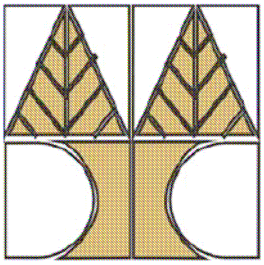


UNIVERSITY OF CYPRUS

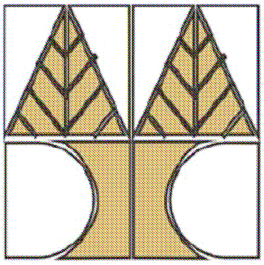
DEPARTMENT OF CHEMISTRY

Doctorate Thesis

New Chemistry of 1,2,3-Dithiazoles

Sophia Stavrou Michaelidou

November 2011



UNIVERSITY OF CYPRUS
DEPARTMENT OF CHEMISTRY

Doctorate Thesis

Sophia Stavrou Michaelidou

Examination Committee:

Prof. Oleg, A. Rakitin, Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, (External Examiner)

Dr. Carlos F. Marcos, Universidad de Extremadura, (External Examiner)

Dr. Nicolas Chronakis, University of Cyprus (Committee Chairman)

Dr. Athanasios Nicolaides, University of Cyprus (Internal Examiner)

Dr. Panayiotis A. Koutentis, University of Cyprus (Project Supervisor)

November 2011

EXPERIMENTAL PROCESSES ACCOMPLISHMENT STATEMENT

Except where noted below the work described within this thesis has been carried out exclusively by Sophia S. Michaelidou at the Organic Chemistry Research Laboratory, in the Department of Chemistry, University of Cyprus under the supervision of Dr. Panayiotis A. Koutentis, (September 2004-May 2010).

The exceptions include: the single x-ray crystallographic studies (performed by Dr. Andrew J. P. White at Imperial College London and Dr. Anastasios J. Tasiopoulos of the Department of Chemistry, University of Cyprus); the elemental analysis of all compounds (performed by Stephen Boyer of London Metropolitan University); high resolution mass spectrometry (performed by John Barton of Imperial College London) and biological studies (performed by A*STAR, Institute of Chemical and Engineering Sciences, Singapore; Dr. Valerie Thiéry, Université de La Rochelle, France; and Dr. Paris A. Skourides, Department of Biological Sciences, University of Cyprus).

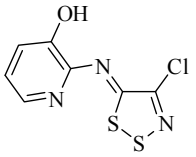
Date

……..

Signature

……..

To my Grandmother Sophia and Uncle Anthony



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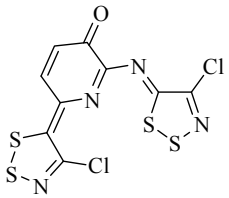

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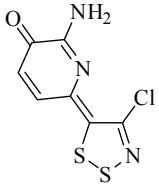

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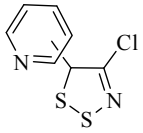

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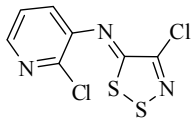
70g (pyrid-3-yl)
70l (pyrid-4-yl)



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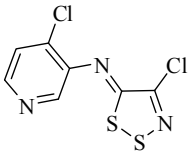

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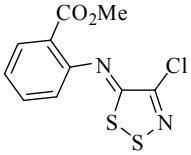

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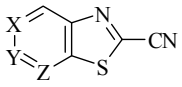

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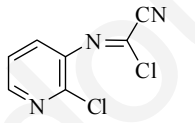
98 (X = Z = CH, Y = N)
99 (X = N, Y = Z = CH)



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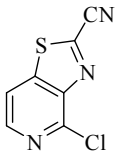

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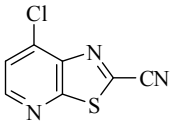

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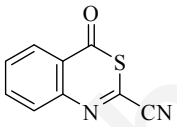

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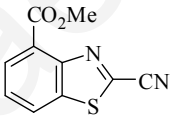

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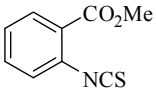

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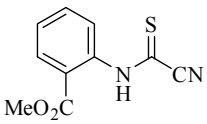

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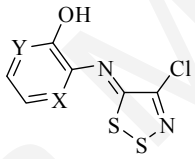
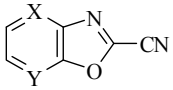


66 (X = Y = CH)
70h (X = CH, Y = N)
70b (X = N, Y = CH)



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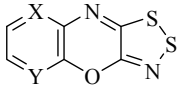

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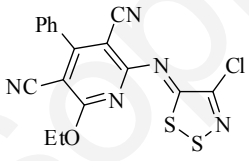

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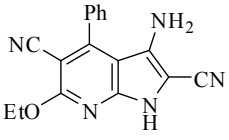

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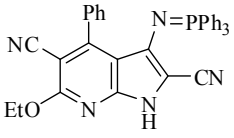

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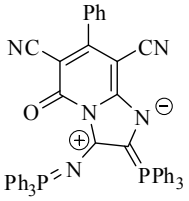

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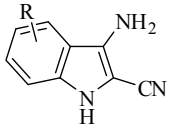


222a-h

a (R = H); **b** (R = 4-O_2N); **c** (R = 4-O_2N-2-Br);
d (R = 5-Cl); **e** (R = 4-Cl); **f** (R = 3-Me); **g** (R = 5-MeO);
h (R = 4,5-$(MeO)_2$)

ABSTRACT

After a general introduction on the synthesis of heterocycles and the chemistry of 1,2,3-dithiazoles (Chapter 1), new chemistry of 1,2,3-dithiazoles is discussed in Chapters 2, 3, 4 and 5. Fourteen new (4-chloro-5*H*-1,2,3-dithiazolylideneamino)azines were synthesized successfully. Dithiazolylidene **70b** was obtained in very low yields because of the side reactions that also gave the highly coloured purple and blue dithiazolylidenes **74** and **76** (Chapter 2).

Chapter 3 focuses on the cyclization reactions of the dithiazolylidenes **70a,g,i,j,l,** and **103** which give the corresponding thiazolopyridine-2-carbonitriles **97**, **98, 99**, (2-chloro-pyridin-3-yl)carbon cyanidimidic chloride **100,** 4-chlorothiazolo[4,5-*c*]pyridine-2-carbonitrile **101**, 7-chlorothiazolo[5,4-*b*]pyridine-2-carbonitrile **102,** 4-oxo-4*H*-benzo[*d*][1,3]thiazine-2-carbonitrile **104**, 2-cyanobenzothiazole-4-carboxylate **105**, 2-isothiocyanatobenzoate **106** and (*Z*)-methyl-2-(cyanothioformanilido)benzoate **107** respectively.

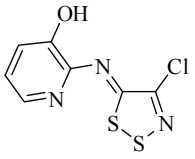
Chapter 4 describes the cyclization reactions of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66**, 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-X-ol (where X = 2 and 3) **70h** and **70b** which afforded the corresponding oxazoles **67**, **118**, **120** and oxazines **114** and **119**. The oxazine **114** and **119** can also rearrange to the corresponding oxazoles **67** and **118**.

Chapter 5 focuses on the chemistry of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** which gives access to a wide range of heterocyclic compounds.

Chapters 6 focuses on the reaction of fully substituted 2-(dithiazolylidene-amino)pyridine **160** with Ph_3P which affords the 3-aminoindole-2-carbonitriles **212**, (2-cyano-indol-3-yl)iminotriphenylphosphorane **213** and 6-cyano-5-oxo-7-phenyl-2,5-bis(tri-phenylphosphino)-imidazo[1,2-*a*]pyridin-4-ium-1-ide **214**. A range of 3-aminoindole-2-carbo-nitriles **222** were synthesized and investigated.

Chapter 7 focuses on the independent synthesis of 3-aminoindole-2-carbonitriles **222** using two different methodologies.

Chapter 8 focuses on the biological studies on the dithiazolylidenes that were carried out from collaborators in Cyprus and abroad. All the products are fully characterized (Chapter 9).



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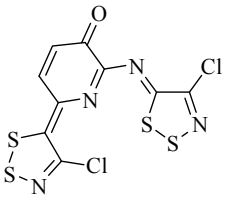

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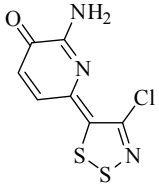

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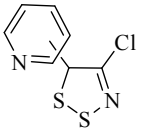
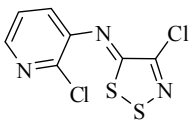
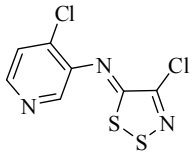




70a (pyrid-2-yl) **70i**
70g (pyrid-3-yl)
70l (pyrid-4-yl)



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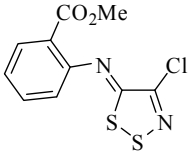

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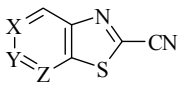

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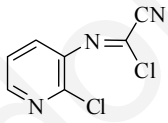
98 (X = Z = CH, Y = N)
99 (X = N, Y = Z = CH)



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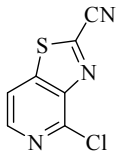

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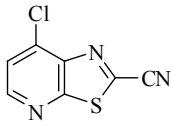

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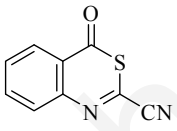

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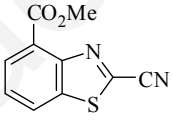

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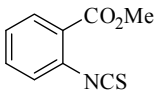

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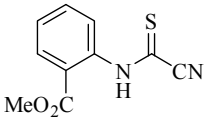

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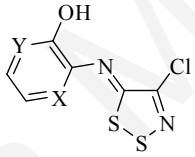
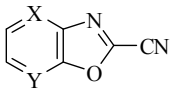
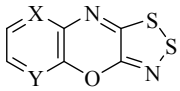


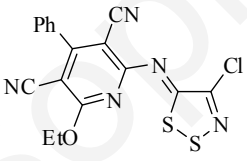
66 (X = Y = CH)
70h (X = CH, Y = N)
70b (X = N, Y = CH)



67 (X = Y = CH)
118 (X = CH, Y = N)
120 (X = N, Y = CH)



114 (X = Y = CH)
119 (X = CH, Y = N)



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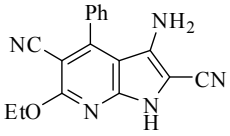

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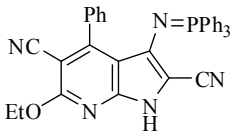

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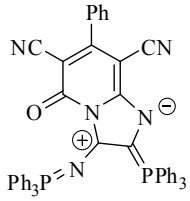

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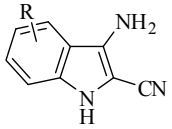

222a-h

a (R = H); **b** (R = 4-O_2N); **c** (R = 4-O_2N-2-Br);
d (R = 5-Cl); **e** (R = 4-Cl); **f** (R = 3-Me); **g** (R = 5-MeO);
h (R = 4,5-$(MeO)_2$)

ΠΕΡΙΛΗΨΗ

Μετά τη σύντομη εισαγωγή (Κεφάλαιο 1) για τις 1,2,3-διθειαζόλες, ακολουθεί περιγραφή νέας χημείας των 1,2,3-διθειαζολών στα Κεφάλαια 2-5. Ένα εύρος από 14 (4-χλωρο-5*H*-1,2,3-διθειαζολυλιδυνεαμινο)αζίνες παρασκευάστηκε. Η διθειαζολυλιδίνη **70b** λήφθηκε σε πολύ χαμηλή απόδοση λόγω σχηματισμού των διθειαζολυλιδινών **74** και **76** (Κεφάλαιο 2).

Το κεφάλαιο 3 εστιάζεται στις αντιδράσεις κυκλοποίησης των διθειαζολιδινών **70a,g,i,j,l,** και **103** τα οποία δίνουν ως προιόντα τα ανάλογα θειαζολοπυριδινο-2-καρβονιτρίλια **97**, **98**, **99**, το (2-χλωροπυριδιν-3-υλ)καρβοκυανιδιμικό χλωρίδιο **100,** το 4-χλωροθειαζολο[4,5-*c*]πυριδο-2-καρβονιτρίλιο **101**, το 7-χλωροθειαζολο[5,4-*b*]πυριδινο-2-καρβονιτρίλιο **100,** 4-οξο-4*H*-βενζο[*d*][1,3]θειαζινο-2-καρβονιτρίλιο **104**, 2-κυανοβενζο-θειαζολο-4-καρβοξυλιο **105**, 2-ισοθειοκυανοβενζοικό **106** και (*Z*)-μεθυλο-2-(κυανοθειο-φορμανιλιδο)βενζοικο **107**.

Το κεφάλαιο 4 εστιάζεται στις αντιδράσεις κυκλοποίησης των διθειαζολιδινών **66**, **70h** και **70b** οι οποίες δίνουν ως προιόντα τις ανάλογες οξαζόλες **67**, **118**, **120** και οξαζίνες **114** και **119**. Οι οξαζίνες **114** και **119** μπορούν να αναδιαταχθούν προς σχηματισμό των ανάλογων οξαζολών **67** και **118**.

Το κεφάλαιο 5 επικεντρώνεται στη χημεία της 2-(4-χλωρο-5*H*-1,2,3-διθειαζολο-5-υλιδυναμινο)-6-αιθοξυ-3,5-δικαρβονιτριλο-4-φαινυλοπυριδίνης **160** η οποία δίνει πρόσβαση σε ένα εύρος από ετεροκυκλικά μόρια.

Το κεφάλαιο 6 εστιάζεται στη αντίδραση της διθειαζολιδίνης **160** με Ph_3P η οποία δίνει ως προιόντα το 3-αμινο-ινδολο-2-καρβονιτρίλιο **212**, (2-κυανοινδολ-3-υλ)ιμινο-τριφαινυλοφοσφωράνιο **213** και 6-κυανο-5-οξο-7-φαινυλο-2,5-δις(τριφαινυλοφωσφινο)-ιμιδαζο[1,2-*a*]πυριδιν-4-ιο **214**. Επιπλέον ένα εύρος από 3-αμινο-ινδολο-2-καρβονιτρίλια **222** συντέθηκε και μελετήθηκε.

Το κεφάλαιο 7 επικεντρώνεται στην ανεξάρτητη σύνθεση των 3-αμινο-ινδολο-2-καρβονιτριλίων **222** χρησιμοποιώντας δύο διαφορετικές μεθοδολογίες.

Το κεφάλαιο 8 επικεντρώνεται στις βιολογικές μελέτες των διθειαζολιδινών που πραγματοποιήθηκαν από συνεργάτες τόσο στην Κύπρο όσο και στο εξωτερικό. Όλα τα προιόντα που συντέθηκαν χαρακτηρίστηκαν πλήρως (κεφάλαιο 9).

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I thank all past and present members of Koutentis Research Group (KRG) particularly Irene, Christos, Harry, Theodosia, Georgia, Andreas and Marina for being so friendly and for their support all these years. Outside the lab I thank Maria, Charalambos and Marios from Dr. Nikos Chronakis laboratory and Dr. Petro Savva from TEPAK for their support and friendship.

Furthermore, I would like to thank my family, especially my husband, and my friends for their love, support and encouragement.

Also I would like to dedicate this thesis to my Grandmother Sophia and Uncle Anthony who passed away while I was working on my PhD.

CONTENTS

Brief Contents

Detailed Contents

ABBREVIATIONS

Å	Ångström unit
Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Alk	alkyl
ANRORC	Addition of Nucleophile Ring Opening Ring Closure
app.	apparent
aq.	aqueous
Ar	argon atmosphere
Bn	benzyl
br	broad
Bz	benzoyl
ca.	approximately (latin: *circa*)
CD_2Cl_2	deuterated dichloromethane
$CDCl_3$	deuterated chloroform
cf.	compare (latin: *confer*)
cm^{-1}	wavelength unit
18-Crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
d	doublet (NMR) or days
2D	two-dimensional
Da	Dalton unit (mass spectrometry)
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	double doublet
ddd	doublet of double doublets
DDQ	2,3-dichloro-5,6-dicyano-4-benzoquinone
decomp.	decomposition

DEPT	distortionless enhancement by polarization transfer
DIBOC	di-*tert*-butyl dicarbonate
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
dppf	1,1′-bis(diphenylphosphino)ferrocene
DSC	Differential Scanning Calorimetry
E	electrophile
e.g.	for example, (Latin: *exempli gratia*)
EI	electron ionization
equiv.	equivalent
Et	ethyl
eV	electron volt unit
FTIR	Fourier transform infrared
g	gas
GCMS	gas chromatography mass spectrometry
gem	geminal
h	hour
Hal	halogen
HOMO	Highest Occupied Molecular Orbital
Hünig's base	diisopropylethylamine
hv	photolysis
Hz	Hertz unit
I_A	Birds aromaticity index
Inf	Inflection
In vacuo	under reduced pressure
i-Pr	isopropyl
IR	infrared
J	coupling constant (measured in Hz)
LDA	lithium diisopropylamide
LG	leaving group
liq.	liquid

lit.	literature
LRMS	Low Resolution Mass Spectrometry
m	multiplet (NMR) or medium (IR)
m/z	mass to charge ration
M^+	molecular ion
Me	methyl
MHz	Megahertz unit
min	minutes
mp	melting point
Ms	methanesulfonyl
MW	microwave
NBS	*N*-bromosuccinimide
nd	no data
nm	nanometer unit
NMR	Nuclear Magnetic Eesonance
n-Pr	*n*-propyl
Nu	nucleophile
^oC	Celsius degrees
ox	oxidation
Ph	phenyl
PhCl	chlorobenzene
PhH	benzene
pK_b	negative log of the base dissociation constant, K_b
ppm	parts per million
psi	pounds per square inch (1 psi equals to 6894.76 Pa)
Py	pyridine
q	quartet
rt	room temperature
rxn	reaction
s	singlet (NMR) or strong (IR)
sat.	saturated
t	triplet

TCNEO	tetracyanoethyleneoxide
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Torr	Torricelli (unit of pressure equal to 1/760 atmosphere)
Ts	4-toluenesulfonyl
TsCl	4-toluenesulfonic chloride
TsOH	4-toluenesulfonic acid
TTF	tetrathiafulvalene
UV	ultraviolet
Vis	visible
W	Watt unit
w	weak (IR)
δ	chemical shift relative to a standard
Δ	heat (Thermolysis)
λ_{max}	maximum wavelength
μL	microlitre unit

CHAPTER 1

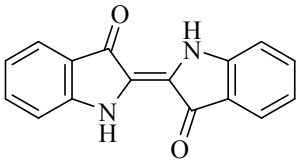
Introduction

Sections

1.1 Introduction

1.1.1 Heteroaromaticity

The term heteroatom refers to any atom other than carbon. Any ring system which contains at least one heteroatom can be described as heterocyclic and such ring systems are well known. Many of them present important properties in various drugs, toxicants, agrochemicals and find applications in material science. The majority of heterocycles contain nitrogen (*e.g.*, indigo dye)[1] or oxygen (*e.g.*, levofloxacin, which is a synthetic chemotherapeutic antibiotic)[2,3] but an increasing number of important compounds are appearing which contain sulfur such as saccharin (artificial sweetener),[4] penicillin (antibiotic),[5] amiphenazole (banned bodybuilding drug),[6,7] tetrathiafulvalene (TTF)[8] and polythiophene (organic conductors).[9]



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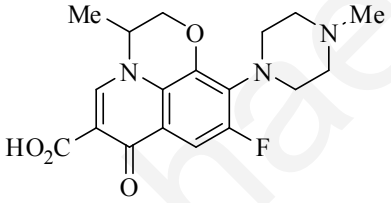
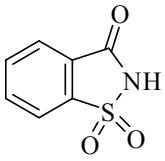
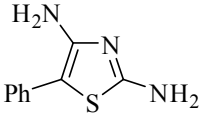


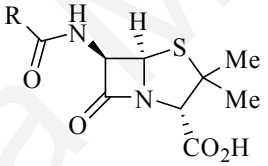
Levofloxacin



Saccharin



Amiphenazole



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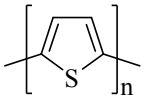
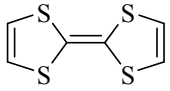


Polythiophene



Tetrathiafulvalene

The unsaturated heterocyclic compounds that obey Hückel's rule (4n+2) are aromatic and therefore they are called heteroaromatic. The replacement of a CH group in benzene by a nitrogen atom gives the 6-membered aromatic heterocycle pyridine. The replacement of an ethylene (CH=CH) group by a NH, O or S gives the 5-membered heteroaromatic compounds pyrrole, furan and thiophene, respectively.

Pyridine **Pyrrole** **Furan** **Thiophene**

The pyridine ring nitrogen is sp^2 hybridized, planar and trigonal with one lone pair in the plane of the ring occupying the space of the C-H bond in benzene (Figure 1). The pyrrole ring nitrogen is also sp^2 hybridized but here the lone pair of electrons is orthogonal to the plane of the ring and participates in electron delocalization. The heteroatoms of furan and thiophene have two lone pairs of electrons, one in the plane of the ring and one orthogonal to the plane of the ring.

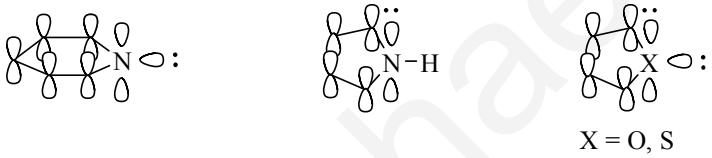
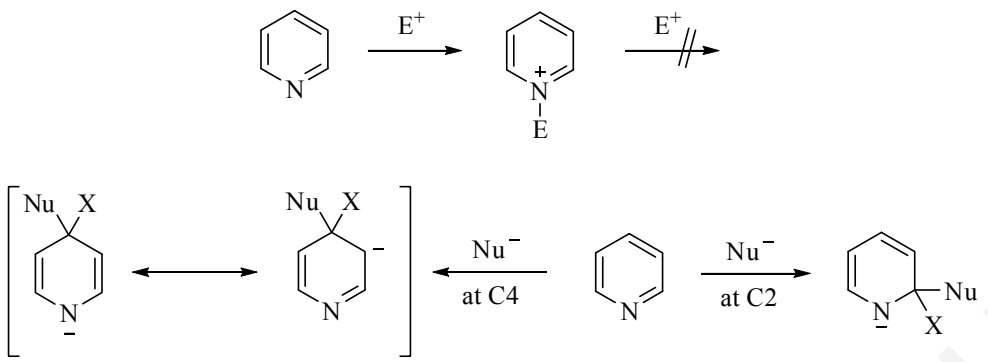


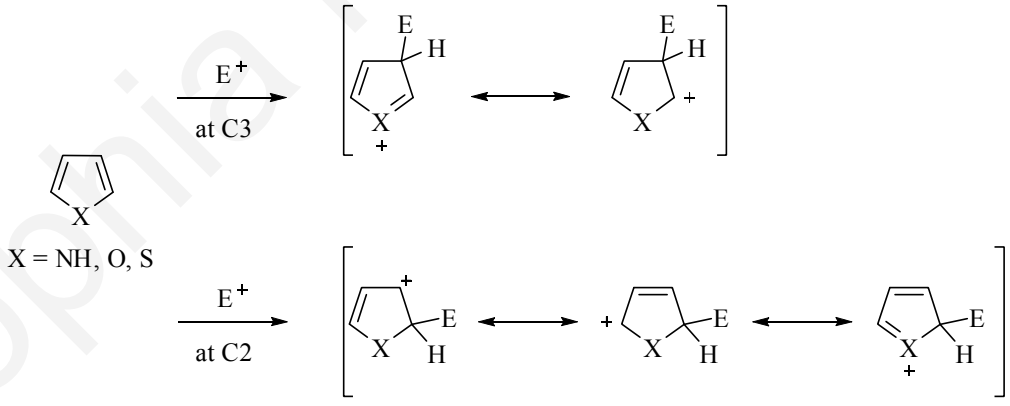
Figure 1. Selected orbital representations of pyridine, pyrrole, furan and thiophene.

The replacement of a benzene CH group by a heteroatom results in significant changes of both the physical and chemical properties. For example pyridine is a weak base ($pK_b = 8.75$)[10] and since the lone pair of electrons on nitrogen cannot be delocalized around the ring, pyridine is nucleophilic *via* the nitrogen atom. The electronegative nitrogen atom makes pyridine less reactive than benzene towards electrophilic aromatic substitution and the nitrogen preferentially attacks the incoming electrophile making the ring even less reactive. Nucleophilic substitution however, which is difficult for benzene, occurs easily on pyridine, particularly at the C2 and C4 positions (Scheme 1). Attack at the C3 position is less favored because the negative charge on the intermediate cannot be stabilized by the electronegative nitrogen atom.



Scheme 1

The lone pair of electrons on the 5-membered heterocycles pyrrole, furan and thiophene are not readily available for protonation since they are delocalized onto the ring and consequently these heterocycles are not basic. The extent of delocalization depends on the electronegativity of the heteroatom. Increased electronegativity reduces the contribution of the lone pair to the delocalization and hence the aromaticity follows the order thiophene > pyrrole > furan. The C2 position is more reactive than the C3 position towards electrophiles because reaction at the C2 position results in better delocalization of the positive charge (Scheme 2). Nucleophilic substitution is relatively rare with thiophene, pyrrole and furan and to facilitate this reaction, these electron rich systems require an activating group just as with benzene.



Scheme 2

Multiple replacements of CH groups are also possible and 5- or 6-membered heterocycles with up to four heteroatoms are common. Therefore, the structural possibilities that arise from the displacement of CH groups by heteroatoms are many. Furthermore, among approximately 20 million chemical compounds identified by the end of the second millennium, more than two-

thirds are fully or partially aromatic and approximately half are heteroaromatic compounds. Heterocycles are important, not only because of their abundance, but their structural diversity leads to a wide range of chemical, biological and physical properties. A consequence of which, is that heterocycles count among their number many natural products, such as vitamins, hormones, antibiotics, alkaloids, as well as pharmaceuticals, herbicides, dyes, and other products of technical importance (corrosion inhibitors, anti-aging drugs, sensitizers, stabilizing agents, etc.).[11] A brief introduction about the synthesis of heterocycles is presented below.

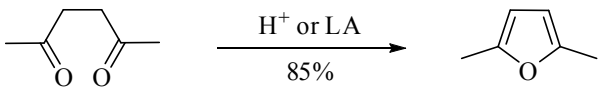
1.2 Synthesis of Heterocyclic Systems

1.2.1 Ring Construction from Acyclic Precursors

One strategy for the synthesis of heterocycles is intramolecular ring construction from an acyclic precursor. This intramolecular cyclization can be achieved either *via* the formation of a C-C or a C-X bond (whereas X = N, O, S). In this category we can find pericyclic (sigmatropic or electrocyclic) or non-pericyclic reactions. Another strategy involves intermolecular ring construction from acyclic precursors. Again the cyclization can be achieved *via* the formation of a C-C or a C-X bond. In this category we can again find both pericyclic (cycloaddition) and non-pericyclic reactions.

1.2.1.1 Intramolecular Ring Construction from Acyclic Precursors via the Formation of a C-C or C-X Bond

A common way to form 5- and 6-membered rings is *via* the formation of a C-X bond using non-pericyclic reactions. An example is the classical Paal-Knorr synthesis of furan **2** that involves the acid catalyzed cyclization of 1,4-dicarbonyl compounds **1** (Scheme 3).[12-15]

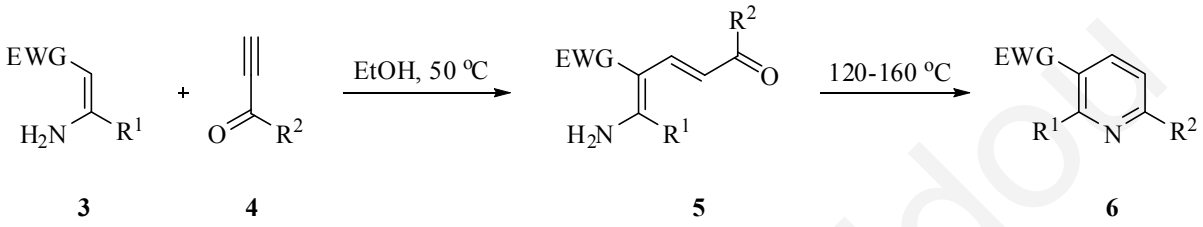


1 **2**

Scheme 3

An example for a hetero-intramolecular ring construction of six-membered rings is the Bohlmann-Rahtz pyridine synthesis. This synthesis allows the generation of substituted pyridines in two steps. Condensation of enamines **3** with ethynylketones **4** leads to an

aminodiene isolable intermediate **5** that, after heat-induced *E*/*Z* isomerization, undergoes a cyclodehydration to yield 2,3,6-trisubstituted pyridines **6** (Scheme 4).[16] The high temperatures which are necessary for the last step, can be avoided by performing the condensation under acidic conditions.[17]

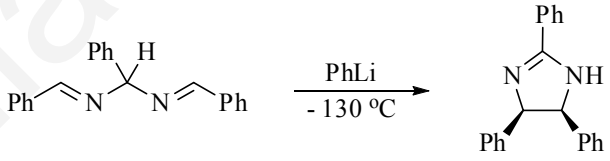


3 **4** **5** **6**

EWG = Electron Withdrawing Group
R^2 = RCO or CN

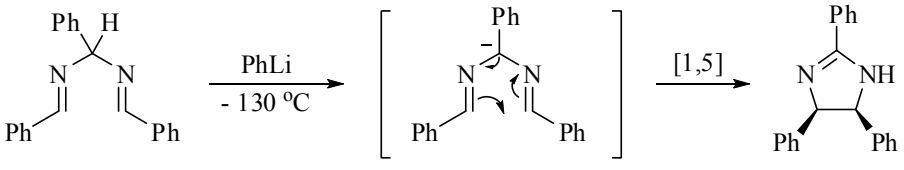
Scheme 4

Another common way to form a ring is through a pericyclic reaction. In the case where the cyclization is intramolecular, the pericyclic reactions are limited into sigmatropic and electrocyclic reactions. An example of a [1,5] sigmatropic intramolecular ring closure *via* the formation of a C-C bond is the cyclization of (*N*,*N*'*E*,*N*,*N*'*E*)-*N*,*N*'-(2-phenylpropane-1,3-diylidene)dianiline **7** which in the presence of a strong base like PhLi can cyclize into (4*R*,5*S*)-2,4,5-triphenyl-4,5-dihydro-1*H*-imidazole **8** (Scheme 5).[18]



7 **8**

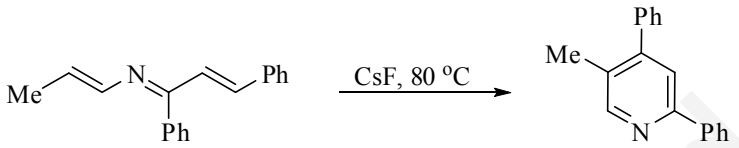
Mechanism



7 **8**

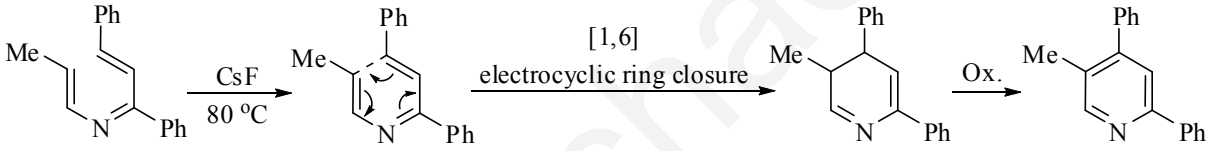
Scheme 5

Another example of a pericyclic reaction used to form a 6-membered ring *via* C-C bond formation is the electrocyclic ring closure of vinyl or aryl 2-azadienes (azatrienes) involving six electrons.[19] For example (1*E*,*NZ*)-*N*-[(*E*)-1,3-diphenylallylidene]prop-1-en-1-amine **9** in the presence of heat cyclizes towards the formation of 5-methyl-2,4-diphenylpyridine **10** in 67% yields (Scheme 6).[19]



9 **10**

Mechanism

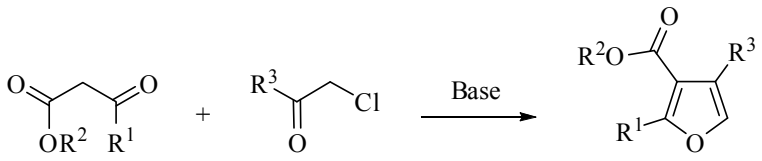


9 **10**

Scheme 6

1.2.1.2 Intermolecular Ring Construction from Acyclic Precursors via the Formation of a C-C or C-X Bond

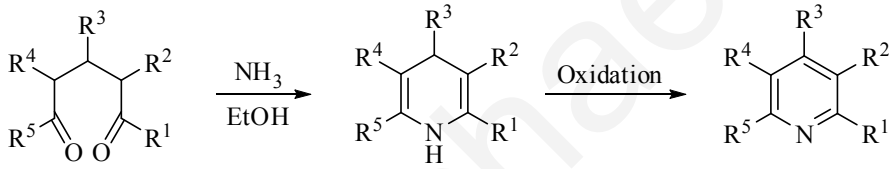
The most common way to synthesize 5- and 6-membered rings is *via* intermolecular ring construction using two or more acyclic precursors. A characteristic example for the ring construction of 5-membered rings is the Fiest-Benary synthesis of furans. *a*-Halocarbonyl compounds **11** can react with 3-oxocarboxylates **12** in the presence of base, to give substituted alkyl 3-furoates **13**[20] in moderate yields (Scheme 7). Potassium hydroxide, pyridine, alkyl amines, sodium acetate or sodium alkoxides can be used as bases.



11 **12** **13**

Scheme 7

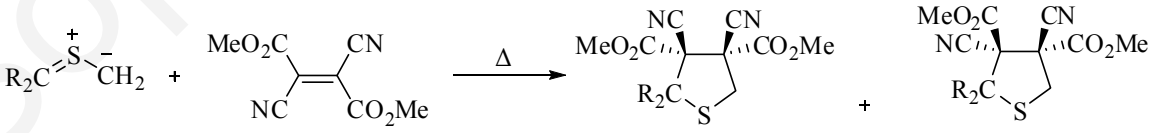
An example for the construction of 6-membered rings is the condensation of 1,5-dicarbonyls with primary amines. For example 1,5-dicarbonyls **14** can react with ammonia and give 1,4-dihydropyridines **15**. These compounds can be oxidized from atmospheric oxygen or by specially introduced oxidants to give substituted pyridines **16** (Scheme 8).[21]



14 **15** **16**

Scheme 8

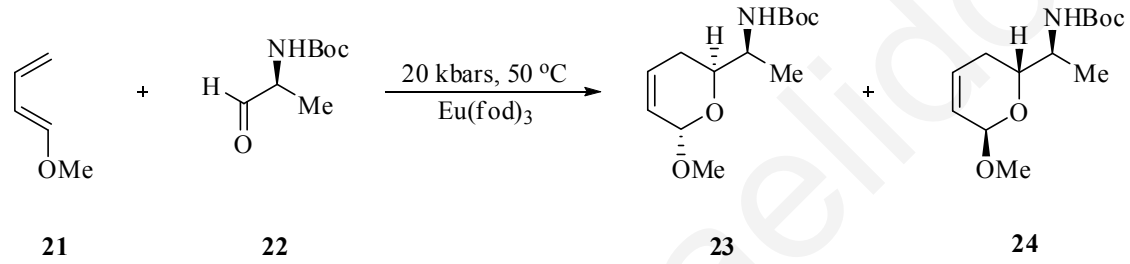
Cyclic compounds can also be prepared *via* pericyclic reactions. An example of a pericyclic reaction is the 1,3-dipolar cycloaddition of substituted methylenesulfonium **17** and dimethyl 2,3-dicyanofumarate **18** to give a mixture of substituted (3*R*,4*S*)-dimethyl-3,4-dicyanodihydro-thiophene-3,4-dicarboxylate **19** and (3*R*,4*R*)-dimethyl 3,4-dicyanodihydrothiophene-3,4-dicarboxylate **20** (Scheme 9).[22-24]



17 **18** **19** **20**

Scheme 9

A popular pericyclic reaction for the preparation of 6-membered heterocyclic rings is the Diels-Alder reaction. This cycloaddition reaction proceeds more efficiently if the diene is electron rich and the dienophile is electron poor. For example (*E*)-1-methoxybuta-1,3-diene **21** can react with (*S*)-tert-butyl 1-oxopropan-2-ylcarbamate **22** to give a mixture of *tert*-butyl (*S*)-1-[(2*S*,6*S*)-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl]ethylcarbamate **23** and *tert*-butyl (*S*)-1-[(2*R*,6*R*)-6-methoxy-3,6-dihydro-2*H*-pyran-2-yl]ethylcarbamate **24** (Scheme 10).[25] In this case the Diels-Alder reaction is promoted by high pressure and Lewis acid catalysis.



21 **22** **23** **24**

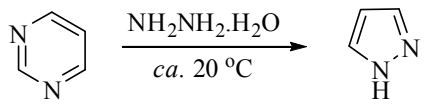
Scheme 10

1.2.2 Ring Transformation

The synthesis of heterocycles *via* ring transformation is one of the most interesting attributes of heterocyclic systems.[26] Small rings (3, 4 or 5-membered) under the appropriate conditions can be transformed to bigger rings (4, 5 or 6-membered, respectively) and *vice versa*. Ring transformations can also occur with retention of ring size. Ring transformations in chemistry are very important because they can give fast access to complex heterocycles that would otherwise be difficult to access *via* classical routes. A large number of these structural rearrangements are triggered by intermediates incorporating positively charged or electron deficient atoms.[27]

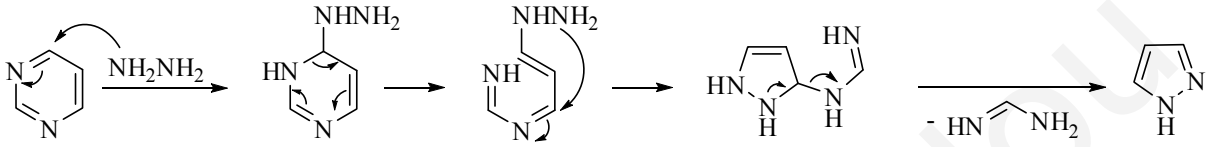
1.2.2.1 Ring Contraction

An example of a ring contraction is the reaction of pyrimidine **25** with hydrazine hydrate at *ca.* 20 °C to give the pyrazole **26** (Scheme 11).[28] This reaction involves a nucleophilic attack of the hydrazine hydrate to the pyrimidine ring **25** at C4 causing ring opening and then ring closure forming the pyrazole **26**.



25 **26**

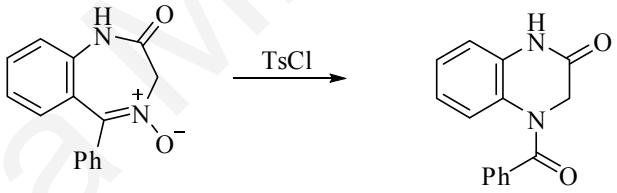
Mechanism



25 **26**

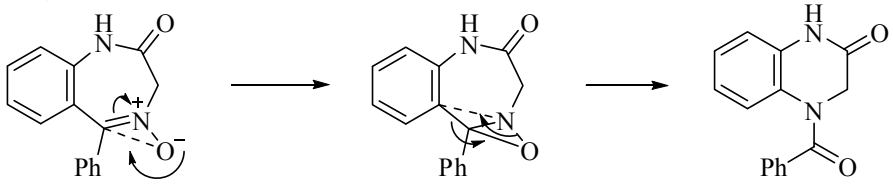
Scheme 11

An example of a ring contraction of a 7-membered ring into a 6-membered ring is the rearrangement of 2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepine 4-oxide **27** which in the presence of TsCl gives 4-benzoyl-3,4-dihydroquinoxalin-2(1*H*)-one **28** as product (Scheme 12).[29]



27 **28**

Mechanism

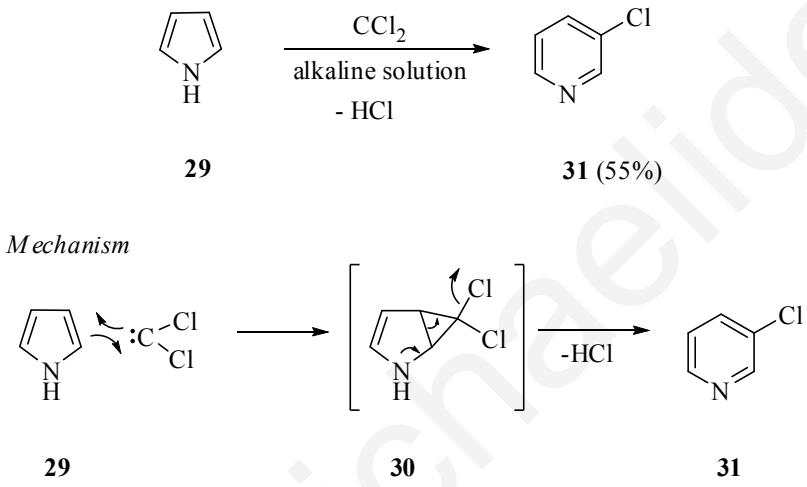


27 **28**

Scheme 12

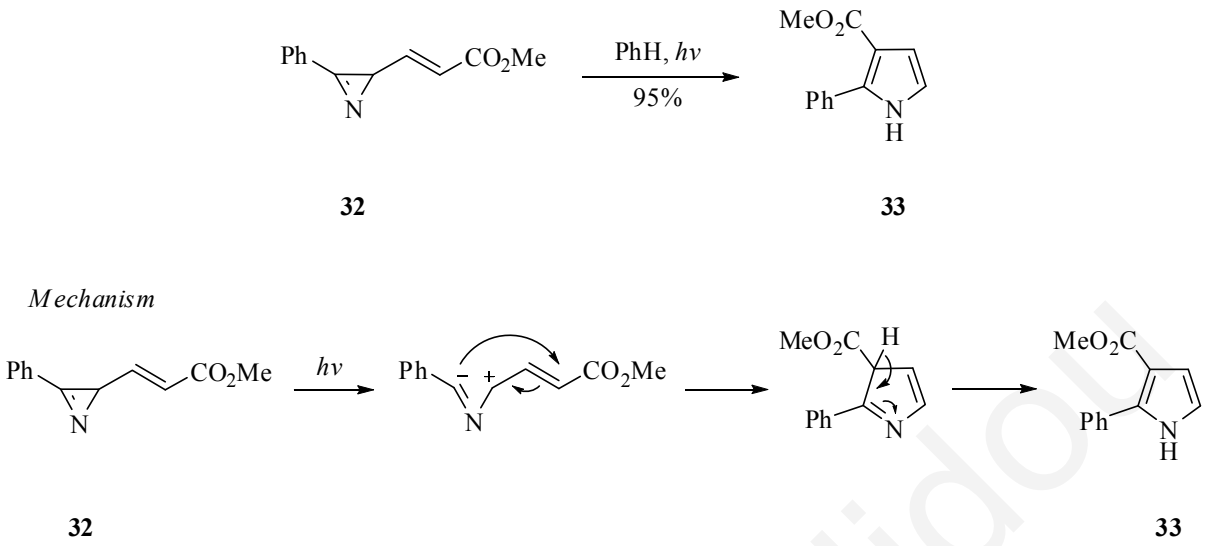
1.2.2.2 Ring Expansion

An example of a ring expansion is the Ciamician-Dennsted rearrangement for the synthesis of pyridines. This rearrangement involves expansion of a pyrrole ring **29** by heating with chloroform or other halogeno compounds in alkaline solution. The intermediate dichlorocarbene adds to the pyrrole to give an unstable dihalogenocyclopropane **30** that rearranges to a 3-halogenopyridine **31** (Scheme 13).[30,31]



Scheme 13

Another characteristic example of a ring expansion is the synthesis of pyrrole from azirines. 2*H*-Azirines that have a 2-vinyl substituent can undergo thermal and photochemical rearrangement to form pyrroles.[32-34] For example, the azirine acrylic ester **32** undergoes photo-rearrangement in benzene to give the pyrrole **33** (Scheme 14).[32]

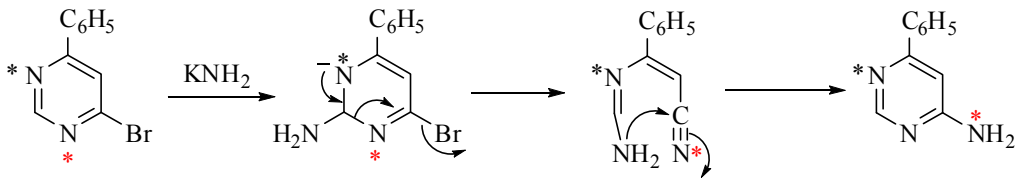


Scheme 14

1.2.2.3 Ring Size Retention (Degenerate)

5- or 6-Membered rings can be transformed to rings with the same number of atoms under the appropriate conditions. When one or more atoms of the heterocyclic ring are replaced with one or more atoms of a reagent in a way that the starting and the product heterocycle are the same but sometimes with different substituents the "rearrangement" is called degenerate (*ipso*) rearrangement.[26,35] Since the starting material and the product can appear unchanged, these types of rearrangements are very difficult to detect and are often overlooked. The only ways to validate this type of rearrangement are by isotopic labeling or by low temperatures NMR studies (Dynamic NMR).

An example of this rearrangement is the reaction of 6-bromo-4-phenylpyrimidine **34** with KNH_2 in NH_3 (l) which gives as a product the 6-amino-4-phenylpyrimidine **35** (Scheme 15). Seemingly the starting pyrimidine is the same as the final pyrimidine but after using labeled ^{15}N in the pyrimidine it was shown that the one ring nitrogen atom was replaced by the nitrogen of the ammonia (Scheme 15).[36]

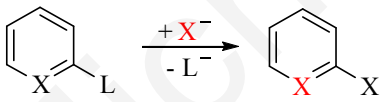


34 **35**

Scheme 15

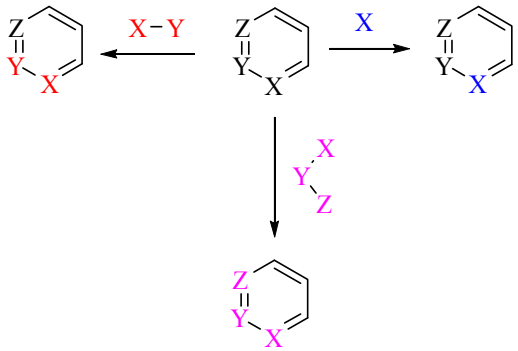
This rearrangement can be divided into two categories:[37]

A) In the first category of the degenerate ring rearrangement, the first step involves a nucleophilic attack of a reagent to the heterocycle, which leads to ring opening and elimination of a leaving group. The next step involves cyclization of the compound leading to replacement of the heteroatom of the ring system by the heteroatom of the reagent. When the leaving group is a substituent of the heterocycle then it is an "external" leaving group (Scheme 16).



Scheme 16

When the leaving group is a part of the heterocyclic system then it is called an "internal" leaving group and can be composed by one or more heteroatoms (Scheme 17).

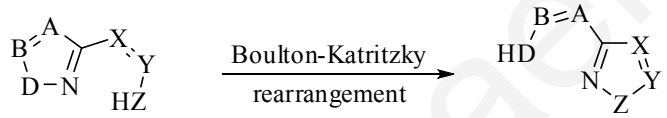


Scheme 17

B) In the second category of degenerate ring transformations, we have participation of the side chain and the heteroatom of the ring is replaced by the same heteroatom which is present

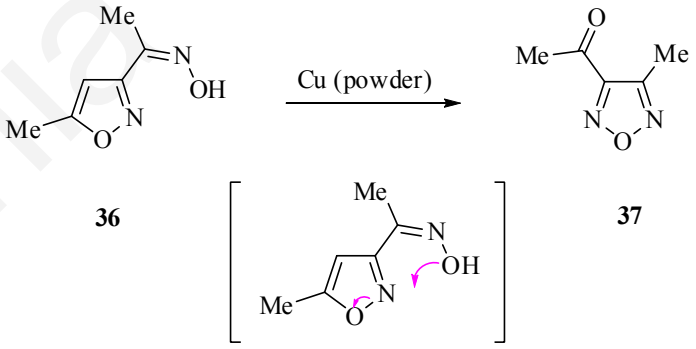
in the side chain. This kind of rearrangement has been observed in 5- and 6-membered aromatic and non-aromatic heterocyclic systems. This rearrangement can be initiated by heating, light as well as by acids or bases.[38]

An example of this category is the Boulton-Katritzky rearrangement. This type of reaction is often initiated by either an acid or a base or under photo irradiation. This reaction has been reported to occur *via* a unimolecular one-step mechanism and suggested to be a [1,9]-sigmatropic rearrangement; but a recent computational study suggests a pseudo-pericyclic reaction. This reaction has been widely used in the synthesis of benzothiazoles, benzofurans, anthranils and indazoles (Scheme 18).[39,40]



Scheme 18

An example of a Boulton-Katritzky ring transformation is the rearrangement of (*Z*)-1-(5-methylisoxazol-3-yl)ethanone oxime **36** to give 1-(4-methyl-1,2,5-oxadiazol-3-yl)ethanone **37** on heating with Cu powder (Scheme 19).[40]



36 **37**

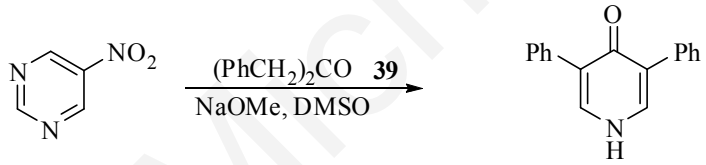
Scheme 19

These types of degenerate rearrangements are also known as invoking the S_N(ANRORC) mechanism. ANRORC stands for **A**ddition of the **N**ucleophile, **R**ing **O**pening and **R**ing **C**losure.[36] Substitution reactions that occur according to the S_N(ANRORC) mechanism and involve a degenerate ring transformation require:

1) That the heterocyclic compound can undergo an initial addition reaction with the nucleophile (which means that the heterocycle is characterized by a considerable π-deficiency).
2) That the nucleophilic displacement takes place with a reagent containing the *same* heteroatom(s) that are present in the heterocycle. The heteroatom in the reagent needs to carry at least one hydrogen atom.[37]

1.2.2.4 Ring Size Retention (Non Degenerate)

If the final ring system is not the same with the starting ring system meaning that they have different number or type of heteroatoms in the ring then the "rearrangement" is called *non-degenerate* rearrangement. An example is the reaction of 5-nitropyrimidine **38** with excess of dibenzylacetone **39** in the presence of NaOMe in DMSO. After 15 h of reaction the product obtained is the 3,5-diphenyl-4-pyridone **40** in 43% yield (Scheme 20).[41]



38 **40**

Scheme 20

Both the starting and final rings have six atoms but the former is a pyrimidine and the latter is a pyridin-4(1*H*)-one. Many non-degenerate reactions involve addition of the nucleophile, ring opening and ring closure. These reactions can be called "ANRORC-type" reactions.

Many reactions of 4-chloro-5*H*-1,2,3-dithiazoles with nucleophiles lead to ANRORC-type non-degenerate ring transformations and even some degenerate ring transformations are known. As such, 1,2,3-dithiazoles are important compounds in heterocyclic synthesis. Furthermore, several dithiazoles show interesting biological and physical properties. For these reasons a brief introduction on 1,2,3-dithiazoles follows.

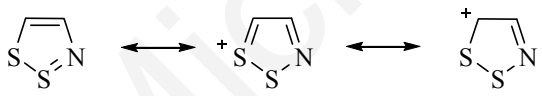
1.3 1,2,3-Dithiazoles

A dithiazole ring is a five membered ring with two carbon atoms, two sulfur atoms and one nitrogen atom. Four types of dithiazoles exist: The 1,2,3-dithiazole,[42] 1,2,4-dithiazole,[43] 1,3,2-dithiazole[44] and 1,3,4-dithiazole[45] represented below as dithiazolium cations (Scheme 21).

1,2,3- 1,2,4- 1,3,2- 1,3,4-

Scheme 21

Our interest focuses on the chemistry of 1,2,3-dithiazoles because of their unusual physical properties, biological activity and synthetic utility. The 1,2,3-dithiazolium ring is planar and 6π aromatic. It can be described by three main resonance forms (Scheme 22),[42] which support considerable electrophilic character at S1, S2 and C5, but not at C4.

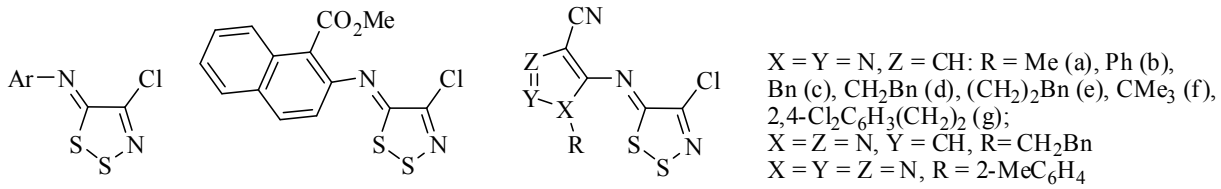


1,2,3-

Scheme 22

1.3.1 Uses of 1,2,3-Dithiazoles

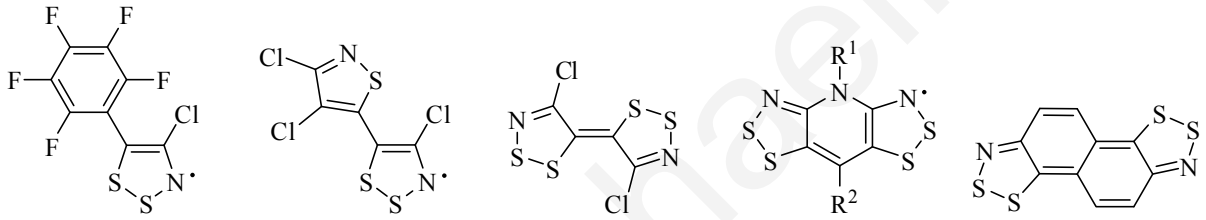
In the biological sciences (dithiazolylideneamino)arenes display antifungal,[46-48] and significant antibacterial activity against gram-positive bacteria.[49,50] The biological activity of these compounds is associated with the presence of the 1,2,3-dithiazole ring, which acts as a powerful inhibitor of several enzymes that are structurally related to serine proteases. They also appear to have herbicidal,[51] ovicidal and insecticidal activities.[46] Some dithiazoles have antitumor activities against human myeloid leucemia and mice leucemia cells[46,51] (Scheme 23).



Antibacterial activities **Antifungal and Antitumor activities**

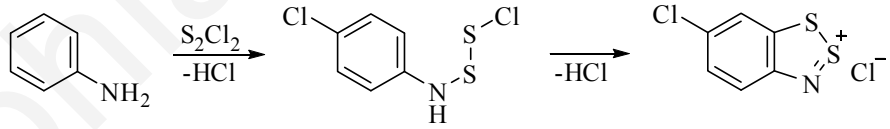
Scheme 23

In the material sciences, several stable 1,2,3-dithiazolyl radicals have been synthesized that are redox active, with potential application in the design of molecular conductors and/or organic magnets.[52-60]



1.3.2 Synthesis of Monocyclic 1,2,3-Dithiazolium Salts

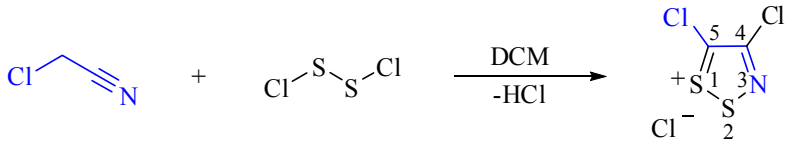
While the reaction of anilines with disulfur dichloride (S_2Cl_2) to give benzo fused dithiazolium salts (Herz salts) **41** (Scheme 24)[61] has been known for over 50 years, the synthesis of monocyclic dithiazolium salts was reported relatively recently.



41

Scheme 24

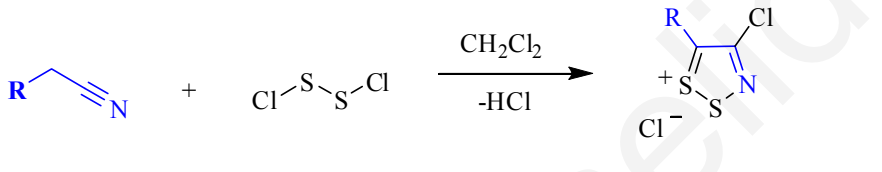
The most well known monocyclic 1,2,3-dithiazolium salt is 4,5-dichloro-1,2,3-dithiazolium chloride **42** (Appel salt). This compound can be synthesized from chloroacetonitrile and disulfur dichloride in DCM. Appel salt **42** is a relatively modern reagent, having been first prepared in the 1980's, and only over the last 20 years has its chemistry been explored and exploited predominantly by Rees and co-workers. It can undergo a variety of reactions initiated by nucleophilic attack at the C5 position (Scheme 25).[42]



42

Scheme 25

1,2,3-Dithiazolium salts **42a-h** can also be obtained from the reaction of other monosubstituted acetonitriles (Scheme 26). [57,61-63]

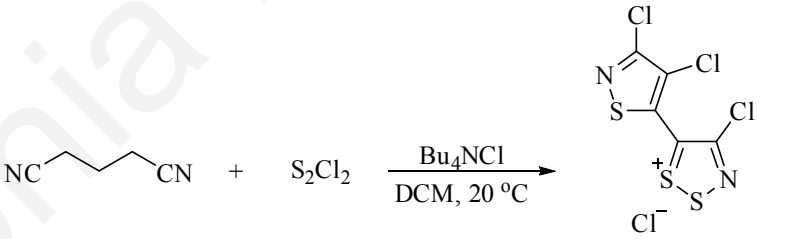


42a-h (20-85%)

R = Cl (**a**), Br (**b**), CN (**c**), SMe (**d**), C_6F_5 (**e**), Ph (**f**), 4-$MeOC_6H_4$ (**g**), 4-$O_2NC_6H_4$ (**h**)

Scheme 26

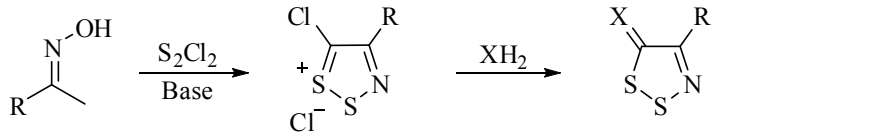
In the case where glutaronitrile **43** was used as starting material and reacted with disulfur dichloride the product isolated was the (isothiazolyl)dithiazolium chloride **44** (Scheme 27).[55]



43 **44** (68%)

Scheme 27

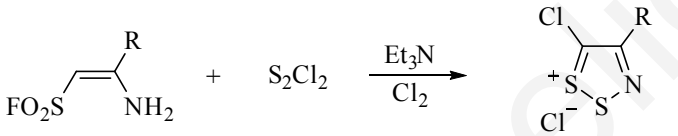
Reaction of substituted (*E*)-acetophenone oxime **45** with disulfur dichloride leads to the formation of the intermediate salt 5-chloro-4-substituted-1,2,3-dithiazol-1-ium chloride **42a-h**[64] which after treatment with water or aniline can form either 4-substituted-1,2,3-dithiazol-5-one **46a** or *N*-(4-substituted-5*H*-1,2,3-dithiazol-5-ylidene)aniline (Scheme 28).[64-68]



45 **42a-h** **46a**, X = O (33%)
46b, X = NPh (24%)

Scheme 28

Moreover, fluorosulfonyl-substituted enamines **47** when reacted with disulfur dichloride form polyfluoroalkyl salts **42i-j** as products (Scheme 29).[69]



47i, R = C_3F_7,
47j, R = $H(CF_2)_5$

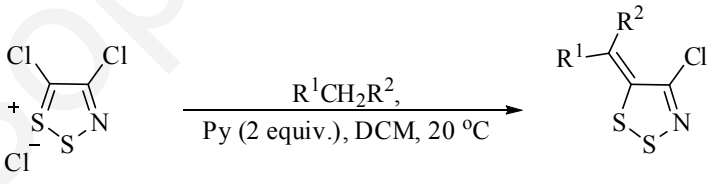
42i (68%)
42j (71%)

Scheme 29

1.3.3 Chemical Reactions of Appel Salt **42**

1.3.3.1 Formation of a C=C Bond at C5

Appel salt **42** readily undergoes nucleophilic attack at the C5 position. For this reason it can react with active methylenes to give (1,2,3-dithiazole-5-ylidene)methanes **48** in good yields (Scheme 30).[70,71] Similarly, cyanoacetic acid esters can react with Appel salt **42** in the presence of pyridine (2 equiv.) at room temperature to give dithiazol-5-ylidenes **48** (Scheme 30).[42]

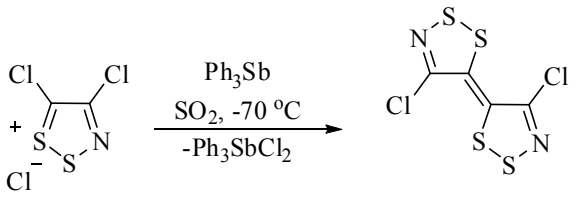


42 **48**

a. $R^1 = R^2 = CN$
b. $R^1 = CN$, $R^2 = CO_2Me$
c. $R^1 = R^2 = CO_2Me$
d. $R^1 = R^2 = SO_2Ph$
e. $R^1 = R^2$ = maleic anhydride
f. $R^1 = R^2$ = pyrimidine-2,4,6 (1*H*,3*H*,5*H*)-trione

Scheme 30

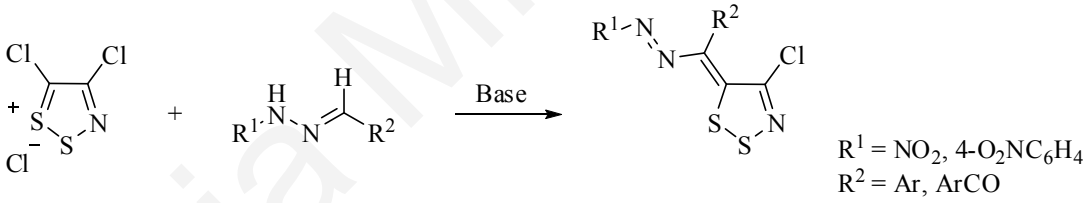
Appel salt **42** can also react with two equivalents of triphenylantimony giving as product the tetrathiadiazafulvalene **49**.[72] The highest yields of **49** was obtained when the reaction took place in liquid SO_2 at -70 ^oC (Scheme 31). This reaction proceeds *via* dimerization of the dithiazolyl radical.



42 **49** (30%)

Scheme 31

Moreover azomethylene derivatives of 1,2,3-dithiazoles can be synthesized by the reaction of Appel salt **42** with *N*-monosubstituted hydrazones **50** (Scheme 32).[73] Their formation probably includes the generation of the carbon anion, under the action of a base, which then adds to the Appel salt **42**.

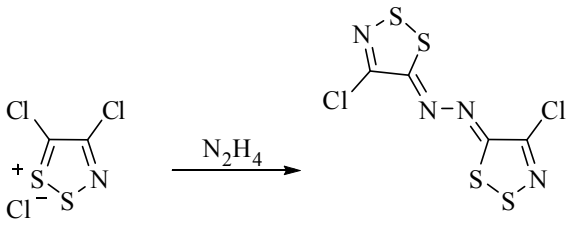


42 **50**

Scheme 32

1.3.3.2 Formation of a C=N Bond at C-5

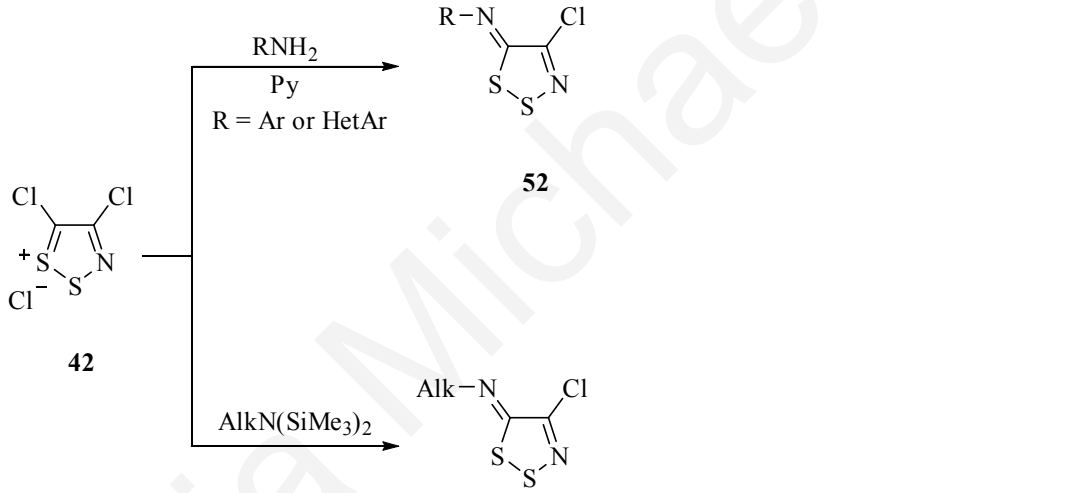
Appel salt **42** can also react with compounds which contain nitrogen atom forming a C=N bond and leading to the synthesis of ylideneamines (imines). When Appel salt reacted with ammonia no obtainable product could be formed. However, reaction with anhydrous hydrazine led to the formation of (1*Z*,2*Z*)-1,2-bis(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene) hydrazine **51** (Scheme 33).[74]



42 **51**

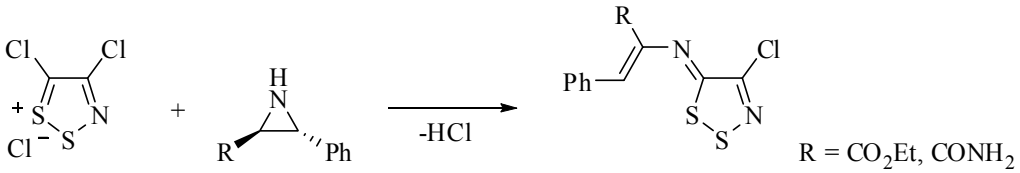
Scheme 33

Moreover, Appel salt **42** can react with aliphatic amines but the obtained yields are low.[42,75] In contrast, reaction with 1° arylamines,[42] quinolinamines and naphthylamines gives (4-chloro-5*H*-1,2,3-dithiazol-5-ylidineamine)arenes **52** in high yields[48,49,76] (Scheme 34).



Scheme 34

An unusual reaction is the reaction of Appel salt **42** with aziridines **53** to form *N*-vinyl-1,2,3-dithiazolylideneamines **54** (Scheme 35).[77]

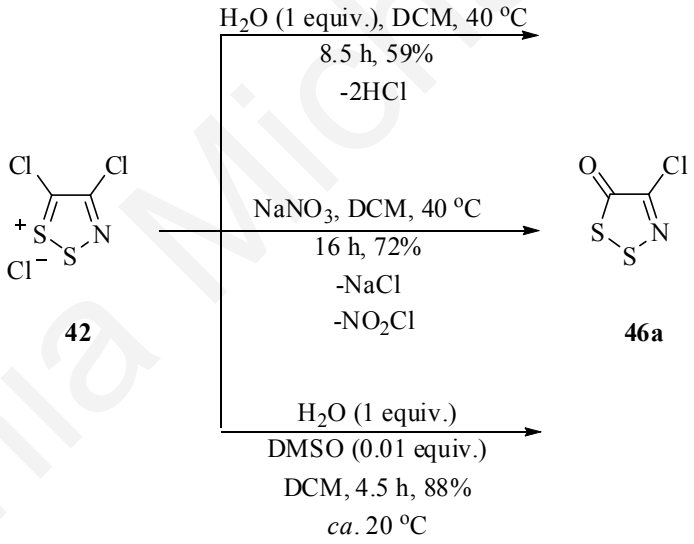


42 **53** **54**

Scheme 35

1.3.3.3 Formation of a C=O Bond at C5

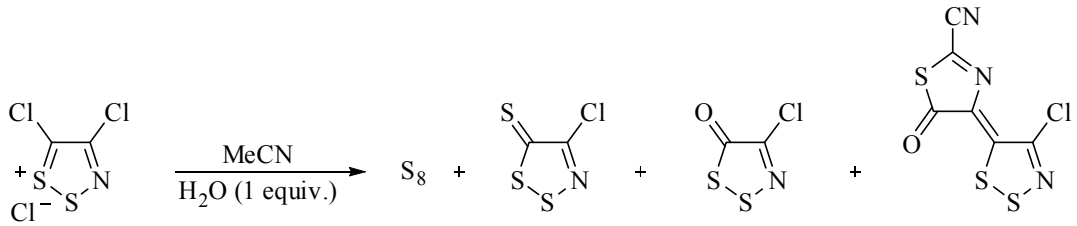
Appel salt **42** can undergo hydrolysis in moist conditions to give 4-chloro-5*H*-1,2,3-dithiazol-5-one **46a** by losing HCl.[42] Similarly, the same compound **46a** can also be obtained when Appel salt **42** reacts with $NaNO_3$ in DCM.[78] Moreover, a new synthetic procedure has been discovered recently which involves the hydrolysis of Appel salt **42** in the presence of catalytic DMSO (Scheme 36).[79]



42 **46a**

Scheme 36

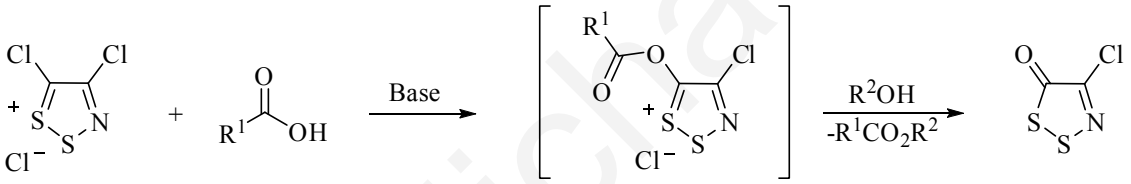
Similarly treatment of Appel salt **42** with wet MeCN gives 4-chloro-5*H*-1,2,3-dithiazol-5-one **46**, as well as 4-chloro-5*H*-1,2,3-dithiazole-5-thione **55** and thiazol-5-one **56** as side products (Scheme 37).[80]



42 **55** (15%) **46** (53%) **56** (13%)

Scheme 37

Reaction of Appel salt **42** with carboxylic acids in the presence of 2,6-lutidine can lead to the formation of 4-chloro-5-(substituted-carbonyloxy)-1,2,3-dithiazol-1-ium **57** which on treatment with alcohols leads to the release of the ester and 4-chloro-5*H*-1,2,3-dithiazol-5-one **46a** (Scheme 38).[81]

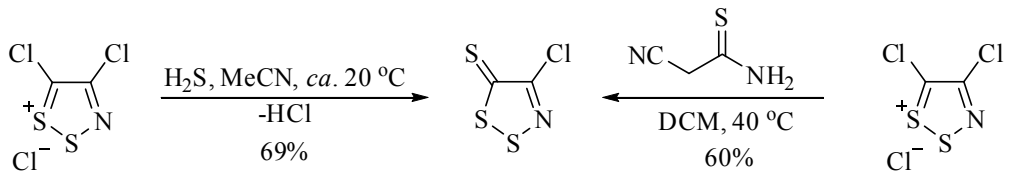


42 **57** **46a**

Scheme 38

1.3.3.4 Formation of a C=S Bond at C-5

As mentioned previously, hydrolysis of Appel salt **42** in wet MeCN can lead to the formation of 4-chloro-5*H*-1,2,3-dithiazole-5-thione **55** (see Section 1.3.3.3, Scheme 37). The dithiazolethione **55**, however, is best prepared by treating Appel salt **42** with either hydrogen sulfide in acetonitrile at room temperature or with 2-cyanothioacetamide in DCM at room temperature (Scheme 39).[42]



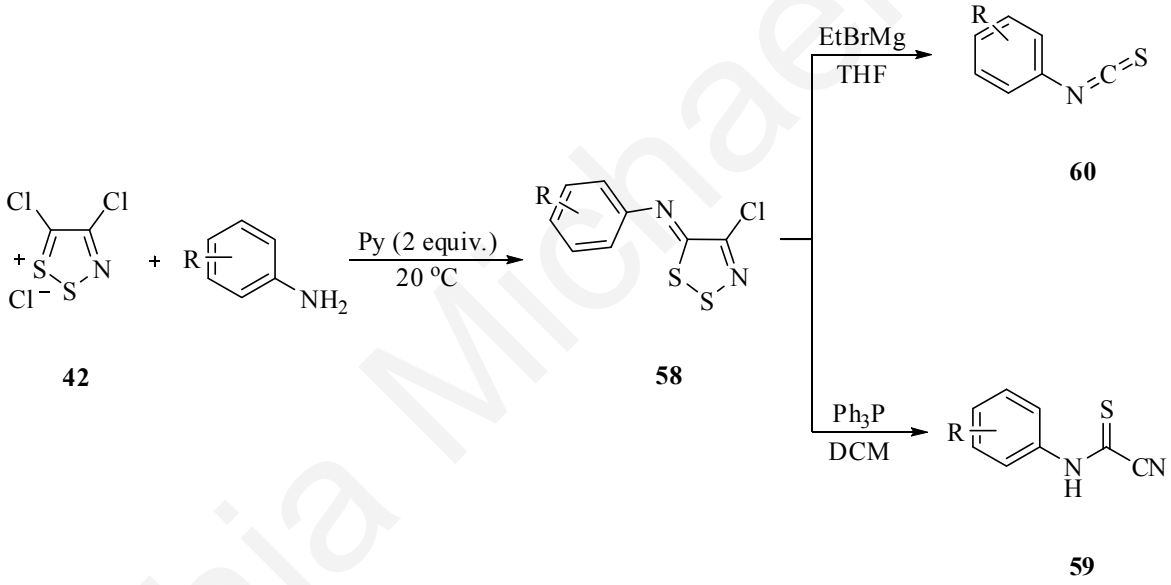
42 **55** **42**

Scheme 39

1.3.4 1,2,3-Dithiazoles in Synthesis

The 1,2,3-dithiazole ring has two particularly weak bonds, the S1-S2 and the S2-N3 bonds 425.3[82,83] and 464.0[10,83] kJ/mol, respectively (homolysis). The weakness of these bonds often leads to their cleavage in the presence of thiophiles and subsequent transformation of the dithiazole into new ring systems or functionalities. The formation of a thermodynamically stable new triple bonded nitrile C≡N (887 kJ/mol)[83] from the N3-C4 ring atoms probably assists in driving these dithiazole fragmentations.

Dithiazolylidenes have been used for the synthesis of acyclic ring systems like cyanothioformanilides **59** and *N*-arylisothiocyanates **60** (Scheme 40) (see also Chapter 6).[84-86]

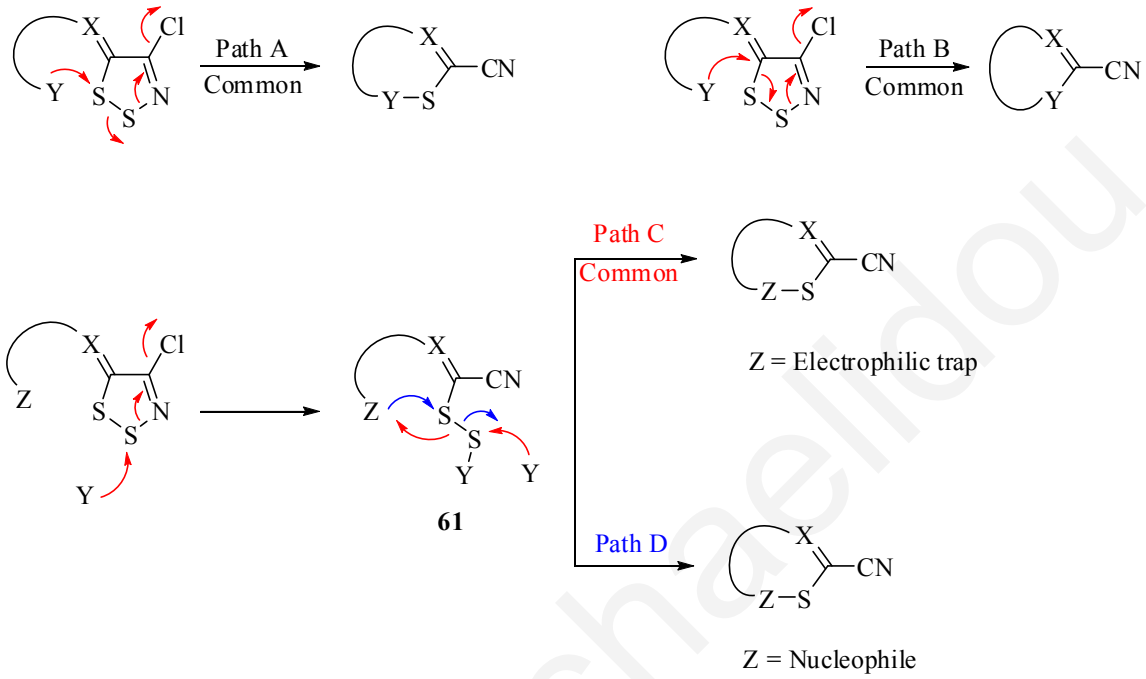


42 **58** **60** **59**

Scheme 40

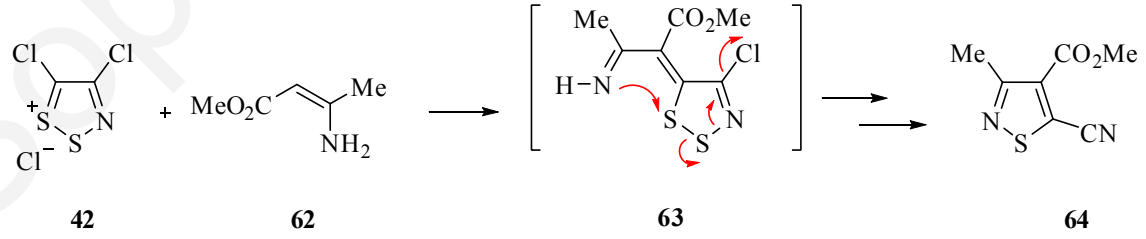
Our interest in 1,2,3-dithiazole chemistry revolves around the construction of dithiazole systems that can be converted into new heterocyclic systems *via* ring transformation. The majority of these ring transformations involve the initial preparation of a neutral dithiazole which supports a potentially nucleophilic side chain or substituent capable of attacking the electrophilic dithiazole at either S1 (Path A) or at C5 (Path B) with subsequent ring opening. Dithiazoles, however, can also be ring opened with the use of soft nucleophiles to afford the disulfide intermediate **61** (Paths C and D) (Scheme 41). This disulfide can be a source of both

electrophilic and nucleophilic sulfur.[87] All these proposed mechanisms belong to the category of non-degenerated ring closures.



Scheme 41

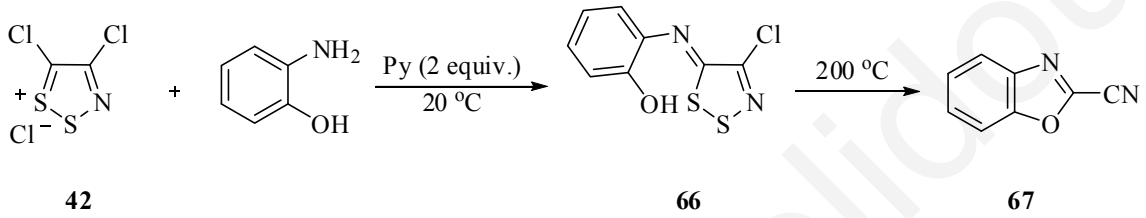
A representative example the first mechanistic route (Path A) is the reaction of Appel salt **42** with methyl-3-aminocrotonate **62** that gives methyl 5-cyano-3-methylisothiazole-4-carboxylate **64** in high yields (78%). The spontaneous transformation of the hypothetical intermediate **63** into the isothiazole system involves nucleophilic attack by the external side chain onto the dithiazole S1 atom (Scheme 42).[88]



Scheme 42

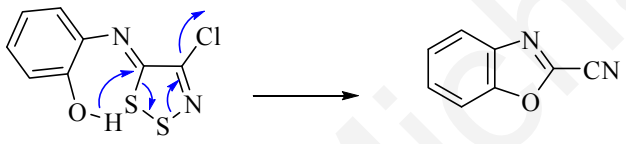
A representative example of the second mechanistic route (Path B) is the reaction of Appel salt **42** with primary aromatic amines to form (4-chloro-5*H*-1,2,3-dithiazol-5-ylidene-

amino)arenes which contain a nucleophilic group in the C2 (*ortho*) position of the arene. This nucleophilic side chain can then attack the dithiazole at C5, causing the ring to open and ring close forming a new heterocycle. For example, 2-aminophenol can react with Appel salt **42** to form (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66**. At high temperatures the *ortho* hydroxyl attacks the dithiazole at C5 to afford benzo[*d*]oxazole-2-carbonitrile **67** in high yields (90%) (Scheme 43).[89]



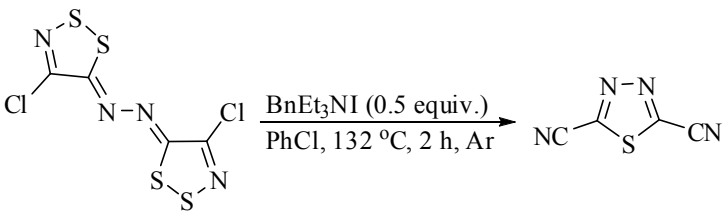
42 **66** **67**

Mechanism



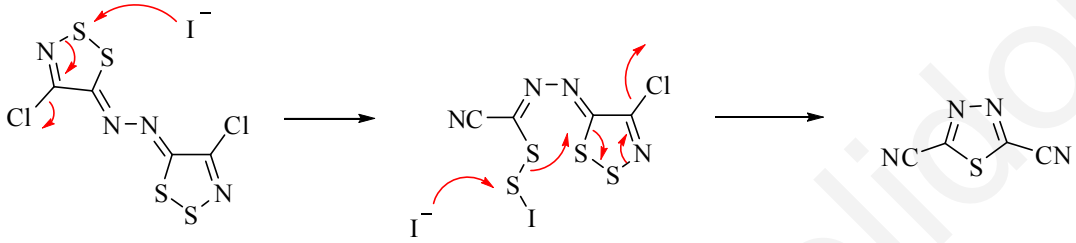
Scheme 43

An interesting example of the third mechanistic pathway (Path C) is the reaction of the bisdithiazole **51** with $BnEt_3NI$ in refluxing PhCl which gives 1,3,4-thiadiazole-2,5-dicarbonitrile **68** (Scheme 44).[90]



51 **68** (78%)

Mechanism

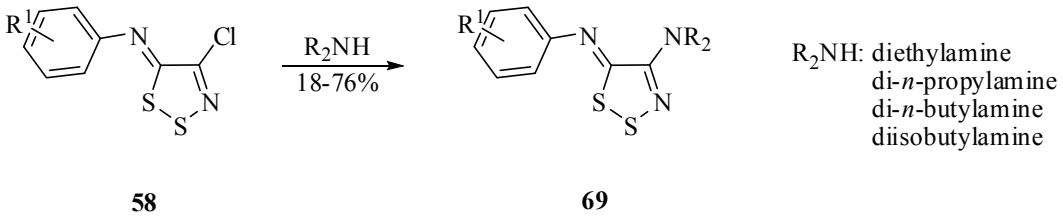


51 **68**

Scheme 44

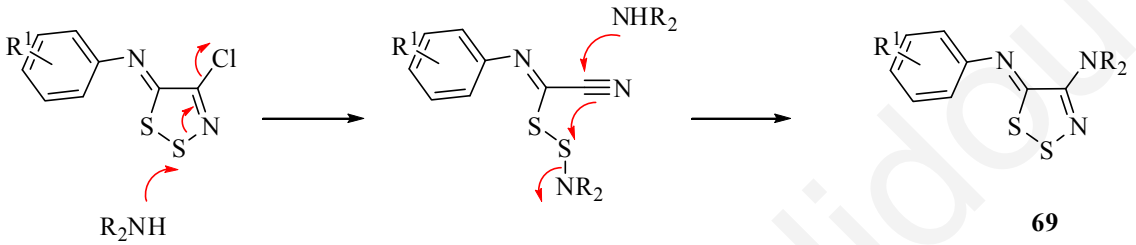
A clear example of the fourth mechanistic route (Path D) has not yet been demonstrated, however, it cannot be excluded that reactions proposed to occur *via* Path B actually involve mixed disulfide intermediates such as those in Path D.

All the examples that were mentioned above were examples of non-degenerate ring transformations of Appel salt **42**. However, there is only one example in the literature which includes a degenerate ring transformation. Substituted dithiazolylidenes **69**, on treatment with secondary acyclic amines, can ring open and ring close to form new dithiazolylidenes **67**. The only difference between the two compounds is that the chlorine atom at the C4 position of the dithiazole ring has been replaced by the secondary acyclic amine (Scheme 45).[91]



58 **69**

Mechanism



Scheme 45

All these transformations of the Appel salt **42** have significant mechanistic interest since they give access in many cases to novel compounds that are difficult to obtain following other procedures. For this reason it was decided to study Appel salt chemistry further and try to discover new transformations and new products.

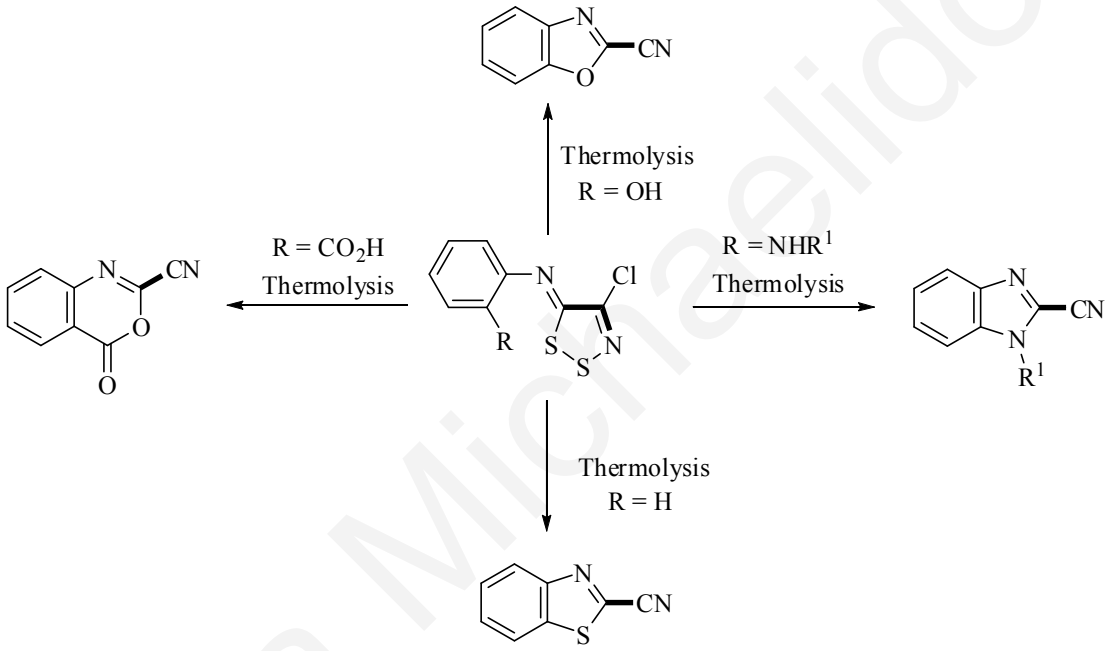
CHAPTER 2

Synthesis of (4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)azines

Sections

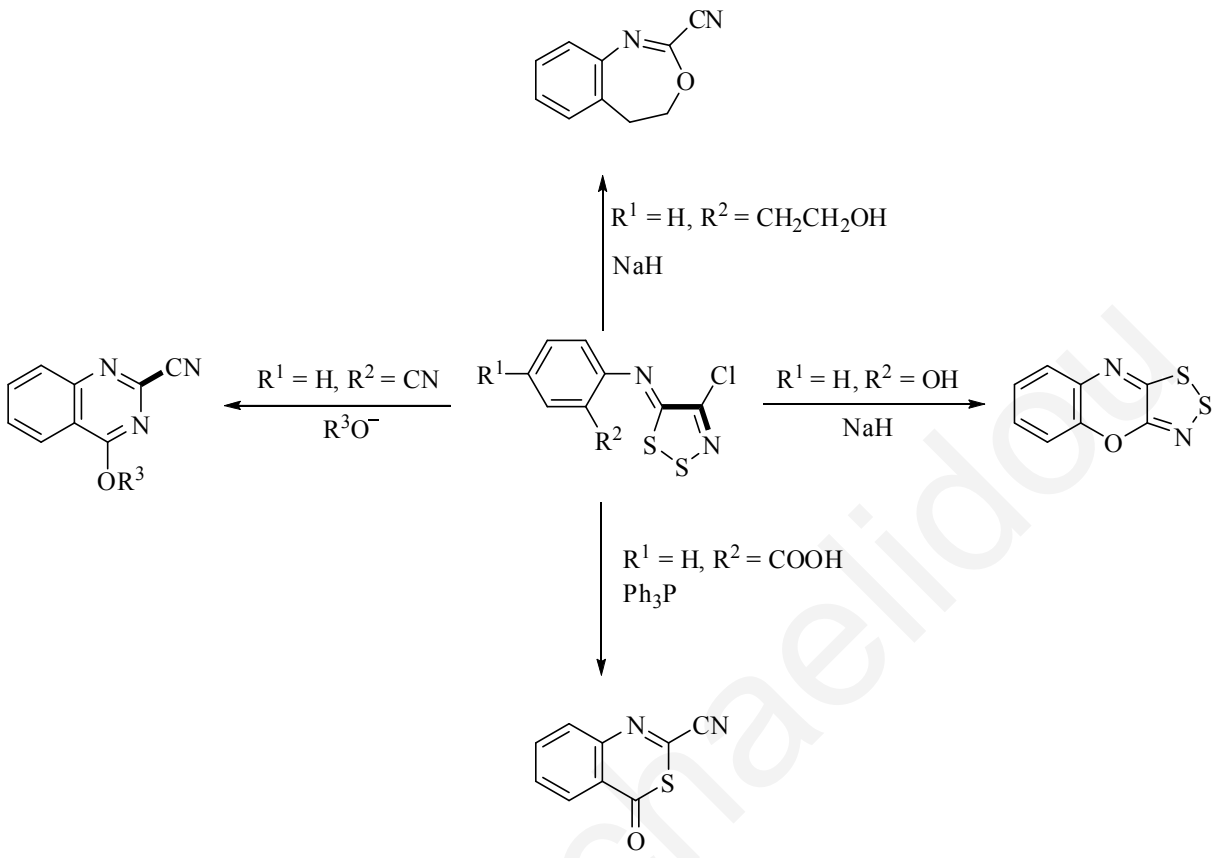
2.1 Introduction

N-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines (dithiazolimines) are useful synthetic scaffolds for the synthesis of heterocycles several of which display significant biological activities.[65,92-93] They are also very useful intermediates for the synthesis of other difficult to access cyano substituted heterocycles.[48,49,70,75,84,94-114] For example, the thermolysis of selected *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines can afford benzothiazoles,[70,94] benzimidazoles,[95] thiazolopyridines,[85] and benzoxazines[96] (Scheme 46).



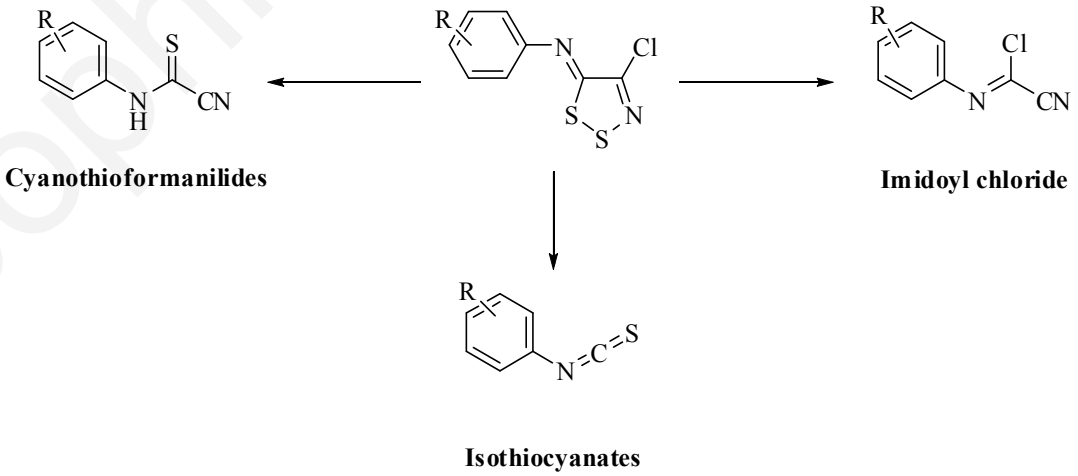
Scheme 46

Moreover *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines in the presence of a strong base or a nucleophile can rearrange towards the formation of 4,5-dihydrobenzo[*d*][1,3]oxazepine-2-carbonitriles,[96,97] benzoxazines,[65,70] quinazolines[84,89,93,98,104] and 4-oxo-4*H*-benzo[*d*][1,3] thiazine-2-carbonitriles[48] (Scheme 47).



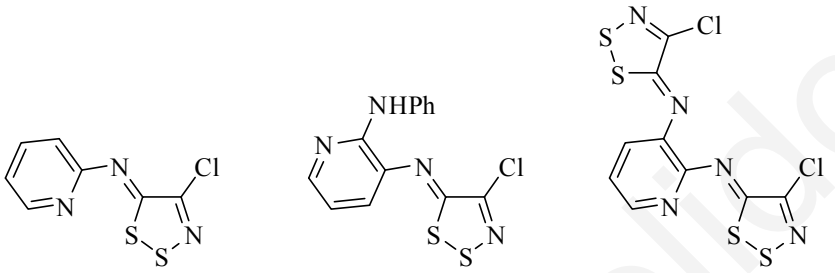
Scheme 47

Acyclic functionalities such as cyanothioformanilides,[48,49,75,84,100,105-116] imidoyl chlorides,[70,75,99-107] and isothiocyanates,[100,108,109] can also be prepared from neutral *N*-(4-chloro -5*H*-1,2,3-dithiazol-5-ylidene)anilines (Scheme 48) (see also Chapter 3, Section 3.1).



Scheme 48

Despite their significant synthetic utility, there are only a few examples of (4-chloro-5*H*-1,2,3-dithiazolylideneamino)azines. To the best of our knowledge the only reported examples are *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine **70a**,[102] N^3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-N^2-phenylpyridine-2,3-diamine **71** and N^2,N^3-bis(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridine-2,3-diamine **72**.[117]



70a **71** **72**

The main reason for this is probably that aminoazines are less readily commercially available compared to the primary anilines and possibly also that electron poor aminoheteroazines, such as aminopyridines, have less nucleophilic character than primary anilines. This leads to low yields of the desired (4-chloro-5*H*-1,2,3-dithiazolylideneamino)azines and/or complex reaction mixtures owing to side reactions that often lead to difficulties in their isolation.

Having all the above in mind and the fact that only a few examples of (4-chloro-5*H*-1,2,3-dithiazolylideneamino)azines exist in the literature it was decided to study their chemistry and see if it was possible to obtain similar high yielding products as in the case of the more electron poor *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines.

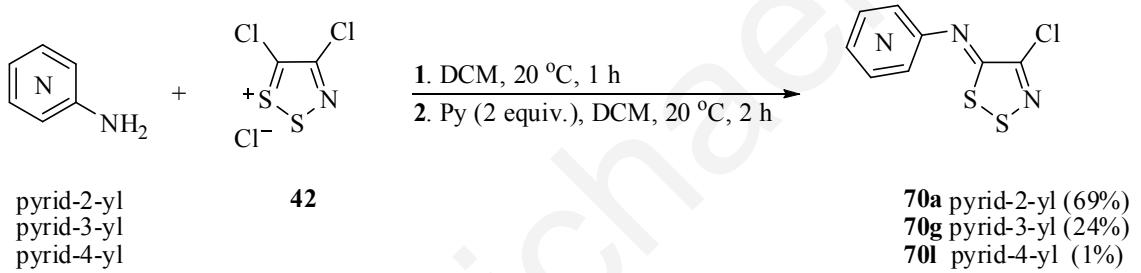
2.2 Synthesis of (4-Chloro-5*H*-1,2,3-dithiazolylideneamino)azines

2.2.1 Optimization Studies on (4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridinamines

Our investigation began with the reaction of the simplest aminoazines, namely aminopyridines, with Appel salt **42** to afford (4-chloro-5*H*-1,2,3-dithiazolylidene)pyridin-X-amines (whereas X = 2, 3 and 4). By focusing on the 2-, 3- and 4-aminopyridines we hoped to see how the position of the pyridyl ring nitrogen affected the reactivity of the aminoazine with

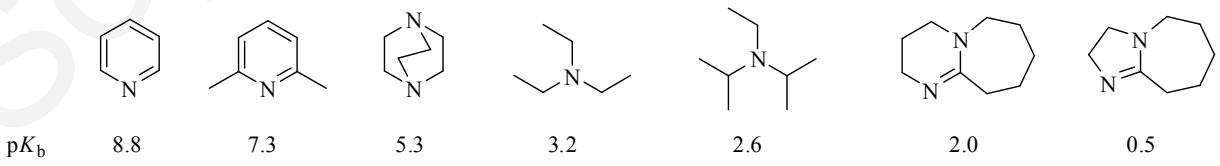
Appel salt **42**. The reaction was optimized with respect to base, temperature, and reaction time (Scheme 49).

Initially the synthesis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridinamines **70a,g,l** was based on a well established literature procedure for the preparation of (dithiazolylideneamino)-arenes,[102] using pyridine (2 equiv.) as base, at *ca.* 20 °C in DCM (Scheme 49). It became clear even at this stage that the product yields were affected by the position of the pyridyl nitrogen: The reaction between 2-amino-, 3-amino- and 4-aminopyridine and Appel salt **42** gave the corresponding *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-X-amine (whereas X = 2, 3, 4) **70a**, **70g** and **70l** in 69, 24 and 1% yields, respectively (Scheme 49).



Scheme 49

To improve the yields of the above reactions we then screened a variety of amine bases. Weakly aromatic amine bases like pyridine (pK_b 8.8)[10] and the more sterically demanding (less nucleophilic) 2,6-lutidine (pK_b 7.3)[10] were included as well as a range of trialkylamines with increasing steric demands, reduced nucleophilicity and increasing basicity *e.g.*, DABCO (pK_b 5.3),[10] Et_3N (pK_b 3.2),[10] and Hünig's base (pK_b 2.6).[10] Moreover, "weakly" nucleophilic strong amidine bases such as DBU (pK_b 2.0)[10] and DBN (pK_b 0.5)[10] were also included.

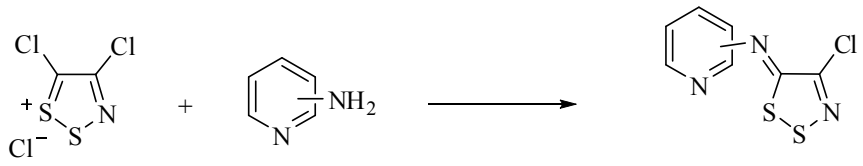


The latter amidine bases DBU and DBN are commonly used to effect base induced dehydrohalogenations and other eliminations to produce C-C and C-heteroatom multiple bonds.[118] As such they are often referred to as non-nucleophilic strong bases.[119] Nevertheless,

a careful search of the literature revealed multiple reports of nucleophilic behaviour for both DBU and DBN, notably in reactions with either phosphorus[120-132] or carbon[133-150] electrophiles to afford adducts sporting new N-P and N-C bonds, respectively (see also Chapter 6, Section 6.3).

The addition of base was necessary to obtain greater than trace quantities of (dithiazol-ylidene)pyridinamines. Furthermore, increasing the reaction time (by 4, 6 and 8 h) before the addition of the base decreased the yields as did increasing the reaction time (by 4, 6 and 8 h) after the addition. Increasing the reaction temperature from 25 to 40 ^{o}C also did not lead to an improvement of the observed yields. The best conditions required mixing Appel salt **42** with the aminopyridine for 1 h at room temperature followed by the addition of amine base (2 equiv.) and a further 2 h of stirring (Table 1).

Table 1. Reaction of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (1 equiv.) with aminopyridine (0.91 mmol) in DCM (4 mL) at *ca.* 20 °C for 1 h and followed by base (2 equiv.) for another 2 h.



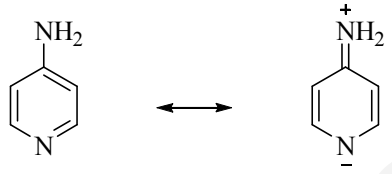
42

70a (pyrid-2-yl)
70g (pyrid-3-yl)
70l (pyrid-4-yl)

Aminopyridine	Base (pK_a)	Yields (%)
Pyrid-2-yl	Pyridine (5.2)	**70a** (69)
Pyrid-2-yl	2,6-Lutidine (6.7)	**70a** (72)
Pyrid-2-yl	DABCO (8.7)	**70a** (55)
Pyrid-2-yl	Et_3N (10.8)	**70a** (69)
Pyrid-2-yl	i-Pr_2NEt (11.4)	**70a** (73)
Pyrid-2-yl	DBU (12.0)	**70a** (58)
Pyrid-2-yl	DBN (13.5)	**70a** (47)
Pyrid-3-yl	Pyridine (5.2)	**70g** (24)
Pyrid-3-yl	2,6-Lutidine (6.7)	**70g** (45)
Pyrid-3-yl	DABCO (8.7)	**70g** (8)
Pyrid-3-yl	Et_3N (10.8)	**70g** (43)
Pyrid-3-yl	i-Pr_2NEt (11.4)	**70g** (57)
Pyrid-3-yl	DBU (12.0)	**70g** (16)
Pyrid-3-yl	DBN (13.5)	**70g** (13)
Pyrid-4-yl	Pyridine (5.2)	**70l** (traces)
Pyrid-4-yl	2,6-Lutidine (6.7)	**70l** (traces)
Pyrid-4-yl	DABCO (8.7)	**70l** (3)
Pyrid-4-yl	Et_3N (10.8)	**70l** (23)
Pyrid-4-yl	i-Pr_2NEt (11.4)	**70l** (13)
Pyrid-4-yl	DBU (12.0)	**70l** (13)
Pyrid-4-yl	DBN (13.5)	**70l** (traces)

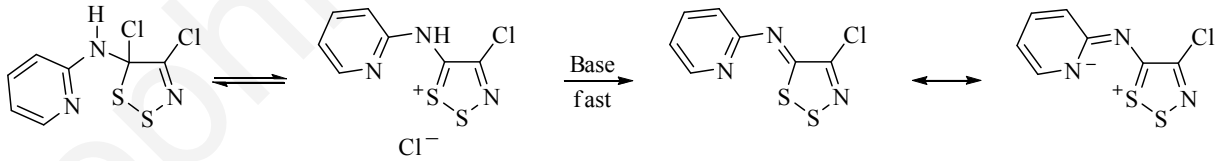
The highest yields of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine **70a** and *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70g** were obtained with Hünig's base, in 73 and 57% yields, respectively, while the highest yield for *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine **70l** (23%) was obtained with Et_3N. As such, the trialkylamines (Hünig's and Et_3N) gave overall better yields of (dithiazolylidene)pyridinamines than either

the aromatic amines (pyridine and lutidine), or the bicyclic amidines (DBN, DBU) and DABCO. The exceptionally low yields of product from the reaction of 4-aminopyridine and Appel salt **42** may be partially explained by the very low nucleophilicity of the primary amine since 4-amino-pyridine favoured a charge separated form rather than a neutral form making the amino group in the C4 position positive charged (Scheme 50).[149] Moreover, 4-amino-pyridine was not very soluble in the solvents tried (DCM, MeOH, EtOH, PhH) and this could also have led to the low product yields.



Scheme 50

Also notable was that the reaction between 2-aminopyridine and Appel salt **42** was less sensitive to the base used which may be due to two factors: 1) The pyrid-2-yl nitrogen's ability to coordinate with the dithiazole sulfur S1 in a "non-bonding" manner[150,151] provided particularly stable (dithiazolylidene)pyridinamines; and 2) the acidity of the proton in intermediate **73** was enhanced by both the neighbouring pyridyl nitrogen and the positively charged dithiazolium ring sulfur.[152,153] Both these features could lead to a very facile base catalysed elimination of HCl (Scheme 51).



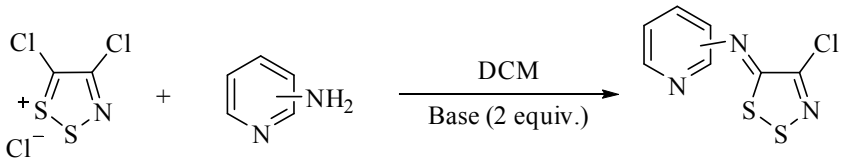
73

Scheme 51

2.2.2 Synthesis of a (4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)azine Library

To investigate this further, a range of substituted aminopyridines and related azines were reacted with Appel salt **42** in the presence of the above amine bases (Table 2).

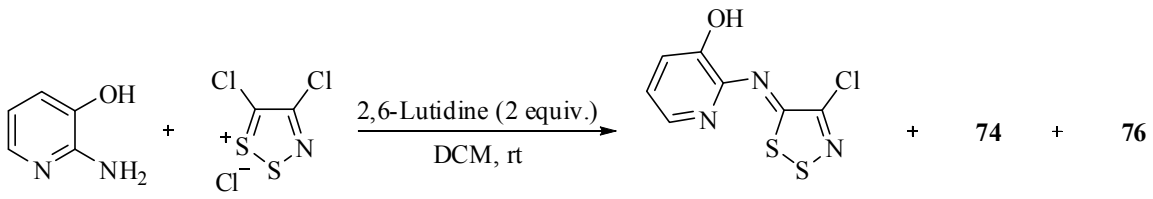
Table 2. Reaction of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (1 equiv.) with aminopyridines (0.91 mmol) in DCM (4 mL) at 20 °C for 1 h and then addition of base (2 equiv.) for another 2 h.



42 **70a-n**

Aminopyridine	Bases (yields)						
	Pyridine	2,6-Lutidine	DABCO	Et_3N	i-Pr_2NEt	DBU	DBN
a (2-NH_2)	69	72	55	69	73	58	47
b (2-NH_2-3-OH)	8	11	9	7	8	7	5
c (2-NH_2-3-OMe)	71	67	55	60	66	42	40
d (2-NH_2-3,5-Cl_2)	69	70	52	44	43	44	39
e (2-NH_2-3,5-Br_2)	65	70	56	48	40	27	15
f (2-NH_2-3-O_2N)	45	62	48	32	14	23	12
g (3-NH_2)	23	45	8	42	57	16	10
h (3-NH_2-2-OH)	53	19	11	9	18	12	5
i (3-NH_2-2-Cl)	75	82	85	71	72	50	45
j (3-NH_2-4-Cl)	65	76	60	70	69	21	19
k (3-NH_2Pyrazine)	65	63	51	63	61	40	36
l (4-NH_2)	traces	traces	3	21	13	13	10
m (4-NH_2-2,6-Me_2)	5	traces	19	22	10	9	5
n (4-NH_2-5-CNPyrimidine)	61	55	35	45	40	39	15

As before the position of the nitrogen atom in the aromatic ring affected the product yields. In the case of 2-amino and 3-amino derivatives the desired (dithiazolylideneamino)azines were obtained in moderate to good yields with the exception of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** which was obtained in only 11% yield. 4-Aminopyridines gave very low yields with all the bases as expected; however, the presence of an additional nitrogen atom *α* to the amine in 4-aminopyrimidine-5-carbonitrile gave a significant increase in the product yields (61%). The observed low yield of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene-amine)pyridin-3-ol **70b** was partially owed to the formation of two other coloured compounds (Scheme 52).

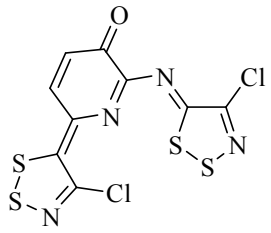


42 **70b**

Scheme 52

2.2.3 Structure Elucidation of Side Products **74** and **76** from Pyridinol Chemistry

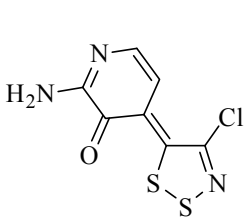
The less polar compound was obtained as a blue powder, mp 288-289 ^{o}C (from DCE). Mass spectrometry supported a tentative molecular weight of 380 Da and a clear two chlorine isotope ratio was observed for the parent ion [*m/z* 384 (M^{+}+4, 2%), 382 (M^{+}+2, 4%), 380 (M^{+}, 8%)], although in the absence of elemental analysis this molecular weight could not be confirmed. UV/vis spectroscopy showed a λ_{max} of 614 nm (log ε 3.52) that suggested the compound had extended conjugation. IR spectroscopy indicated an absence of nitriles, amines or hydroxyl functionality. Finally, owing to solubility problems ^{1}H and ^{13}C NMR spectroscopic data could not be obtained. On this limited data and the tentative structural assignment for the second compound **76** (see below) we suspect that this compound to be the bis-dithiazole **74**.



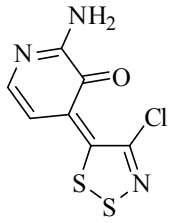
74

The second compound **76** was obtained as lusterous bronze coloured gold prisms, mp > 300 ^{o}C (from DCE). Mass spectrometry supported a molecular weight of 245 Da [*m/z* (EI) 245 (M^{+}, 28%)]. ^{1}H NMR spectroscopy identified one D_2O exchangeable broad resonance integrating 2 at 7.10 ppm, indicating the presence of a 2^{o} amino group and this was supported by IR bands at 3300 cm^{-1}. UV/vis spectroscopy showed a λ_{max} at 612 nm (log ε 3.35) suggesting the compound had extended conjugation. ^{1}H NMR spectroscopy also identified 2 resonances

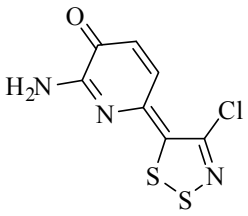
which belonged to aromatic hydrogens [8.50 (*J* 9.6 Hz) and 6.34 (*J* 9.9 Hz) ppm] integrating 1 and 2, respectively. Four possible structures fitted this data.



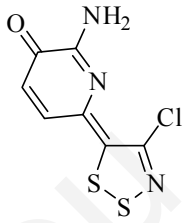
75a



75b



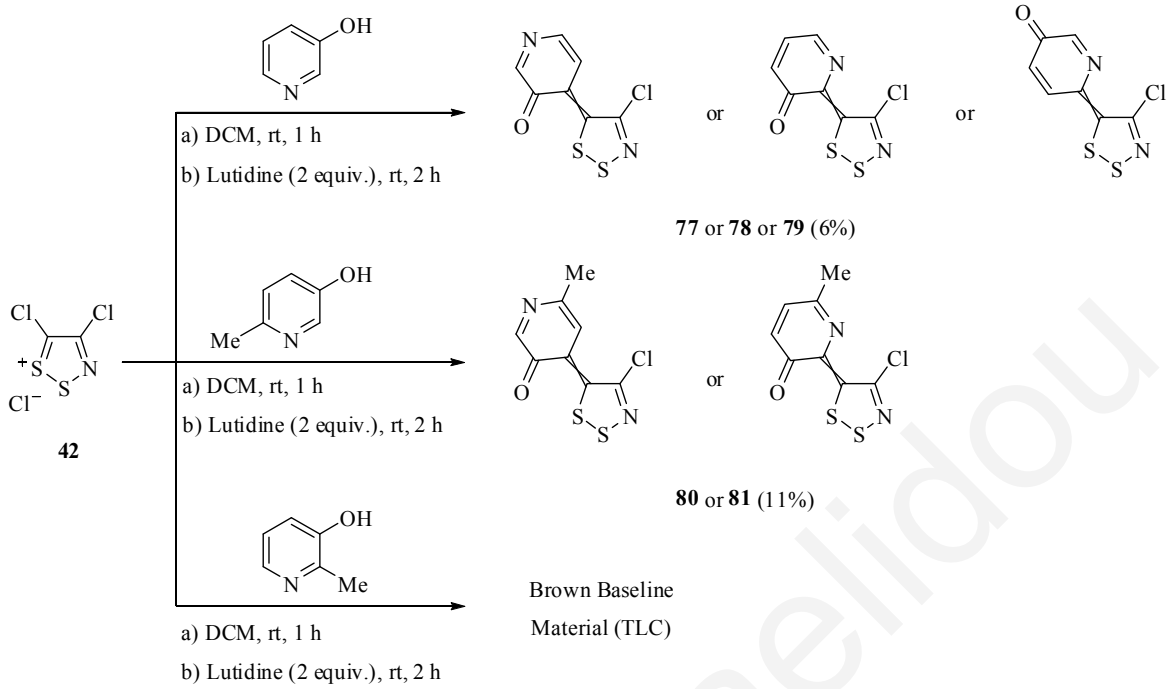
76a



76b

The large ^{1}H NMR coupling's *J* 9.6 and 9.9 Hz supported structures **76a** and **76b** since substituted pyridines are known to have larger $^{3}J_{H2H3}$ couplings than $^{3}J_{H1H2}$ (7-9 *vs* 4-6 Hz).[154] As such the above data tentatively eliminated the possible C4 ylidene structures but could not differentiate the possible *E/Z* geometry of the C-6 pyridinylidene **76a-b**. Nevertheless, the steric compression between the pyridyl H5 and the dithiazole chlorine could disfavour structure **76a** over structure **76b** which only has the interaction of the pyridyl nitrogen's lone pair and the dithiazole chlorine to contend with.

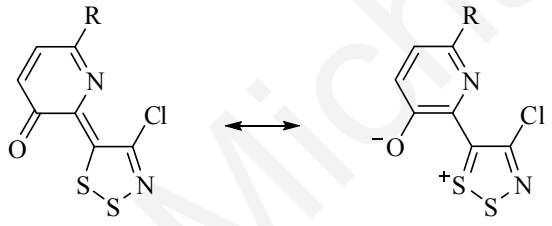
To further investigate the formation of the two coloured compounds, three pyridinols were left to react with Appel salt **42** in DCM in the presence of 2,6-lutidine (2 equiv.) (Scheme 53).



Scheme 53

In the first case, reaction of pyridin-3-ol with Appel salt **42** led to the formation of a compound isolated by chromatography (DCM) as a purple powder, mp > 300 ^{o}C (from cyclohexane/DCE). Microanalysis (C, 36.6; H, 1.2; N, 12.0%) and LR (EI) mass spectrometry supported the molecular formula $C_7H_3ClN_2OS_2$; a clear chlorine isotope ratio was observed in the parent ion [*m/z* 232 (M^++2, 37%), 230 (M^+, 90%)]. UV/vis spectroscopy indicated extensive conjugation with a λ_{max} of 517 nm (log ε 3.06). The ^{1}H NMR spectrum identified 3 double doublets which belonged to aromatic hydrogens [δ_H 8.39 (*J* 3.45, 1.65 Hz), 7.63 (*J* 9.0, 3.6 Hz) and 7.56 (*J* 9.0, 1.5 Hz) ppm] suggesting a 2,3-disubstituted pyridine. ^{13}C NMR spectroscopy in CD_2Cl_2 gave only three clear CH signals at 142.6, 130.9 and 128.2 ppm. However, owing to poor solubility of the compound, better data could not be obtained. IR spectroscopy failed to identify any 1^{o} or 2^{o} amino, hydroxyl, cyano or carbonyl functional groups. The lack of a carbonyl stretch in the FTIR data could be explained by the existence of "non-bonding" interactions between the dithiazole S1 sulfur the oxygen atom of the carbonyl group suggesting that both were syn orientated.[92,155] As such the purple product was tentatively identified as (*E*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3(2*H*)-one **78** (Scheme 53).

Similarly the reaction of 6-methylpyridin-3-ol with Appel salt **42** gave a compound isolated by chromatography (DCM) as a purple powder, mp > 300 ^{o}C (from cyclohexane/DCE). Microanalysis (C, 39.3; H, 2.1; N, 14.6%) and LR (EI) mass spectrometry supported the molecular formula $C_8H_5ClN_2OS_2$; a clear chlorine isotope ratio was observed in the parent ion [*m/z* 246 (M^++2, 22%), 244 (M^+, 53%)]. UV/vis spectroscopy indicated extensive conjugation with a λ_{max} at 536 nm (log ε 2.48). The ^{13}C NMR spectroscopy showed eight separate carbon resonances of which two were aromatic CH carbons and one CH_3 (DEPT-135 studies). ^{1}H NMR spectroscopy identified 2 doublets which belonged to aromatic hydrogens [δ_H 7.63 (*J* 8.4 Hz) and 7.47 (*J* 9.0 Hz) ppm] supporting a 2,3,6-trisubstituted pyridine. IR spectrometry failed again to support the existence of the carbonyl group indicating the existence of "non-bonding" interactions between the dithiazole S1 sulfur and the oxygen atom of the carbonyl group[92] (Scheme 54). Having this data in mind the purple compound was tentatively identified as (*E*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-6-methylpyridin-3(2*H*)-one **81**.

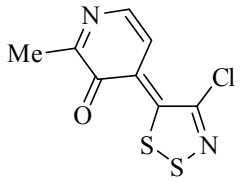


78 R = H,
81 R = Me

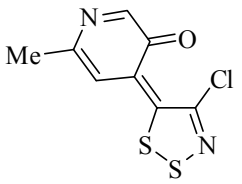
78	λ	log ε	**81**	λ	log ε
	233	3.53		231	3.10
	291 inf	3.28		308	2.99
	354 inf	2.76		367 inf	2.43
	517	3.06		536	2.48

Scheme 54

In contrast, the reaction of 2-methylpyridin-3-ol and Appel salt **42** gave a brown intractable polar mixture (baseline on TLC) possibly belonging to salts. No trace of the expected C2 or C4 adducts (*Z*)-4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-methylpyridin-3(4*H*)-one **82** and (*E*)-4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-6-methylpyridin-3(4*H*)-one **83** were observed.



82



83

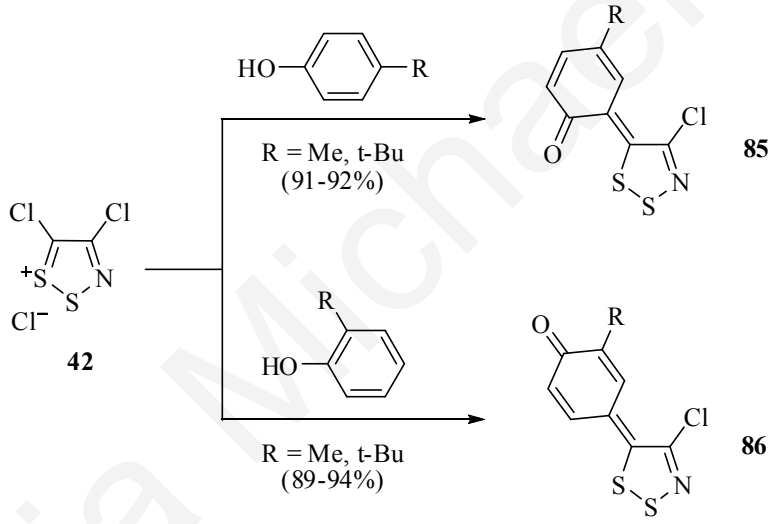
The formation of (*E*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3(2*H*)-one **78** and (*E*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-6-methylpyridin-3(2*H*)-one **81** was owed to electrophilic attack on the aromatic ring at the enolic C2 carbon atom *ortho* to both the carbonyl and to the pyridyl nitrogen. The *E* geometry of the ylidene bond was tentatively assumed owing to the possibility of the non-bonding interaction between the dithiazole S1 and the carbonyl; the intense colours of the products supported a strong contribution of the proposed charge separated resonance structures. Attack was probably favoured *via* the pyridyl C2 over the C4 positions owing to the smaller steric interaction between the dithiazole chlorine and the pyridyl N lone pair *vs* the pyridyl H5 (*cf.* compound **76b**).

If all four reactions were repeated in DCM at reflux temperature the same products were obtained in very similar yields. In contrast when refluxing DCE was used then different results were obtained only in the case of pyridin-3-ol. Reaction of pyridin-3-ol and Appel salt **42** in refluxing DCE after 5 min gave (*Z*)-4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3(4*H*)-one **78** (6%) as before. However, if the reaction was left to proceed longer, then compound **78** slowly disappeared and a second purple compound appeared and after 5 h, only the second purple compound **84** could be observed (TLC). This compound was obtained as purple prisms, mp 160-161 ^{o}C (from cyclohexane). Mass spectrometry indicated a possible molecular weight of 293 Da; a clear chlorine isotope ratio was observed in the parent ion [*m/z* 295 (M^{+}+2, 2%), 293 (M^{+}, 5%)], however, in the absence of elemental analysis data this molecular weight could not be confirmed. UV/vis spectroscopy gave a λ_{max} at 550 nm (log ε 3.00) indicating extensive conjugation. The ^{13}C NMR spectrum showed nine separate carbon resonances of which seven were quaternary carbons and two were aromatic CH (DEPT-135 studies). The ^{1}H NMR spectrum identified two doublets which belonged to aromatic hydrogens [δ_H 7.79 (*J* 9.0 Hz) and 7.57 (*J* 8.4 Hz) ppm] suggesting a 2,3,5-trisubstituted pyridine. IR spectroscopy did not

show any known characteristic peaks. The above data was not sufficient to elucidate a possible structure for this compound.

Having carried out this study, it can be concluded that the pyridine-3-ols favor to react *via* the C2 position. However, when this position is blocked like in the case of 2-methylpyridin-3-ol then no C4 adduct is recovered.

In the literature such reactions are known; Appel salt treated with *p*- and *o*-substituted phenols gave the analogous purple coloured *ortho* and *para* quinonemethides **85** and **86**, respectively (Scheme 55).[42]



Scheme 55

2.3 Summary

The main conclusion from this research is that (4-chloro-5*H*-1,2,3-dithiazolylideneamino)azines can be obtained in similar to lower yields as *N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines. It was also found that the position of the nitrogen on the aromatic ring of the initial amine affects the yield of the expected products. More specifictly a range of (4-chloro-5*H*-1,2,3-dithiazolylideneamino)azines was synthesized and the reaction conditions were optimized with respect to base, temperature and reaction time. Seven amine bases with different structures and pK_b's were used for the optimization. Addition of base was needed to obtain greater than traces quantities of the dithiazolylidenes. The best reaction times were found to be 1 h at room temperature before the addition of base (2 equiv.) and then an

additional 2 h of stirring at room temperature. Fourteen heteroazinyl were successfully synthesized. Dithiazolylidene **70b** was obtained in very low yields because of the side reactions that also gave the highly coloured purple and blue dithiazolylidenes **74** and **76**. Future work could focus on the chemistry of Appel salt **42** with pyridine-3-ols in an effort to understand what favours the observed regioselectivities.

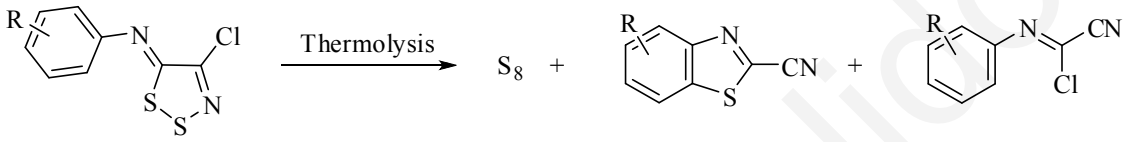
CHAPTER 3

Ring Transformations of (4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)arenes

Sections

3.1 Introduction

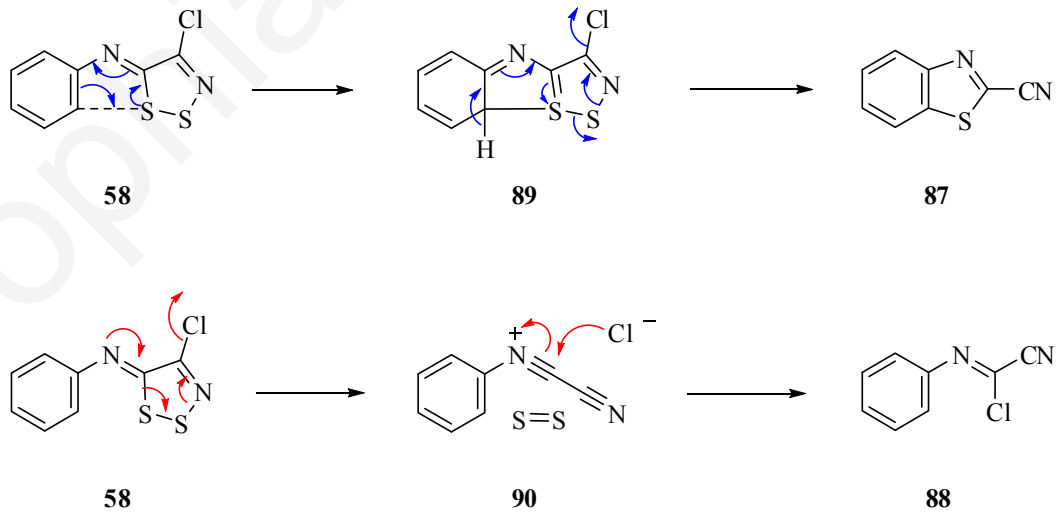
N-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines (*N*-aryl 4-chloro-5*H*-1,2,3-dithiazolimines) can undergo ring transformations to afford other heterocycles.[70,85,94-96] In particular thermolysis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines **58** affords benzo[*d*]thiazole-2-carbonitriles **87** as main products but when the phenyl ring is substituted with electron withdrawing groups then the main product isolated is *N*-(chlorocyanomethylidene)aniline **88** (Scheme 56).[70,75,94,100-107,156-158]



58 **87** **88**

Scheme 56

Mechanisms for the formation of both products have been proposed (Scheme 57).[70] In the first case the aryl ring attacks the dithiazole at S1 to give intermediate **89** that fragments releasing $1/8S_8$, HCl and the benzothiazole **87**. In the second case, the nitrogen of the exocyclic imine releases electron density towards the dithiazole causing fragmentation to give the nitrilium intermediate **90**, which traps chloride to give the imidoyl chloride **88**.



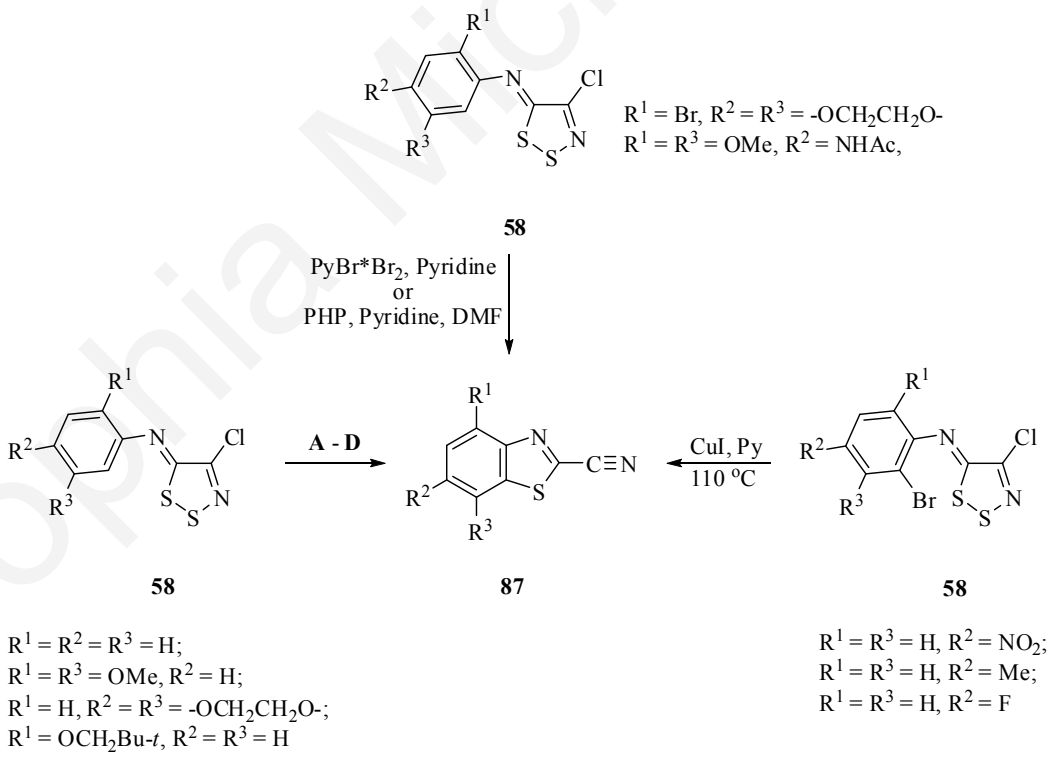
58 **89** **87**

58 **90** **88**

Scheme 57

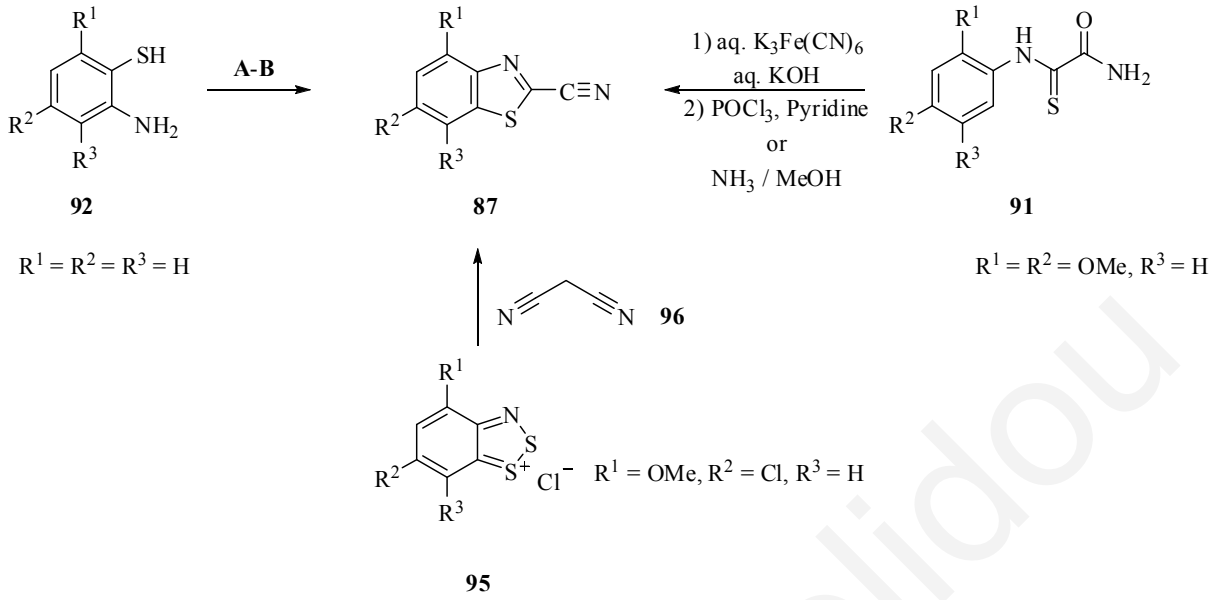
Benzothiazole is a privileged bicyclic ring system since many derivatives possess useful biological properties such as anti-viral,[159] anti-bacterial,[160-162] anti-allergic[163] anti-diabetic,[164] antitumor,[165] anti-inflammatory,[166] anthelmintic,[167] and anti-HIV.[167] As such, benzothiazoles have appeared as core structures in a diverse range of pharmaceuticals.[170]

While there are many routes to benzothiazoles, there are only a few routes to benzothiazole-2-carbonitriles and aside from the thermolysis of *N*-(dithiazol-5-ylideneamino)anilines (Scheme 58) these involve reactions of 2-(2,4-substituted-phenylamino)-2-thioxoacetamide **91** with aq. $K_3Fe(CN)_6$ and $POCl_3$,[170,173] reactions of 2-aminobenzenethiol **92** with either ethyl 3-chloro-3-oxopropanoate **93** in the presence of Et_3N, $NaNO_2$, aq HCl, aq NaOH, 157 ^oC[171] or with ethyl carbonochloridoimidate **94** in $CHCl_3$, isopentylnitrite, HCl, dioxane, NaN_3, DMF and AcOH.[172] Finally this benzothiazole **87** can be synthesized from 6-chloro-4-methoxy-benzo[*d*][1,2,3]dithiazol-1-ium chloride **95** and malononitrile **96** (Scheme 59).[174] These routes include many synthetic steps and expensive starting materials.



A: T = 150-160 ^oC or **B**: PhMe or **C**: NMP, 150 ^oC or **D**: NMM, 150 ^oC

Scheme 58



A: 93
1) Et_3N, rt;
2) $NaNO_2$, aq HCl;
3) aq. NaOH, 95 °C;
4) 157 °C

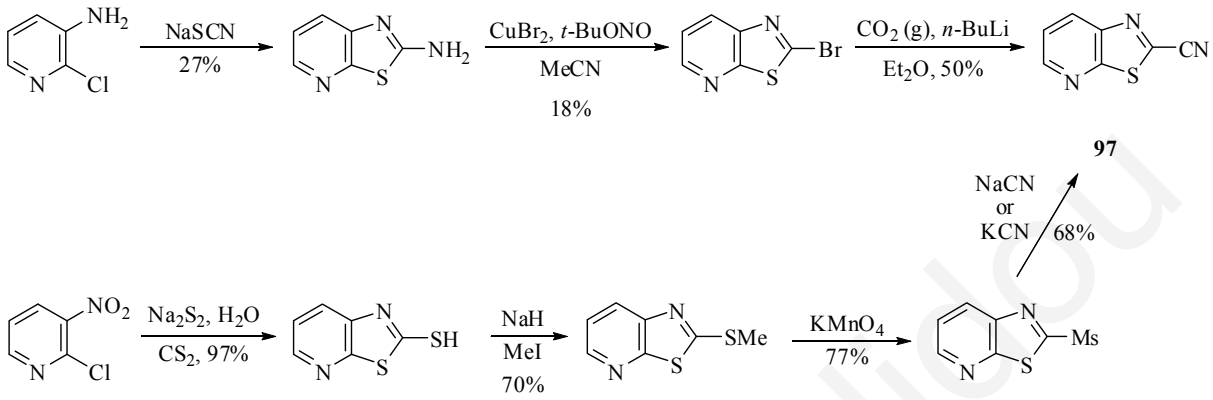
B: 94
1) $CHCl_3$, 16 h, rt;
2) Isopentylnitrite, HCl, dioxane;
3) NaN_3, DMF, 5 h;
4) AcOH, 16 h, rt

Scheme 59

By comparison the thermolysis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines **58**, [70,75,94,100-107,156-158] can be performed neat, in the presence of either PhMe,[158] NMP[103,104] or NMM,[175] and in the presence of copper (I) iodide in pyridine at 110 °C,[94,101,158,175-182] or pyBr*Br_2 in either pyridine or in DMF in a microwave reactor.[158,179] The conversion of (dithiazolylidene)anilines **58** into benzothiazole-2-carbonitriles **87** *via* thermolysis is thus advantageous because it includes only two steps: a) preparation of the (dithiazolylidene)anilines **58** from readily available inexpensive anilines and Appel salt **42** and b) an often high yielding and comparatively clean thermolysis reaction.

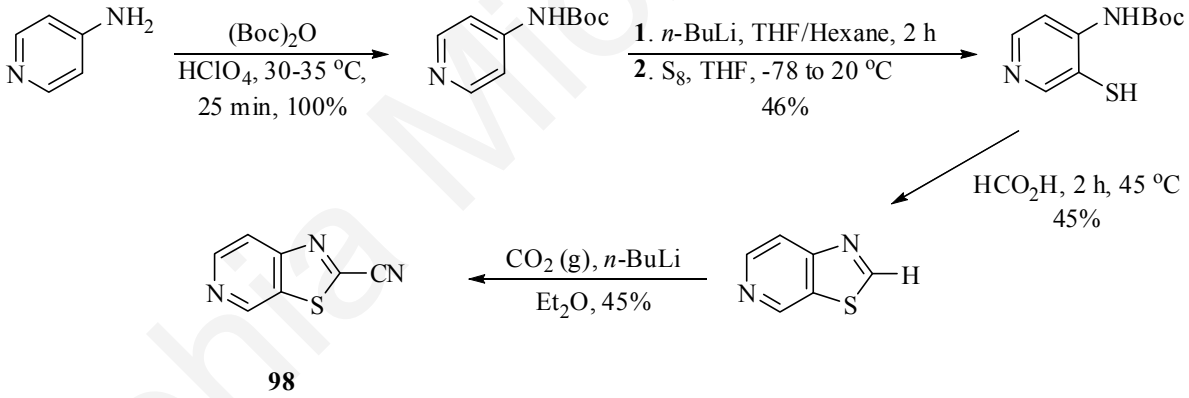
Despite these advantages there are surprisingly no studies on the thermolysis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridinamines (see Scheme 49, Chapter 2) which could potentially afford useful thiazolopyridine-2-carbonitriles. Interestingly, of the four possible thiazolo-pyridine-2-carbonitriles only two have been reported: Thiazolo[5,4-*b*]pyridine-2-

carbonitrile **97** has been prepared from the analogous 3-amino-2-chloropyridine or 2-chloro-3-nitropyridine (Scheme 60).[183-189]



Scheme 60

Thiazolo[5,4-*c*]pyridine-2-carbonitrile **98** has been prepared from 4-aminopyridine and di-*tert*-butyl dicarbonate (DIBOC) (Scheme 61).[189]



98

Scheme 61

Several thiazolopyridines have interesting promising biological profiles including inhibition of kinases,[178,183,185,192-213] intercalation of DNA,[214,215] and as cytotoxic,[205,214,216-217] anti-proliferative,[215] antiparasitic,[217,220] antibacterial,[208-209,221-223] antibiotic,[209,224] antimicrobial,[225] antifungal,[226-228] antiviral[205] and as anticoagulant agents.[183] Some examples of these biologically active compounds are shown in Figure 2.

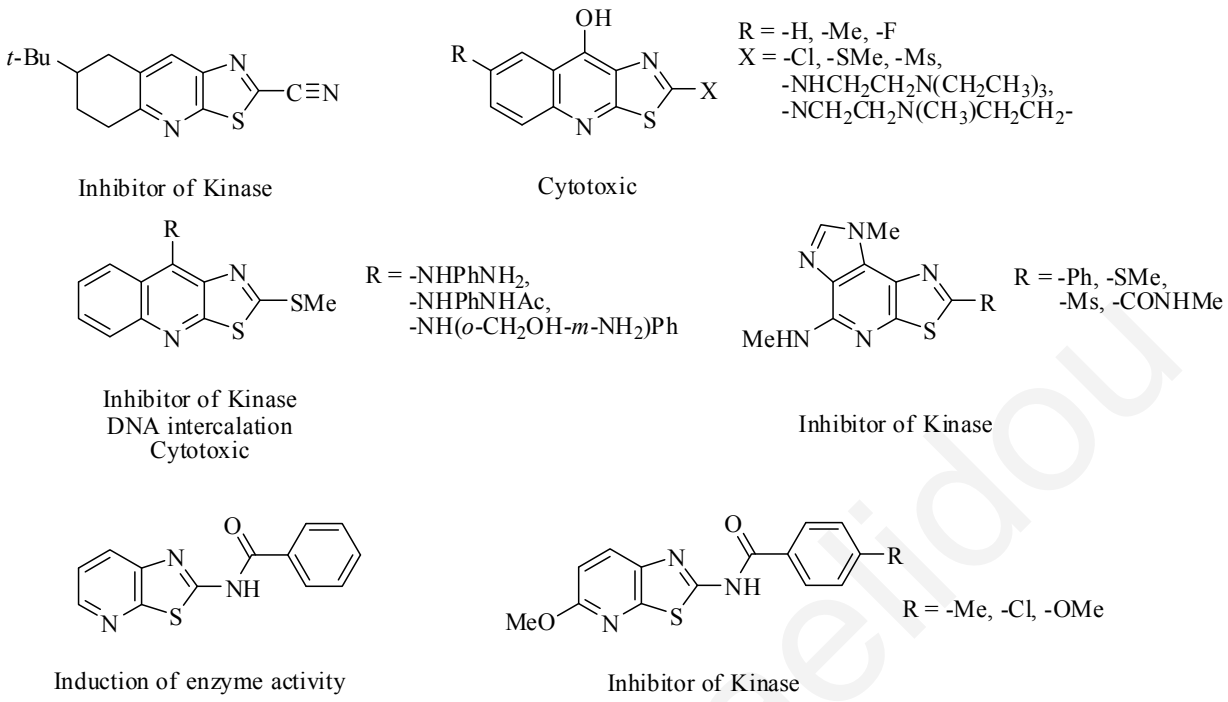
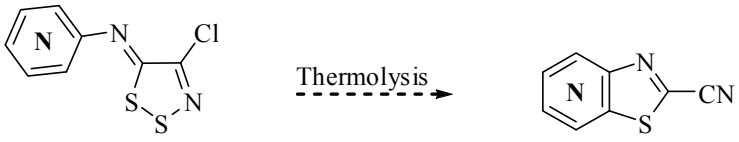


Figure 2. Examples of biologically active thiazolopyridines.

Since there are no examples in the literature of thermolysis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridinamines it was decided to study this ring transformation and see if the same products as in the thermolysis of *N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines can be obtained in similar yields. Also another reason for this investigation is the biological importance of thiazolopyridines. Initialy the thermolysis reactions of the simplest pyridyl analogues *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-X-amine **70a**, **70g**, **70l** (whereas X = 2, 3 and 4, respectively) (Chapter 2), were investigated in the hope that a short route to a variety of thiazolopyridines could be accessed (Scheme 62).



70a,g,l **97-99**

Scheme 62

3.2 Synthesis of Thiazolopyridine-2-carbonitriles Starting from *N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-X-amines 70a,g,l (Where X = 2, 3, 4)

3.2.1 *via* Thermolysis

Typically the thermolysis of dithiazolylidenes is carried out at 150-160 ^{o}C in a preheated Wood's metal bath[70,75,94,100-107,156-158] however, to facilitate the present study the decomposition temperatures of the (dithiazolylidene)pyridinamines **70a,g,l** (230, 150 and 180 ^{o}C, respectively) were measured using Differential Scanning Calorimetry (DSC) (Figure 3).

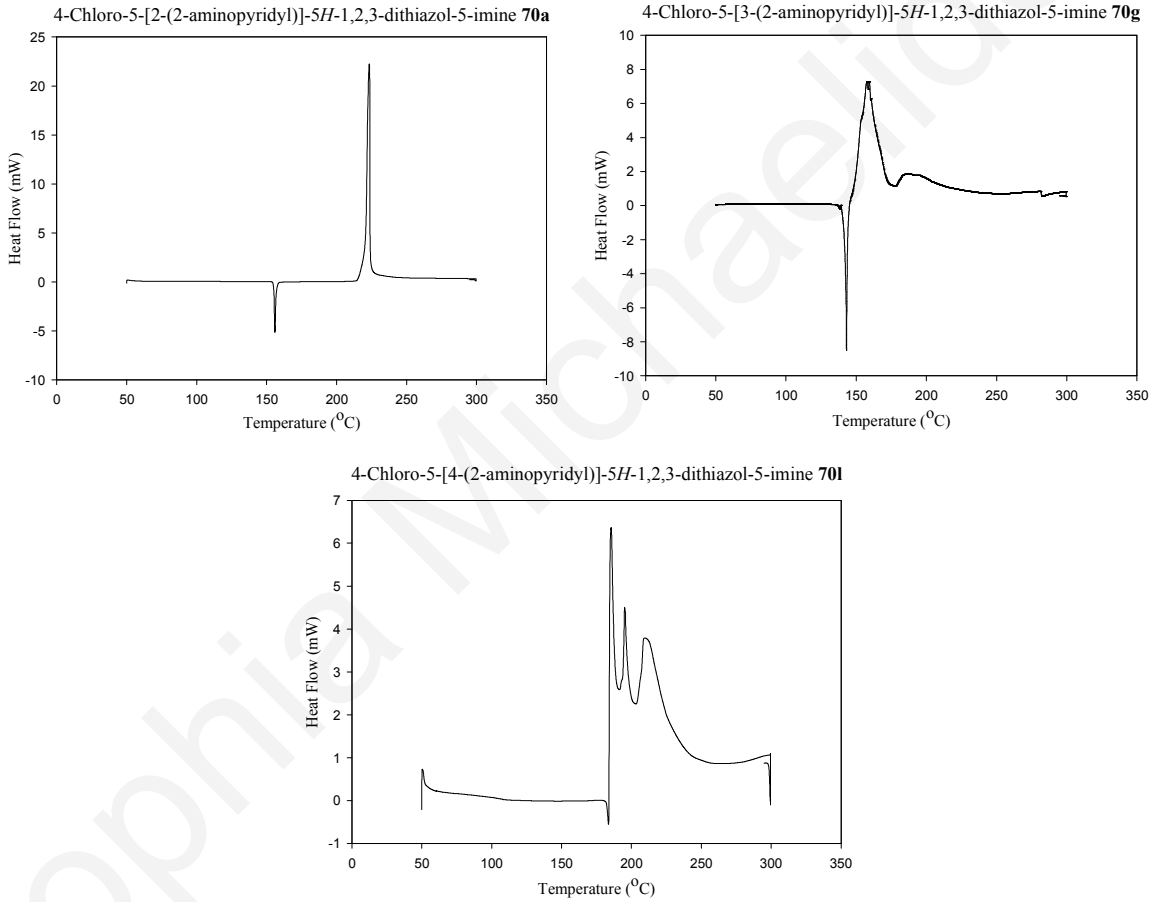
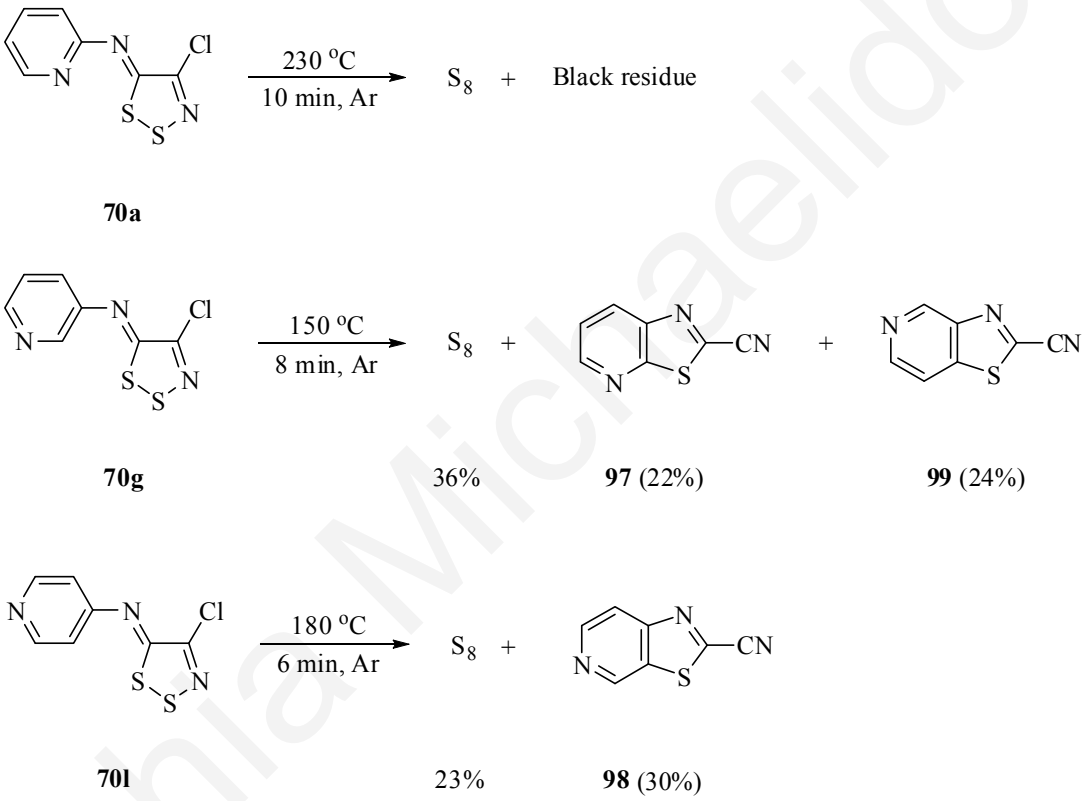


Figure 3 DSC of *N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine **70a**, *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70g** and *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine **70l**. The three samples were heated from 25-350 ^{o}C using a rate of 5 ^{o}C/min under an argon atmosphere in hermetically sealed aluminium pans.

N-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine **70a** was heated neat at *ca.* 230 ^{o}C in an argon atmosphere for 10 min giving S_8 and an intractable black residue that could not be

chromatographed. Heating *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70g** at *ca.* 150 °C for 8 min under argon atmosphere, however, gave S_8 (36%), thiazolo[5,4-*b*] pyridine-2-carbonitrile **97** (22%) and thiazolo[4,5-*c*]pyridine-2-carbonitrile **99** (24%). Thermolysis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine **70l** at *ca.* 180 °C for 6 min gave S_8 (23%) and thiazolo[5,4-*c*]pyridine-2-carbonitrile **98** (30%). Diluting the reaction mixtures with Dowtherm as a high boiling solvent (bp 257 °C) did not simplify the reaction mixtures or lead to improved product yields (Scheme 63).

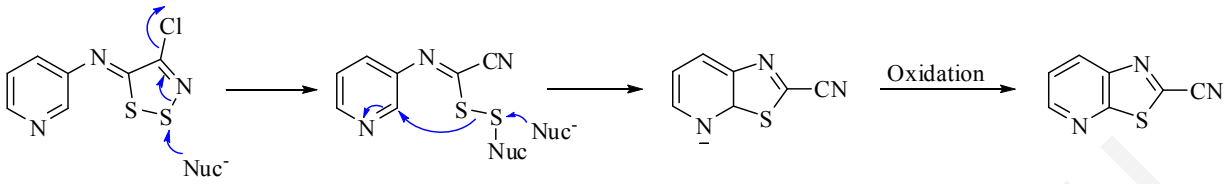


Scheme 63

3.2.2 *via* Thiophile Assisted ANRORC

The low yields of the desired thiazolopyridines were expected, since the pyridyl was by comparison to the phenyl substituents less electron rich and according to the mechanism proposed by Rees,[70] less likely to form the initial C-S bond of the thiazole (Scheme 57, Section 3.1).[70] In light of the comparative π-electron deficiency of pyridine the thiophile assisted nucleophilic ring opening-ring closure (ANRORC)[79,88] style ring transformation of dithiazoles[48,70,85,89,94,95,96,98,120,230] was considered in an effort to improve the product yields

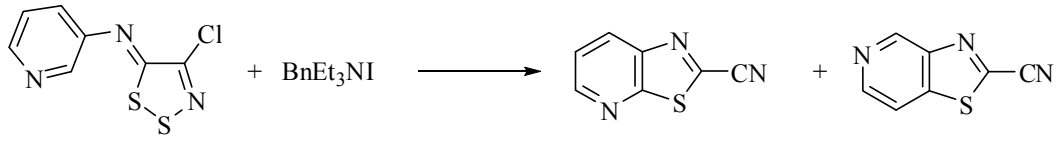
particularly where the released nucleophilic S1 atom could be trapped at either of the pyridyls electrophilic sites C2 or C4 (Scheme 64).



Scheme 64

Initially $BnEt_3NX$ (X = Cl, Br, I) were investigated. These reactions were optimized with respect to the equivalents of the reagent and solvent. The solvents that were screened were PhH, PhMe, PhCl and xylene since this reaction needed high temperatures to proceed. In the case of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine **70a** the complexity of the reaction prohibited the isolation of any desirable products. When *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70g** was treated with $BnEt_3NI$ (0.05 or 1 equiv.) the two expected products were formed in similar to slightly improved yields than in the case of the thermolysis. In the case whereas chloride or bromide were used (1 equiv.) in PhCl for 24 h, the two products were obtained only in traces and the starting material was recovered in a range of 78-85% (Table 3).

Table 3. Reaction of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70g** (0.22 mmol) with $BnEt_3NI$ (1 equiv.) in dry solvent (2 mL) under anhydrous conditions, at reflux temperatures.



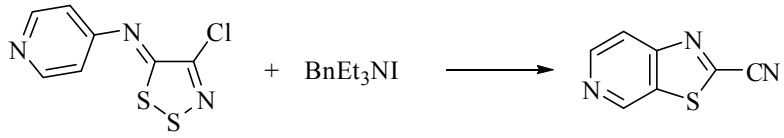
70g **97** **99**

Solvent	Temp. (°C)	Time (h)	Yields (%) **97**	**99**
PhH	80	24	22	46
PhMe	110	2.3	17	32
PhCl	132	0.67	25	29
PhCl[a]	132	20	37	40
xylene	145	0.67	35	42

[a] $BnEt_3NI$ (5%) was used.

When *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine **70l** was treated with $BnEt_3NI$ (0.05 or 1 equiv.) the expected thiazolo[5,4-*c*]pyridine-2-carbonitrile **98** was obtained in low to moderate yields (Table 4). Use of chloride or bromide failed to give a complete reaction.

Table 4. Reaction of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine **70l** (0.22 mmol) with $BnEt_3NI$ (1 equiv.) in dry solvent under anhydrous conditions, at reflux temperatures.



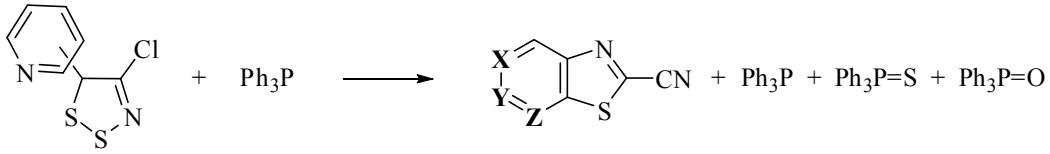
70l **98**

Solvent	T (°C)	Time (h)	Yield (%)
PhH	80	24	Traces
PhMe	110	3	18
PhCl	132	0.5	41
PhCl[a]	132	28	39
xylene	145	0.25	21

[a] $BnEt_3NI$ (5 mol%) was used.

The next thiophilic reagents that were used were free Ph_3P and polymer bound Ph_3P. Reaction of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-X-amines (whereas X = 2, 3 and 4) with free Ph_3P gave only baseline or recovered starting materials, but when polymer bound Ph_3P (2, 3, or 4 equiv.) was used the expected thiazolopyridines were obtained in similar yields as the reaction with $BnEt_3NI$. Again *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine **70a** failed to give any expected product giving only recovered starting material (85%) even when polymer bound Ph_3P was used. The best yields were 38% for thiazolo[5,4-*b*]pyridine-2-carbo-nitrile **97** and 32% for thiazolo[4,5-*c*]pyridine-2-carbonitrile **99** starting from *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70g** and 36% for thiazolo[5,4-*c*]pyridine-2-carbonitrile **98** starting from *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine **70l** (Table 5).

Table 5. Reaction of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-X-amine **70a,g,l** (0.22 mmol) with either Ph_3P (2, 3 or 4 equiv.) or polymer bound Ph_3P (2, 3 or 4 equiv.) in DCM.



70a,g,l

97 (X = Y = CH, Z = N)
98 (X = Z = CH, Y = N)
99 (X = N, Y = Z = CH)

Starting imine	Ph_3P (equiv.)	Pyridothiazole	Yields (%) Ph_3P	Ph_3P=S	Ph_3P=O
Pyrid-2-yl **70a**	2[a]	-[c]	-	-	-
Pyrid-2-yl **70a**	2[b]	-[d]	79	-	-
Pyrid-2-yl **70a**	3[a]	-[d]	-	-	-
Pyrid-2-yl **70a**	3[b]	-[d]	82	-	-
Pyrid-2-yl **70a**	4[b]	-[d]	88	-	-
Pyrid-3-yl **70g**	2[a]	-	-	93	44
Pyrid-3-yl **70g**	2[b]	**97** (38), **99** (25)	-	-	-
Pyrid-3-yl **70g**	3[a]	-	-	91	33
Pyrid-3-yl **70g**	3[b]	**97** (34), **99** (32)	-	-	-
Pyrid-3-yl **70g**	4[a]	**97** (17), **99** (19)	24	68	22
Pyrid-3-yl **70g**	4[b]	**97** (15), **99** (18)	-	-	-
Pyrid-4-yl **70l**	2[a]	-[e]	-	-	-
Pyrid-4-yl **70l**	2[b]	-[e]	-	-	-
Pyrid-4-yl **70l**	3[a]	-[e]	-	-	-
Pyrid-4-yl **70l**	3[b]	**98** (36)	-	-	-
Pyrid-4-yl **70l**	4[a]	**98** (30)	-	-	-
Pyrid-4-yl **70l**	4[b]	**98** (18)	-	-	-

[a]Free Ph_3P; [b]polymer bound Ph_3P (3 mmol / g Ph_3P loading, crosslinked with 2% DVB, 200-400 mesh); [c]a yellow baseline was formed; [d]No desired product, only baseline material; [e]Starting material was recovered in 28, 16 and 14% respectively.

The last thiophilic reagent that was used was DBU which can act as a thiophilic reagent to open dithiazoles,[120-132] however, in all three cases only baseline material was formed.

3.3 Synthesis of Thiazolopyridine-2-carbonitriles Starting from X-Chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amines 70i,j (Where X = 2, 4)

3.3.1 *via* Thermolysis

A closer look to the proposed ANRORC type mechanism mentioned above, indicated that an oxidation step was needed to regain aromaticity and as such adjusting the oxidation level of the starting 3-aminopyridine by introducing a chlorine substituent at either C2 or at C4 on the pyridyl ring was expected to avoid the need for an oxidative rearomatization and assist in both facilitating and directing the ring closure to give the thiazolopyridines (see Scheme 64).

In light of this, the above reactions were repeated using this time 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** and 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-pyridin-3-amine **70j** as starting materials. DSC studies indicated the decomposition temperature of dithiazolylideneamines **70i** and **70j** to be *ca.* 150 and 180 ^{o}C, respectively (Figure 4).

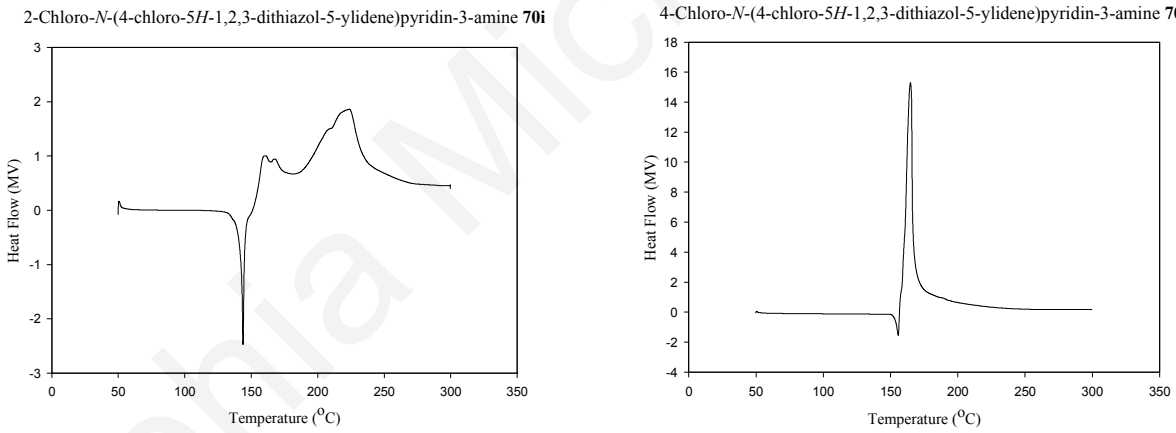
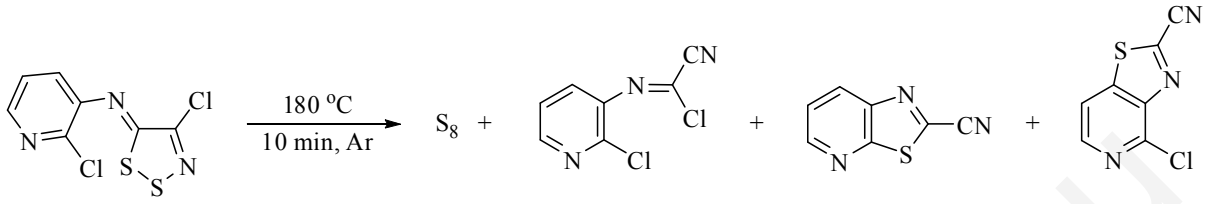


Figure 4: DSC of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** and 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70j**. The two samples were heated from 25-350 ^{o}C using a rate of 5 ^{o}C/min under an argon atmosphere in hermetically sealed aluminium pans.

Thermolysis of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** at 180 ^{o}C for 10 min under an argon atmosphere gave S_8 and three other products: The first product was identified to be the expected product in the thermolysis of dithiazolylideneamines supporting electron poor aromatic rings,[70] *N*-(chlorocyanomethylidene)-2-chloropyridine **100**.

The second product was the expected thiazolopyridine **97** and the third product was 4-chloro-thiazolo[4,5-*c*]pyridine-2-carbonitrile **101** (Scheme 65).

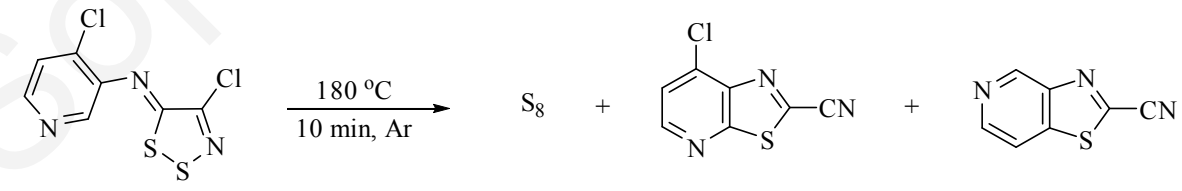


70i 35% **100** (77%) **97** (10%) **101** (15%)

Scheme 65

4-Chlorothiazolo[4,5-*c*]pyridine-2-carbonitrile **101** was obtained as colourless needles, mp 161-162 °C (from cyclohexane). Microanalysis (C, 42.8; H, 1.2; N, 21.6%) and mass spectrometry supported the formula $C_7H_2ClN_3S$ [*m/z* 195 (M^+, 100%)]. The ^{13}C NMR spectrum showed six separate carbon resonances of which three were quaternary carbons as supported by DEPT-135 studies. The presence of a cyano group was supported by an IR band at ν(C≡N) 2241 cm^{-1} and a carbon signal at 115.8 ppm. The ^1H NMR spectrum identified two resonances which belonged to aromatic hydrogens (8.52 and 7.90 ppm). The signal at δ_H 8.52 ppm was observed as doublet (*J* 5.5 Hz) and the signal at δ_H 7.90 was also observed as doublet (*J* 5.6 Hz).

Similarly thermolysis of 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70j** at *ca.* 180 °C for 10 min in anhydrous conditions gave S_8 and 2 other products: 7-chloro-thiazolo[5,4-*b*]pyridine-2-carbonitrile **102** and the expected thiazolopyridine **99** (Scheme 66).



70j 30% **102** (22%) **99** (44 %)

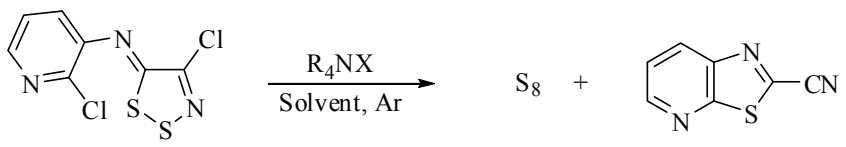
Scheme 66

7-Chlorothiazolo[5,4-*b*]pyridine-2-carbonitrile **102** was obtained as colourless cotton fibers, mp 177-178 ^{o}C (from cyclohexane). Microanalysis (C, 42.9; H, 1.0; N, 21.6%) and mass spectrometry supported the formula $C_7H_2ClN_3S$ [*m*/*z* 195 (M^+, 100%)]. The ^{13}C NMR spectrum showed six separate carbon resonances of which three were quaternary carbons as supported by DEPT-135 studies. The presence of a cyano group was supported by an IR band at ν(C≡N) 2234 cm^{-1} and a carbon signal at 112.1 ppm. The ^{1}H NMR spectrum identified two resonances which belonged to aromatic hydrogens (8.70 and 7.66 ppm). The signal at δ_H 8.70 ppm was observed as doublet (*J* 5.0 Hz) and the signal at δ_H 7.66 was also observed as doublet (*J* 5.0 Hz).

3.3.2 *via* Thiophile Assisted ANRORC

Reaction of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** with $BnEt_3NX$ (X = Cl, Br, I) gave as only product the thiazolopyridine **97** in moderate to quantitative yields. The reaction was optimized with respect to equivalents of reagents and different solvents. When the reaction took place in atmospheric air then the reaction mixture was complex and the desired product was obtained in moderate to low yields. When the reaction took place in anhydrous conditions and in dry and degassed solvent then the product was received in high yields (Table 6).

Table 6. Reaction of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** (0.19 mmol) with R_4NX in the presence of solvent (2 mL) in anhydrous conditions.

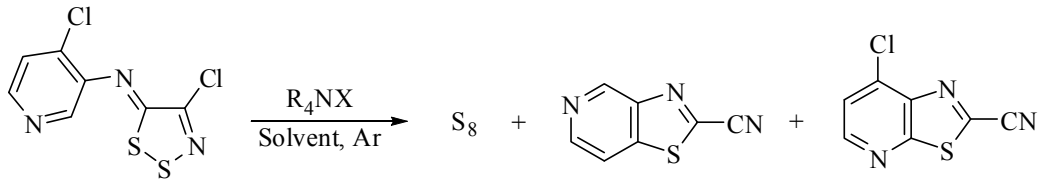


70i **97**

R_4NX (equiv.)	Time (h)	Solvent (°C)	Yields (%) S_8	**97**
$BnEt_3NI$ (1)	20 min	PhCl (132)	84	66
$BnEt_3NI$ (1)	10 min	xylene (145)	86	60
$BnEt_3NI$ (0.5)	1	PhCl (132)	99	92
$BnEt_3NI$ (0.25)	4	PhCl (132)	100	89
$BnEt_3NI$ (0.05)	24	PhCl (132)	83	98
$BnEt_3NI$ (0.05)	26	PhH (80)	90	99
$BnEt_3NI$ (0.05)	22	PhMe (110)	89	95
$BnEt_3NI$ (0.05)	20	xylene (145)	88	96
Et_4NBr (0.05)	24	PhCl (132)	98	92
$BnEt_3NCl$ (0.05)	48	PhCl (132)	90	88

Similar treatment of 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70j** with $BnEt_3NI$ gave as product the expected thiazolopyridine **99** in high yields. In contrast when $BnEt_3NCl$ or $BnEt_3NBr$ was used then some 7-chlorothiazolo[5,4-*b*]pyridine-2-carbonitrile **102** was also formed as side-product in low yields (Table 7).

Table 7. Reaction of 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70j** (0.19 mmol) with R_4NX in solvent (2 mL) under anhydrous conditions.



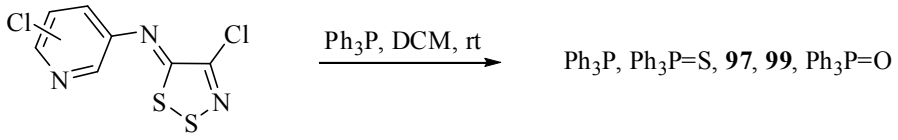
70j **99** **102**

R_4NX (equiv.)	Solvent (^oC)	Time (h)	Yields (%) S_8	**99**	**102**
$BnEt_3NI$ (1)	PhH (80)	3 d	90	92	0
$BnEt_3NI$ (1)	PhMe (110)	17	92	96	0
$BnEt_3NI$ (1)	PhCl (132)	2	90	94	0
$BnEt_3NI$ (1)	xylene (145)	50 min	89	91	0
$BnEt_3NI$ (0.05)	PhH (80)	24	91	95	0
$BnEt_3NI$ (0.05)	PhMe (110)	22	95	97	0
$BnEt_3NI$ (0.05)	PhCl (132)	20	96	99	0
$BnEt_3NI$ (0.05)	xylene (145)	20	95	98	0
Et_4NBr (0.05)	PhCl (132)	30	88	86	6
$BnEt_3NCl$ (0.05)	PhCl (132)	35	80	66	26

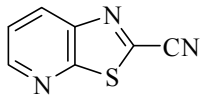
In an effort to obtain these thiazolopyridines without the need for chromatography, the reactions of dithiazolylideneamines **70i** and **70j** with $BnEt_3NI$ (5 mol%) in dried and degassed PhCl were repeated and on completion the reaction mixtures were left to cool to room temperature followed by the addition of polymer bound Ph_3P (2 equiv.). The mixtures were then left stirring at ambient temperature for 24 h, followed by filtration of the polymer to give the desired products in same yields as before.

Treatment of the two X-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine (whereas X= 2, 4) **70i** and **70j** with Ph_3P gave the expected Ph_3P=S and Ph_3P=O as well as the thiazolopyridines, but the yields were lower than in the case were $BnEt_3NI$ was used as a thiophilic reagent. Similarly, when polymer bound Ph_3P was used the expected products were obtained in analogous yields as in the case when free Ph_3P was used (Table 8).

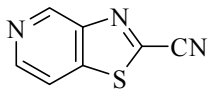
Table 8. Reactions of X-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** and **70j** (0.19 mmol) with Ph_3P and polymer bound Ph_3P in DCM (2 mL).



70i-j



97



99

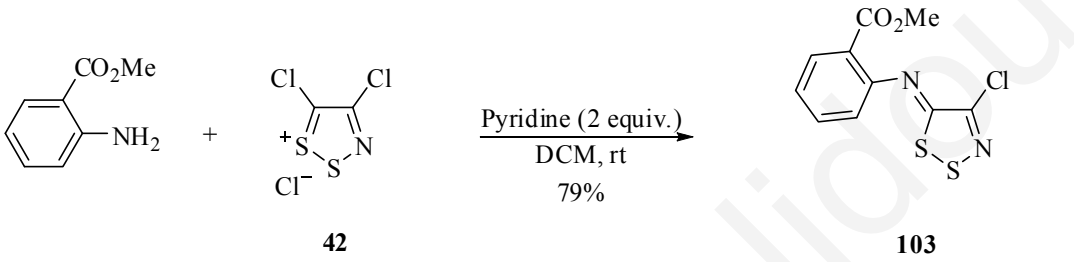
Starting imine	Ph_3P (equiv.)	Temp. (^oC)	Time (min)	Yields (%) Ph_3P	Ph_3P=S	**97**	**99**	Ph_3P=O
2-Cl-3-Pyridyl **70i**	2[a]	20	120	-	80	28	-	60
4-Cl-3-Pyridyl **70j**	2[a]	20	15	-	51	-	28	42
2-Cl-3-Pyridyl **70i**	2[a]	40	15	-	75	42	-	55
4-Cl-3-Pyridyl **70j**	2[a]	40	10	-	70	-	57	62
2-Cl-3-Pyridyl **70i**	3[a]	20	60	10	65	25	-	50
4-Cl-3-Pyridyl **70j**	3[a]	20	10	17	58	-	26	48
2-Cl-3-Pyridyl **70i**	4[a]	20	30	25	60	18	-	45
4-Cl-3-Pyridyl **70j**	4[a]	20	5	35	57	-	14	49
2-Cl-3-Pyridyl **70i**	2[b]	20	2 d	-	-	16	-	-
4-Cl-3-Pyridyl **70j**	2[b]	20	3 d	-	-	-	20	-
2-Cl-3-Pyridyl **70i**	3[b]	20	45	-	-	14	-	-
4-Cl-3-Pyridyl **70j**	3[b]	20	60	-	-	-	17	-
2-Cl-3-Pyridyl **70i**	4[b]	20	10	-	-	10	-	-
4-Cl-3-Pyridyl **70j**	4[b]	20	20	-	-	-	17	-

[a] Free Ph_3P; [b]polymer bound Ph_3P (3 mmol / g Ph_3P loading, crosslinked with 2% DVB, 200-400 mesh)

The last thiophilic reagent that was used was DBU. Reaction of the 2-chlorodithiazol-ylideneamine **70i** with DBU (3 equiv.) in dry DCM at *ca.* 0 ^oC or at *ca.* -86 ^oC gave the expected thiazolopyridine **97** (50 and 53%, respectively) and the imidoylchloride **100** (24 and 20%, respectively). In the case of the 4-chlorodithiazolylideneamine **70j**, only the desired thiazolopyridine **99** was formed in 59 and 62% yields, respectively.

3.4 Synthesis of 3,1-Benzothiazin-4-ones

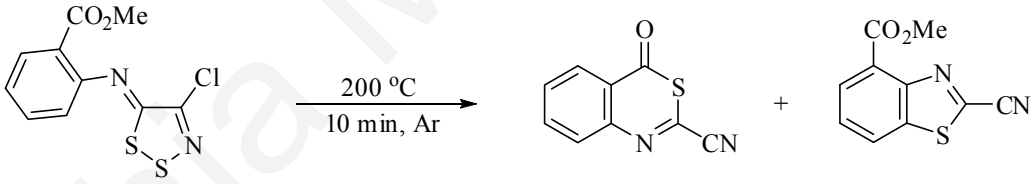
Having the above results in mind it was decided to repeat this chemistry using a dithiazol-ylideneamine which had a different electrophilic trap in the C2 position (carboxylate group). For this purpose, (*Z*)-methyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate **103** was synthesized starting from the readily available methyl anthranilate[42,48,84,113,231,232] (Scheme 67).



42 **103**

Scheme 67

Thermolysis of the (dithiazolylideneamino)benzoate **103** at *ca.* 200 °C for 10 min under an argon atmosphere gave 4-oxo-4*H*-benzo[*d*][1,3]thiazine-2-carbonitrile **104** together with the expected methyl 2-cyanobenzothiazole-4-carboxylate **105** in 25 and 35% yields, respectively (Scheme 68).



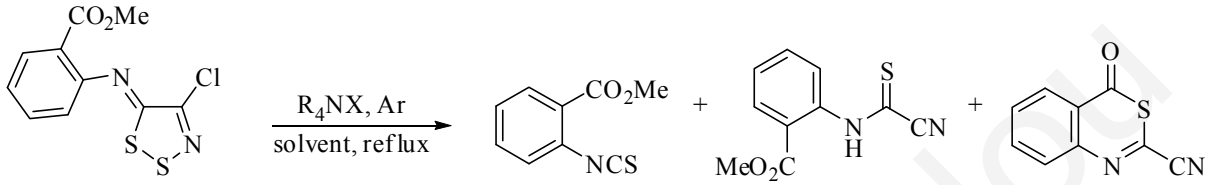
103 **104** (25%) **105** (35%)

Scheme 68

The isolation of both benzothiazinone **104** and benzothiazole **105** from the thermolysis of (*Z*)-methyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate **103** implied that two competing mechanisms were operating. The ring closure to benzothiazole **105** requires the dithiazole ring sulfur S1 to have electrophilic character, while the ring closure to the benzothiazinone **104** requires the dithiazole ring sulfur S1 to have nucleophilic character. Traces of chloride released during the degradation could have activated an ANRORC type ring transformation.[89] As such, the (dithiazolylideneamino)benzoate **103** was treated with

various tetraalkylammonium halides in the hope that the yield of benzothiazinone could be improved (Table 9).

Table 9. The reaction of (*Z*)-methyl-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate **103** (0.17 mmol) with R_4NX in anhydrous solvent (2 mL) at reflux under argon atmsophere.



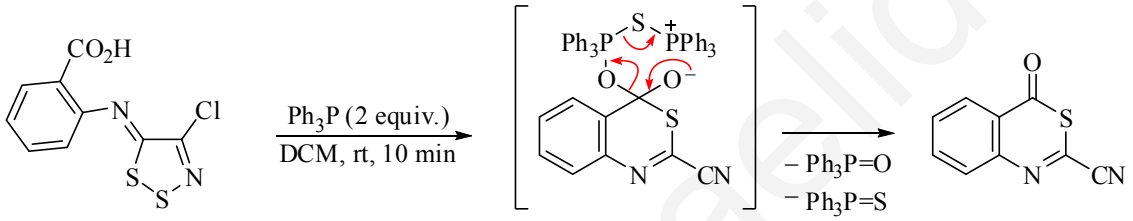
103 **106** **107** **104**

R_4NX (equiv.)	Solvent (°C)	Time (h)	Yields (%) **106**	**107**	**104**
$BnEt_3NCl$ (0.05)	PhCl (132)	15.5	-	88	-
Et_4NBr (0.05)	PhCl (132)	14.5	-	55	-
$BnEt_3NI$ (0.05)	xylene (145)	16	-	98	-
$BnEt_3NI$ (0.05)	PhCl (132)	16	-	99	-
$BnEt_3NI$ (0.05)	PhMe (110)	20	-	98	-
$BnEt_3NI$ (0.05)	PhH (80)	24	-	95	-
$BnEt_3NI$ (1)	xylene (145)	0.33	-	46	42
$BnEt_3NI$ (1)	PhCl (132)	0.33	38	31	-
$BnEt_3NI$ (1)	PhMe (110)	0.75	-	61	24
$BnEt_3NI$ (1)	PhH (80)	21	-	27	52

The reactions gave three main products, the first was methyl 2-isothiocyanatobenzoate **106**, the second was methyl (Z)-methyl-2-(cyanothioformanilido)benzoate **107** and the third was the expected compound **104**. The use of catalytic amounts of halide (5 mol%) gave only recoveries of S_8 and the cyanothioformanilide **107**. Increasing the nucleophilicity of the halide from chloride to iodide led to higher yields of the cyanothioformanilide **107** but increasing the reaction temperature by changing the solvent from refluxing PhH to xylene did not significantly shorten the reaction times. On increasing the quantity of iodide (1 equiv.) the reactions became more complex affording the isothiocyanate **106** and the benzothiazinone **104** at the expense of the cyanothioformanilide **107**. Presumably, these side products formed directly from the cyanothioformanilide **107** that can undergo intramolecular cyclization to give the benzothiazinone **104** or eliminate HCN to give the isothiocyanate **106**. All these reactions also gave S_8 and typically this was removed by chromatography. However, in the reaction

with catalytic iodide that afforded quantitatively the cyanothioformanilide **107** it was demonstrated that the addition of thiophilic polymer bound Ph_3P allowed the high yielding isolation of the cyanothioformanilide **107** by a simple filtration of the polymer resin.

Rees *et al.*,[84,113] reported the mild and quantitative conversion of the iminocarboxylic acid **108** into the benzothiazinone **104** on treatment with Ph_3P (2 equiv.) and proposed that the phosphonium salt side products helped activate the carboxylic acid towards cyclization possibly *via* the tentative intermediate **109** (Scheme 69).

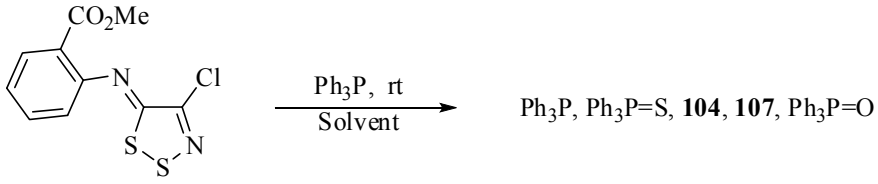


108 **109** **104** (96%)

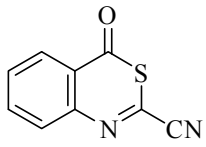
Scheme 69

The above reaction indicated that use of Ph_3P could lead to a high yielding formation of benzothiazinone **104**. Similar treatment of (*Z*)-methyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate **103** with free or polymer bound Ph_3P, however, gave the cyanothioformanilide **107** as the major product together with some benzothiazinone **104** (Table 10).

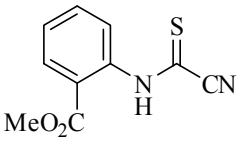
Table 10. Treatment of (*Z*)-methyl-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate **103** (0.17 mmol) with Ph_3P and polymer bound Ph_3P in solvent (2 mL).



103



104



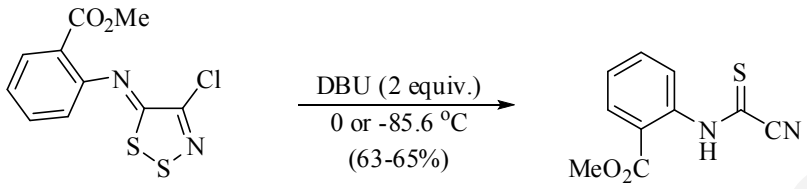
107

Ph_3P (equiv.)	Solvent (^oC)	Time (min)	Yields (%)				
			Ph_3P	Ph_3P=S	**104**	**107**	Ph_3P=O
2[a]	DCM (rt)	10	-	84	41	54	73
2[a]	DCM (40)	2	-	80	10	55	70
2[a]	MeOH (rt)	5	-	85	6	76	70
2[a,c]	DCM (rt)	10	-	85	-	65	74
2[a,c]	MeOH (rt)	5	-	89	-	90	80
2[b]	DCM (rt)	48 h	-	Incomplete Reaction			
3[a]	DCM (rt)	8	-	80	10	57	75
3[a]	DCM (40)	5	-	Complex Mixture			
3[b]	DCM (0)	35	-	-	8	80	-
3[b]	DCM (rt)	30	-	-	15	62	-
4[a]	DCM (rt)	5	-	79	15	40	75
4[a]	DCM (40)	5	-	Complex Mixture			
4[b]	DCM (rt)	20	-	-	9	72	-

[a]Free Ph_3P; [b]Polymer bound Ph_3P (3 mmol / g Ph_3P loading, crosslinked with 2% DVB, 200-400 mesh; [c] TosH (1 equiv.) was added to the reaction mixture.

The highest yield of cyanothioformanilide **107** (90%) was obtained when the reaction took place in MeOH, in the presence of *p*-TsOH (1 equiv.). When the reaction took place in DCM at *ca*. 20 ^oC then the yield of the cyanothioformanilide **107** decreased and the benzothiazinone **104** was obtained in its highest yield (41-42%).

Finally, treatment of the methyl ester dithiazolylidene **103** with DBU (2 equiv.) at either *ca.* 0 ^{o}C or at *ca.* -86 ^{o}C, in dry DCM, gave only the cyanothioformanilide **107** in 63% and 65% yields, respectively (Scheme 70).



103 **107**

Scheme 70

3.5 Summary

Thermolysis of *N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-X-amines (whereas X = 2, 3, 4) **70a,g,l** gave thiazolo[5,4-*b*]pyridine-2-carbonitrile **97**, thiazolo[4,5-*c*]pyridine-2-carbonitrile **99** and thiazolo[5,4-*c*]pyridine-2-carbonitrile **98** in low yields. Thermolysis of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** and 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70j** gave in the first case (2-chloropyridin-3-yl)carbon cyanidimidic chloride **100,** pyridothiazole **97** and 4-chlorothiazolo[4,5-*c*]pyridine-2-carbonitrile **101** and in the second case 7-chlorothiazolo[5,4-*b*]pyridine-2-carbonitrile **102** and pyridothiazole **99** respectively. Treatment with $BnEt_3NI$ (0.05 equiv.) in PhCl gave the pyridothiazole **99** and pyridothiazole **97** in quantitative yields. The same chemistry was also repeated in the case of (*Z*)-methyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate **103**. Thermolysis gave 4-oxo-4*H*-benzo[*d*][1,3]thiazine-2-carbonitrile **104** and methyl 2-cyanobenzothiazole-4-carboxylate **105** in low yields while, treatment with $BnEt_3NI$ (0.05 equiv.) in PhCl gave only (Z)-methyl-2-(cyanothioformanilido)benzoate **107** in quantitative yields**.** Treatment with free of polymer bound Ph_3P gave only compound **107** in high yields. The highest yield (90%) was observed when *p*-TsOH (1 equiv.) was also used in methanol. As future work, more analogues can be synthesized. The conclusion from all the above is that ring opening *via* thiophile assisted ANRORC can be advantageous and is thus a useful tool for this chemistry.

CHAPTER 4

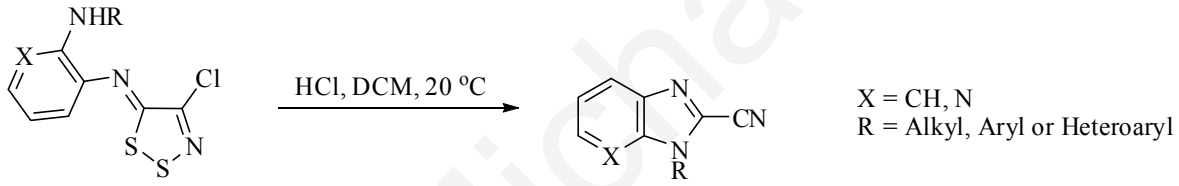
Ring Transformations of 2-Hydroxy-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidineamino)arenes

Sections

4.1 Introduction

In Chapter 3 we examined the thermal and thiophile assisted ring transformation of (4-chloro-5*H*-1,2,3-dithiazolylideneamine)arenes bearing *N*-arenes with electrophilic sites. The study led to the quantitative ring transformation of 2-chloro- and 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** and **70j** into thiazolo[5,4-*b*]pyridine-2-carbonitrile **97** and thiazolo[5,4-*c*]pyridine-2-carbonitrile **98**, respectively (Chapter 3, Section 3.2.1). In contrast, there are also several examples of (4-chloro-5*H*-1,2,3-dithiazol-5-ylidineamino)arene ring transformations that involve a nucleophilic *ortho* substituent.

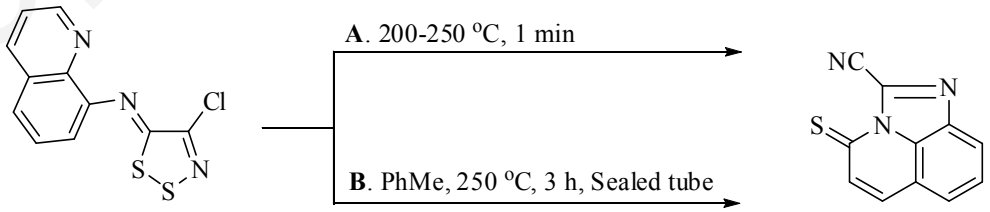
For example, dithiazolylideneamines which have an arene bearing a nucleophilic *ortho* secondary amine **110** can cyclize to afford the analogous imidazole-2-carbonitrile **111** (Scheme 71).[95,117]



110 **111**

Scheme 71

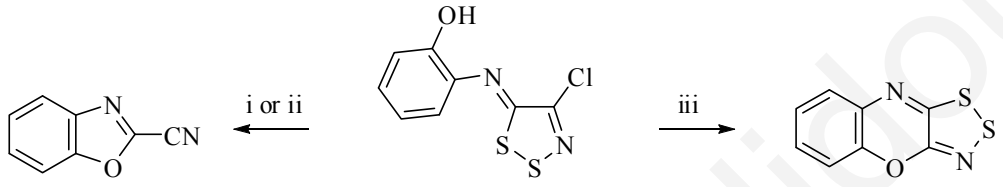
Substituted *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)quinolin-8-amines **112** when heated neat at 200-250 °C for 1 min or for concentrated solutions in a minimum of PhMe in a sealed tube at *ca.* 250 °C for 3 h cyclize to form 4-thioxo-4*H*-imidazo[4,5,1-*ij*]quinoline-2-carbonitriles **113** (Scheme 72).[233-234]



112 **113**

Scheme 72

Moreover, 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** which can be prepared in 83% from Appel salt **42** and 2-aminophenol when heated neat at *ca.* 200 °C for 1 min[75,235] or in NMP at 150 °C under microwave irradiation[7] gives benzo[*d*]oxazole-2-carbonitrile **67** in 90 and 69% yields, respectively. More interestingly, treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** with NaH in dry THF gave not the expected benzoxazole but surprisingly benzo[*b*][1,2,3]dithiazolo [5,4-*e*][1,4]oxazine **114** (Scheme 73).[70]

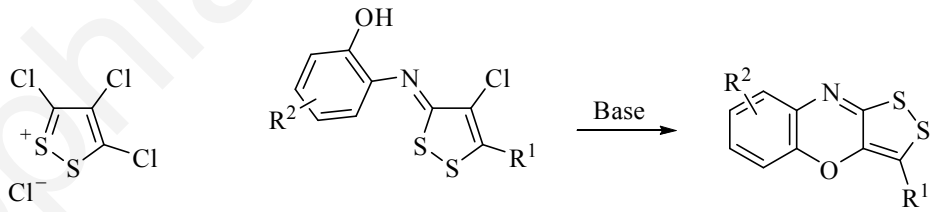


67 **66** **114**

Reagent and conditions: i) 200 °C, 1 min, 85%; ii) NMP, 150 °C, MW (250 W), 1 min, 69%; iii) NaH (2 equiv.), THF (dry), reflux, 2 h 68%.

Scheme 73

An analogous base (NaH or Hünig's base in THF or K_2CO_3 in MeCN) catalysed cyclization involved the 2-(4-chloro-3*H*-1,2-dithiol-3-ylideneamino)phenols **116**, prepared from 3,4,5-trichloro-1,2-dithiolium chloride **115**[238] and 2-aminophenols, to give 1,2-dithiolo[4,3-*b*][1,4]benzoxazines **117**, in moderate yields (39–45%) (Scheme 74).[237]



115 **116** **117**

Scheme 74

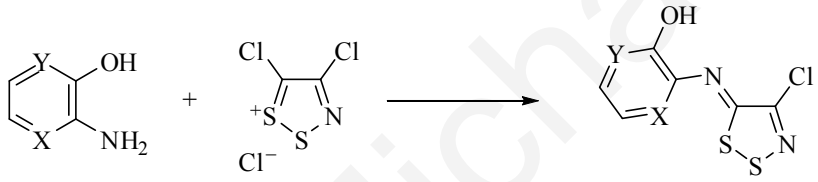
This ring closure of (dithiazolylideneamino)phenol **66** into benzoxazine **114** is a rare example of the substitution of the dithiazoles C4 chloro substituent[91,238] and one of only two examples of a cyclization onto C4 that maintains the integrity of the dithiazole ring.[238] In light of this and our access to 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66**, 3-(4-chloro-5*H*-

1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** and 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** we decided to probe this chemistry further, investigate the formed products and try to propose mechanistic pathways for their formation.

4.2 Ring Transformations of 2-Hydroxy-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)arenes

4.2.1 Synthesis of Fused Oxazoles and Oxazines

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66**, together with two new aza analogues, 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** and 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** were prepared from 4,5-dichloro-1,2,3-dithiazolium chloride **42** and the corresponding *ortho* hydroxyl amino arenes (see Chapter 2, Section 2.2.2) (Scheme 75).



(X = Y = CH) (X = CH, Y = N) (X = N, Y = CH)

42

66 (X = Y = CH), 95%
70h (X = CH, Y = N), 53%
70b (X = N, Y = CH), 11%

Reagents and conditions: (a) stirring at rt for 1 h; (b) Base (2 equiv.), DCM, *ca* 20 ^{o}C, 2 h

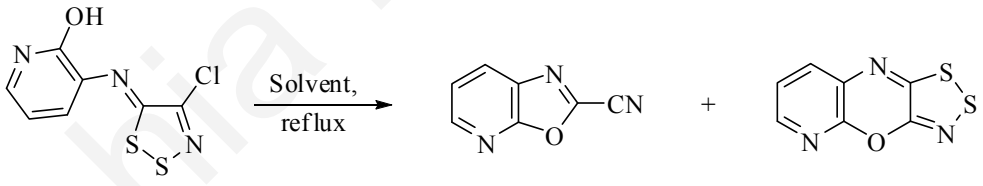
Scheme 75

4.2.1.1 Thermal Studies

Thermolysis of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** under argon atmosphere at *ca.* 200 ^{o}C for 5 min, gave the expected benzo[*d*]oxazole-2-carbonitrile **67** in 85% yield together with S_8 (90%), which closely agreed with the literature yield (90%).[70] Repetition of the reaction in a microwave reactor (250 W) at *ca.* 200 ^{o}C (P = 100 Psi) for 1 min afforded the desired benzoxazole **67** in somewhat lower yield (61%) together with a black intractable polar residue (baseline on TLC). Treatment with NaH (2 equiv.) in dry THF for 2 h at reflux temperature gave the expected benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114** in 65% yield which was also closely in agreement with the literature yield (68%).[70]

Able to reproduce the reported literature we subsequently investigated the analogous reactions of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** and 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b**. Interestingly, early observations during their isolation and purification gave some indication of their thermal stability. Both 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** and 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70h** could be recrystallized from warm cyclohexane to give clean yellow cotton fibers but in contrast, 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70b** was unstable in warm cyclohexane and cyclized into oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** in 60% yield and also gave traces of [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119**. For this reason, the purification of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70b** was carried out *via* precipitation from pentane. Moreover when 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-pyridin-2-ol **70h** was left to boil in PhH, PhMe, PhCl and xylene oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** and [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** were formed. In the case of PhH and PhMe the oxazolo[5,4-*b*]pyridine **118** and pyridoxazine **119** were obtained only in traces while in PhCl and xylene pyridoxazine **119** was obtained again in traces while oxazolo[5,4-*b*]pyridine **118** was obtained in 72 and 84% yields, respectively (Table 11).

Table 11. Thermal stability of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h**.



70h **118** **119**

Solvent	Temp. (°C)	Yields (%)	
		118	**119**
c-C_6H_{12}	80	60	Traces
PhH	80	Traces	Traces
PhMe	110	Traces	Traces
PhCl	131	72	Traces
Xylene	139	84	Traces

To further investigate the stability of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** DSC studies were carried out. The DSC studies showed a melting point at 106.4 ^{o}C (onset peak at 100.1 ^{o}C) and two exothermic peaks at 109.3 (onset peak at 107.2 ^{o}C) and 145.0 ^{o}C (onset peak at 142.5 ^{o}C), respectively indicating the formation of two different decomposition products (Figure 5).

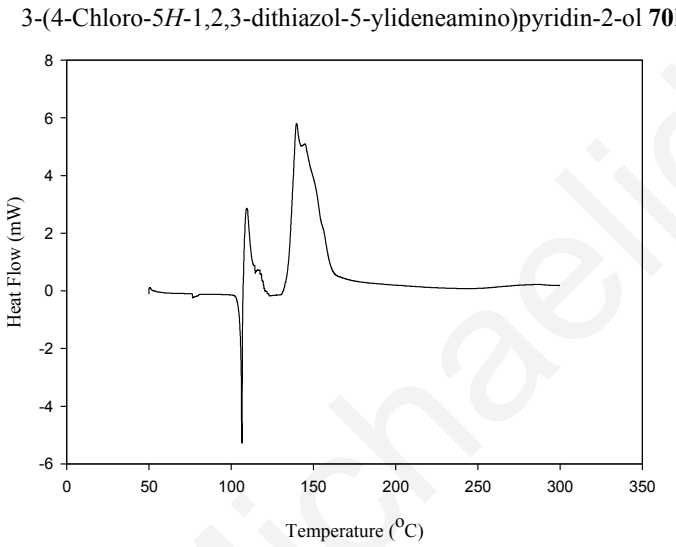


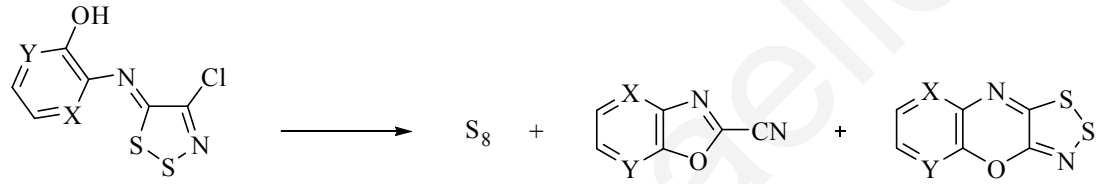
Figure 5: Melting and decomposition onset and peak temperatures of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** measured by DSC in aluminium hermetically sealed pans under argon with a 5 ^{o}C/min heating rate.

Thermolysis of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** at *ca.* 200 ^{o}C for 2 min gave S_8 (90%), oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** (66%) and [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** (1%). Repetition of the reaction in a microwave reactor at *ca.* 200 ^{o}C for 2 min gave a black residue (baseline on TLC) and the oxazolo[5,4-*b*]pyridine **118** in 45%, while treatment of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** with NaH in dry THF at reflux gave the pyridoxazine **119** in 42% yield and traces of the oxazolo[5,4-*b*]pyridine **118** (Table 12). Increasing the equivalents of NaH to 4 and 6 did not help improve the yield since pyridoxazine **119** was obtained in 32 and 31% yields, respectively.

Thermolysis of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** at *ca.* 200 ^{o}C for 5 min gave as products S_8 (90%) and oxazolo[4,5-*b*]pyridine-2-carbonitrile **120** (84%)

(Table 12). Repetition of the reaction in a microwave reactor at 200 °C (P = 100 Psi) for 5 min gave the oxazolo[4,5-*b*]pyridine **120** in 66% yield. Treatment with NaH in dry THF at reflux, however, gave oxazolo[4,5-*b*]pyridine **120** and not the expected [1,2,3]dithiazolo[5,4-*e*] pyrido[3,2-*b*][1,4]-oxazine **121**. The best yield of oxazolo[4,5-*b*]pyridine **120** (88%) was obtained when 2 equivalents of NaH were used. Less equivalents of NaH (1.1 equiv.) gave the oxazolo[4,5-*b*]pyridine **120** in 53% while use of more equivalents (3 and 4) gave the oxazolo[4,5-*b*]pyridine **120** in 62 and 60%, respectively.

Table 12. Thermolysis of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)arenes **66, 70b, 70h** (0.20 mmol) and reactions with NaH in THF (2 mL).

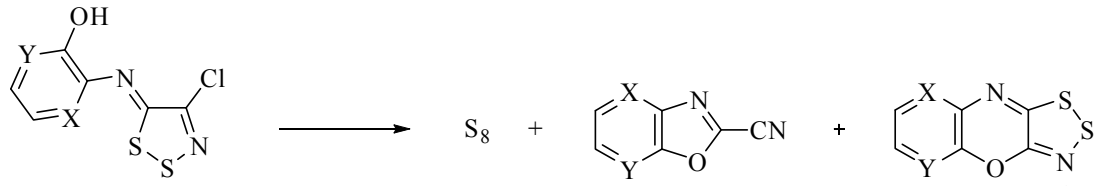


66, 70b, 70h **67, 118, 120** **114, 119, 121**

X	Y	Conditions	Yields (%)		
			S_8	**67/118/120**	**111/116/118**
CH	CH	200 °C, 1 min, argon	60	**67** (85)	-
CH	CH	NaH (2 equiv.), THF, reflux, 2 h	55	**67** (65)	-
CH	N	200 °C, 2 min, argon	90	**118** (66)	**119** (1)
CH	N	NaH (1.1 equiv.), THF, reflux, 2 h	traces	**118** trace	**119** (42)
N	CH	PhH, reflux, 24 h	traces	**120** trace	-
N	CH	PhMe, reflux, 24 h	traces	**120** trace	-
N	CH	PhCl, reflux, 16 h	85	**120** (72)	-
N	CH	xylene, reflux, 12 h	90	**120** (84)	-
N	CH	200 °C, 5 min, argon	90	**120** (84)	-
N	CH	NaH (1.1 equiv.), THF, reflux, 2 h	65	**120** (53)	-
N	CH	NaH (2 equiv.), THF, reflux, 1.5 h	88	**120** (88)	-

Based on the acidity of the phenolic hydroxyl group (pK_a = 9.71)[239] we considered modifying the reaction conditions by simply treating the dithiazoles with organic amine bases in the hope that a simpler procedure to the oxazines could be developed (Table 13).

Table 13. Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)arenes **66, 70b, 70h** (0.20 mmol) and base in solvent (2 mL) at *ca*. 20 °C.



66 (X = Y = CH)
70h (X = CH, Y = N)
70b (X = N, Y = CH)

67 (X = Y = CH)
118 (X = CH, Y = N)
120 (X = N, Y = CH)

114 (X = Y = CH)
119 (X = CH, Y = N)
121 (X = N, Y = CH)

X	Y	Base (equiv)	Solvent	Time (d)	Yields (%) S_8	**67/118/112**	**111/116/118**
CH	CH	Pyridine (4)	DCM	2	ir[a]	ir[a]	ir[a]
CH	CH	Lutidine (4)	DCM	5	traces	**67** (5)	**114** (95)
CH	CH	DABCO (4)	DCM	5	traces	**67** (5)	**114** (95)
CH	CH	Et_3N (1.1)	DCM	0.5	8	**67** (8)	**114** (91)
CH	CH	Et_3N (1.1)	EtOH	0.7	15	**67** (11)	**114** (41)
CH	CH	i-Pr_2NEt (1.1)	DCM	0.5	traces	**67** (1)	**114** (93)
CH	CH	DBU (1.1)	DCM	0.2	15	**67** (11)	**114** (84)
CH	N	Pyridine (1.1)	DCM	10	nr[b]	nr[b]	nr[b]
CH	N	Dabco (1.1)	DCM	7	traces	traces	**119** (60)
CH	N	Et_3N (1.1)	DCM	7	traces	traces	**119** (63)
CH	N	i-Pr_2NEt (1.1)	DCM	7	traces	traces	**119** (63)
CH	N	DBU (1.1)	DCM	10	traces	traces	**119** (51)[c]
N	CH	Pyridine (1.1)	DCM	7	traces	traces	-
N	CH	Dabco (1.1)	DCM	7	traces	traces	-
N	CH	Et_3N (1.1)	DCM	4	86	**120** (76)	-
N	CH	i-Pr_2NEt (1.1)	DCM	4	85	**120** (73)	-
N	CH	DBU (1.1)	DCM	6	75	**120** (64)	-

[a] Incomplete Reaction (recovered SM 87%); [b] No reaction, recovered SM (90%); [c] Based on recovered SM (67%).

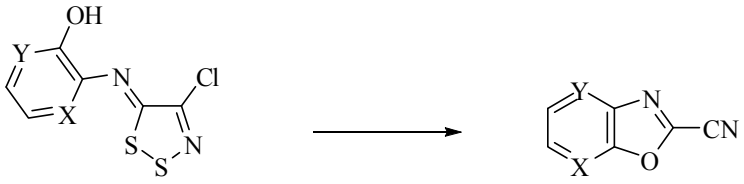
The reaction time and the base equivalents needed to drive the reaction to completion were influenced by the base strength. The use of weak aromatic bases required at least 4 equivalents and extended reaction times to drive the reaction to completion. The use of 1, 2 and 3 equivalents led to incomplete reactions and after 48 h the starting dithiazole was recovered in 90, 65 and 45% yields, respectively. Stronger trialkylamines such as Et_3N (pK_b 3.2)[10] or Hünig's base (pK_b 2.6)[10] and bicyclic amidine bases such as DBU (pK_b 2.0)[10] needed only 1.1 equivalents of base and gave the faster reactions.

Treating 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** with selected amine bases in DCM gave benzoxazine **114** as the major product in high yields and benzoxazole **67** as a secondary minor product. Similar to 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** and 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** with pyridine and DABCO (1.1 or 2 equiv.) at *ca.* 20 ^{o}C gave mainly recovered starting dithiazole and traces of oxazolo[4,5-*b*]pyridine **120**. However, unlike 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene-amino)phenol **66** and 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** treatment of the 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** with stronger bases such as Et_3N, Hünig's base and DBU (2 equiv.) at *ca.* 20 ^{o}C for several days gave not the expected pyridoxazine **121** but the oxazolo[4,5-*b*]pyridine **120** in 76, 73 and 64%, respectively. Nevertheless, when 2 g of the starting dithiazole **70b** and an excess of base (Et_3N) (5 mL) were used then an orange compound was formed (50%). This compound was stable in silica and was isolated using dry flash chromatography but after a few hours the compound decomposed forming sulfur and the oxazolo[4,5-*b*]pyridine **120**. For this reason the only data obtained were LRMS spectrometry which indicated a molecular weight of *m/z* 209 Da, which was in agreement with the molecular weight of [1,2,3]dithiazolo[5,4-*e*]pyrido [3,2-*b*][1,4]oxazine **121**.

4.2.1.2 Thiophile Studies

Other methods for investigating dithiazole ring transformations include the use of thiophiles such as phosphines.[70,49,84,89,97,98,100,114] The reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** with Ph_3P (1-4 equiv.) gave the benzoxazole **67** together with the expected Ph_3P=S and Ph_3P=O, however, the benzoxazole **67** co-ran on silica with the Ph_3P=S and as such their chromatographic separation could not be achieved. The problem was overcome by using polymer bound Ph_3P (2, 3, 4 equiv.) and in this manner benzoxazole **67** was obtained in moderate yields (39-55%) by a simple filtration of the polymer resin. Treatment of (dithiazolylideneamino)pyridin-3-ol **70b** with Ph_3P (1-4 equiv.) or polymer bound Ph_3P (4 and 5 equiv.) gave only traces of the oxazolo[4,5-*b*]-pyridine **120**. While in contrast treatment of (dithiazolylideneamino)pyridin-2-ol **70h** with either Ph_3P (1-4 equiv.) or either polymer bound Ph_3P (4 and 5 equiv.) gave no reaction and the starting material was recovered (90-95%) (Table 14).

Table 14. Treatment of dithiazoles **66, 70b, 70h** (0.20 mmol) with polymer bound Ph_3P in DCM (2 mL) at *ca*. 20 °C.



66 (X = Y = CH)
70h (X = CH, Y = N)
70b (X = N, Y = CH)

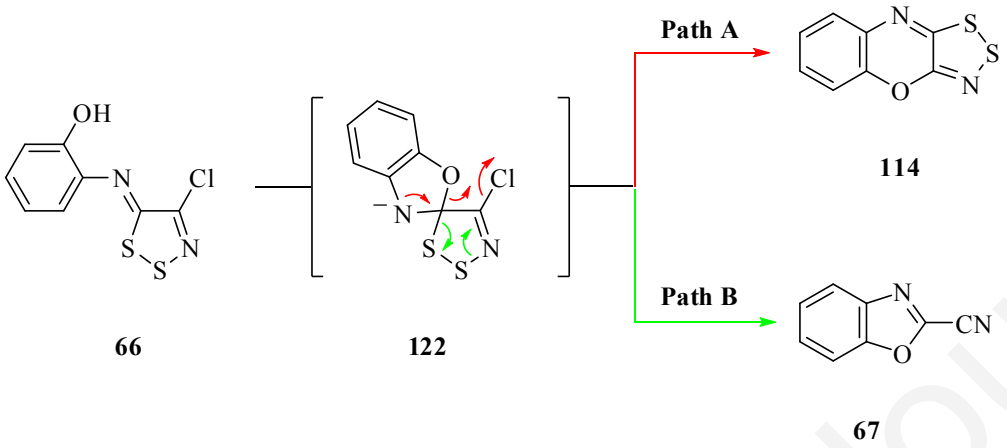
67 (X = Y = CH)
118 (X = CH, Y = N)
120 (X = N, Y = CH)

X	Y	Polymer bound Ph_3P[a] (equiv.)	Time (h)	Yield (%)
CH	CH	2	48	**67** (55)
		3	7 min	**67** (40)
		4	5 min	**67** (39)
CH	N	4	48	ir[b]
		5	48	ir[b]
N	CH	4	48	ir[b]
		5	48	ir[b]

[a] Polymer bound Ph_3P 3 mmol / g Ph_3P loading, crosslinked with 2% DVB, 200-400 mesh; [b] Incomplete Reaction, traces of product

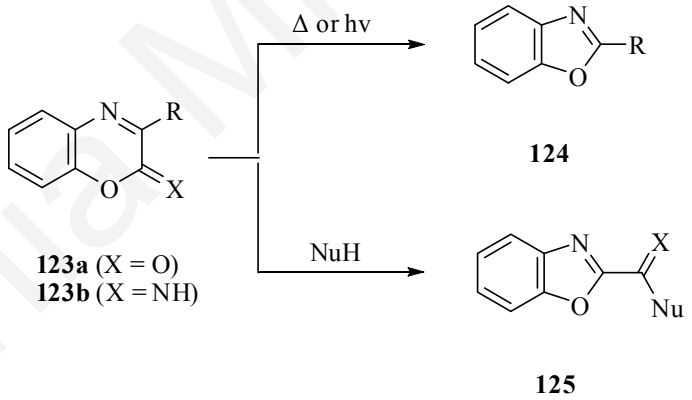
4.2.2 Mechanistic Rationale

A rational mechanism for the formation of both the oxazoles and the oxazines must take into account that the dithiazole C5 position is more electrophilic than the C4 position. As such, it is probable that on base catalysed deprotonation the *ortho* hydroxyl group cyclizes onto the electrophilic C5 position to give a spirocyclic intermediate **122** that can fragment *via* pathway A to form the oxazine or *via* pathway B to form the oxazole (Scheme 76).[70]



Scheme 76

There was also the possibility that the benzoxazine **114** could decompose to give benzoxazole **67** and sulfur. Ring contractions of 2*H*-benzo[*b*][1,4]oxazin-2-ones **123a** (X = O)[163,240-249] and 2*H*-benzo[*b*][1,4]oxazin-2-imines **123b** (X = NH)[250] into benzoxazoles have been reported, and are typically initiated by either thermolysis,[247,248] photolysis[240,246] or by nucleophiles such as hydroxide,[241-243,250] alcohols,[245] alkylamines[244,245,249] and hydrazines[163,249] (Scheme 77).



Scheme 77

Control studies indicated that heating benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114** or [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** in neat PhCl at *ca.* 132 °C, led to no decomposition indicating that both compounds were stable under these conditions. Nevertheless, DSC studies on the benzoxazine **114** showed that the decomposition temperature was 276.1 °C (onset peak at 274.6 °C), while DSC studies on

[1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]-oxazine **116** showed only two endothermic peaks at 224.0 ^{o}C (onset peak at 222.4 ^{o}C) and 265.2 ^{o}C (onset peak at 263.8 ^{o}C) (Figure 6).

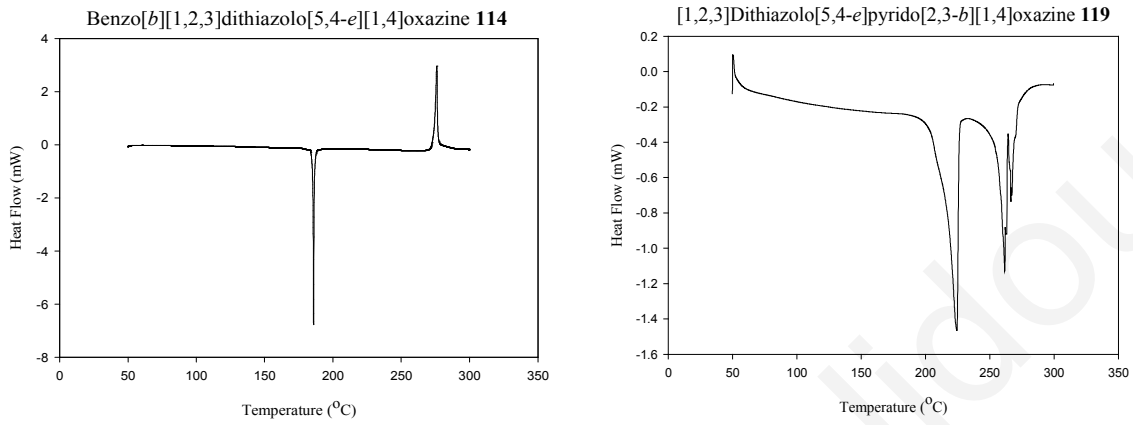
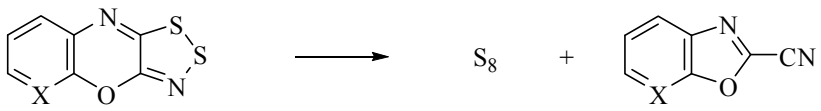


Figure 6 Decomposition onset and peak temperatures of benzo[*b*][1,2,3]dithiazolo[5,4-*e*] [1,4]-oxazine **114** and [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** measured by DSC in aluminium hermetically sealed pans under argon with a 5 ^{o}C/min heating rate.

Thermolysis of the benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114** or [1,2,3]dithiazolo [5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** at *ca.* 275 and 230 ^{o}C, respectively gave the benzo[*d*]oxazole-2-carbonitrile **67** and oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** in 27 and 65% yields, respectively. Attempts to lower the reaction temperatures needed to encourage ring contraction included the addition of additives such as pyridine, $TsOH.H_2O$ and $BnEt_3NCl$ (Table 15).

Table 15. Stability tests of [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **114** and [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** (0.14 mmol).



114 (X = CH)
119 (X = N)

67 (X = CH)
118 (X = N)

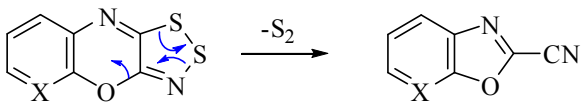
Solvent	Additive (equiv)	Temp. (°C)	Time (h)	X	S_8 (%)	**67, 118** (%)
neat	-	275	7 min	CH	55	**67** (27)
neat	-	230	10 min	N	97	**118** (65)
isoquinoline	-	150	24	CH	nr[a]	nr[a]
isoquinoline	-	150	24	N	nr[a]	nr[a]
PhCl	-	132	24	CH	nr[a]	nr[a]
PhCl	-	132	24	N	nr[a]	nr[a]
PhCl	pyridine (1)	132	24	CH	nr[a]	nr[a]
PhCl	pyridine (1)	132	24	N	nr[a]	nr[a]
PhCl	Et_3N (1)	132	24	CH	85	**67** (45)
PhCl	Et_3N (1)	132	24	N	80	**118** (40)
PhCl	$TsOH.H_2O$ (1)	132	24	CH	nr[a]	nr[a]
PhCl	$TsOH.H_2O$ (1)	132	2	N	83	**118** (49)
PhCl	$TsOH.H_2O$ (0.05)	132	10	CH	nr[a]	nr[a]
PhCl	$TsOH.H_2O$ (0.05)	132	20	N	86	**118** (50)
PhMe	$TsOH.H_2O$ (1)	110	24	CH	nr[a]	nr[a]
PhMe	$TsOH.H_2O$ (1)	110	3	N	41	**118** (47)
PhCl	$BnEt_3NCl$ (1)	132	12	CH	71	**67** (35)
PhCl	$BnEt_3NCl$ (1)	132	5	N	38	**118** (42)

[a] No Reaction

As such, when PhCl solutions of benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114** or [1,2,3]-dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** were heated at reflux (*ca.* 132 °C) in the presence of pyridine (1 equiv.) both oxazines were stable but in the presence of Et_3N they were converted to the benzoxazole **67** and oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** respectively. Moreover, when $TsOH.H_2O$ (1 equiv.) was added in either PhCl at *ca.* 132 °C or in PhMe at *ca.* 110 °C the pyridoxazine **119** was converted to the oxazolo[5,4-*b*]pyridine **118** while the benzoxazine **114** was stable. In fact only catalytic amounts of $TsOH.H_2O$ (5 mol%) were needed to trigger the ring contraction of the pyridoxazine **119**. When $BnEt_3NCl$ (1 equiv.) was used as additive in PhCl heated to reflux then both oxazoles **67** and **118** were isolated in 35 and 42% yields, respectively together with some S_8.

Formally the transformation of the oxazine to the oxazole required the loss of diatomic sulfur (S_2) and tentatively this can occur *via* a concerted pericyclic-type extrusion (mechanism A) or *via* a stepwise mechanism that involves ring opening-ring closing steps (mechanism B) (Scheme 78). In the latter mechanism, the oxazine nitrogen lone pair could release electron density into the dithiazole ring leading to fragmentation *via* loss of S_2 and formation of a highly electrophilic nitrilium carbonitrile intermediate **126**. This could subsequently trap the phenoxide (where X = CH) or the pyridoxide (where X = N) to give the observed oxazoles **67** and **118**, respectively (Scheme 78). The addition of $TsOH.H_2O$ could assist the ring transformation by protonating the pyridyl nitrogen and thus facilitating cleavage of the C-O bond. When $BnEt_3NCl$ was added an alternative mechanism (mechanism C) could be possible that involved thiophilic attack on the dithiazole ring sulfur to give intermediate **127** which subsequently eliminates sulfur and cyclizes to the observed oxazoles. Similar thiophilic reactions between tetraalkylammonium halides and neutral dithiazoles leading to ANRORC-style[26,35] ring transformations have been reported.[71,88]

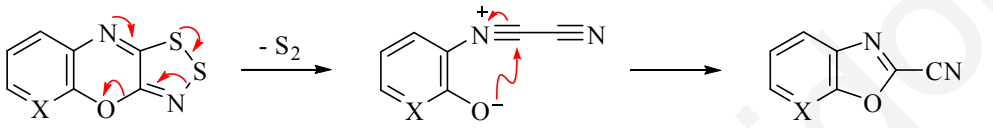
Mechanism A



114 (X = CH)
119 (X = N)

67 (X = CH)
118 (X = N)

Mechanism B

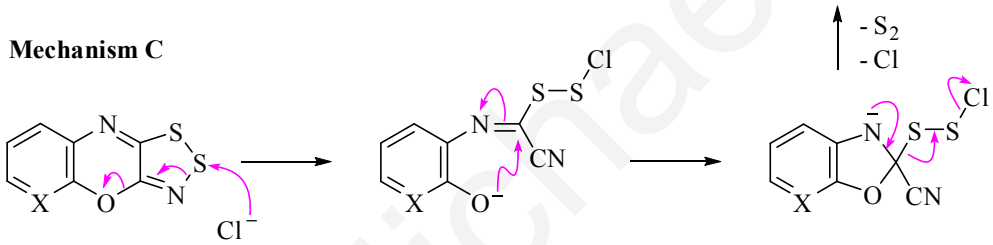


114 (X = CH)
119 (X = N)

126

67 (X = CH)
118 (X = N)

Mechanism C



114 (X = CH)
119 (X = N)

127

67 (X = CH)
118 (X = N)

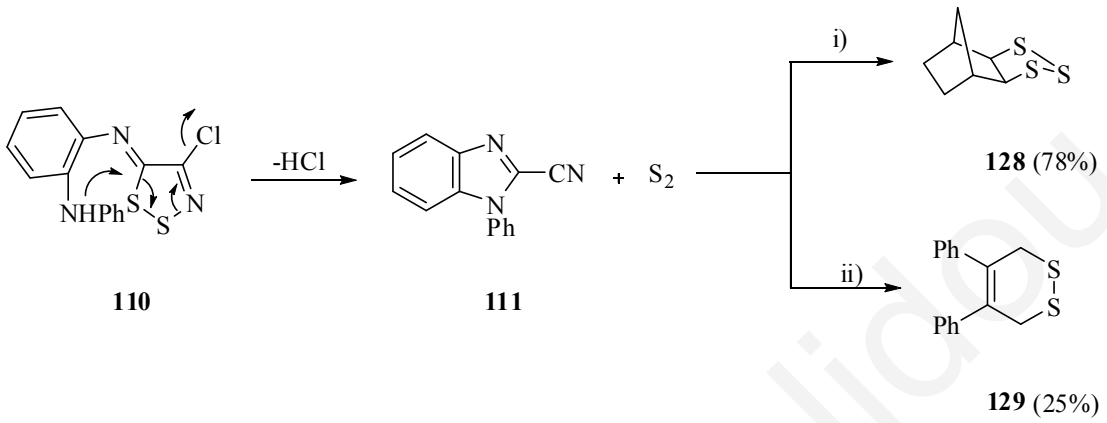
Scheme 78

A tentative explanation for the failure to isolate the isomeric pyridoxazine **121** in the reactions of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** could be that this compound on forming rearranged rapidly to the oxazolo[4,5-*b*]pyridine **120**. The presence of the two nitrogen atoms in the two neighbouring carbons could be a reason for the fast rearrangement. This is now under further study.

4.2.3 Trapping Studies

S_2 has been trapped using norbornene and 2,3-diphenylbutadiene to afford the 1,2,3-trithiole **128** and the Diels-Alder adduct 4,5-diphenyl-3,6-dihydro-1,2-dithiine **129**, respectively.[95,117] Thermolysis of (*Z*)-N^1-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-N^2-phenylbenzene-1,2-diamine **110** at *ca.* 140-150 ^oC gives 1-phenyl-1*H*-benzo[*d*]imidazole-2-carbonitrile **111** and S_2 which

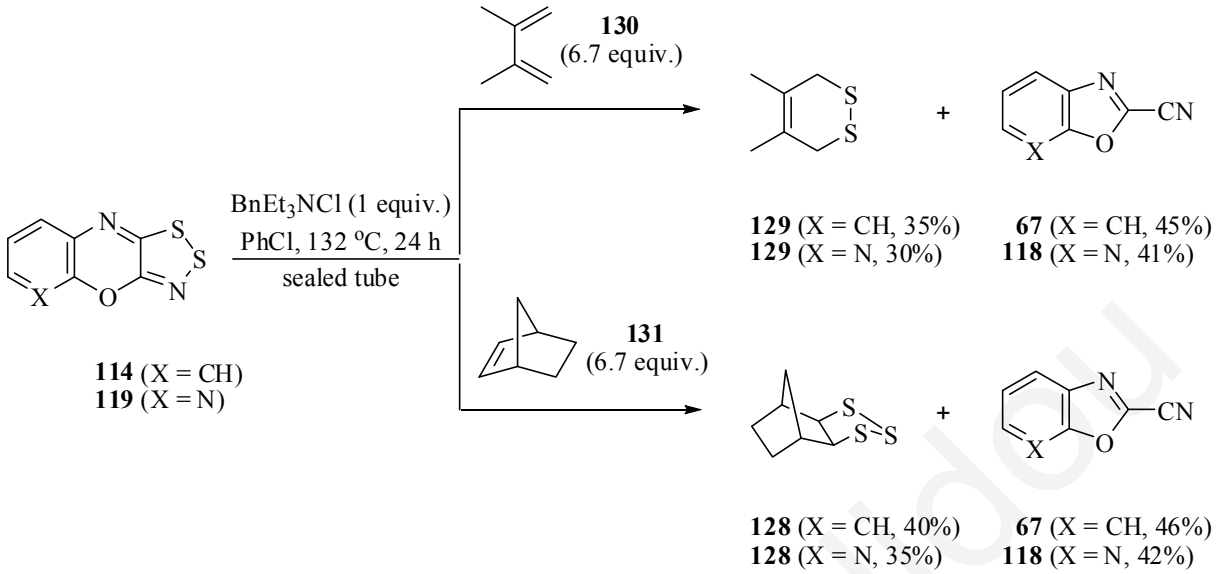
was trapped using norbornene and 2,3-diphenylbutadiene to give the sulfur adducts **128** and **129** in 78 and 25% yields, respectively (Scheme 79).[95,117]



Reagents and Conditions: i) norbornene (6.7 equiv.), 140-150 °C, 4 h, sealed tube; ii) 2,3-diphenyl-1,3-butadiene (6.7 equiv.), 140-150 °C, 3 h, sealed tube.

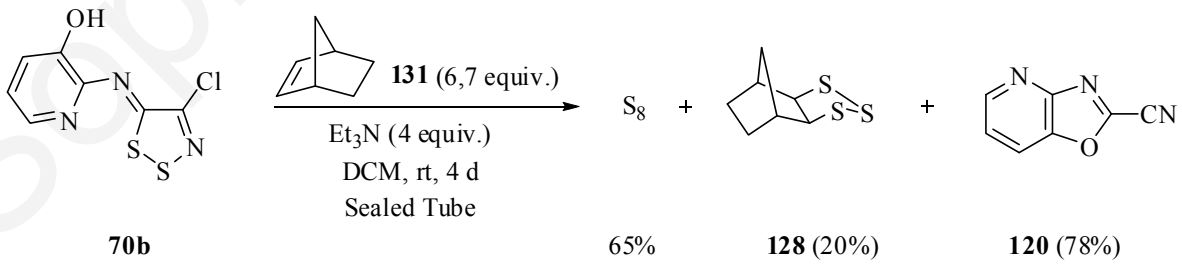
Scheme 79

To support the proposed loss of S_2 during the transformation of the oxazines to oxazoles, the thermolysis reactions of benzoxazine **114** and pyridoxazine **119** were repeated in the presence of either 2,3-dimethylbuta-1,3-diene **130** or 2-norbornene **131** (6.7 equiv.) in a sealed tube at *ca.* 140 °C (preheated Wood's metal bath). However no desired 4,5-dimethyl-3,6-dihydro-1,2-dithiine **129**[251] or (3a*S*,4*R*,7*S*)-hexahydro-4,7-methano-benzo[*d*][1,2,3]trithiole **128**[252] were isolated. For this reason it was decided to repeat the reaction of benzoxazine **114** and pyridoxazine **119** with $BnEt_3NCl$ in refluxing PhCl in a sealed tube at *ca.* 140 °C (preheated Wood's metal bath). After 24 h the starting oxazines were consumed (by TLC) and the analogous oxazoles were isolated in 45-46 and 41-42% yields, respectively together with either 4,5-dimethyl-3,6-dihydro-1,2-dithiine **129** in 35 and 30% yields, or (3a*S*,4*R*,7*S*)-hexahydro-4,7-methanobenzo[*d*][1,2,3]trithiole **128** in 40 and 35% yields, respectively (Scheme 80). Care must be taken though, since the trapping of sulfur using these reagents merely supports the release of a reactive source of sulfur and is not confirmation of the formation of S_2.



Scheme 80

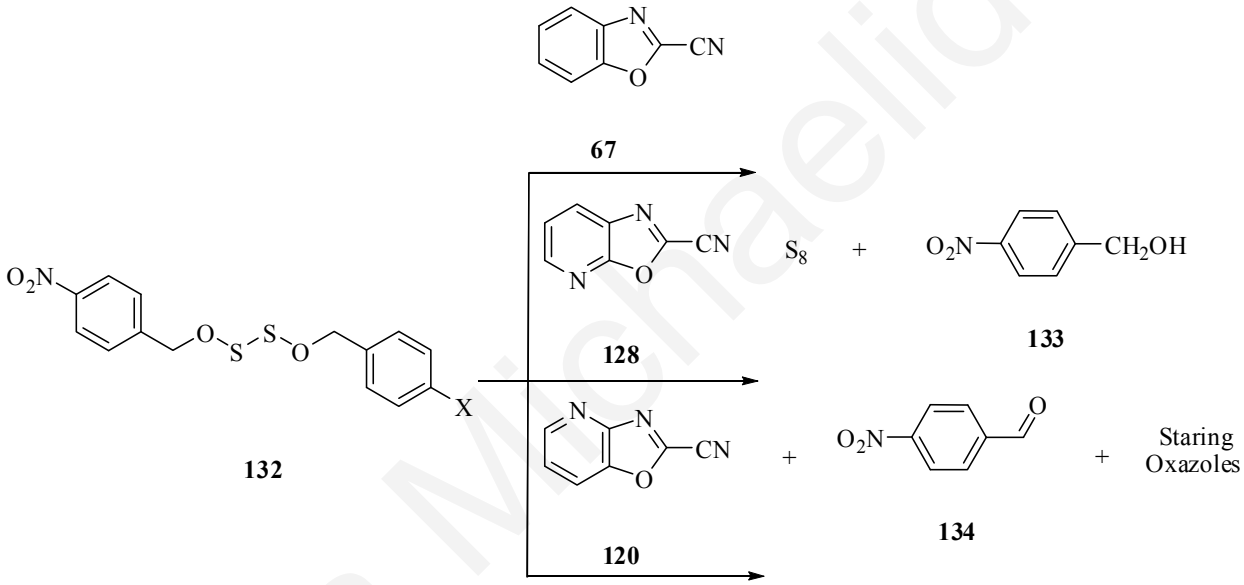
In an attempt to find out if the pyridoxazine **121** is formed during the reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** with base, the reaction with Et_3N (4 equiv.) in refluxing DCM was repeated in a sealed tube in the presence of norbornene **131** (6.7 equiv.) (Scheme 81). After 4 d, S_8 (65%), 1,2,3-trithiole **128** (20%) and oxazolo[4,5-*b*]pyridine **120** (78%) were isolated. The formation of a small quantity of 1,2,3-trithiole **128** suggested that some reactive sulfur source was released possibly indicating the formation of the pyridoxazine **121**. However, control studies indicated that even treatment of S_8 with norbornene (6.7 equiv.) gave recovered S_8 (65%) and 1,2,3-trithiole **128** in 20% yield, in very similar ratios as those above (Scheme 80) strongly suggesting that during the ring transformation of pyridoxazine **121** to oxazolo[4,5-*b*]pyridine **120** only S_8 had formed.



Scheme 81

Having trapped S_2 during the transformation of oxazines to oxazoles we considered the possibility of carrying out the reverse reaction. Treating the oxazoles with an S_2 precursor,

such as 1,2-bis(4-nitrobenzyloxy)disulfane **132**[251,253-268] could afford the dithiazolo-oxazines. As such, solutions of 1,2-bis(4-nitrobenzyloxy)disulfane **132** and oxazoles **67**, **118** and **120** in PhH were heated to reflux for 24 h but only traces of S_8, recovered starting materials (90, 85, 88%, respectively), *p*-nitrobenzyl alcohol **133** (80, 85 and 88% respectively) and traces of *p*-nitrobenzaldehyde **134** (identified by TLC) were obtained (Scheme 82). Repetition of the reaction in either CCl_4 or PhCl also gave similar results as previously. Similarly treatment of the three oxazoles with S_2Cl_2 (1 equiv.), $BuEt_3NCl$ (1 equiv.) and DABCO (1 equiv.) in dry DCM at *ca* 20 ^oC gave no reaction.



Scheme 82

4.3 Summary

Thermolysis of the dithiazolylidenes **66**, **70h** and **70b** at *ca.* 200 ^oC afforded benzo[*d*]oxazole-2-carbonitrile **67**, oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** and oxazolo[4,5-*b*]pyridine-2-carbonitrile **120** in high yields, respectively. Treatment of the dithiazolylidenes **66**, **70h** and **70b** with NaH in dry THF afforded benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114**, [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** and oxazolo[4,5-*b*]pyridine **120** respectively. Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** with polymer bound Ph_3P gave the benzoxazole **67** in 39-55% yield by a simple filtration of the polymer. Stabilities tests on the benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114** and [1,2,3]-dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]-oxazine **119** showed that thermolysis reactions or in PhCl solutions in the presence of either Et_3N (1 equiv.) or $BnEt_3NI$ (1 equiv.) gave the

corresponding oxazoles in moderate yields and we were able to propose three mechanistic pathways. Repetition of the two reactions in the presence of either 2,3-dimethylbuta-1,3-diene **130** or 2-norbornene **131** (6.7 equiv.) in PhCl in the presence of $BnEt_3NI$ (1 equiv.) in a sealed tube gave after 24 h the expected oxazoles, together with either 4,5-dimethyl-3,6-dihydro-1,2-dithiine **129** or (3*aS*,4*R*,7*S*)-hexahydro-4,7-methanobenzo[*d*][1,2,3]trithiole **128**. Control studies with norbornene indicated that the pyridoxazine **121** is formed during the reaction of the dithiazolylidene **70b** with base but ring contracts fast to the oxazolo[4,5-*b*]pyridine **120**. As future work the non-formation of [1,2,3]dithiazolo[5,4-*e*]pyrido[3,2-*b*][1,4]oxazine **121** could be investigated further to identify why it was not formed and what conditions could favor its formation.

CHAPTER 5

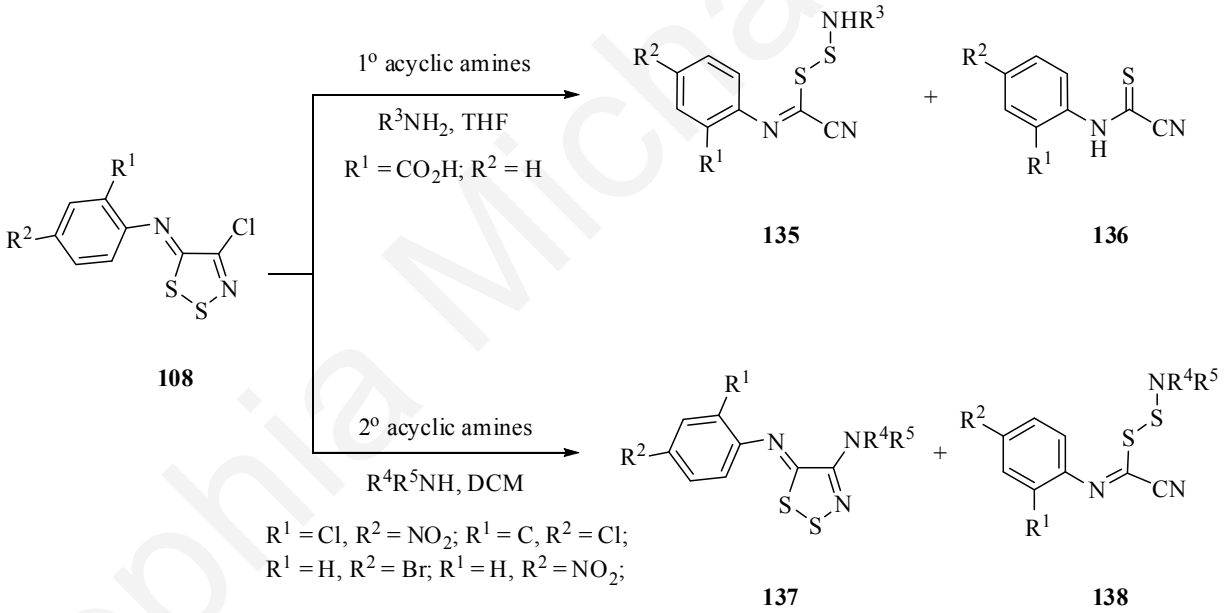
Synthesis of 2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile and its Reactivity towards Selected Nucleophiles

Sections

5.1 Introduction

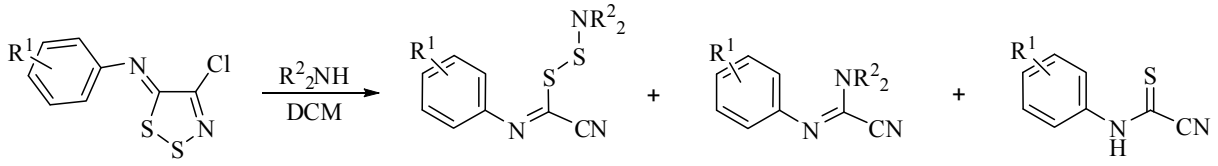
A wide variety of heteroatom nucleophiles such as 1°, 2° or 3° amines, alkoxides, alkylthiols and phosphines have been used as thiophiles to ring open 4-chloro-5*H*-1,2,3-dithiazoles and some of this chemistry is reviewed below.

Treatment of 2-[(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)amino]benzoic acid **108** ($R^1 = CO_2H$, $R^2 = H$) with 1° acyclic amines like *t*-butylamine causes the dithiazole ring to open and afford the mixed disulfide **135** and the cyanothioformanilide **136** (Scheme 83).[107] (Dithiazolylideneamino)arenes can also react with 2° acyclic amines to give new (dithiazolylideneamino)arenes **137** where the chlorine atom at the C4 position of the dithiazole ring has been displaced by the 2° amine.[91,102] This was not considered to be *via* direct substitution of the 4-chloro but *via* an ANRORC type mechanism involving the disulfide **138**.



Scheme 83

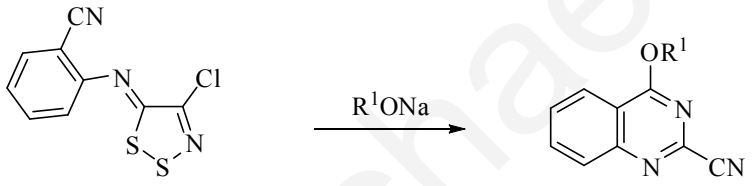
The reaction of (dithiazolylideneamino)arenes **58** with cyclic 2° dialkylamines was a little more complex affording the mixed disulfide **139**, the amidines **140** and the cyanothioformanilides **141** depending on both the aryl substituents and the specific amine (Scheme 84).[102,261-262]



58 **139** (R_2N = piperidinyl) **140** (R_2N = pyrrolidinyl) (R_2N = morpholinyl) **141**

Scheme 84

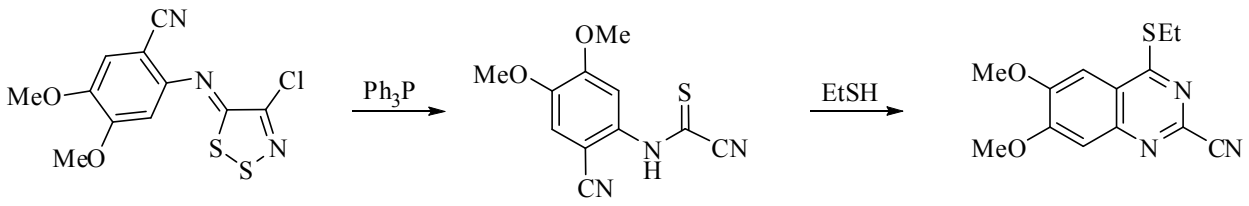
When the arene supports an *ortho* cyano substituent then treatment of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142a** with nucleophiles such as alkoxides affords 4-alkoxyquinazoline-2-carbonitriles **143** in good yields (Scheme 85).[48,89,98,230]



142a **143**

Scheme 85

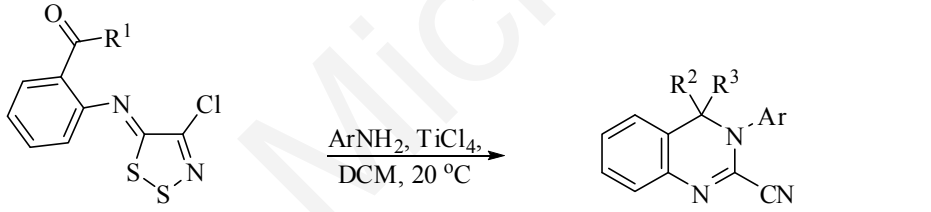
More recently, this alkoxide mediated ring transformation of dithiazoles has also been achieved with (dithiazolylideneamino)pyrazole, -imidazole and -triazole carbonitriles to afford the corresponding 1*H*-pyrazolo[3,4-*d*]pyrimidine-6-carbonitrile, 9*H*-purine-2-carbonitrile and 3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidine-5-carbonitriles, respectively.[93] Interestingly, 4-(ethylthio)-6,7-dimethoxyquinazoline-2-carbonitrile **145** has also been prepared from 2-cyano-4,5-dimethoxycyanothioformanilide **144h** and ethylthiol indicating that these dithiazole fragmentation products could be intermediates in this ring transformation (Scheme 86).[48,98]



142h **144h** **145**

Scheme 86

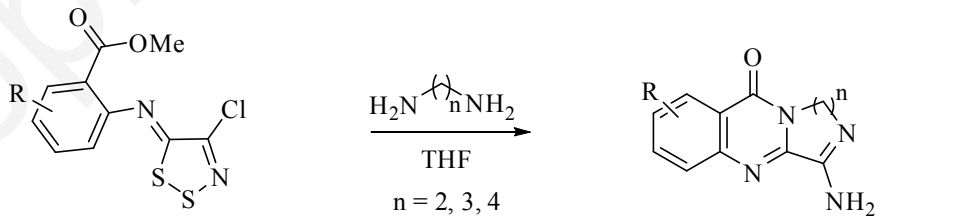
Moreover quinazolines can be synthesized from substituted anilines and Appel salt **42**.[48,89,98,106,230,260] For example they can be prepared by treatment of 2-carboxy substituted 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzenes **146** with anilines in the presence of $TiCl_4$ in DCM to give 4-hydroxy-3,4-diphenyl-3,4-dihydroquinazoline-2-carbonitrile **147a** or 4-oxo-3-phenyl-3,4-dihydro-quinazoline-2-carbonitrile **147b** (Scheme 87)[263,264] or with diaminoalkanes to give substituted 1-amino-3*H*-pyrazino[2,1-*b*]quinazolin-6(4*H*)-ones **148** (Scheme 88).[231,265,266]



146 (R^1 = OMe)
(R^1 = Ph)

147a (R^2 = Ph; R^3 = OH)
147b (R^2 = R^3 = O)

Scheme 87

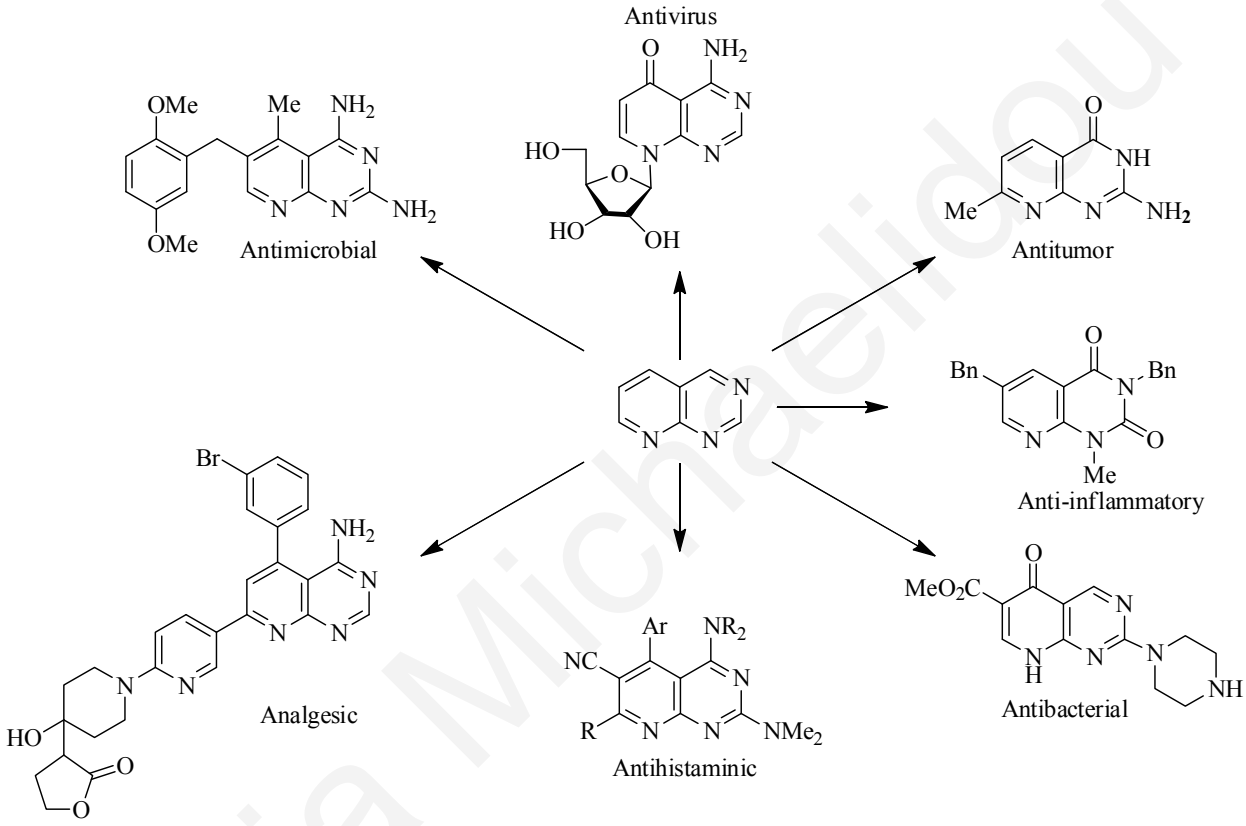


146

148 n = 1, 2, 3 and 4

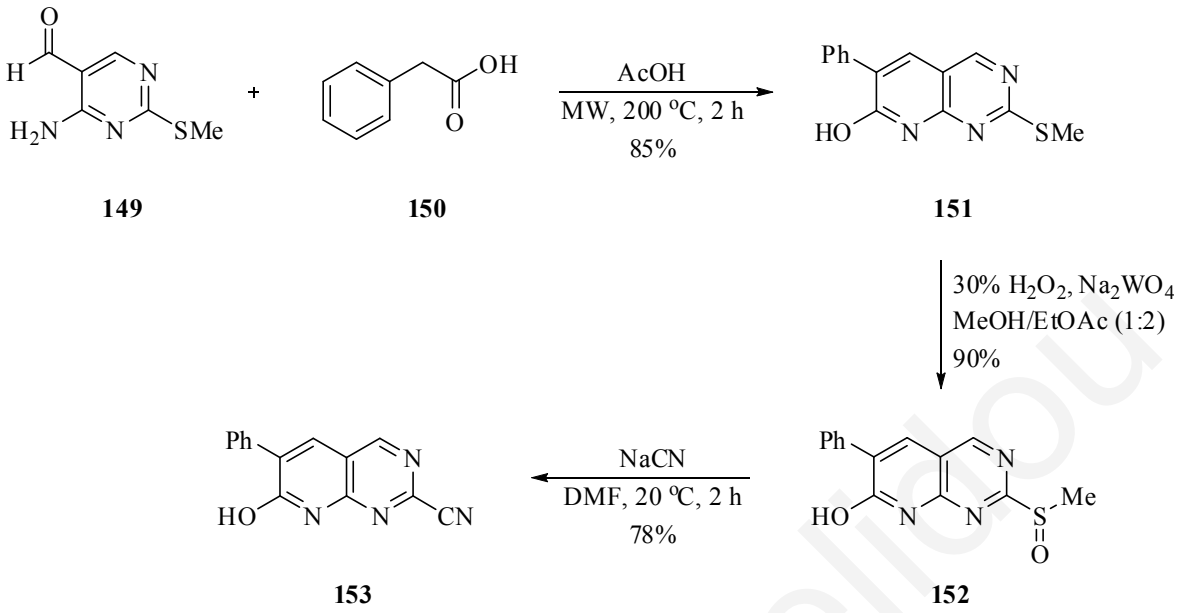
Scheme 88

In principal this ring transformation could be used to prepare pyrido[2,3-*d*]pyrimidines several of which display potentially useful biological properties, including antiviral,[267] antitumor,[268] anti-inflammatory,[269] antibacterial,[270,273] antihistamininic,[271] and analgesic[272] activities (Scheme 89).



Scheme 89

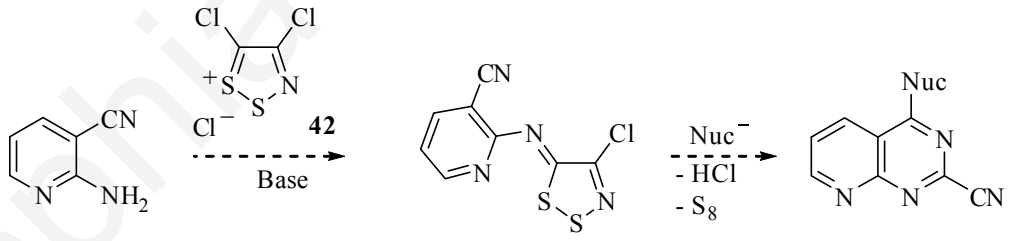
In the literature, only a few examples of pyrido[2,3-*d*]pyrimidine-2-carbonitriles exist and their synthesis involves substitution of different leaving groups at the C2 position of the pyrimidine ring (Scheme 90).[274,275]



149 **150** **151** **152** **153**

Scheme 90

Having all these literature data in mind it was decided to treat the dithiazolylidenes with amines and investigate the possible formation of pyrido[2,3-*d*]pyrimidines or other products. However, preparation of pyrido[2,3-*d*]pyrimidines using Appel salt chemistry would require access to 2-aminonicotinonitrile **154**[276] (Scheme 91). 2-Aminonicotinonitrile **154** is known but its synthesis involves many synthetic steps or expensive starting materials.[276,277]

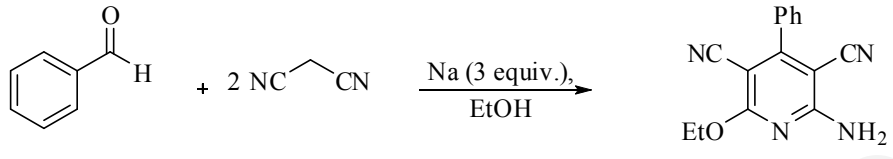


154 **155** **156**

Scheme 91

As such the structurally more complex but synthetically more feasible penta-substituted 2-amino-3,4-dicyano-5-phenyl-6-ethoxypyridine **159** was prepared from benzaldehyde **157** and malononitrile **158** in the presence of Na in EtOH (Scheme 92).[278] 2-Amino-3,4-dicyano-5-phenyl-6-ethoxypyridine **159** displays the necessary functionality, and interestingly has wide

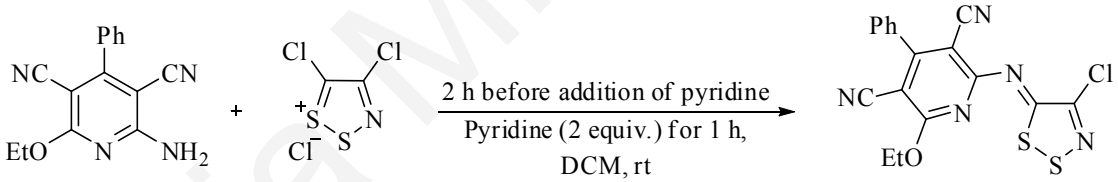
biological activity: It has a high conductance-type Ca activated K channel opening effect that acts as a smooth muscle relaxant for the bladder, and is useful in treating pollakluria and urinary incontinence.[278-281]



157 **158** **159** (50%)

Scheme 92

Treatment of 2-amino-3,5-dicyano-6-ethoxy-4-phenylpyridine **159** with Appel salt **42**, in DCM at *ca.* 20 ^{o}C for 2 h followed by the addition of pyridine (2 equiv.) for another 1 h gave the expected 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** in 88% yield as yellow-orange cotton fibers, mp 264-265 ^{o}C (from PhMe) (Scheme 93).



159 **42** **160** (88%)

Scheme 93

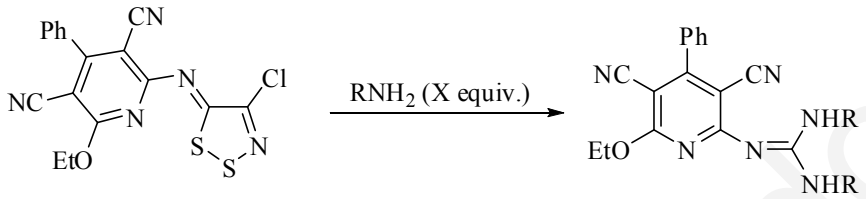
5.2 Reactions with Nucleophiles

5.2.1 Reaction with 1^{o} Amines

Treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** with the 1^{o} alkylamines *n*-butylamine or benzylamine (4 equiv.) in DCM at reflux gave as product 1,3-di-*n*-butyl- and 1,3-dibenzyl-2-(3,5-dicyano-6-ethoxy-4-phenyl-pyridin-2-yl)guanidines **161a** and **161b** in 32 and 82% yields, respectively. However treatment with the less nucleophilic 1^{o} arylamine aniline (8 equiv.) both in DCM and in PhMe, heated at

reflux gave no reaction and the starting material was recovered in 89 and 90% yields, respectively (Table 16).

Table 16. Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** with primary amines.



160 **161a-b**

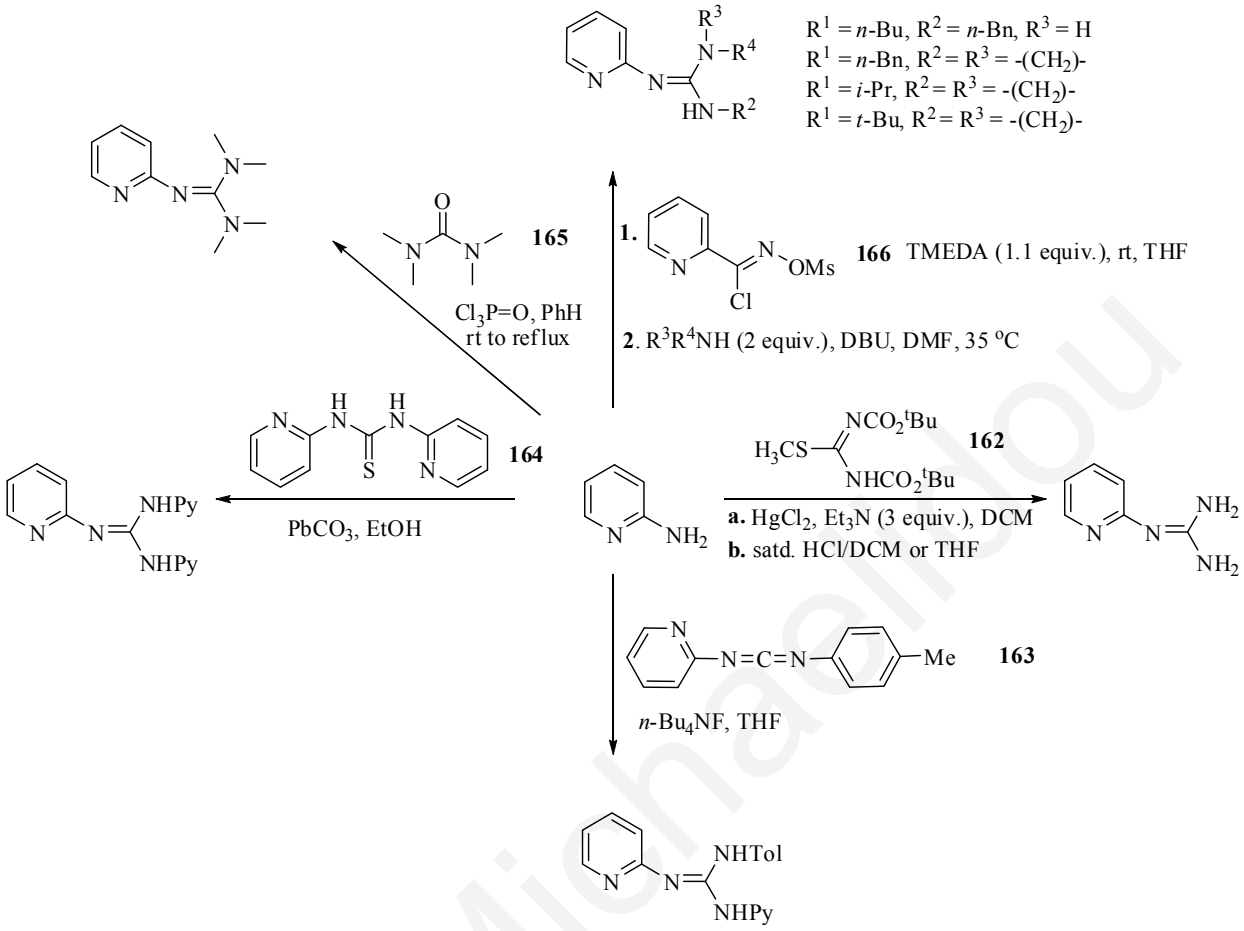
RNH_2 (equiv.)	Solvent	Time (h)	Temp (^oC)	Yields (%)
n-$BuNH_2$ (4)	DCM	4	40	**161a** (32)
$BnNH_2$ (4)	DCM	7	40	**161b** (82)
$PhNH_2$ (4)	DCM	24	40	-[a]
$PhNH_2$ (8)	DCM	24	40	-[a]
$PhNH_2$ (8)	PhMe	24	110	-[a]

[a] Starting material was recovered in 94, 89 and 90% yields respectively.

1,3-Di-*n*-butyl-2-(3,5-dicyano-6-ethoxy-4-phenylpyridin-2-yl)guanidine **161a** was obtained as colourless needles, mp 204-205 ^oC (from EtOH). Microanalysis (C, 68.9; H, 7.4; N, 20.0%) and mass spectrometry supported the formula $C_{24}H_{30}N_6O$ [*m/z* (EI) 418 (M^+, 100%)]. ^{13}C NMR spectroscopy showed twenty separate carbon resonances of which five were aromatic, four were CH_2 and two were CH_3 as supported by DEPT studies. The presence of cyano groups was supported by IR band at $\nu(C{\equiv}N)_s$ 2222 cm^{-1} and two carbon signals at 116.7 and 115.6 ppm. ^1H NMR spectroscopy showed the presence of twenty eight protons of which five were aromatic (7.52-7.47 ppm). The ethoxy group was also present in the spectrum with a triplet at 0.94 (3H, t, *J* 7.3 Hz) and a quarter at 4.34 ppm (2H, q, *J* 7.1 Hz). Another multiplet was present at the range 1.68-1.36 ppm integrating twelve and corresponding to the six CH_2 of the two butylamines added to the compound. The presence of 2^o amino groups was only supported by IR bands at $\nu(N\text{-}H)_s$ 3337 cm^{-1}.

1,3-Dibenzyl-2-(3,5-dicyano-6-ethoxy-4-phenylpyridin-2-yl)guanidine **161b** was obtained as colourless prisms, mp 230-231 ^{o}C (from EtOH). Microanalysis (C, 74.2; H, 5.5; N, 17.6%) and mass spectrometry supported the formula $C_{30}H_{26}N_6O$ [*m/z* (EI) 486 (M^+, 80%)]. ^{13}C NMR spectroscopy showed seventeen separate carbon resonances of which six were aromatic and four were quaternary carbons as supported by DEPT studies. The presence of cyano groups was supported by IR band at $\nu(C\equiv N)_s$ 2222 cm^{-1} and two carbon signals at 116.7 and 115.3 ppm. ^{1}H NMR spectroscopy showed the presence of thirty protons of which fifteen were aromatic (7.55-7.33 ppm), suggesting the addition of two phenyl groups to the compound. The ethoxy group was also present in the spectrum with a triplet at 1.03 (3H, t, *J* 6.9 Hz) and a quarter at 3.76 (2H, q, *J* 6.9 Hz). Another peak was present at 4.57 ppm integrating four and corresponding to the two CH_2 of the benzylamine. ^{1}H NMR spectroscopy also identified two D_2O exchangeable broad resonances integrating 1 at 9.31 and 8.25 ppm indicating the presence of 2^o amino groups and this was supported by IR bands at $\nu(N\text{-}H)_s$ 3335 cm^{-1}.

In the literature this type of pyridoguanidines can usually be synthesized from 2-amino-pyridine and reagents like *N*,*N*'-bis(*t*-butoxycarbonyl)-*S*-methylisothiourea **162** in the presence of $MgCl_2$,[282] *N*-[(p-tolylimino)methylene]pyridin-2-amine **163** in the presence of *n*-Bu_4NF,[283] 1,3-di(pyridin-2-yl)thiourea **164** in the presence of lead carbonate,[284,285,288] 1,1,3,3-tetra-methylurea **165** in the presence of trichlorophosphate[286,287] and with *N*-(methylsulfonyloxy) picolinimidoyl chloride **166** with TMEDA in the presence of DBU in dry DMF[289] (Scheme 94).

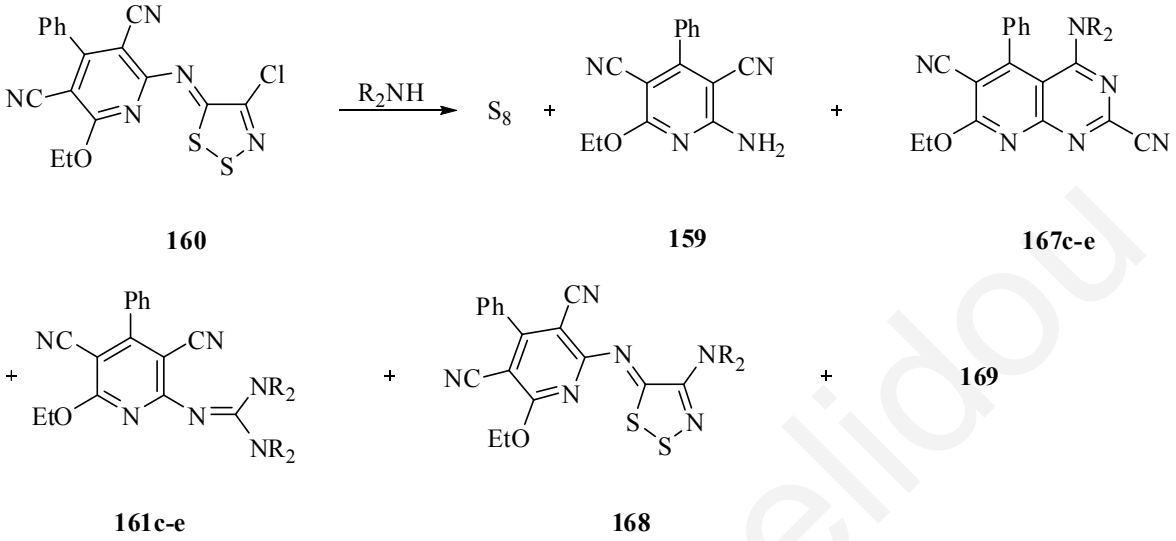


Scheme 94

5.2.2 Reactions with Acyclic 2° Amines

Treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** with the reactive diethylamine, di-*n*-propylamine and dibenzylamine gave as main product the analogous pyrido[2,3-*d*]pyrimidines **167** in moderate to high yields. It is worthy of note that the reaction with diethylamine also led to the formation of 2-[4-(diethyl-amino)-5*H*-1,2,3-dithiazol-5-ylideneamino]-6-ethoxy-4-phenylpyridine-3,5-dicarbo-nitrile **168** and a deep green coloured compound **169**. Reaction with diisopropylamine gave an incomplete and complex reaction while reaction with the sterically hindered and non nucleophilic diphenylamine unsurprisingly gave no reaction (Table 17).

Table 17. Treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** (0.125 mmol) with acyclic secondary amines.



R_2NH (equiv.)	Solvent	T (^oC)	Time (d)	Yields (%) **S_8**	**159**	**167**	**161**	**168**	**169**
Et_2NH (2)	DCM	40	5	100	11	80	nd[a]	11	9
Et_2NH (3)	DCM	40	2 h	87	11	88	nd[a]	4	2
Et_2NH (4)	DCM	40	3.5 h	86	6	84	nd[a]	5	2
n-Pr_2NH (4)	DCM	40	4 h	97	nd[a]	73	nd[a]	nd[a]	nd[a]
Bn_2NH (20)	DCM	40	3	nr[b]	nr[b]	nr[b]	nr[b]	nr[b]	nr[b]
Bn_2NH (20)	PhH	110	2	97	15	50	nd[a]	nd[a]	nd[a]
i-Pr_2NH (20)	DCM	40	2	ir[c]	ir[c]	ir[c]	ir[c]	ir[c]	ir[c]
i-Pr_2NH (20)	PhH	110	2	ir[c]	ir[c]	ir[c]	ir[c]	ir[c]	ir[c]
Ph_2NH (20)	DCM	40	2	nr[b]	nr[b]	nr[b]	nr[b]	nr[b]	nr[b]
Ph_2NH (20)	PhH	110	2	nr[b]	nr[b]	nr[b]	nr[b]	nr[b]	nr[b]

[a] No Data; [b] No Reaction; [c] Incomplete and complex reaction

The reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** with diethylamine and di-*n*-propylamine needed four equivalents to consume the starting dithiazolylidene and give the 4-aminopyrido[2,3-*d*]pyrimidines **167c-e** in high yields, in contrast with the dibenzylamine reaction which needed twenty equivalents and only gave the analogous 4-aminopyrido[2,3-*d*]pyrimidines **167e** in a modest 50% yield. In the

case of dibenzylamine the presence of the two benzyl groups introduce some steric hindrance which decreased the nucleophilicity of the amine. When diphenylamine was used no reaction was observed presumably because the two phenyl groups draw electron density away from the amino group, decreasing significantly its nucleophilicity.

2-[4-(Diethylamino)-5*H*-1,2,3-dithiazol-5-ylideneamino]-6-ethoxy-4-phenylpyridine-3,5-di-carbonitrile **168** was obtained as red prisms, mp 174-175 ^{o}C (from EtOH). Microanalysis (C, 57.9; H, 4.7; N, 19.3%) and mass spectrometry supported the formula $C_{21}H_{20}N_6OS_2$ [*m/z* (EI) 436 (M^+, 83%)]. UV/vis spectroscopy showed a λ_{max} at 531 nm (log ε 3.07), supporting extensive conjugation. ^{13}C NMR spectroscopy showed seventeen separate carbon resonances of which three were aromatic and six were quaternary carbons as supported by DEPT NMR studies. The presence of cyano groups was supported by an IR band at $\nu(C\equiv N)_s$ 2224 cm^{-1} and two carbon signals at 115.1 and 114.1 ppm. DEPT NMR studies also supported the presence of CH_2 and CH_3 groups. ^{1}H NMR spectroscopy showed the presence of twenty hydrogens of which five were aromatic (7.58-7.26 ppm). The ethoxy group was also present in the spectrum with a triplet at 1.59 (3H, t, *J* 7.1 Hz) and a quartet at 4.81 (2H, q, *J* 7.1 Hz). The ethyl chain was supported by a triplet at 1.27 (6H, t, *J* 7.0 Hz) and a quartet at 3.93 (4H, q, *J* 7.0 Hz).

The green compound **169** was obtained as bronze prisms, mp > 300 ^{o}C (from DCE). Microanalysis (C, 63.3; H, 4.8; N, 20.1%) supported a formula $C_{44}H_{40}N_{12}O_2S_2$ ^{1}H NMR spectroscopy showed the presence of forty hydrogens of which ten were aromatic in the range of 7.59-7.26 ppm suggesting the presence of two phenyl groups in the molecule. Two ethoxy groups were present in the compound since the triplet peak at 3.75 ppm corresponded to two CH_3 groups and the quartet at 4.90 ppm corresponded to two CH_2 groups. ^{1}H NMR spectroscopy also showed two multiplets at 1.87-1.83 and 1.40-1.32 ppm integrating to eight and twelve hydrogens, respectively, which suggested that two diethylamine groups were incorporated into the structure.

The above spectroscopic data were not sufficient to determine the structure of this compound. For this reason a single crystal was grown which was suitable for an X-ray crystallographic analysis. A few milligrams of the green compound were slowly recrystallized from warm DCE

and left to stand at room temperature. After about 7 d a rectangular crystal was obtained and single crystal X-ray crystallographic analysis showed that the green compound had a molecular weight of 833 Da and that it was the quinoidal 2,2'-bithiazole **169** (Figure 7).

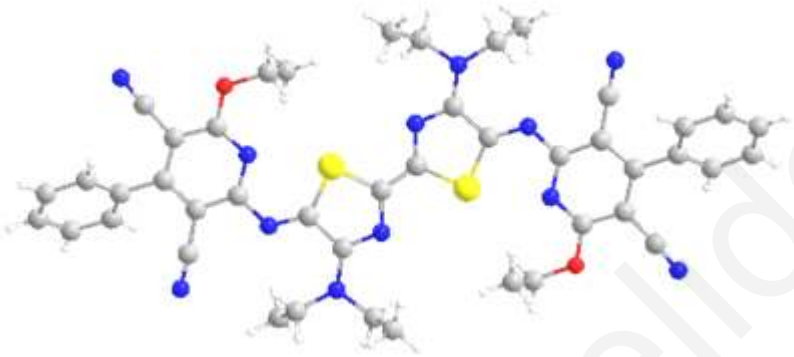
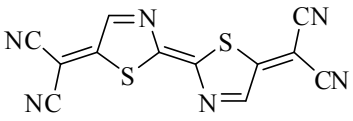


Figure 7. X-ray structure of quinoidal 2,2'-bithiazole **169**.

The X-ray also showed that this molecule was not exactly planar. It is possible that one of the functional groups of the molecule affected the planarity.

A search in the literature showed the presence of (*E*)-2,2'-(5*H*,5'*H*-[2,2'-bithiazolylidene]-5,5'-diylidene)dimalononitrile **170**[290] that had a similar quinoidal 2,2'-bithiazole structure as the green bithiazole **169**.



170

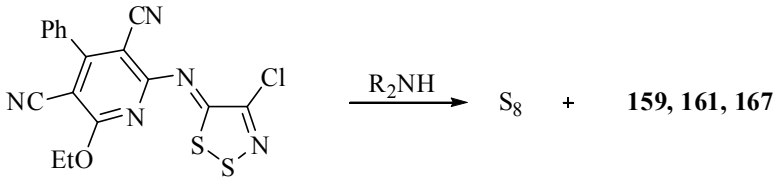
Bithiazole **170** is a strong electron acceptor. The nitrogen atoms on the thiazole rings enhance its acceptor ability and also work as a functional part for heteroatom contacts. It was recrystallized from DCM giving lustrous blue-black crystals (mp > 500 ^{o}C) indicating extended π-conjugation. This compound has two sharp strong absorption peaks at λ_{max} 553 nm (log ε 4.85) and 513 nm (log ε 4.47) which is a characteristic of bis-quinonoid type acceptors. It is very stable at ambient temperature but reacts quickly with nucleophilic reagents. The

cyclic voltammograph of this bithiazole showed two reversible one-electron reduction waves. The reduction potentials $E^1_{1/2}$ = +0.34 V and $E^2_{1/2}$ = +0.01 V are higher than those of TCNQ ($E^1_{1/2}$ = 0.22 V and $E^2_{1/2}$ = -0.35 V) indicating that the bithiazole **170** is a very strong acceptor owing to the electron-withdrawing effect of the C≡N groups. This result indicates that introduction of nitrogen atoms is a useful method for increasing acceptor abilities without using extra substituents. The differences between the first and second reduction potential ΔE decrease in **170** (ΔE = 0.33 V) compared to that of TCNQ (ΔE = 0.57 V), suggesting the decrease in on-site Coulomb repulsion in **170** due to the extended π-conjugation. The strong electron acceptability and small on-site Coulombic repulsion indicate the superiority of **170** as an acceptor for organic conductors. The X-ray of this bithiazole **170** showed that it has a planar geometry. If we compare the bithiazole **170** with the quinoidal bithiazole **169** which is an almost planar compound with extensive conjugation, we can conclude that it is also possible the quinoidal 2,2'-bithiazole **169** to be a strong electron acceptor and can find uses in the material sciences.

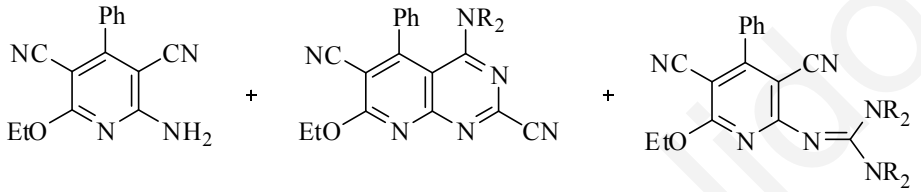
5.2.3 Reactions with Cyclic 2^o Amines

Treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** with cyclic 2^o dialkylamines pyrrolidine, piperidine and morpholine gave as products S_8, 4-aminopyrido[2,3-*d*]pyrimidines **167f-h**, 2-aminopyridine **159** and 2-(diamino-1-ylmethyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitriles **161f-h** (Table 18).

Table 18. Treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **160** (0.125 mmol) with cyclic secondary amines.



160



159 **167f-h** **161f-h**

R_2NH (equiv.)	Solvent	T (^oC)	Time (h)	Yields (%) **S_8**	**159**	**167**	**161**
-$(C_2H_4)_2NH$ (2[a])	DCM	20	48	86	4	47	6
-$(C_2H_4)_2NH$ (2[a])	DCM	40	48	94	9	50	12
-$(C_2H_4)_2NH$ (2)	PhH	110	22	94	5	76	18
-$(C_2H_4)_2NH$ (4)	DCM	20	0.25	61	8	64	17
-$(C_2H_4)_2NH$ (4)	DCM	40	0.17	95	6	78	14
-$(C_2H_4)_2NH$ (20)	DCM	40	144	86	11	5	62
-$(CH_2)_5NH$ (2[a])	DCM	40	72	81	5	45	1
-$(CH_2)_5NH$ (4)	DCM	40	3.5	94	10	74	11
-$(CH_2)_5NH$ (8)	DCM	40	2	94	6	73	7
-$(CH_2)_5NH$ (20)	DCM	40	192	95	11	15	65
-$O(C_2H_4)_2NH$ (2)	DCM	40	14	nr[b]	nr[b]	nr[b]	nr[b]
-$O(C_2H_4)_2NH$ (4)	DCM	40	13	89	12	77	2
-$O(C_2H_4)_2NH$ (4)	PhH	110	6	92	16	65	1
-$O(C_2H_4)_2NH$ (8)	DCM	40	1.5	97	20	41	2
-$O(C_2H_4)_2NH$ (20)	DCM	40	72	92	15	5	60

[a] Incomplete Reaction, recovered SM (50 and 40% respectively); [b] No Reaction.

The best yields of the 4-aminopyrido[2,3-*d*]pyrimidines **167f-h** were obtained when four equivalents of base were used in refluxing DCM. In addition the three reactions had a significant difference in the time that was needed for each to come to completion. The

reaction with pyrrolidine was the fastest (10 min) while the reaction with morpholine was the slowest (13 h), which was in agreement with the nucleophilicity of the three amines. Pyrrolidine is a five member ring in contrast with piperidine and morpholine which are six member rings making it a better nucleophile because of its small size and the easier availability of the NH group towards nucleophilic attack. The nucleophilicity of the nitrogen in morpholine is inductively deactivated by the oxygen atom in the ring (Figure 8).

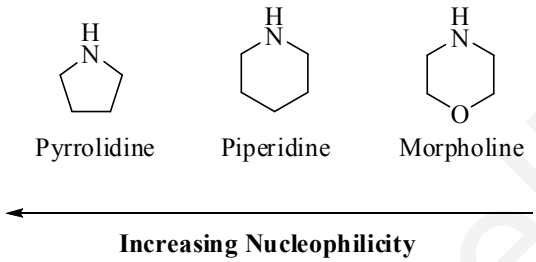
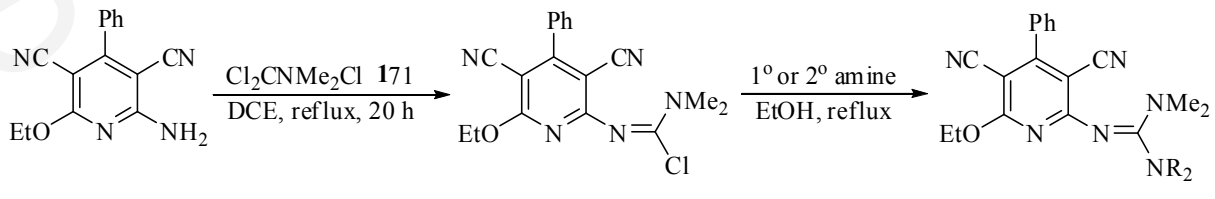


Figure 8. Structure of the three cyclic amines and their relative nucleophilicities

Furthermore, when excess amine was used (20 equiv.) the yields of 4-aminopyrido[2,3-*d*] pyrimidines **167f-h** decreased significantly while the yields of 2-aminoguanidinopyridines **161f-h** increased. This suggested that the formation of the 2-aminoguanidinopyridines **161f-h** were possibly derived from the 4-aminopyrido[2,3-*d*]pyrimidines **167f-h** and not from the starting dithiazole **160**.

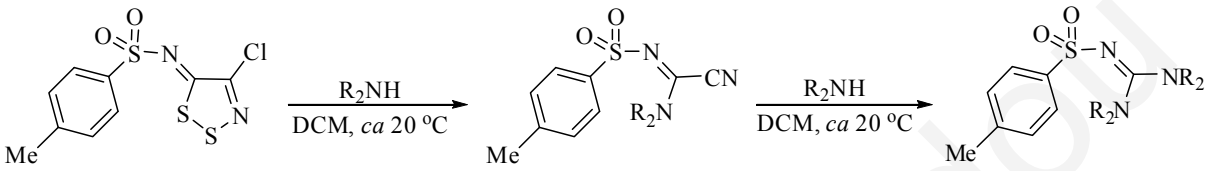
Interestingly, similar 2-aminoguanidinopyridines **173** have previously been prepared in two steps from the 2-aminopyridine **159** and *N*,*N*-dichlorodimethyliminochloride **171** in refluxing DCE, which initially affords (*E*)-*N*'-(3,5-dicyano-6-ethoxy-4-phenylpyridin-2-yl)-*N*,*N*-dimethylcarbamimidic chloride **172**, the subsequent treatment of which with either 1° or 2° amines affords the analogous guanidines **173** (Scheme 95).[279]



159 **172** **173**

Scheme 95

(*Z*)-*N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methylbenzenesulfonamide **174** can form the analogous *N*-(diaminoalkylate)-4-methyl-benzenesulfonamide **176** in moderate to high yields (40-99%) when treated with 2° amines. This reaction passes through a (*Z*)-*N*'-tosyl-carbamimidoyl cyanide intermediate **175** (Scheme 96).[261]

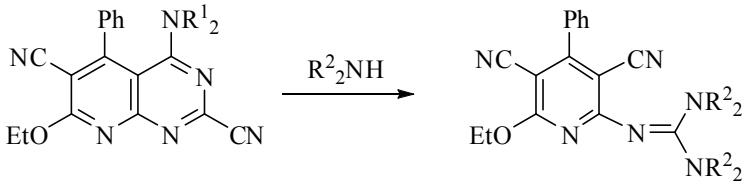


174 **175** **176**

Scheme 96

In our case, however, the analogous cyanothioformamide intermediate was not observed, supporting the suggestion that the formation of the 2-aminoguanidinopyridines **161f-h** derived from the 4-aminopyrido[2,3-*d*]pyrimidines **167f-h**. To the best of our knowledge, there were no examples in the literature where a pyrimidine ring can open to form a 2-amino-guanidonopyridine. Treatment of the three 4-aminopyrido[2,3-*d*]pyrimidines **167f-h** with excess of the corresponding 2° amine, gave as products the expected 2-aminoguanidinopyridines **161f-h** in low to moderate yields (Table 19).

Table 19. Reaction of 4-aminopyrido[2,3-*d*]pyrimidines **167f-h** (0.135 mmol) with excess of 2° amines.



167f-h **161f-h**

R^2_2NH (equiv.)	Solvent	T (°C)	Time (d)	Yields (%)
-$(C_2H_4)_2NH$ (18)	DCM	40	6 h	63
-$(C_2H_4)_2NH$ (20)	DCM	40	5 h	65
-$(C_2H_4)_2NH$ (30)	DCM	40	3.5 h	65
-$(CH_2)_5NH$ (18)	DCM	40	6	9
-$(CH_2)_5NH$ (20)	DCM	40	6	18
-$(CH_2)_5NH$ (20)	EtOH	78	8	15
-$(CH_2)_5NH$ (30)	PhMe	110	6	20
-$(CH_2)_5NH$ (40)	PhMe	110	6	21
-$O(C_2H_4)_2NH$ (40)	DCM	40	6	-[a]
-$O(C_2H_4)_2NH$ (18)	EtOH	78	2	28
-$O(C_2H_4)_2NH$ (20)	PhMe	110	6	78
-$O(C_2H_4)_2NH$ (30)	PhMe	110	6	74

[a] Incomplete reaction, recovered starting material (75%).

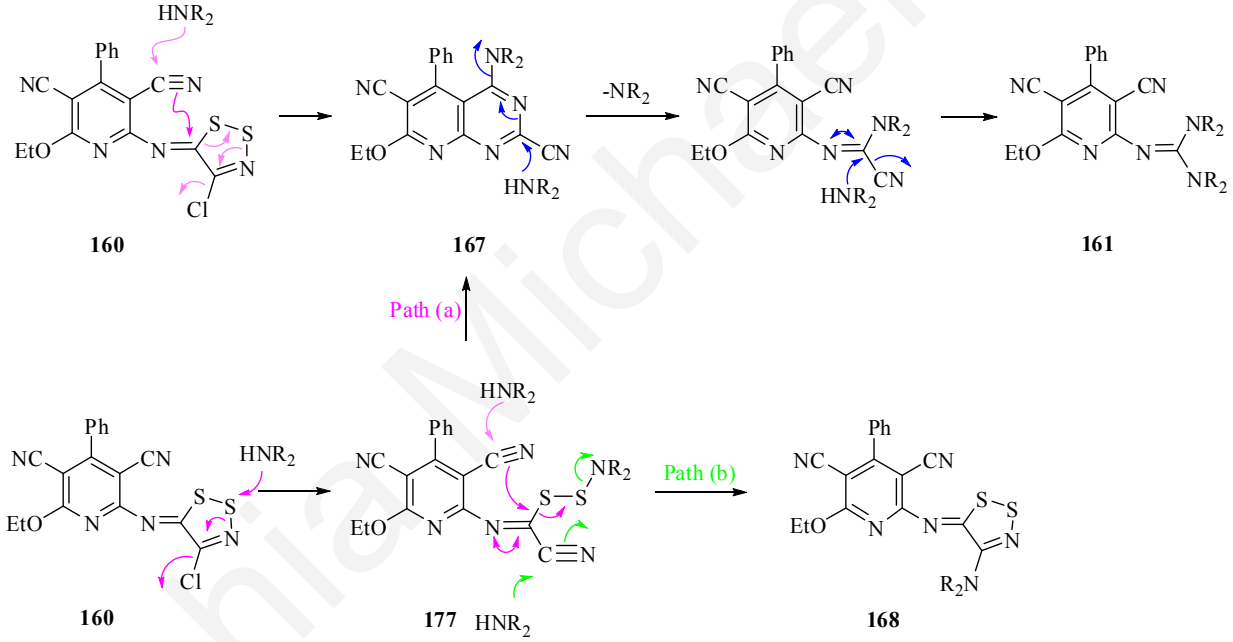
The reaction times for the transformation of the 4-aminopyrido[2,3-*d*]pyrimidines **167f-h** were in line with the nucleophilicity of the 2° amines: Pyrrolidine gave the product in the shortest time while piperidine and morpholine needed higher temperatures and longer reaction times.

5.2.4 Mechanistic Rationale for the Formation of Compounds **161, 167-169**.

4-Aminopyrido[2,3-*d*]pyrimidines **167** can be obtained *via* two possible mechanistic pathways. The first involves a nucleophilic addition of the amine to the cyano group at the pyridine C3 position. The nitrogen of the cyano group can then attack the dithiazole C5 position causing fragmentation and elimination of S_2 and HCl to give the 4-aminopyrido [2,3-*d*]pyrimidines **167**. The second mechanistic pathway involves a nucleophilic attack of the amine to the S2 position of the dithiazole ring causing it to form the disulfide intermediate **177**. A second amine can then attack the cyano group at the pyridine C3 position and the

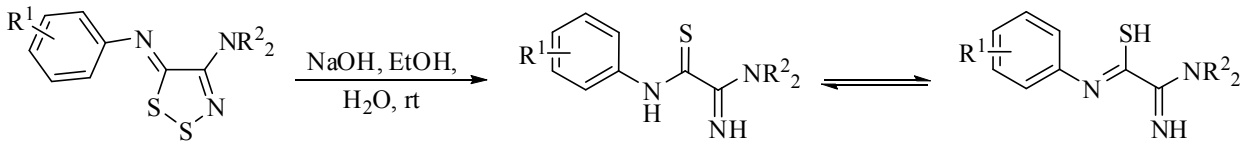
nitrogen of the cyano group can attack the carbon next to the sulfur on the dithiazole ring causing the ring closure and elimination of S_2.

The 2-aminoguanidinopyridines **161** can be formed by a nucleophilic attack of the amine to the C2 position of the pyridine ring of the 4-aminopyrido[2,3-*d*]pyrimidine **167** causing the ring to open followed by a second amine attack and elimination of HCN. The dithiazolylidene **168** can be formed by a nucleophilic attack of the amine to the S2 position of the dithiazole ring causing it to open and form the mixed disulfide intermediate **177**. A second amine can then add to the cyano group to give an amidine that cyclizes onto the S2 atom, eliminating the first amine and affording the dithiazolylidene **168** (Scheme 97).



Scheme 97

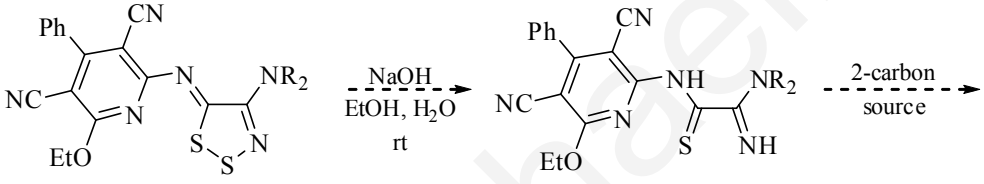
A review of the literature to find possible information regarding the mechanism for the formation of the green compound **169** revealed that treatment of the dithiazolylidene **178** with NaOH in EtOH leads to ring opening of the dithiazole forming the reddish *N*'-aryl-thiocarbamoyl-*N*,*N*-dialkylamidine **180** in good to excellent yields (68-99%) (Scheme 98).[291]



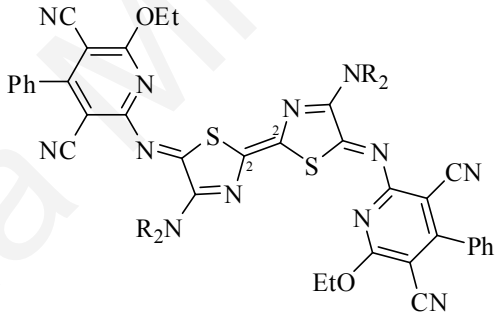
178 **179** **180**

Scheme 98

It is possible that something similar happened to 2-[4-(diethylamino)-5*H*-1,2,3-dithiazol-5-ylideneamino]-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **168** to give the intermediate **181** which reacts with a two carbon source to give the green compound **169** (Scheme 99).



168 **181**



169

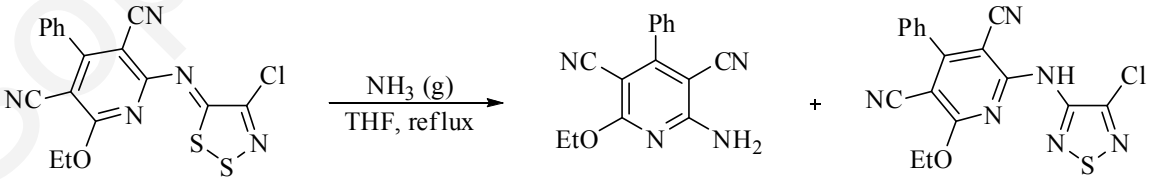
Scheme 99

The origin of the two ethene carbons was quite interesting. One possibility was that they derived from the solvent. To verify this suggestion the reaction was repeated using a variety of solvents. Dry and deoxygenated DCM, $CDCl_3$, CH_2Br_2, CH_2BrI, $ClCH_2CH_2Cl$ (DCE), $CHBr_3$ and $CHCl_2CHCl_2$ were used as solvents. The only reaction that gave the green compound was the reaction that took place in dry and deoxygenated DCM. This was surprising since DCM was a one carbon source and other dihalomethanes which had better leaving groups failed to give this product. Insufficient time was available to pursue this reaction further.

5.2.5 Reaction with other Nucleophiles

5.2.5.1 Reaction with Ammonia

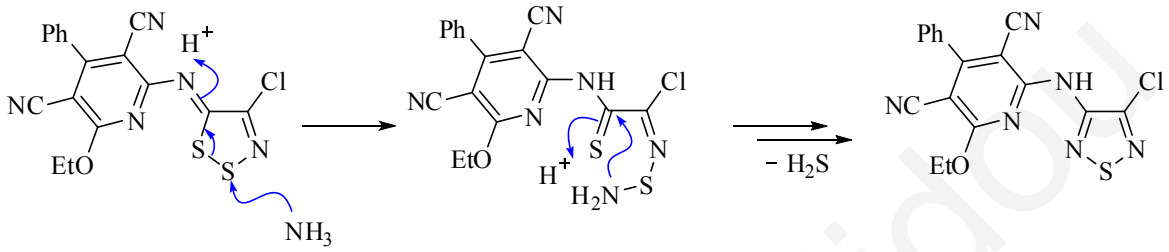
Treatment of the dithiazolylidene **160** with excess of NH_3 (g) in refluxing DCM or PhMe gave no reaction and the starting material was recovered in 90 and 85% yields, respectively. In contrast, when the reaction was carried out in refluxing THF or EtOH two colourless compounds were formed. The first one was identified to be the 2-aminopyridine **159** and was obtained in 36 and 12% yields, respectively. The second one was obtained as colourless cotton fibers, mp 178-179 ^{o}C (from cyclohexane/EtOH). Microanalysis (C, 53.4; H, 2.8; N, 22.2%) and mass spectrometry supported the formula $C_{17}H_{11}ClN_6OS$ [*m/z* (EI) 382 Da (M^+, 100%)]. ^{13}C NMR spectroscopy showed fifteen separate carbon resonances of which three were aromatic, belonging to the phenyl group and six were quaternary carbons as supported by DEPT NMR studies. The presence of the ethoxy group was also supported by DEPT studies. The presence of cyano groups was supported by IR bands at $\nu(C\equiv N)_s$ 2224 and 2214 cm^{-1} and two carbon signals at 114.6 and 113.7 ppm. ^{1}H NMR spectroscopy showed the presence of eleven hydrogens of which five were aromatic (7.58 ppm) in a broad single peak indicating the overlap of the aromatic protons. The presence of the ethoxy group was supported by a triplet at 1.45 (3H, t, *J* 7.1 Hz, C*H*$_3$) and a quartet at 4.54 ppm (2H, q, *J* 7.1 Hz, C*H*$_2$O). ^{1}H NMR spectroscopy also identified one D_2O exchangeable broad resonance integrating 1 at 8.07 ppm indicating the presence of a 2^{o} amino group and this was supported by an IR band at 3387m cm^{-1}. This colourless compound was identified to be 2-(4-chloro-1,2,5-thiadiazol-3-ylamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **182** and was obtained in 28% yield when the reaction was carried out in THF and 20% yield when the reaction was carried out in EtOH (Scheme 100).



160 **159** (36%) **182** (28%)

Scheme 100

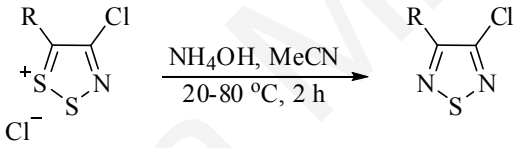
A possible mechanistic rationale involves nucleophilic attack of the ammonia at the S2 atom of the dithiazole, causing ring opening and formation of the disulfide intermediate **183**. The amine that is bound to the S2 atom can now attack the carbon next to the S1 atom causing a ring closure and elimination of H_2S (Scheme 101).



160 **183** **182**

Scheme 101

In the literature, there are only a few examples of the synthesis of 1,2,5-thiadiazoles from dithiazoles: Treatment of an acetonitrile solution of the 1,2,3-dithiazoles **184** with aqueous ammonia gives as products the corresponding 1,2,5-thiadiazoles **185**[63] (Scheme 102).

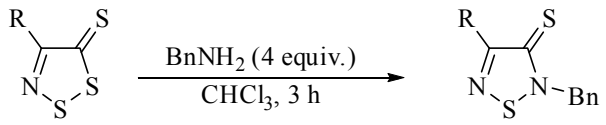


184 **185**

a, R = Cl, 0%
b, R = CN, 7%
c, R = SMe, 0%
d, R = Ph, 36%
e, R = 4-$O_2NC_6H_4$, 26%

Scheme 102

Furthermore, the reaction of 4-substituted-5*H*-1,2,3-dithiazole-5-thione **186** with benzylamine or other primary amines in chloroform gives 2-benzyl-4-substituted-1,2,5-thiadiazole-3(2*H*)-thione **187** as a product, in moderate yields[292,293] (Scheme 103).



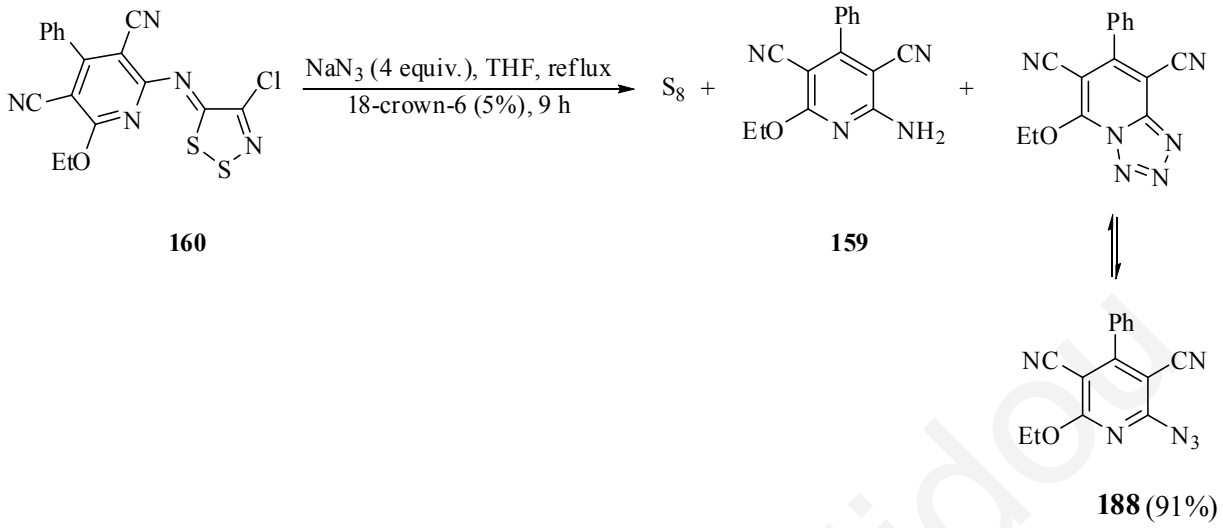
186 **187**

a. R = Ph, 56%
b. R = 4-FC_6H_4, 58%
c. R = 4-$MeOC_6H_4$, 54%
d. R = 4-$O_2NC_6H_4$, 43%
e. R = Me, 62%
f. R = 2-thienyl, 65%
g. R = 2-benzofuryl, 49%

Scheme 103

5.2.5.2 Reaction with Sodium Azide

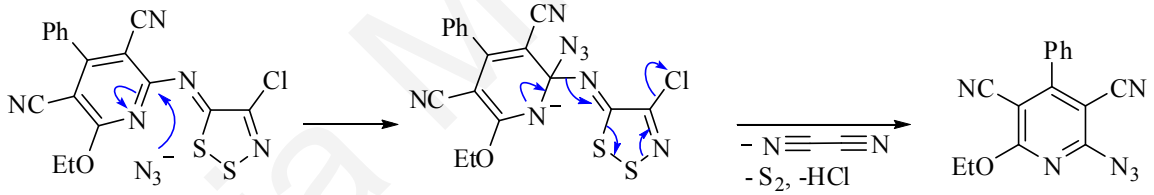
Treatment of dithiazolylidene **160** with sodium azide in the presence of 18-crown-6 (5 mol%) in THF or in the absence of 18-crown-6 in DMF at reflux gave traces of the 2-aminopyridine **159** and another light orange compound. This compound was obtained as light orange cubes, mp 145-146 ^{o}C (from cyclohexane/EtOH). Microanalysis (C, 62.0; H, 3.5; N, 29.1%) and mass spectrometry supported the formula $C_{15}H_{10}N_6O$ [*m/z* (EI) 290 (M^+, 72%)]. ^{13}C NMR spectroscopy showed thirteen separate carbon resonances of which three were aromatic, belonging to the phenyl group, one CH_2 and one CH_3 belonging to the ethoxy group and four quaternary carbons as supported by DEPT studies. The presence of cyano groups was supported by IR band at $\nu(C{\equiv}N)_s$ 2230 cm^{-1} and two carbon signals at 113.1 and 113.0 ppm. ^{1}H NMR spectroscopy showed the presence of ten protons of which five were aromatic (7.58-7.50 ppm) and the presence of the ethoxy group was supported by a triplet at 1.51 (3H, t, *J* 7.1 Hz, C*H*$_3$) and a quartet at 4.62 ppm (2H, q, *J* 7.1 Hz, C*H*$_2$O). This colourless compound was identified to be 5-ethoxy-7-phenyltetrazolo[1,5-*a*]pyridine-6,8-dicarbonitrile **188** (Scheme 104).



160 **159** **188** (91%)

Scheme 104

A possible mechanistic rationale involves a nucleophilic attack of the azide group at the C2 position of the pyridine ring forcing the breaking of the aromaticity. The pyridine ring in an attempt to gain back its aromaticity, instead of eliminating the azide group eliminates the dithiazole ring possibly as S_2, HCl and cyanogen, forming the product (Scheme 105).



160 **189** **188**

Scheme 105

5.2.5.3 Reaction with Halides or Alkoxides

Treatment of the dithiazolylidene **160** with tetraalkylammonium chloride (10 mol% or 2 equiv.) in either refluxing PhMe or PhCl or treatment with anhydrous HBr[112] or HCl[95] in either THF or PhMe at *ca.* 20 °C or reflux gave no reaction and the starting material was recovered in high yields (90-95%). Treatment of the dithiazolylidene **160** with Na in EtOH or MeOH[70,75,84,89,93,95,96,98,179] gave complex reaction mixtures and no desired product could be isolated.

5.3 Summary

2-Amino-3,4-dicyano-5-phenyl-6-ethoxypyridine **159** treated with Appel salt **42** gave 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** in 88% yield. Treatment of this compound with *n*-$BuNH_2$ and $BnNH_2$ gave the guanidines **161a** and **161b** in 32 and 82% yields, respectively. In contrast, treatment of the dithiazolylidene **160** with diethylamine, di-*n*-propylamine or dibenzylamine gave the analogous 4-aminopyrido[2,3-*d*]pyrimidines **167c-e** in high yields. With diethylamine, two more products were obtained, the dithiazolylidene **168** and the quinoidal-2,2'-bithiazole **169** whose structure was identified using a single crystal x-ray crystallography. Treatment of the dithiazolylidene **160** with pyrrolidine, piperidine or morpholine gave the analogous 4-amino-pyrido[2,3-*d*]pyrimidines **167f-h**, 2-aminopyridine **159** and 2-(di-amino-1-ylmethylene-amino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitriles **161f-h**. Treatment of 4-aminopyrido [2,3-*d*]pyrimidines **167f-h** with excess of amine led to 2-(diamino-1-ylmethylene-amino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitriles **161f-h**. Moreover, treatment of the dithiazolylidene **160** with NH_3 (g) in THF gave 2-(4-chloro-1,2,3-thiadiazol-3-ylamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **182** in 28% yield while treatment with NaN_3 afforded 5-ethoxy-7-phenyltetrazolo[1,5-*a*]pyridine-6,8-dicarbonitrile **188** in 91% yield. As we can conclude treatment of the dithiazolylidene **168** with a range of nucleophilic amines can give access to a range of unexpected products. As future work, the same chemistry can be repeated using 2-amino-nicotinonitrile which now is commercially available, investigate the mechanism for the formation of products that can be obtain from this compound and compare them with the products that were formed during the reactions of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine **160**. Also the chemistry of the quinoidal 2,2'-bithiazole **169** could be explored in more detail in terms of investigating the mechanism of formation and synthesis of derivatives.

CHAPTER 6

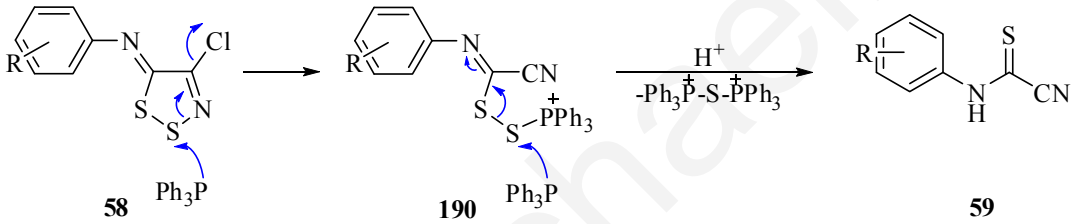
Synthesis of 3-Aminoindole-2-carbonitriles from 2-(4-Chloro-5*H*-1,2,3-dithiazolylideneamino)benzonitriles

Sections

6.1 Introduction

Our interest in 1,2,3-dithiazole chemistry revolves around the construction of dithiazole systems that can be converted into new heterocyclic systems *via* ring transformation. One way to ring open dithiazoles, is to use soft nucleophiles and especially thiophiles (Chapter 5).

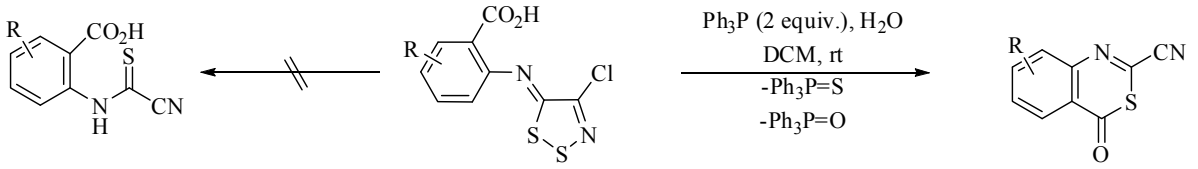
One thiophile that has been used extensively is triphenylphosphine (Ph_3P), which reacts with neutral (4-chloro-5*H*-1,2,3-dithiazolylideneamino)arenes **58** to give in most cases cyanothioformanilides **59** (Scheme 106).[49,70, 84,89,97,98,100,114] This transformation was assisted by traces of water, since hydrolysis of the $(Ph_3P)_2S^{2+}$ $2Cl^-$ side product afforded more stable $Ph_3P{=}S$, $Ph_3P{=}O$ and HCl.



R = H (70%), 2-CN (50%), 2-CO_2Me (71%), 4-MeO (81%), 4,5-$(MeO)_2$ (98%), 2-CN-4,5-$(OMe)_2$ (76%), 2-CO_2Me-4,5-$(OMe)_2$ (93%), 1,4-dioxime (80%)

Scheme 106

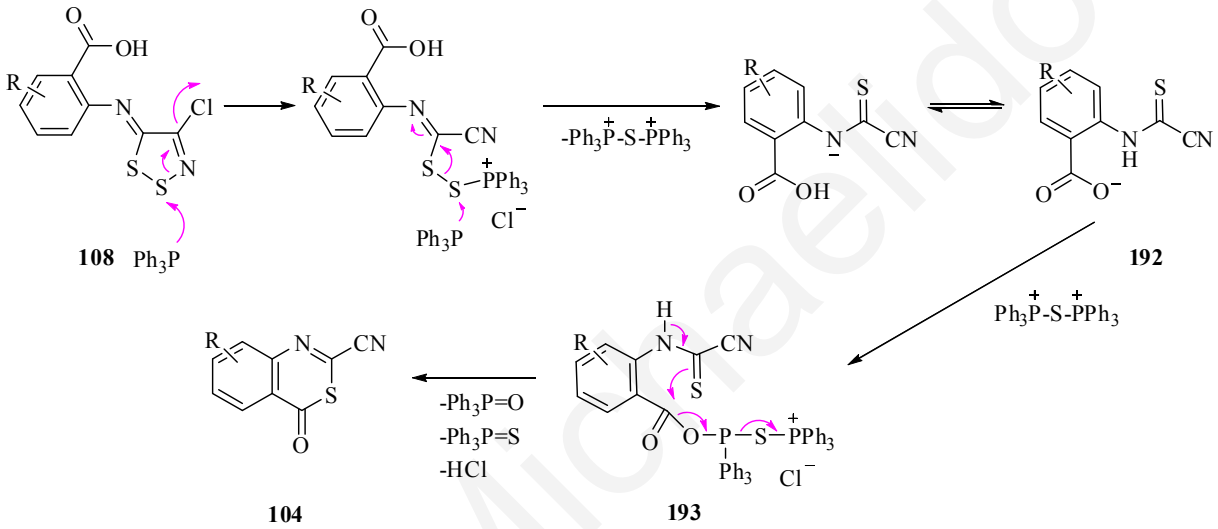
Rees *et al*., treated substituted (4-chloro-5*H*-1,2,3-dithiazolylideneamino)benzoic acids **108** with Ph_3P and surprisingly obtained the cyclized 2-cyano-3,1-benzothiazin-4-ones **104** and not the expected cyanothioformanilide **191**.[84,108,109,114] The proposed mechanism for the formation of the 2-cyano-3,1-benzothiazin-4-one **104** involved the formation of the activated intermediate **192** that can undergo a reaction with the $(Ph_3P)_2S^{2+}$ species giving the intermediate **193**, which can then undergo an intramolecular reaction to give the corresponding cyclized compound **104** (Scheme 107).[84,294]



191 **108** **104**

R = H, 4-Cl, 4,5-diOMe

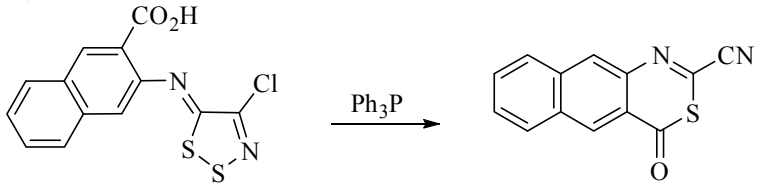
Proposed Mechanism



108 **192** **104** **193**

Scheme 107

Similarly, when the imino naphthoic acid derivative **194** was treated with Ph_3P it gave the corresponding naphthothiazinone **195** in 24% yield (Scheme 108).[84] The mechanism for the formation of the thiazinone **195** is presented in the previous scheme (Scheme 107).

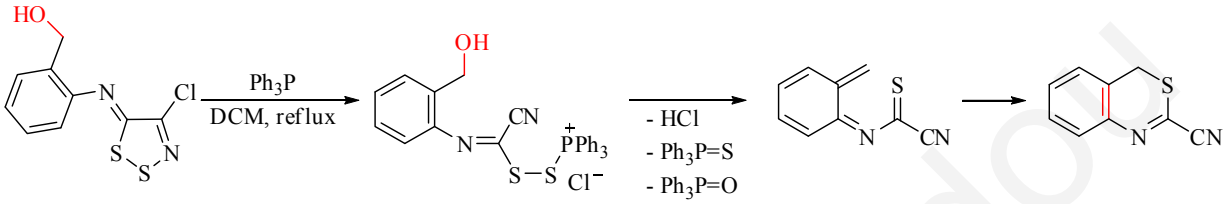


194 **195**

Scheme 108

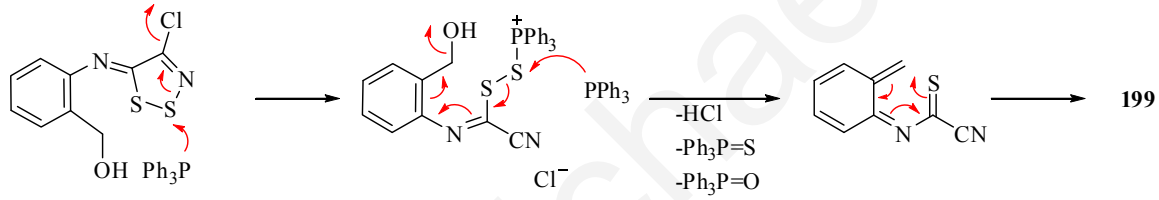
When an *ortho* hydroxymethyl group was present in the (*Z*)-[2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenyl]methanol **196**, treatment with Ph_3P (2 equiv.) in DCM at reflux, gave the

benzothiazine **199** in good yields.[96] The proposed reaction mechanism invoked an initial attack of the Ph_3P at the dithiazole S2 position to give the mixed disulfide intermediate **197**, which then suffers attack by a second Ph_3P on the S2 atom eliminating $Ph_3P{=}S$ and $Ph_3P{=}O$ and forming the active intermediate **198** that cyclized to the benzothiazine **199** (Scheme 109).



196 **197** **198** **199**

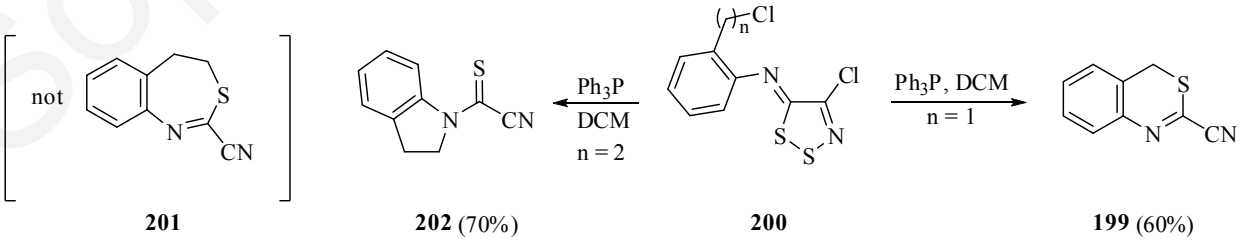
Proposed Mechanism



196 **197** **198**

Scheme 109

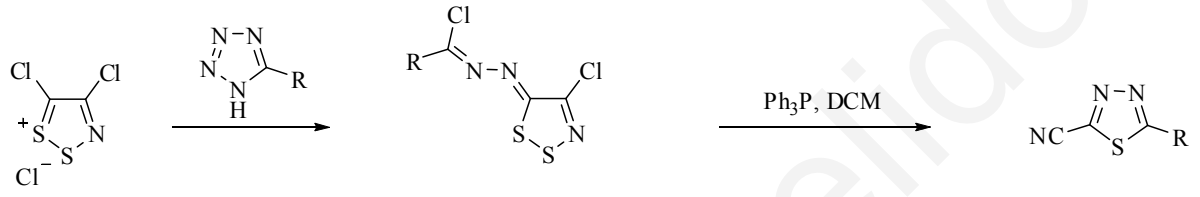
Similar treatment of the chloromethyl compound **200** with Ph_3P (2 equiv.) in refluxing DCM gave as product the analogous benzothiazine **199** in 60% yield. In contrast, treatment of the chloroethyl analogue **200** with Ph_3P (2 equiv.) in refluxing DCM did not give the expected benzothiazepine **201** but instead gave the *N*-(cyanothioformyl)indoline **202** in 70% yield (Scheme 110).[295]



201 **202** (70%) **200** **199** (60%)

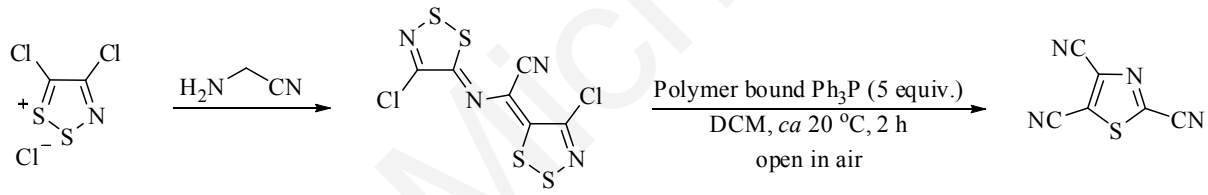
Scheme 110

Polymer bound Ph_3P has also been used to transform neutral 4-chloro-5*H*-1,2,3-dithiazoles **203** into the corresponding thiadiazole **204**.[88] Dithiazole ring can also be used as a source of electrophilic trap. For example, 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-(*Z*)-4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)acetonitrile **205**,[85,90,116] can be attacked by a second phosphine releasing a nucleophilic sulfur which is subsequently trapped by the electrophilic C5 positions of the neighboring dithiazole giving the thiazole **206** (Scheme 111).



42 **203** **204**

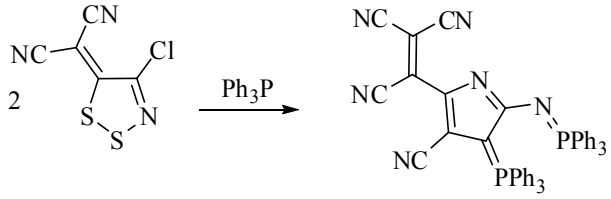
R = Ph (82%), 4-$O_2NC_6H_5$ (92%), 4-$MeOC_6H_4$ (99%), 4-NCC_6H_4 (72%), PhO (75%), $ClCH_2CH_2$ (90%), MeS (73%), 2-Thienyl (76%)



42 **205** **206** (76%)

Scheme 111

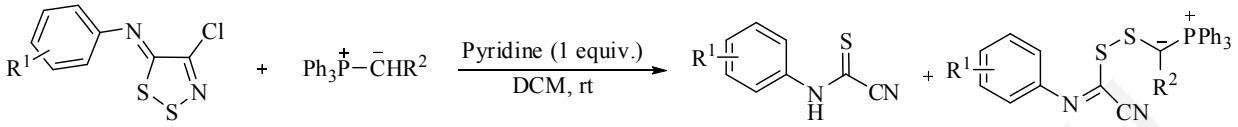
In addition, when Ph_3P reacts with (4-chloro-5*H*-1,2,3-dithiazolylidene)malononitrile **207** the deep blue coloured 3*H*-pyrrole **208** was obtained *via* a complex transformation (Scheme 112).[296]



207 **208**

Scheme 112

1,2,3-Dithiazoles **58** have also been treated with stable phosphoraneylidenes **209** (Wittig reagents) to afford both the cyanothioformanilides **59** and the unusual dithiomethylenephosphorane **210** (Scheme 113).[113,297,298]

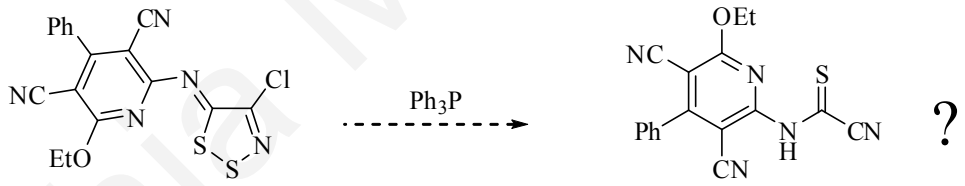


58 **209** **59** **210**

R^1 = 4-MeO; 4-Me; 2-Cl; 4-Cl; 4-Br; 4-O_2N; 2-Me, 4-O_2N; 2-CN; 3-O_2N; 4-O_2N;
R^2 = CO_2Et; Ac; 4-ClC_6H_4CO; CN

Scheme 113

From the above survey it can be seen that the phosphine mediated cleavage of 4-chloro-*5H*-1,2,3-dithiazoles can afford both useful cyanothioformanilides and also unexpected ANRORC like ring transformations to yield new heteroarenes. These reactions are often influenced by the substitution patterns of the dithiazoles. As such we chose to probe the reaction of Ph_3P with the heavily functionalized (dithiazolylidene)pyridine-2-amine **160** in the hope of discovering new dithiazole chemistry (Scheme 114).



160 **211**

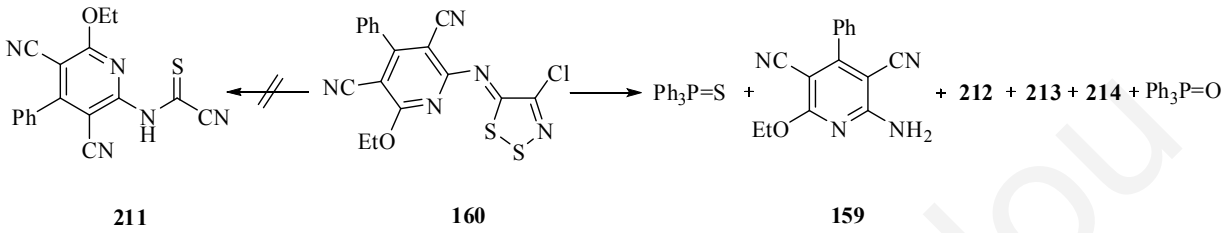
Scheme 114

6.2 Reaction of 2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile 160 with Ph_3P

6.2.1 Synthesis of a Fully Substituted Indole

When 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-di-carbonitrile **160** was treated with the usual Ph_3P (2 equiv.) in DCM the reaction was incomplete and the starting material was recovered in 90% yield. Increasing the amount of Ph_3P to four equivalents led to the consumption of the starting material and the formation of 2-

aminopyridine **159** together with three unknown products, in addition to the expected $Ph_3P=S$ and $Ph_3P=O$ (Scheme 115). No trace of the expected 2-cyano cyanothioformanilide **211** was observed.

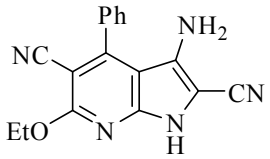


Reagents and Conditions: Ph_3P (4 equiv.), DCM, *ca.* 20 °C

Scheme 115

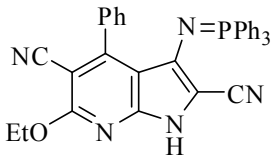
Compound **212** was obtained as yellow prisms, mp 191-192 °C (from cyclohexane/EtOH). Microanalysis and mass spectrometry supported the formula $C_{17}H_{13}N_5O$ [*m/z* (EI) 303 (M^+, 84%)]. The starting material ($C_{17}H_{10}ClN_5OS_2$) had therefore lost ClS_2 and gained 3H. UV/vis spectroscopy showed a λ_{max} at 372 nm (log ε 3.39). ^{13}C NMR spectroscopy gave fifteen separate carbon resonances of which three (130.4, 129.2 and 128.3 ppm) represented Ph CH peaks, one (63.8 ppm) represented one CH_2 peak and one (14.3 ppm) represented CH_3 peak as supported by DEPT studies. The three aromatic Ph CH peaks belonged to the phenyl on the C4 position of the pyridine ring and the CH_2, CH_3 peaks belonged to the ethoxy group on the C6 position of the pyridine ring. ^{13}C NMR spectroscopy also tentatively identified two cyano carbons at 115.2 and 113.8 ppm which were supported by IR bands at $\nu(C\equiv N)_s$ 2234 and 2203 cm^{-1}. ^1H NMR spectroscopy identified two D_2O exchangeable broad resonance intergrating one at 8.31 ppm and two at 3.74 ppm indicating the presence of 1° and 2° amino groups and this was supported by IR bands at ν(NH) 3345 cm^{-1} and $\nu(NH_2)$ 3231 cm^{-1}. ^1H NMR spectroscopy also gave a quartet peak at 4.51 ppm corresponding to two protons and a triplet peak at 1.47 ppm corresponding to three protons, typical for an ethoxy substituent. In the aromatic region two multiplets were present in the range of 7.59-7.56 and 7.52-7.48 ppm, respectively one corresponding to three protons and the other one to two protons. Also, in the ^1H NMR spectrum of the product NH and NH_2 groups were present at 8.31 (1H, br s, N*H*), and 3.74 (2H, br s, NH_2). This compound was also stable to solutions (DCM) of either Ph_3P, $Ph_3P=S$, $Ph_3P=O$ or S_8 at *ca.* 20 °C. Having all this in mind it was concluded that this

compound could be the 3-amino-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-*b*]-pyridine-2,5-dicarbonitrile **212**.



212

Compound **213** was obtained as colourless cubes, mp 285-286 ^{o}C (from cyclohexane/EtOH). Microanalysis (C, 74.5; H, 4.6; N, 12.4%) showed a large carbon percentage and mass spectrometry gave a large molecular weight [*m/z* (EI) 563 Da (M^+, 100%)], suggesting that a carbon rich fragment had added to the system. The only carbon rich source was Ph_3P. ^{31}P NMR spectroscopy gave one peak at 10.2 ppm confirming the presence of phosphine. With this information in hand, microanalysis and the mass spectrometry the formula $C_{35}H_{26}N_5OP$ was proposed. UV/vis spectroscopy showed a λ_{max} at 351 nm (log ε 3.88). The ^{13}C NMR spectrum, was complicated by extensive P-C coupling, however, a total of twenty-two independent carbon resonances of which nine were quaternary (DEPT) were identified, which suggested the presence of a Ph_3P group together with the phenyl group. The presence of the cyano groups was supported by an IR bands at $\nu(C{\equiv}N)_s$ 2229 and 2219 cm^{-1} and carbon signals at 119.0 and 117.3 ppm. The most up field carbon resonance 100.3 ppm indicated the absence of sp^3 hybridized carbons. ^{1}H NMR spectroscopy failed to identify D_2O exchangeable signals. The aromatic area was complex representing twenty five hydrogens (7.83-7.22 ppm). The peaks belonging to the ethoxy group were also present in the spectrum. Comparing the above data with the data obtained for the pyrrolo[2,3-*b*]pyridine **212** it was concluded that this compound was 3-aminophosphorane-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-2,5-dicarbonitrile **213**.



213

Compound **214** was obtained as yellow prisms, mp 316-318 ^{o}C (from EtOH). Microanalysis (C, 77.0; H, 4.5; N, 8.8%) showed a large carbon percentage. Similarly mass spectrometry showed a large molecular weight [*m/z* (EI) 795 Da (M^{+}, 80%)] suggesting that a carbon rich fragment such as Ph_3P had added to the system. ^{31}P NMR spectroscopy indicated two similar phosphorus environments at 13.9 and 8.0 ppm in the range for phosphonium ylides, $Ph_3P{=}CR_2$, with no ^{31}P-^{31}P coupling. Microanalysis in combination with mass spectrometry and ^{31}P NMR spectroscopy, supported the formula $C_{51}H_{35}N_5OP_2$. UV/vis spectroscopy gave an absorption [λ_{max} (DCM) 398 nm (log ε 3.65)] that indicated an extensive chromophore. ^{13}C NMR spectroscopy showed a complex aromatic region. The ethoxy group was absent as supported by DEPT studies. The presence of two cyano groups were supported by peaks at 119.0 and 117.3 ppm and IR band at $\nu(C{\equiv}N)_s$ 2205 cm^{-1}. IR spectroscopy also showed aromatic C-H stretching at $\nu(C\text{-}H)_s$ 3080 and 3056 cm^{-1} and a very strong peak belonging to a carbonyl group at $\nu(C{=}O)_s$ 1639 cm^{-1}. ^{1}H NMR spectroscopy also gave a complex aromatic multiplex area (7.83-7.18 ppm) of the Ph_3P groups.

Compound **214** was stable in basic (LiOH in MeOH, EtOH, THF) and acidic media (TsOH or HCl in MeOH, EtOH, THF) at room temperature. The above spectroscopic data were not sufficient to enable structure determination. As such single crystals of yellow colour and rhombic shape were grown from warm saturated EtOH by slow cooling and single crystal X-ray crystallography identified the compound as 6-cyano-5-oxo-7-phenyl-2,5-bis(triphenylphosphino)imidazo[1,2-*a*]pyridin-4-ium-1-ide **214** (Figure 9).

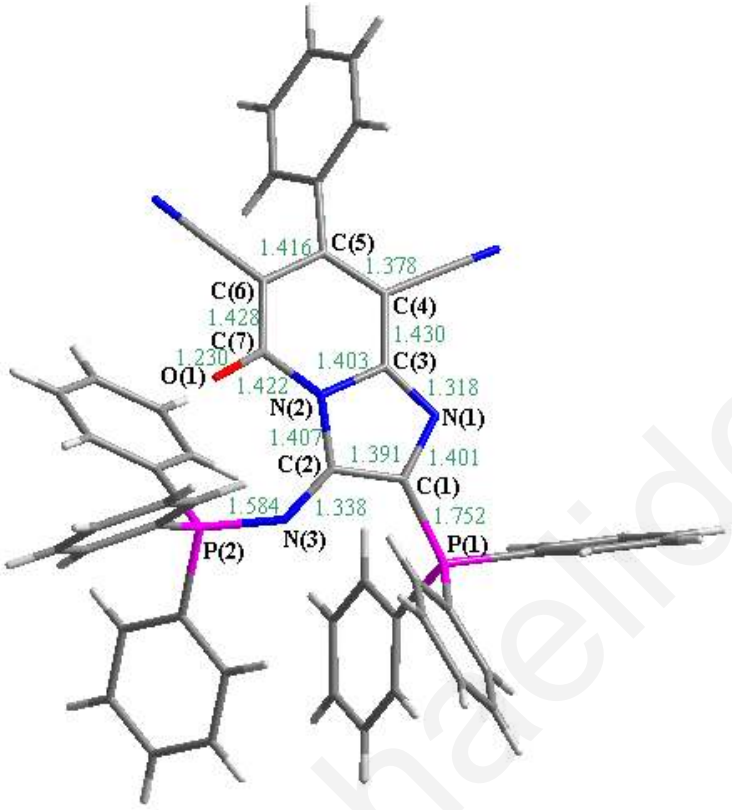
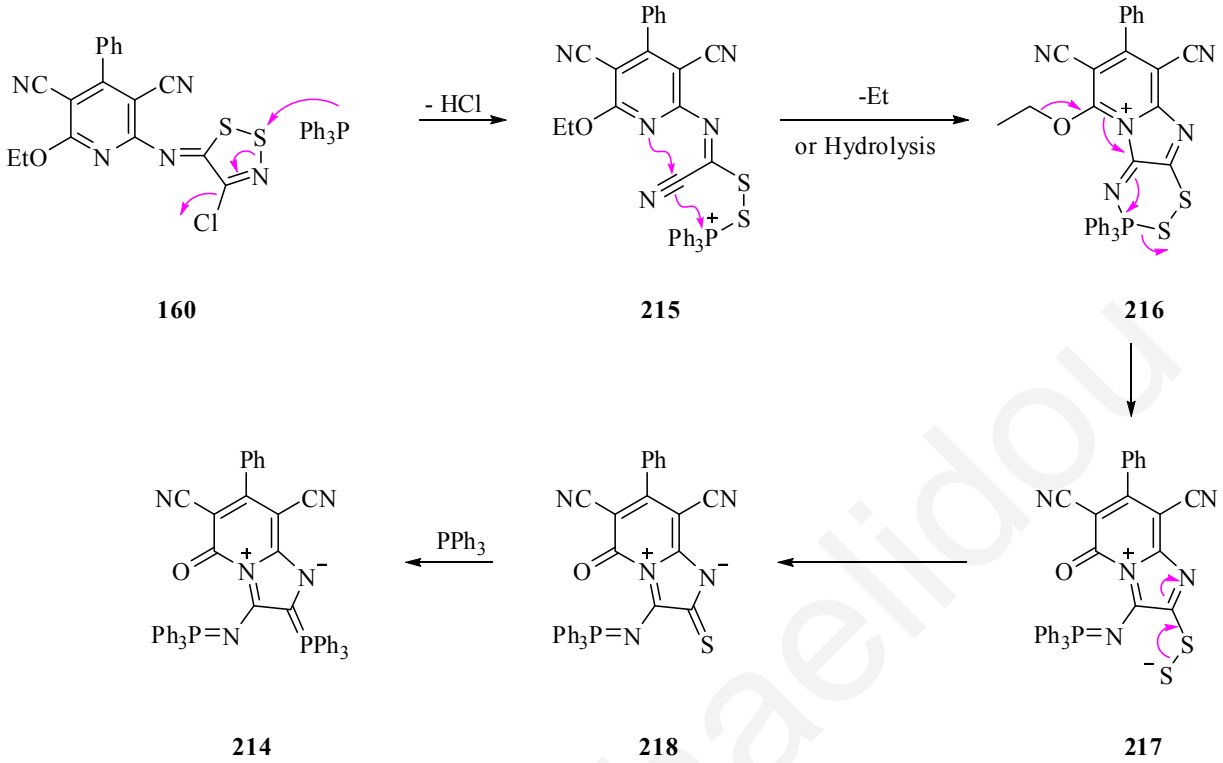


Figure 9 X-ray structure of 6-cyano-5-oxo-7-phenyl-2,5-bis(triphenylphosphino)imidazo [1,2-*a*]pyridin-4-ium-1-ide **214** showing bond lengths (Å) in green [P_1-C_1 1.752(2); P_2-N_3 1.5838(17); O_1-C_7 1.231(3); N_1-C_3 1.318(3); N_1-C_1 1.401(3); N_2-C_3 1.403(3); N_2-C_2 1.407(3); N_2-C_7 1.421(3); N_3-C_2 1.338(3); C_1-C_2 1.391(3); C_3-C_4 1.430(3); C_4-C_5 1.378(3); C_5-C_6 1.416(3); C_6-C_7 1.428(3) Å].

The X-ray structure of 6-cyano-5-oxo-7-phenyl-2,5-bis(triphenylphosphino)imidazo[1,2-*a*] pyridin-4-ium-1-ide **214** showed that the ethoxy substituent of the starting pyridine ring was transformed into a carbonyl group. The dithiazole ring suffered a ring transformation to give an imidazole ring fused to the pyridine ring and having as substituents two Ph_3P groups. The compound is not planar with the phenyl groups out of the plane (by 45°) The ylide nature of compound **35** is further demonstrated by the patterns of bonding in the molecule. The P(1)-C(1) bond has clear partial double bond character [1.752(2) Å] though is longer than the reported for triphenylphosphonium cyclopentadienylide [1.718(2) Å].[299,300] The bond lengths within the pyrrole ring indicate a pattern of delocalization extending between P(1) and N(3) *via* N(1). The P=N double bond length is typical at 1.584(17) Å (typical P=N bond length is 1.55-1.57 Å)[301] and the bond lies close to the plane of the pyrrole ring. The C(7)-O(1) bond

[1.231(3) Å] is a typical carbonyl bond (typical C=O bond length is 1.23-1.26 Å).[301] The N(1)-C(1) and N(2)-C(2) bonds [1.401(3) and 1.407(3) Å respectively] are shorter than a typical C-N bond (1.47-1.48 Å)[301] because of the N(1) is negative charged and the C(2) is positive charged. Similarly the C(1)-C(2) bond [1.391(3) Å] is shorter than a typical Csp^3-Csp^3 bond (1.54 Å)[301] because of the positive charged C(2) The N(1)-C(3) bond [1.318(3) Å] is longer than a typical C=N bond (1.29 Å)[301] because of the negative charged N(1).

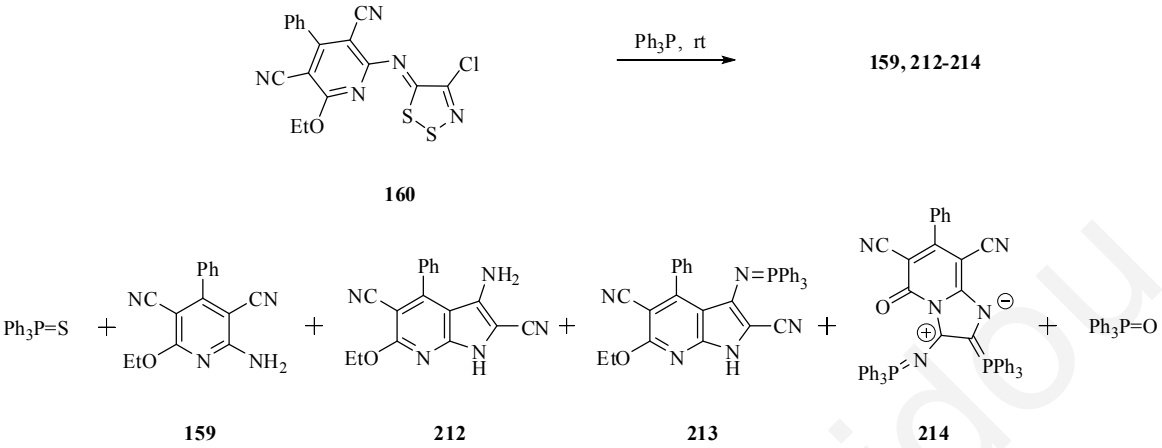
Having in mind the mechanism for the formation of [4-cyano-5-tricyanovinyl-2-(triphenyl-phosphoraneylideneamino)-3*H*-pyrrol-3-ylidene]triphenylphosphorane **208**[296] a mechanism for the synthesis of the bisphosphine compound **214** was proposed. One Ph_3P can attack the dithiazole S2 position causing it to open, eliminate HCl and form the disulfur intermediate **215**. The phosphonium cation that forms activates tandem cyclization from the nitrogen of the pyridine ring to the cyano group and then to the phosphonium group leading to the formation of the intermediate **216**. The formation of the pyridinium cation also activates a de-ethylation of the ethoxy group (or hydrolysis) in the C5 position of the pyridine ring leading to the formation of compound **217**. This compound can then possibly lose S_8 *via* a sulfur chain extension mechanism[302] and form compound **218** which after a nucleophilic attack of a Ph_3P group can give the bisphosphine compound **214** as final product (Scheme 116).



Scheme 116

After the characterization and identification of all the unknown compounds the reaction was repeated using DCM as solvent at ambient temperature and also at reflux temperature (Table 20). The main product in both cases was the pyrrolopyridine **212** in 60 and 56% yields, respectively, while the iminophosphorane **213** and the imidazopyridinium **214** were obtained only in low yields. Less than four equivalents of Ph_3P (2 and 3 equiv.) led to incomplete consumption of the dithiazolylideneamine **160** which could be recovered in 90 and 85% yields, respectively. More than four equivalents (5-7 equiv.) led to more complex mixtures and unreacted Ph_3P was also isolated from the reaction mixture. Changing the solvent to CCl_4, $CHCl_3$ and CH_2Br_2 gave lower yields of the pyrrolopyridine **212**. In the case of CH_2Br_2 the iminophosphorane **213** was isolated in a higher yield (38%) than in DCM (26%). In the case when CCl_4 was used, the starting dithiazole was very insoluble and no reaction occurred and the starting material was recovered in 95% yield. When the Ph_3P was replaced by other phosphites like $(EtO)_3P$, $(PhO)_3P$ and $(i\text{-}PrO)_3P$ (4-5 equiv.) the reaction hardly progressed and the starting material was recovered in 85-90% yields.

Table 20. Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** (0.13 equiv.) with Ph_3P (4 equiv.).

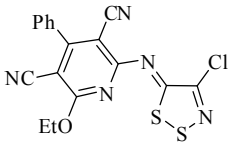


Solvent	Time (d)	Temp. (°C)	Yields (%)					
			Ph_3P=S	**159**	**212**	**213**	**214**	**Ph_3P=O**
DCM	3	20	93	7	60	26	5	74
DCM	1	40	95	21	56	19	4	75
CH_2Br_2	2	20	60	1	49	38	3	48
$CHCl_3$	3	20	60	22	13	11	2	78
CCl_4	3	20	nr[a]	nr[a]	nr[a]	nr[a]	nr[a]	nr[a]

[a] No Reaction, solubility problems

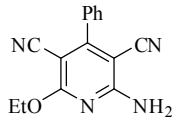
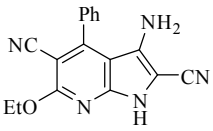
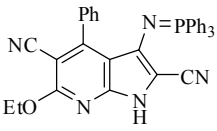
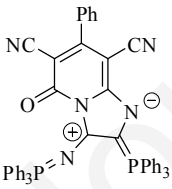
The highest yield of the pyrrolopyridine **212** was obtained when DCM was used as solvent. Also, Ph_3P=O was obtained in 74-78% yield, suggesting that this reaction needed some water. To check this suggestion, the reaction was repeated using freshly distilled DCM and adding equivalents of water to the reaction mixture (Table 21). When no water was added to the reaction mixture, pyrrolopyridine **212** was obtained only in 47% yield whilst iminophosphorane **213** was obtained in 30% yield. When 2 equivalents of water were added to the reaction mixture then the yield of pyrrolopyridine **212** increased to 70% whilst the yield of the iminophosphorane **213** decreased in 17%. Further addition of equivalents of water did not change the product ratios.

Table 21. Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **160** (0.13 mmol) with Ph_3P (4 equiv.) in dry DCM.



160

Ph_3P, DCM → **159, 212-214**

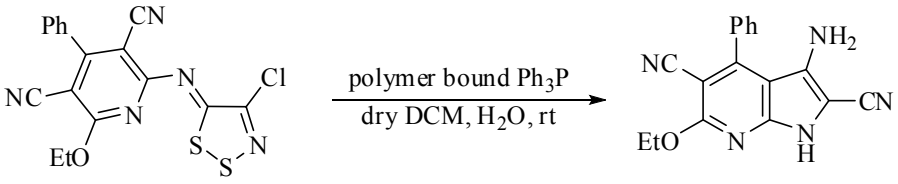
$Ph_3P{=}S$ +  +  +  +  + $Ph_3P{=}O$

159 **212** **213** **214**

Time (h)	H_2O (equiv.)	Temp. (^oC)	Yields (%)					
			$Ph_3P{=}S$	**159**	**212**	**213**	**214**	**$Ph_3P{=}O$**
48	0	20	96	9	47	30	14	62
8	1	20	98	12	55	17	6	75
8	2	20	96	17	70	17	1	78
3	3	20	96	18	63	17	3	80
8	2	40	97	19	57	13	2	85

To avoid the undesirable side products from the Ph_3P ($Ph_3P{=}S$ and $Ph_3P{=}O$), and also try to obtain high yields of the pyrrolopyridine **212**, polymer bound Ph_3P (5 equiv.) was used as reagent. In this case a clean solution of the pyrrolopyridine **212** was obtained by a simple filtration of the polymer. Evaporation of the solvent gave the pyrrolopyridine **212** in 62% yield. Additional amounts of polymer did not however improve the yield of pyrrolopyridine **212** (Table 22).

Table 22. Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **160** (0.13 mmol) with polymer bound Ph_3P in dry DCM in the presence of H_2O (2 equiv.).

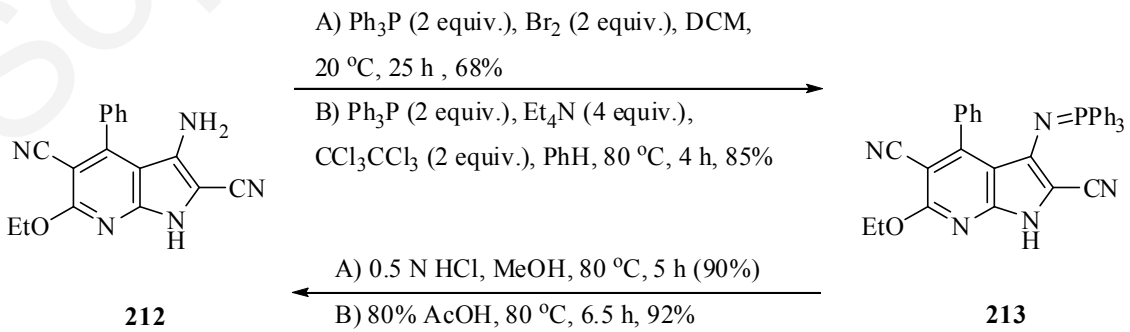


160 **212**

polymer bound Ph_3P (equiv.)	Time (d)	Yield (%)
4	ir[a]	ir[a]
5	3	62
6	3	55

[a]ir Incomplete reaction

Control reactions were performed to see if the pyrrolopyridine **212** could react with Ph_3P forming the iminophosphorane **213** and similarly if the iminophosphorane **213** could hydrolyze to the pyrrolopyridine **212**. Formation of a Ph_3P=N bond is well known in the literature.[308] Reaction of the pyrrolopyridine **212** (0.07 mmol) with either Ph_3P (2 equiv.) in the presence of Br_2 (2 equiv.) in DCM (2 mL) at ambient temperature or either Ph_3P (2 equiv.) in the presence of Et_3N (4 equiv.) and hexachloroethane (2 equiv.) in dry PhH gave the expected iminophosphorane **213** in 68 and 85% yield, respectively. Similarly hydrolysis of the iminophosphorane **213** (0.04 mmol) in the presence of either 0.5 N HCl in MeOH (2 mL) at 80 °C or either in the presence of 80% AcOH (2 mL) at 80 °C gave the expected pyrrolopyridine **212** in 90 and 92% yields, respectively (Scheme 117).



212 **213**

Scheme 117

This is the first time that an indolic system has been observed in the 1,2,3-dithiazole chemistry and so far, there have been only two reports of substituted 3-aminoindole-2-carbonitriles.[304,305] With this in mind and taking into consideration the biological importance of indoles[306] it was decided to investigate further this reaction and try to propose a mechanism for the ring transformation.

6.2.2 Simplification of the Reaction

Simplifying the starting dithiazole could provide useful information for this unusual ring transformation. For the pyrrolopyridine **212** to be formed, the minimum requirement was the presence of a 2-(dithiazolylideneamino)benzonitrile. As such, various 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitriles **142a-h** were prepared from substituted 2-amino-benzonitriles **219a-h** (anthranilonitriles) and Appel salt **42** (Table 23).

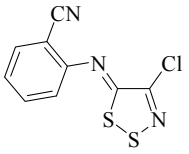
Table 23. Reaction of anthranilonitriles **219a-h** (0.65 mmol) with 4,5-dichloro-1,2,3-dithiazolium chloride **42** (1 equiv.) in DCM at *ca.* 20 °C for 1 h followed by treatment with pyridine (2 equiv.) at *ca.* 20 °C for 2 h.

219a-h **42** **142a-h**

219 (R)	Yields **139** (%)
219a (H)	**142a** (92)
219b (6-Me)	**142b** (91)
219c (5-O_2N)	**142c** (80)
219d (3-Br-5-O_2N)	**142d** (73)
219e (4-Cl)	**142e** (87)
219f (5-Cl)	**142f** (86)
219g (4-MeO)	**142g** (74)
219h (4,5-$(MeO)_2$)	**142h** (76)

The simplest of these analogues 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142a** was treated with Ph_3P under a variety of conditions to determine the optimum conditions for the formation of the expected indole **222a** (Table 24).

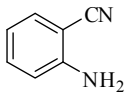
Table 24. Treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142a** (0.20 mmol) with Ph_3P (1-4 equiv.) in dry DCM (2 mL) at *ca*. 20 °C.



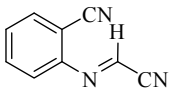
Ph_3P, H_2O → **219-223**

142a

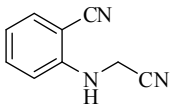
Ph_3P=S



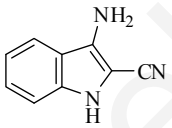
219



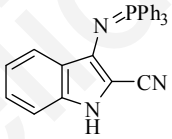
220



221a



222a



223a

Ph_3P=O

Ph_3P (equiv.)	H_2O (equiv.)	Time (min)	Yields (%)[a]							
			Ph_3P	**Ph_3P=S**	**219**	**220**	**221**	**222**	**223**	**Ph_3P=O**
1	2	5	36	42	9	-	-	-	-	44
2	2	5	17	41	8	-	-	-	-	48
3	2	5	-	68	13	-	-	10	11	70
4	0	30	-	86	8	2	6	20	22	81
4	1	5	-	77	11	8	10	40	15	81
4	2	5	-	77	13	7	7	39	16	80
4	3	1	-	77	18	9	7	43	15	77

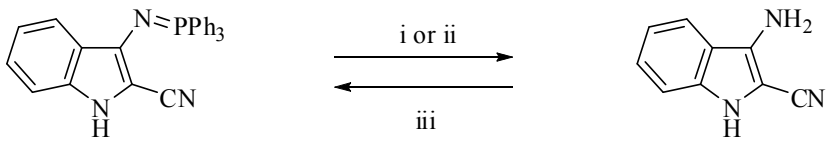
[a] Yields based on recovered starting 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142a**

Treatment of a solution of the dithiazolylideneamine **142a** in dry DCM at *ca.* 20 °C with Ph_3P (4 equiv.) rapidly gave Ph_3P=S, anthranilonitrile **219**, 2-(cyanomethylamino)benzonitrile **221a**, 3-aminoindole-2-carbonitrile **222a**, (2-cyanoindol-3-yl)iminotriphenylphosphorane **223a** and Ph_3P=O. As the equivalents of water added to the reaction mixture were increased, the yield of iminophosphorane **223a** decreased while that of the 3-aminoindole **222a** increased. The overall yields of indoles (**222a** + **223a**) remained relatively steady. Furthermore, a new compound **220a** was isolated in low yield which was relatively unstable and identified as 2-(cyanomethyleneamino)benzonitrile **220a**.

3-Aminoindole-2-carbonitrile **222a** was obtained as light yellow cotton fibers, mp 172-173 °C (from cyclohexane/EtOH). Microanalysis and mass spectrometry supported the formula

$C_9H_7N_3$ [*m/z* (EI) 157 Da (M^+, 100%)]. ^{13}C NMR spectroscopy showed nine separate carbon resonances of which five were quaternary carbons as supported by DEPT studies. The presence of a cyano group was supported by an IR band at $\nu(C\equiv N)_s$ 2212 cm^{-1} and a carbon signal at 116.2 ppm. The most upfield carbon resonance (86.6 ppm) indicated the absence of sp^3 hybridized carbons. ^1H NMR spectroscopy identified two D_2O exchangeable broad resonances integrating 1:2 at 10.67 and 5.71 ppm indicating the presence of 2^o and 1^o amino groups and this was supported by IR bands at $\nu(N\text{-}H)_s$ 3356 and 3309 cm^{-1}. Two possible structures that fitted this data were the known 2-aminoindole-3-carbonitrile (mp 188 ^oC)[312] and the unknown isomer 3-aminoindole-2-carbonitrile **222a**. A comparison of the spectroscopic data eliminated the possibility of the former indole structure that also deviated from the carbon and nitrogen connectivity of the starting (dithiazolylideneamino)benzonitrile.

(2-Cyano-1*H*-indol-3-yl)iminotriphenylphosphorane **223a** was obtained as colourless needles, mp 183-184 ^oC (from PhH). Microanalysis and mass spectrometry gave the formula $C_{27}H_{20}N_3P$ [*m/z* (EI) 417 Da (M^+, 100%)]. The presence of the phosphorous atom was supported by ^{31}P NMR spectroscopy which gave a single phosphorus resonance at 5.48 ppm, typical of a phosphorane. The ^{13}C NMR spectrum was complicated by extensive P-C coupling, however, a total of 13 independent carbon resonances of which six were quaternary (DEPT) could be identified, suggesting the presence of a Ph_3P group. The presence of a cyano group was supported by an IR band at $\nu(C\equiv N)_s$ 2203 cm^{-1} and a carbon signal at 117.4 ppm. The most up field carbon resonance (95.9 ppm) indicated the absence of sp^3 hybridized carbons. ^1H NMR spectroscopy identified only one D_2O exchangeable signal at 10.75 ppm, that was very similar to the indole NH observed in the 3-aminoindole-2-carbonitrile **222a** described above, however stretching frequencies to support this 2^o amino function were notably absent from the IR spectra. Tentatively, the structure of the iminotriphenylphosphorane **223a** was proposed. Confirmation of the assignment was achieved *via* the clean interconversion of iminotriphenylphosphorane **223a** into 3-aminoindole-2-carbonitrile **222a** (Scheme 118).



223a **222a**

Reagents and conditions: (i) 0.5 N HCl, MeOH, 80 °C, 32 h, 93%; (ii) 80% AcOH, 80 °C, 6.5 h, 92%; (iii) Ph_3P (2 equiv.), C_2Cl_6 (2 equiv.), Et_3N (4 equiv.), dry PhH, 80 °C, 6 h, 91%.

Scheme 118

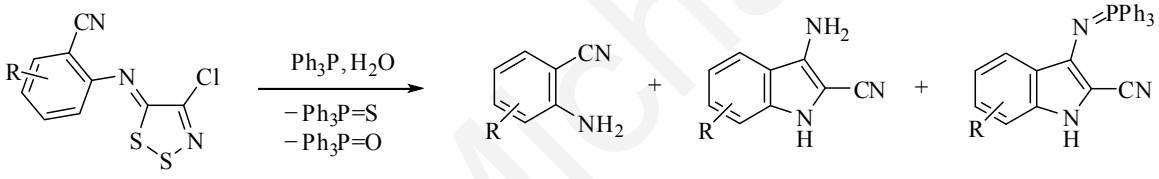
2-(Cyanomethyleneamino)benzonitrile **220a** was obtained as colourless cotton fibers, mp 75-76 °C (from cyclohexane). Microanalysis and mass spectrometry supported the formula $C_9H_5N_3$ [*m/z* 155 Da (M^+, 28%)]. The presence of a cyano group was supported by an IR band at $\nu(C{\equiv}N)_s$ 2234 cm^{-1} and stretching frequencies could not be observed for any 1° or 2° amino functionality. The ^{13}C NMR spectrum showed nine separate carbon resonances of which four were quaternary carbons (DEPT-135 studies). Two of the quaternary signals (δ_C 118.3 and 116.2 ppm) were typical of cyano carbons, tentatively supporting the presence of two nitrile groups. The ^1H NMR spectrum identified five resonances, four of which clearly belonged to aromatic hydrogens (7.78, 7.68, 7.50 and 7.18 ppm) of a 1,2-disubstituted benzene ring. The signal at δ_H 7.63 ppm, however, was observed as a singlet. Based on the above data two possible structures could be proposed which maintained the carbon and nitrogen connectivity of the starting dithiazolylidene **142a**, the 2-(cyanomethyleneamino)benzonitrile **220a** or the quinazoline-2-carbonitrile **224**. Fortunately, the latter compound **224** was known [mp 162-164 °C, ^1H NMR ($CDCl_3$) $\delta_{H\text{-}4}$ 9.55 ppm] and had been prepared *via* an unambiguous route starting from 2-chloroquinazoline.[119]

220a **224**

It was worthy of note that the use of more than4 equivalents of Ph_3P did not give better yields and in the absence of water, the consumption of starting (dithiazolylideneamino)benzonitrile

142a was slow. Furthermore, replacing the Ph_3P with either triethyl-, triphenyl- or triisopropylphosphites led to little or no reaction and the starting dithiazole could be recovered almost quantitatively. Similarly as before the highest yield of the desired indole was obtained when 4 equivalents of Ph_3P were used in dry DCM in the presence of 2 equivalents of water. With this in mind the reaction of the remaining seven (dithiazolylideneamino)benzonitriles with Ph_3P was explored (Table 25). Interestingly the 5-nitro and 4-chloro substituted analogues gave the corresponding indoles in relatively high and useful yields 75 and 71%, respectively. Nevertheless the electron rich methoxy substituted analogues gave little to no yield of indoles. In the case of the 4,5-dimethoxy substituted (dithiazolylideneamino) benzonitrile **142h** the known 2-cyano-4,5-dimethoxy cyanothioformanilide **144h** was isolated in 36% yield together with an unknown compound **225**.

Table 25. Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazolylidenamino)benzonitriles **142a-h** (0.2 mmol) with Ph_3P (4 equiv.) and H_2O (2 equiv.) in distilled DCM (2 mL) at *ca.* 20 °C for 5 min under a $CaCl_2$ drying tube.



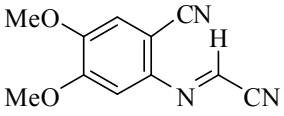
142a-h **219a-h** **222a-h** **223a-h**

142a-g (R)	Yields (%)				
	$Ph_3P=S$	**219a-g**	**222a-g**	**223a-g**	$Ph_3P=O$
142a (H)	74	**219a** (13)	**222a** (39)	**223a** (16)	80
142b (5-O_2N)	99	**219b** (8)	**222b** (75)	**223b** (0)	95
142c (3-Br-5-O_2N)	78	**219c** (43)	**222c** (41)	**223c** (15)	67
142d (4-Cl)	92	**219d** (25)	**222d** (71)	**223d** (0)	93
142e (5-Cl)	96	**219e** (27)	**222e** (32)	**223e** (0)	93
142f (6-Me)	79	**219f** (30)	**222f** (6)	**223f** (0)	65
142g (4-MeO)	79	**219g** (14)	**222g** (7)	**223g** (0)	75
142h (4,5-$(MeO)_2$)[a]	77	**219h** (0)	**222h** (0)	**223h** (0)	81

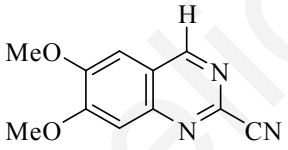
[a] 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **225** and 2-cyano-4,5-dimethoxy cyanothioformanilide **144h** were isolated in 15 and 36% yields, respectively.

Compound **225** was obtained as yellow cotton fibers, mp 170-171 °C (from cyclohexane). Microanalysis and mass spectrometry supported the formula $C_{11}H_9N_3O_2$ [*m/z* (EI) 215 Da (M^+, 100%)]. The presence of a cyano group was supported by an IR band at $\nu(C\equiv N)_s$ 2230

cm^{-1} and stretching frequencies could not be observed for any 1^o or 2^o amino functionality. The ^{13}C NMR spectrum showed 11 separate carbon resonances of which six were quaternary carbons as supported by DEPT studies. Three aromatic CH carbon resonances were identifiable (137.4, 114.5 and 101.8 ppm) and ^1H NMR spectroscopy confirmed the presence of three aromatic H resonances with singlets at 8.17, 7.51 and 7.31 ppm. Two possible structures can be proposed from the above spectroscopy data: The first one is the 2-(cyano-methyleneamino)-4,5-dimethoxybenzonitrile **225** and the second one is the 6,7-dimethoxy-quinazoline-2-carbonitrile **226**.

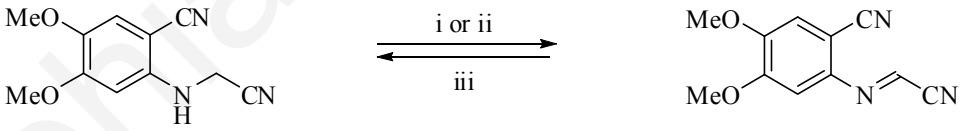


225



226

To verify the correct structure, the two proposed compounds were independently synthesized. Compound **225** was prepared *via* the mild oxidation of 2-(cyanomethylamino)-4,5-dimethoxy-benzonitrile **227** using either NBS or CaOCl,[119] and treatment of 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **225** with $NaBH_4$ in dry MeOH led to its facile conversion back to 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **227** (Scheme 119).

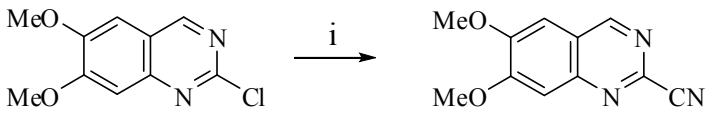


227 **225**

Reagents and conditions: (i) NBS (1 equiv.), $CaCl_2$ (0.5 equiv.), $Ca(OH)_2$ (2.1 equiv.) in CCl_4 at 55 ^oC, 2 d, (32%); (ii) CaOCl (1.5 equiv.), $CaCl_2$ (0.2 equiv.), $Ca(OH)_2$ (2 equiv.) in DCM at rt, 4 d (50%); (iii) $NaBH_4$ (1.2 equiv.) in dry MeOH, rt, 10 min (91%).

Scheme 119

6,7-Dimethoxyquinazoline-2-carbonitrile **226** was prepared from 2-chloro-6,7-dimethoxy-quinazoline **228**[314] using NaCN (2 equiv.) and DABCO (1 equiv.) in DMSO (Scheme 120).[31]



228 **226**

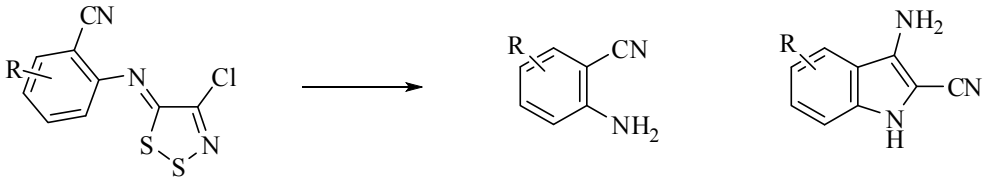
Reagents and conditions: i) NaCN (2 equiv.), DABCO (1 equiv.) in DMSO at 75 ^{o}C, 10 h (38%), or at rt, 7 d, (40%).

Scheme 120

DSC studies (5 ^{o}C/min) of isomers **225** and **226** gave considerably different thermal behaviour; the cyanomethyleneamino **225** gave no melting point and only a decomposition peak at 177.0 ^{o}C (onset 175.4 ^{o}C) while the quinazoline **226** showed a sharp melting point at 303.4 ^{o}C (onset 301.3 ^{o}C) and was followed by an immediate decomposition at 310.3 ^{o}C (onset 305.7 ^{o}C). Furthermore, unlike the cyanomethyleneamine **225** the isomeric 6,7-dimethoxyquinazoline-2-carbonitrile **226** was stable to $NaBH_4$ in dry MeOH. The spectral data of the independently prepared sample of isomer **225** was identical to that isolated from the reaction of (dithiazolylideneamino)benzonitrile **142h** with Ph_3P, confirming the identity of compound **225**.

In light of the reactions complexity, in particular the phosphine side-products, the use of polymer bound Ph_3P was again investigated as an alternative phosphine source. Although significantly more expensive, the use of polymer bound phosphine could give reaction mixtures devoid of "free" Ph_3P=S and Ph_3P=O. Previously, (see Section 6.2.1) the use of at least 5 mol equivalents of polymer bound Ph_3P in the presence of water (2 equiv.) at *ca.* 20 ^{o}C was shown to be advantageous. Under these semi-optimized conditions a variety of substituted 2-(4-chloro-5*H*-1,2,3-dithiazolylideneamino)benzonitriles **142a-h** were reacted with polymer bound Ph_3P (Table 26).

Table 26. Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazolylidineamino)benzonitriles **142a-h** (0.2 mmol) with polymer bound Ph_3P (5 equiv.) and water (2 equiv.) in distilled DCM (2 mL) at *ca.* 20 °C for 24 h.

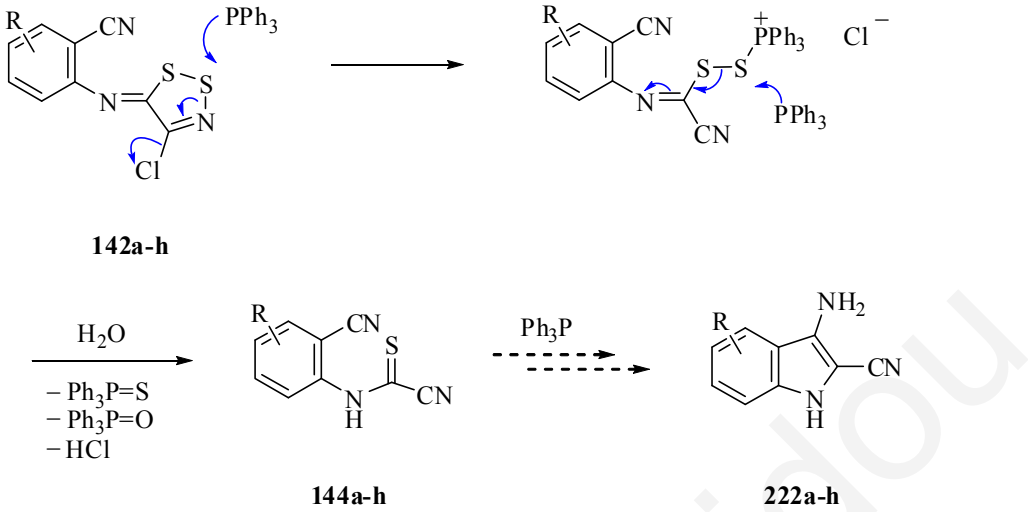


142a-h **219a-h** **222a-h**

	Yields (%)	
142	**219**	**222**
142a (H)	**219a** (7)	**222a** (26)
142b (5-O_2N)	**219b** (5)	**222b** (55)
142c (3-Br-5-O_2N)	**219c** (27)	**222c** (27)
142d (4-Cl)	**219d** (10)	**222d** (39)
142e (5-Cl)	**219e** (8)	**222e** (13)
142f (6-Me)	**219f** (27)	**222f** (27)
142g (4-MeO)	**219g** (36)	**222g** (29)
142h (4,5-$(MeO)_2$)	**219h** (52)	**222h** (0)

The reaction mixtures involving polymer bound Ph_3P were less complex, affording only the desired aminoindolecarbonitriles and some anthranilonitriles. Interestingly, the (dithiazolylideneamino)benzonitriles **142c**,**f-h** gave significant recoveries of the corresponding anthranilonitriles **219c**,**f-h**, respectively. While the use of polymer bound Ph_3P facilitated the chromatographic isolation of the desired indoles the overall yields were poor to moderate.

A potential mechanism for the formation of the 3-aminoindole-2-carbonitriles involved nucleophilic attack by the thiophilic Ph_3P at the S2 atom of dithiazole causing the ring to open and form a mixed disulfide intermediate. A second Ph_3P can then attack the same sulfur atom forming 2-cyano cyanothioformanilide **144a**, which can later transform into the 3-aminoindole compound (Scheme 121).



Scheme 121

According to this suggestion an important intermediate for this reaction was the 2-cyano cyanothioformanilide **144a-h**. However, this compound was not observed during the reaction of (dithiazolylideneamino)benzonitriles **142a-h** with Ph_3P. To investigate its role as an intermediate in the above reactions it was decided to synthesize it and treat it with Ph_3P.

6.3 Synthesis of 2-Cyano Cyanothioformanilides

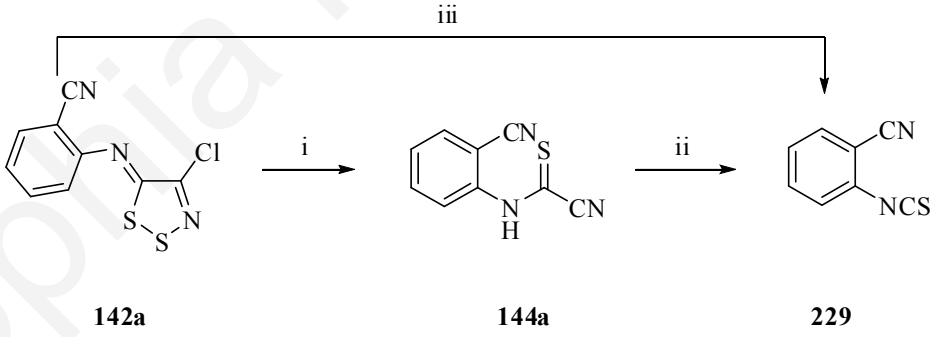
Cyanothioformanilides are traditionally prepared by the reaction of *N*-aryl isothiocyanates with cyanide,[232,234,310-317] or bis(dialkylamino)acetonitriles[318] and also *via* dethiohydration of *N*-aryldithiooxamides,[317,319] thionation-dethiohydration of *N*-arylthiooxalamides,[319] and thionation-dehydration of aryloxalamides.[319] More recent methods involve treating 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzenes with either the oxidising agent *m*-CPBA,[105] the reducing agent $NaBH_3CN$,[110] or with nucleophilic (thiophilic) reagents such as aq. NaOH,[75] NH_2OH,[106] *t*-$BuNH_2$,[107] tryptamine,[111] *o*-aminophenethylamine and *o*-phenylenediamine,[112] triphenylphosphoraneylidenes,[113] Ph_3P in moist DCM[48,49,84,100,108,114-116] and with the use of EtMgBr (1 equiv.).[108,109]

While the use of Ph_3P (2 equiv.) was reported to give good yields of the cyanothioformanilides it was not possible to obtain 2-cyano cyanothioformanilide **144a** from the reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142a** despite the preparation of the 4,5-dimethoxy analogue in high yield.[49] Nevertheless, Kim *et al.*, successfully isolated 2-cyano cyanothioformanilide **144a** from the reaction of the dithiazolylidene **142a** with either

$NH_2OH.HCl$ (4 equiv.) in pyridine at *ca.* 20 °C for 4 h (27%)[106] or as a side product from reaction with phosphorane-ylidenes in low yield (8%).[113]

In our hands the conditions of Kim *et al*.,[106] were successfully reproduced giving the desired 2-cyano cyanothioformanilide **144a** in moderate yield. Replacement of pyridine with other bases (Et_3N, Hünig's base) gave similar yields. However, in the case when DBU was used as base then the desired product was obtained in quantitative yield. It was also found that if the dithiazole **142a** was treated only with DBU in the absence of $NH_2OH.HCl$ again the desired product was obtained in quantitative yield, indicating that in this case $NH_2OH.HCl$ was not necessary. This result was notable and required further study.

Treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142a** with only DBU (3 equiv.) in DCM at *ca.* -5 °C gave near quantitative conversion of the dithiazole **142a** into 2-cyano cyanothioformanilide **144a** and no sulfur formation could be observed by TLC. The use of an additional equivalent of DBU led to the clean formation of 2-isothiocyanatobenzonitrile **229**, which could also be formed directly from a pure sample of 2-cyano cyanothioformanilide **144a** (Scheme 122). No reaction occurred between the dithiazolylidene **142a** and 3 equiv. of either pyridine, DABCO, DMAP or Et_3N in DCM at *ca.* 20 °C.



142a **144a** **229**

Reagents and conditions: (i) DBU (3 equiv.), DCM, -5 °C, 5 min, 93%; (ii) DBU (1 equiv.), 20 °C, 0.5 h, 95%; (iii) DBU (4 equiv.), DCM, -5 to +20 °C, 0.5 h, 96%.

Scheme 122

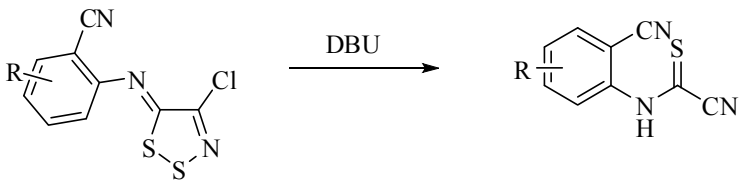
The high yielding formation of the isothiocyanate **229** was worthy of note; since 1995 only four reports have appeared on the conversion of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzenes into *N*-aryl isothiocyanates. These have involved the use of either

m-CPBA,[107] EtMgBr (2 equiv.) in hot dry THF under argon atmosphere,[100,108,109] or NaH (2.2 equiv.) in dry THF at 67 °C for 18 h.[108] Furthermore, only two methods have appeared on the conversion of cyanothio-omanilides into *N*-aryl isothiocyanates using either EtMgBr (2 equiv.) in hot dry THF under argon atmosphere,[108,109] or in neat 2,6-lutidine using microwave irradiation.[108] Despite this, the conversion of the cyanothioformanilide **144a** into the isothiocyanate **229** in the presence of DBU (1 equiv.) was not surprising. A quick screen of alternative 3° amine bases (1 equiv.) in DCM at *ca.* 20 °C showed that pyridine was unreactive, DABCO or DMAP led to incomplete conversion after 2 d, and that Et_3N could affect the conversion slowly (10 h) to give the isothiocyanate **229** in 65% yield. The unusual reactivity of dithiazole towards DBU was however, at first unclear. None of the alternative bases screened (pyridine, DABCO, DMAP, and Et_3N) under similar reaction conditions (base 3 equiv. at *ca.* 20 °C in DCM) showed any reactivity.

DBU and DBN are commonly used to effect base induced dehydrohalogenations and other eliminations to produce C-C and C-heteroatom multiple bonds.[118] As such these bicyclic amidines are often referred to as non-nucleophilic strong bases.[119] Nevertheless, a careful search of the literature revealed multiple reports of nucleophilic behaviour for both DBU and DBN, notably in reactions with either phosphorus[119-132] or carbon[133-148] electrophiles to afford adducts sporting new N-P and N-C bonds, respectively. On the basis that under identical conditions DMAP failed to react with the 1,2,3-dithiazole **142a** it can be qualitatively said that DBU was a more powerful nucleophile, or at least more thiophilic towards the dithiazolylidene **142a**. Similar differences between the reactivity of DMAP and DBU have been reported.[320] The enhanced nucleophilicity was not altogether unsurprising considering the enamine like character of the bicyclic amidine.[321-322]

In general the reaction of the dithiazoles **142a-h** with DBU (3 equiv.) at *ca.* -5 °C gave rapidly the desired 2-cyano cyanothioformanilides **144a-h** in high yield (Table 27). In a couple of examples where the yield was significantly lower than 90% the reactions could be initiated at *ca.* -78 °C and under these conditions the products were obtained in yields > 90%. The only exception was the 3-bromo-(dithiazolylideneamino)-5-nitrobenzonitrile **142c** which gave complex reaction mixtures even at *ca.* -78 °C and no desired product could be isolated.

Table 27. Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino) benzonitriles **142a-h** (0.40 mmol) with DBU (3 equiv.) in dry DCM (2 mL).

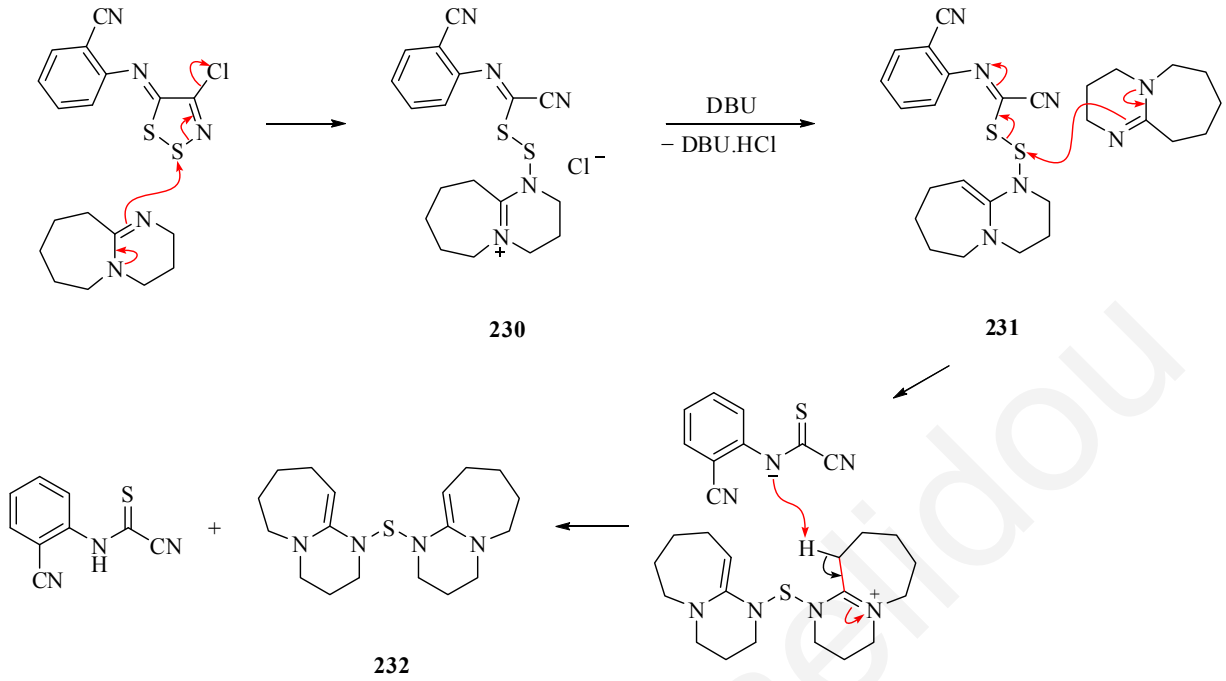


142a-h **144a-h**

142	Temp. (ºC)	Time (min)	Yields **144** (%)
142a (H)	-5	5	**144a** (93)
142b (5-O_2N)	-5	10	**144b** (69)
142b (5-O_2N)	-78 to + 20	45	**144b** (93)
142c (3-Br-5-O_2N)	-78 to + 20	60	**144c** (nd)[a]
142d (4-Cl)	-5	15	**144d** (82)
142d (4-Cl)	-78 to + 20	35	**144d** (91)
142e (5-Cl)	-5	15	**144e** (87)
142f (6-Me)	-5	5	**144f** (94)
142g (4-MeO)	-5	15	**144g** (95)
142h (4,5-$(MeO)_2$)	-5	15	**144h** (88)

[a] No isolable product could be optained

A potential mechanism involves nucleophilic attack *via* the DBU amidine nitrogen at the dithiazole S2 ring sulfur and subsequent ring opening affords the mixed disulfide **230**. A second equivalent of DBU could then abstract HCl to give the neutral disulfide **231**. Further nucleophilic attack by a third equivalent of DBU could cleave the disulfide S-S bond to ultimately give the cyanothioformanilide and the neutral sulfane **232** (Scheme 123).



Scheme 123

It is worthy of note that the sulfane sulfur could migrate from N to C6 and similar N-P to C6-P migrations have been reported with DBU adducts.[128] While isolation of the anticipated sulfane **232** was unsuccessful, the need of 3 equivalents of DBU was confirmed, since the use of less equivalents gave incomplete conversion of the starting dithiazolylidene. The absence of S_8 from the reaction mixture tentatively added support to the entrapment of the sulfur possibly as the sulfane.

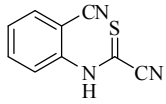
6.3.1 Reaction of 2-Cyano Cyanothioformanilides with Ph_3P

After succeeding the high yielding synthesis of the desired 2-cyano cyanothioformanilides **144a-h** the next step was to treat a pure sample of 2-cyano cyanothioformanilide **144a** (R = H) with Ph_3P to determine whether it was a possible intermediate in the dithiazole to indole conversion.

Treatment of a solution of the cyanothioformanilide **144a** in dry DCM at *ca.* 20 ^{o}C with Ph_3P (2 equiv.) gave the same products as the reaction of (dithiazolylidneneamino)benzonitrile **142a** with Ph_3P. Similarly as before, increasing the equivalents of water added to the reaction mixture the yield of iminophosphorane **223a** decreased while that of the 3-aminoindole **222a**

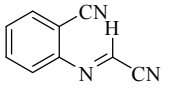
increased. This reaction however, was optimized further with respect to solvent (PhH, PhMe, MeOH) (Table 28).

Table 28. Reaction of cyanothioformanilide **144a** with Ph_3P (2 equiv.) under a $CaCl_2$ drying tube.

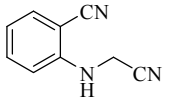


144a

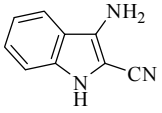
Ph_3P (2 equiv.) → Ph_3P=S, **220**-**223**, Ph_3P=O



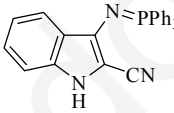
220a



221a



222a



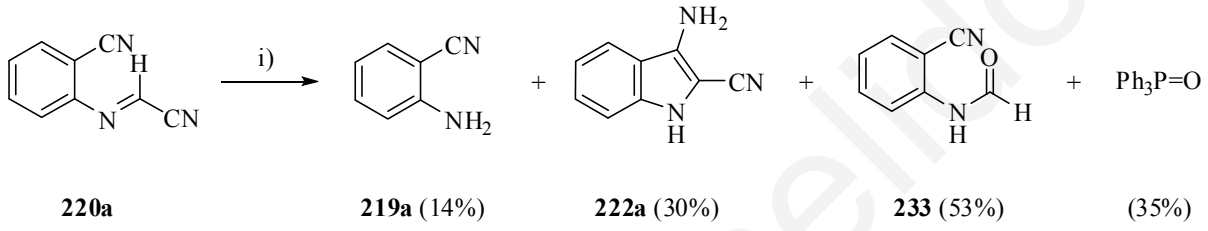
223a

H_2O (equiv.)	Solvent	Temp. (^oC)	Time (min)	Yields (%) **Ph_3P=S**	**220a**	**221a**	**222a**	**223a**	**Ph_3P=O**
0	DCM	20	5	78	-	20	-	70	54
1	DCM	20	3	80	-	25	6	63	58
2	DCM	20	1	80	7	30	13	50	70
3	DCM	20	1	80	6	25	21	48	71
0	PhH	20	5	84	11	38	3	45	69
0	PhH	40	5	78	5	23	1	69	49
0	PhH	80	1	87	6	traces	9	79	34
0	PhMe	20	3	86	6	17	5	68	51
0	PhMe[a]	20	10	79	-	28	58	7	80
0	PhMe	110	1	86	3	5	7	81	32
0	MeOH	20	70	45	9	63	-	23	49
0	MeOH[b]	20	60	69	4	59	5	23	71
0	MeOH[a]	20	50	72	-	9	90	-	80
0	MeOH	60	5	52	5	61	1	27	51

[a] PTSA (1 equiv.) was added to the reaction mixture.
[b] PTSA (5 mol%) was added to the reaction mixture.

When dry PhH or PhMe were used as solvents, increasing the reaction temperature significantly raised the yield of the iminophosphorane **223a** to 79 and 81%, respectively, and gave total indole recoveries (**222a** + **223a**) approaching 90%. In the presence of *p*-toluene-sulfonic acid (PTSA) (1 equiv.) the reaction in PhMe at *ca.* 20 ^oC gave mainly 3-aminoindole-2-carbonitrile **222a** rather than the iminophosphorane **223a**. It was rationalized that the use of a protic solvent such as MeOH could lead to the formation of lesser amounts of indole products and greater amounts of the cyanomethylene **221a** and this was indeed the case although some indole products were still obtained. In this case the addition of catalytic quantity of PTSA (5 mol%) made little difference to the product distribution however, the

addition of PTSA (1 equiv.) gave rather surprisingly 3-aminoindole-2-carbonitrile **222a** in 90% yield. To better understand this result pure samples of compounds **220a**, **221a** and **223a** were dissolved in MeOH and treated with Ph_3P (2 equiv.) and PTSA (1 equiv.) at *ca.* 20 ^oC, respectively. After 24 h of reaction, compounds **221a** and **223a** proved to be stable. Compound **220a**, however, was consumed after 5 h and chromatography gave unreacted Ph_3P (59%), anthranilonitrile **219a** (14%), 3-aminoindole-2-carbonitrile **222a** (30%), *N*-(2-cyanophenyl) formamide **228** (53%) and Ph_3P=O (35%) (Scheme 124).



220a **219a** (14%) **222a** (30%) **233** (53%) (35%)

Reagents and conditions: i) Ph_3P (2 equiv.), PTSA (1 equiv.) in MeOH at rt, 5 h.

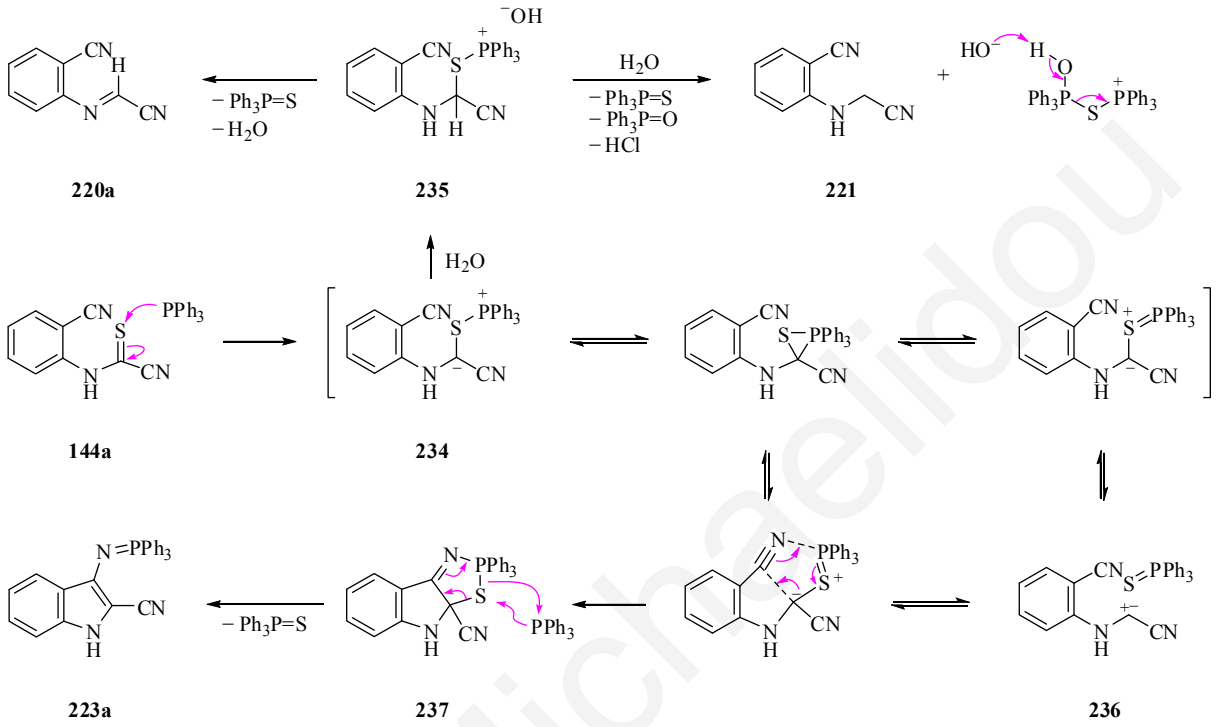
Scheme 124

The identity of the latter compound *N*-(2-cyanophenyl)formamide **233** was confirmed *via* an independent synthesis from anthranilonitrile **219a**, formic acid and zinc oxide according to a known procedure.[327] When the reaction was performed in the absence of Ph_3P, only anthranilonitrile **219a** and *N*-(2-cyanophenyl)formamide **233** were obtained. This unexpected transformation of the dithiazolylidene **142a** into the indole **222a** requires a formal reduction, and this could have been possibly mediated by the Ph_3P.

6.3.2 Mechanistic Rationale

Thiophilic Ph_3P could attack the cyanothioformanilide **144** at sulfur and in the absence of water the zwitterion **234** could form, which would be expected to be in equilibrium with the thiaphosphirane, other ring opened zwitterionic forms and even possibly the carbene. Similar thiaphosphiranes, have previously been proposed[323-327] and recently the first single crystal x-ray structure of a thiaphosphirane was reported.[328] Protonation of the zwitterion **234** could generate a new phophonium species **235** that could then suffer a second attack by Ph_3P on sulfur, followed by protonation, to release the observed (2-cyanomethylamino)benzonitrile **221**. Alternatively, the phosphonium species **235** could eliminate Ph_3P=S to give the observed

imine **220a** although this could also form from the carbene **236** *via* a 1,2-H-shift (Scheme 125).



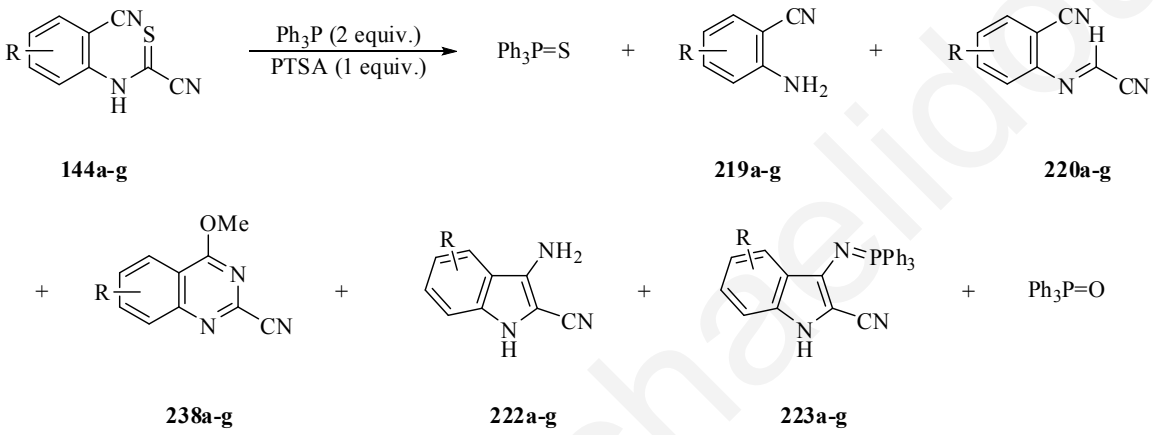
Scheme 125

The formation of the indoles was more speculative. Tentatively the zwitterion **234** could add to the *ortho* cyano group either stepwise or *via* a cycloaddition to yield a heteroarene **237** that could fragment to the iminophosphorane **223a**. Hydrolysis of the iminophosphoranes **223a** can give the observed indole **222a** and it has been shown previously that these two species can be readily inter-converted in high yield. The proposed cycloadditions were tentatively supported by the high iminophosphorane recoveries in PhH and PhMe at reflux while, in MeOH and PTSA (1 equiv.) the possibility that the *ortho*-cyano group was converted into an imidate prior to a stepwise cyclization could explain the high yields of 3-aminoindole-2-carbonitrile **222a**. Attempts to improve the transformation in MeOH by replacing PTSA by mild Lewis acids such as Cs_2CO_3 or $ZnCl_2$ gave mainly (2-cyanomethylamino)benzonitrile **221** in 65-67% yields.

6.3.3 Synthesis of Derivatives

The best conditions for the synthesis of the 3-aminoindole-2-carbonitrile **222a** required Ph_3P (2 equiv.) and PTSA (1 equiv.) in the presence of MeOH at *ca.* 20 °C. These conditions were subsequently used for the synthesis of the 3-aminoindole-2-carbonitriles **222b-g** (Table 29).

Table 29. Reaction of cyanothioformanilides **144a-g** with Ph_3P (2 equiv.) in the presence of PTSA (1 equiv.) in wet MeOH at rt under a $CaCl_2$ drying tube.



144a-g **219a-g** **220a-g**

238a-g **222a-g** **223a-g**

144a-g (R)	Time (h)	**Ph_3P=S**	**219**	**220**	**238**	**222**	**223**	**Ph_3P=O**
144a (R = H)	0.17	72	**219a** (8)	**220a** (0)	**238a** (0)	**222a** (90)	**223a** (0)	80
144b (R = 4-O_2N)	1	77	**219b** (24)	**220b** (0)	**238b** (0)	**222b** (40)	**223b** (21)	78
144b (R = 4-O_2N)	6	80	**219b** (25)	**220b** (0)	**238b** (0)	**222b** (65)	**223b** (0)	77
144d (R = 5-Cl)	1	82	**219d** (26)	**220d** (0)	**238d** (0)	**222d** (72)	**223d** (0)	81
144e (R = 4-Cl)	1	68	**219e** (0)	**220e** (0)	**238e** (23)	**222e** (75)	**223e** (0)	76
144f (R = 3-Me)	1	80	**219f** (24)	**220f** (0)	**238f** (0)	**222f** (75)	**223f** (0)	82
144g (R = 5-MeO)	1	80	**219g** (37)	**220g** (0)	**238g** (0)	**222g** (63)	**223g** (0)	76
144h (R = 4,5-$(MeO)_2$)	1	59	**219h** (27)	**220h** (0)	**238h** (19)	**222h** (0)	**223h** (0)	62
144h (R = 4,5-$(MeO)_2$)	1[a]	52	**219h** (0)	**220h** (23)	**238h** (0)	**222h** (0)	**223h** (31)	50

[a] The reaction took place in PhMe at reflux.

In nearly all cases the expected 3-aminoindole-2-carbonitriles **222a-g** were formed together with Ph_3P=S, Ph_3P=O and some recovered substituted anthranilonitriles **219a-g**. Some anomalous results were evident: First, the 2-cyano-4-nitro substituted cyanothioformanilide **144b** gave a mixture of 3-amino-5-nitroindole-2-cabonitrile **222b** (40%) together with the iminophosphorane **223b** (21%) but extending the reaction time to 6 h led to the latter's conversion into the 3-amino-5-nitroindole-2-cabonitrile **222b** (65%). Secondly, the 4-chloro-

2-cyano cyanothioformanilide **144e** gave a moderate yield of 6-chloro-4-methoxyquinazoline-2-carbonitrile **238e** (23%). Finally, and the most notable exception, 2-cyano-4,5-dimethoxy-phenyl cyanothioformanilide **144h** gave 4,5-dimethoxyanthranilonitrile **219h** (30%) and 4,6,7-trimethoxyquinazoline-2-carbonitrile **238h** (19%) and no indole products in MeOH. Nevertheless, in anhydrous PhMe at reflux, in the absence of PTSA, 2-cyano-4,5-dimethoxyphenyl cyanothioformanilide **144h** gave some (2-cyano-5,6-dimethoxyindol-3-yl)-iminotriphenylphosphorane **223h** (31%) together with some 2-(cyano-methyleneamino)-4,5-dimethoxybenzonitrile **220h** (23%). While the 4-methoxy substituted quinazoline-2-carbonitriles have been previously prepared from cyanothioformanilides simply on treatment with base in MeOH.[98]

Since the byproducts from the transformation of 2-cyano cyanothioformanilide **144** into 3-aminoindole-2-carbonitrile **222** were in most cases similar or identical to those isolated from the dithiazolylidene **142** to indole **222** transformation it can be postulated that the latter transformation involved a cyanothioformanilide intermediate or at least a closely related structure. The overall yields of the cyanothioformanilide to indole conversion were notably higher (63-90%) than those reported for the related dithiazolylidene reaction (7-75%), presumably owing to a shorter reaction pathway. Despite this, the dimethoxy substituted cyanothioformanilide **144g** gave very low yields of indoles [**222g** (0%), **223g** (31%)], similar to the analogous dithiazolylidene reaction. Electron donating substituents such as methoxy groups clearly did not favor the formation of the anticipated indoles.

6.4 Summary

Fully substituted 2-(dithiazolylideneamino)pyridine **160** reacted with Ph_3P in dry DCM in the presence of water (2 equiv.) to give 2-aminopyridine **159**, the 3-aminoindole-2-carbonitriles **212**, (2-cyanoindol-3-yl)iminotriphenylphosphorane **213** and 6-cyano-5-oxo-7-phenyl-2,5-bis(tri-phenylphosphino)imidazo[1,2-*a*]pyridin-4-ium-1-ide **214**. A range of 3-aminoindole-2-carbonitriles **222** were synthesized in moderate to good yields starting from the analogous (dithiazolylideneamino)benzonitriles **142a-h**. The unexpected formation of 3-aminoindole-2-carbonitiriles **222** through the 1,2,3-dithiazole chemistry opens the doors for further mechanistic studies as well as towards the synthesis of new heteroaromatic systems.

Moreover it an important intermediate for the dithiazolylidene to indole transformation was tentatively identified as 2-cyano cyanothio-formanilide **144a**. Seven 2-cyano cyano-thioformanilides **144a-h** were synthesized in high yields from dithiazolylidenes **142a-h** using DBU in dry DCM at low temperatures (0 or -78 ^{o}C). In almost all cases treatment of 2-cyano cyanothioformanilides **144** with Ph_3P (2 equiv.) and TsOH (1 equiv.) in MeOH at rt gave the analogous indoles in high yields. Dimethoxy dithiazolylidene **144h**, which was the exception, did not give the expected indole product but gave 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **225**. This compound was also independently synthesized. DBU was found to be a very important thiophilic reagent. Future work could focus on the synthesis of 6-cyano-5-oxo-7-phenyl-2,5-bis(triphenylphosphine)imidazo[1,2-*a*]pyridine-4-ium-1-ide **214** and its mechanism of formation.

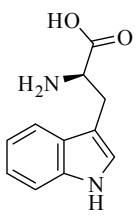
CHAPTER 7

Independent Synthesis of 3-Aminoindole-2-carbonitriles

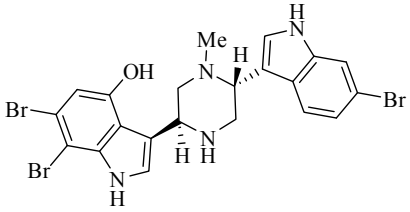
Sections

7.1 Introduction

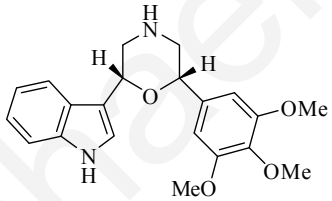
Surprisingly, the reaction of 2-(4-chloro-5*H*-1,2,3-dithiazolylideneamino)benzonitriles **142a-h** or 2-cyano cyanothioformanilides **144a-h** with Ph_3P gave 3-aminoindole-2-carbonitriles **222a-h** (Chapter 6). 3-Aminoindole-2-carbonitriles are potentially useful building blocks since indoles are important in both the biological[306,331-338] and material sciences.[1,339-341] Furthermore, many natural products contain the indole ring system,[342,343] [*e.g.*, the amino acid tryptophan, (precursor of neurotransmitter serotonin),[344] Dragmacidin (cytotoxic),[345] and Chelonin A (anti-inflammatory)].[346] Several indole derivatives are also well known commercial dyes, the most famous example being Indigo (blue colour in jeans),[306] and also natural pigments (*e.g.*, melanin).[347,348]



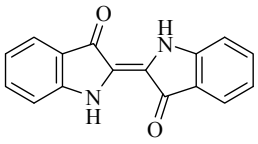
Tryptophan



Dragmacidin

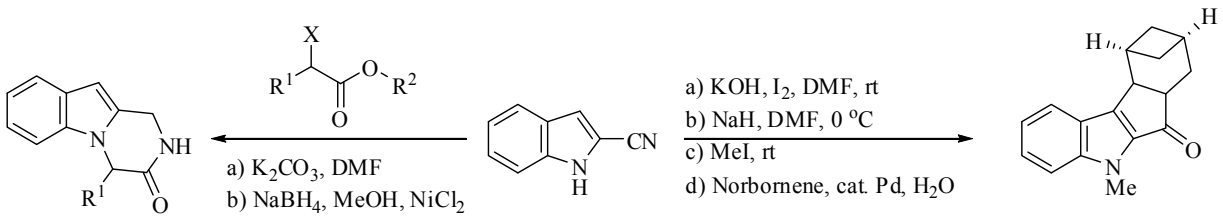


Chelonin A



Indigo

More specifically, several substituted 2-cyanoindoles are important intermediates in the synthesis of biologically active compounds,[349,350] they are components of fragrances[351] and they are used to prepare larger heteroarenes. For example, treatment of 2-cyanoindole **239** with a substituted propanoate in the presence of K_2CO_3 and $NaBH_4$ leads to the formation of the pyrazino[1,2-*a*]indol-3(4*H*)-one **240**[352] while treatment with KOH, NaH, MeI and norbornene leads to the formation of the heterocyclic annulation product **241**,[353] whose skeleton is related to that of a key intermediate in the synthesis of a natural product, yuehchukene, and its analogues[354] (Scheme 126).

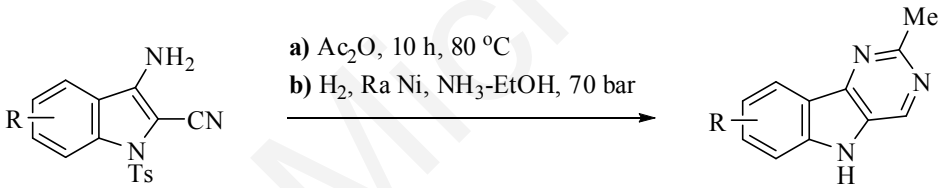


240 (60-65%) **239** **241** (77%)

a. R^1 = Me, R^2 = Et, X = Br or OH;
b. R^1 = Ph, R^2 = Me, X = OMs;

Scheme 126

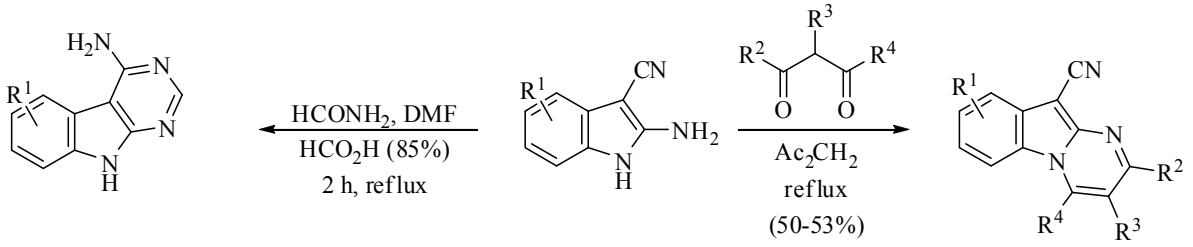
In addition, 3-amino-1-tosylindole-2-carbonitriles **242** have been used as building blocks for pyrimido[5,4-*b*]indoles (Scheme 127).[305] These compounds can be used to treat diseases of the central nervous system *e.g.*, insomnia, anxiety, unrest, fear, epilepsy and seizures.[355] They also find uses as analgesics, vasodilators, antihypoxants, anti-inflammatory agents and inotropics.[87,356]



242 **Pyrimido[5,4-*b*]indoles**

Scheme 127

Interestingly, the isomeric 2-aminoindole-3-carbonitriles **243** are more readily available,[307,357-359] and are useful scaffolds for the construction of pyrimido[1,2-*a*]indoles,[360] and pyrimido[4,5-*b*]indoles (Scheme 128).[358,361-363] Different derivatives of these compounds can find uses as medicines against oxidative stress[364] and HIV,[365] as cytotoxic agents,[365] as neuroprotective,[366] as antioxidants[367] and as adenosine receptors.[362,368]



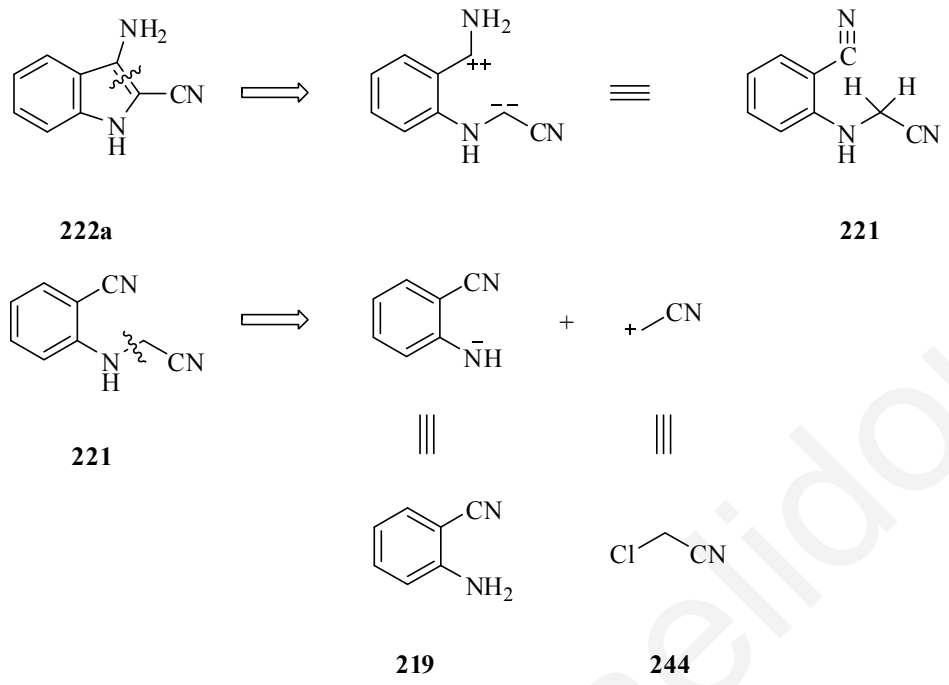
Pyrimido[4,5-*b*]indole **243** **Pyrimido[1,2-*a*]indole**

$R^1 = O_2N$; R^2 = Me, CF_3; R^3 = H, Et; R^4 = Me, OEt, OH

Scheme 128

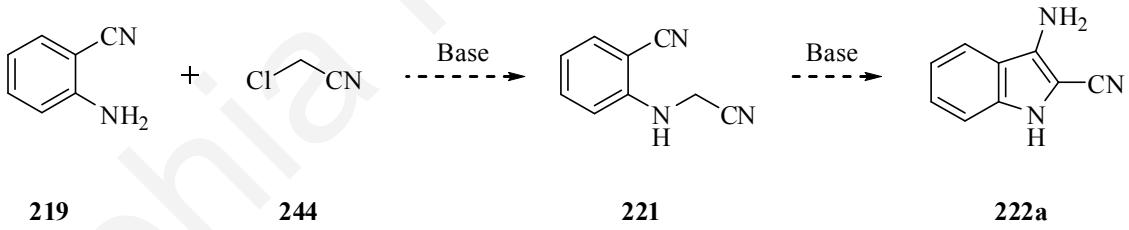
The formation of 3-aminoindole-2-carbonitriles **222** *via* dithiazole chemistry was of mechanistic interest but from a preparative stand point had two main disadvantages: 1) the formation of side products and 2) the need for chromatography. Furthermore, electron rich derivatives such as the dimethoxyindole **222g** could not be prepared in good yields. For this reason it was decided to develop an independent synthetic route that could provide access to the electron rich analogues and give the expected products in high yields.

Retrosynthesis of the 3-aminoindole-2-carbonitrile **222a** revealed a potential Thorpe-Ziegler cyclization of the cyanomethylene **221** that can come from anthranilonitrile **219** (Scheme 129).



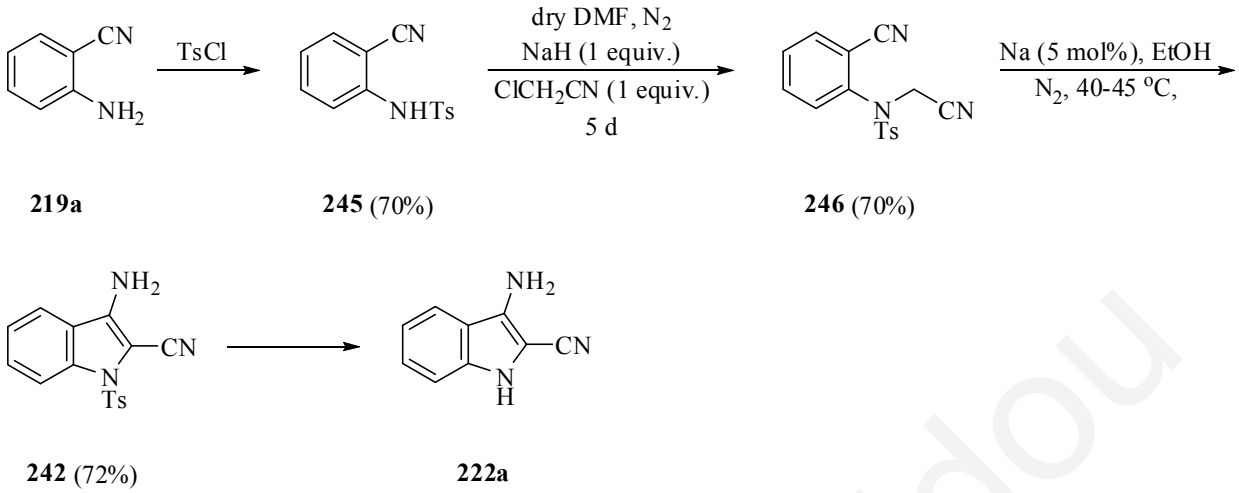
Scheme 129

The forward synthesis could involve the reaction of 2-aminobenzonitrile **219** (anthranilonitrile) with chloroacetonitrile **244**, forming the cyanomethylene **221** cyclization of which can afford 3-aminoindole-2-carbonitrile **222a** (Scheme 130).



Scheme 130

Fortunately, a 4-step synthesis of 3-aminoindole-2-carbonitrile **222a** similar to that proposed above was reported.[304] In the first step anthranilonitrile **219a** was protected with TsCl while in the second step cyanomethylation was achieved using chloroacetonitrile **244** and NaH in dry DMF. The third cyclization step was carried out with Na in dry THF. Experimental details of the fourth deprotection step, removal of the tosyl group (Scheme 131), however, were not described, neither was data provided to support the identity of the 3-aminoindole-2-carbonitrile **222a**.

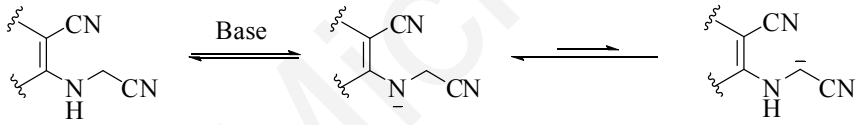


219a **245** (70%) **246** (70%)

242 (72%) **222a**

Scheme 131

The protection of the amino group in the first step was essential for the cyclization reaction to take place since the anion formed by the base abstraction of the NH proton was more stable than the methylide (Scheme 132).[369,370]



Scheme 132

7.2 Synthesis of 3-Amino-1-tosyl-1*H*-indole-2-carbonitrile

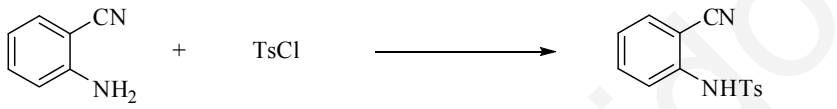
7.2.1 Protection of 2-Aminobenzonitrile using TsCl

Direct cyanomethylation of 2-aminobenzonitrile **219a** was attempted using chloroacetonitrile **244**. 2-Aminobenzonitrile **219a** (0.42 mmol) was treated with chloroacetonitrile **244** (1 equiv.) in the presence of base (Et_3N, Hünig's base, DBU, KH) in different solvents (DCM, THF, EtOH). In almost all cases no desired product was obtained and the starting material was recovered in 90-95% yield, or as in the case with Et_3N (2 equiv.) in EtOH at reflux a brown baseline was observed possibly belonging to the formation of salts.

After failing to achieve the direct cyanomethylation of 2-aminobenzonitrile **219a** using chloroacetonitrile **244**, it was decided to follow the literature procedure and mono *N*-tosylate.[371,372] The reaction of 2-aminobenzonitrile **219a** (8.47 mmol) and TsCl (1 equiv.) in refluxing EtOH (10 mL) in the presence of Et_3N (1 equiv.) gave no reaction and the starting

material was recovered in 90% yield. Reaction of 2-aminobenzonitrile **219a** (8.47 mmol) and TsCl (1 equiv.) in solventless (neat) conditions either using conventional or microwave heating gave the desired product in moderate yields but some starting material was always recovered.[373] Using pyridine as solvent at 100 °C led to full consumption of the 2-amino-benzonitrile **219a** and provided the desired product **245** in high yield (87%)[373-379] (Table 30).

Table 30. Reaction of 2-aminobenzonitrile **219** (8.47 mmol) and TsCl (1 equiv.).



219 **245**

TsCl (equiv.)	Temp. (°C)	Pressure (Psi)	Time (min)	Solvent	Conditions	Yields (%) **219**	**245**
0.65	145	66	20	neat	Microwave Reactor	20	65 (68)[a]
0.65	117	115	20	neat	Microwave Reactor	14	80 (86)[a]
0.65	187	285	20	neat	Microwave Reactor	Traces of products	
0.65	120	0	20	neat	Microwave Reactor	12	75 (77)[a,b]
1	150	0	30	neat	Conventional Heating	4	58 (61)
1	200	0	30	neat	Conventional Heating	5	68 (71)
1	100	0	5 h	Pyridine	Conventional Heating	-	87

[a] Based on recovered starting material; [b] Open Vessel.

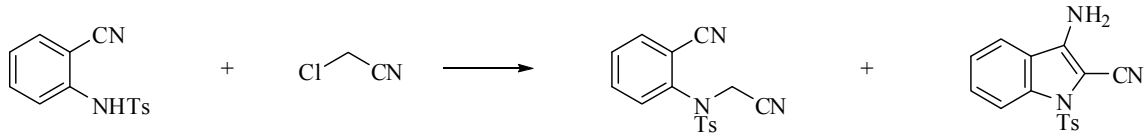
When pyridine was used as solvent, the desired product was obtained after a single extraction with aqueous HCl (5%) to remove the pyridine and subsequent recrystallization (cyclohexane/EtOH) of the residue isolated from the organic phase. No chromatography was needed for a 1 g (8.47 mmol) scale reaction.

7.2.2 Reaction of *N*-(2-Cyanophenyl)-4-methylbenzenesulfonamide with Chloroacetonitrile.

After the successful chromatography free synthesis of *N*-(2-cyanophenyl)-4-methylbenzene-sulfonamide **245** in high yield, the next step was the cyanomethylation (Table 31). When excess chloroacetonitrile **244** was used (120 or 209 equiv.) in the presence of K_2CO_3 (0.5, 1 and 2 equiv.), the desired product was obtained in high yields (88-99%). If less K_2CO_3 (0.1 equiv.) was used then no reaction occurred and the starting material was recovered in 93% yield. When the reaction was carried out in EtOH, a mixture of products was obtained: The less polar product (TLC, R_f = 0.67 hexane/DCM, 1:1) was the expected *N*-(2-cyanophenyl)-4-

methyl-benzene-sulfonamide **246** and the more polar product (TLC, R_f = 0.33, hexane/DCM, 1:4) was the cyclized 3-amino-1-tosyl-1*H*-indole-2-carbonitrile **242**. When the reaction in EtOH was left to proceed for a longer period of time (24 h) then *N*-(2-cyanophenyl)-4-methyl-benzenesulfonamide **246** was transformed completely to 3-amino-1-tosyl-1*H*-indole-2-carbo-nitrile **242** (87%).

Table 31. Reaction of *N*-(2-cyanophenyl)-4-methylbenzenesulfonamide **245** (0.18 mmol) with chloroacetonitrile **244**.



245 **244** **246** **242**

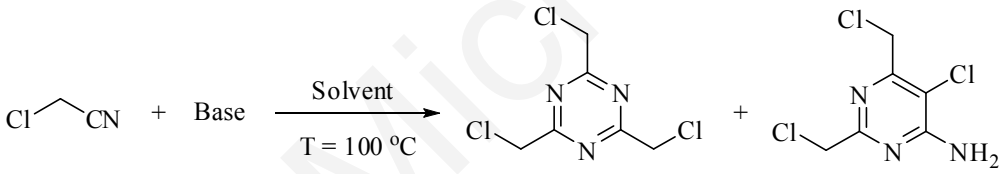
$ClCH_2CN$ (equiv.)	Base (equiv.)	Solvent (mL)	Temp. (°C)	Time (h)	Yields (%) **245**	**246**	**242**
209	-	neat	65	24	-	87	-
209	K_2CO_3 (2)	neat	65	0.5	-	98	-
120	K_2CO_3 (2)	neat	65	40 min	-	93	-
120	K_2CO_3 (2)	DMF[e] (1)	65	24	-	99	-
120	K_2CO_3 (2)	THF (1)	60	48	-	98	-
120	K_2CO_3 (1)	THF (1)	65	1.3	-	95	-
120	K_2CO_3 (2)	EtOH (1)	65	24	-	-	87
120	K_2CO_3 (2)	EtOH (1)	20	12	-	30	54
120	K_2CO_3 (1.5)	EtOH (1)	65	4d	-	23	49
120	K_2CO_3 (1.2)	EtOH (1)	65	48	-	-	81
120	K_2CO_3 (1)	EtOH (1)	65	2	-	91	-
120	K_2CO_3 (0.5)	EtOH (1)	65	48	-	88	-
120	K_2CO_3 (0.1)	EtOH (1)	65	7d	93[a]	-	-
120	Cs_2CO_3 (2)	EtOH (1)	65	24	-[b]	-	-
120	-	EtOH (1)	65	24	83[a]	-	-
60	K_2CO_3 (2)	EtOH (1)	65	24	-	-	88
30	K_2CO_3 (2)	EtOH (1)	65	24	-	-	72
20	Cs_2CO_3 (2)	EtOH (1)	65	48	50[a]	-	-
18	K_2CO_3 (2)	EtOH (1)	65	24	-	-	72
15	Cs_2CO_3 (2)	EtOH (1)	65	24	67[a]	-	-
15	K_2CO_3 (2)	EtOH (0.5)	65	24	-	-	71
15	K_2CO_3 (2)	EtOH (0.25)	65	24	-	-	62
2	Cs_2CO_3 (2)	EtOH (1)	65	24	62[a]	-	-
2	K_2CO_3 (4)	EtOH (1)	65	48	85[a]	-	-
2[c]	K_2CO_3 (2)	DMF[e] (1)	65	1	-	60	-
2[c]	K_2CO_3 (2)	DMF[e] (1)	65	20 min	-	80	-
2[d]	K_2CO_3 (2)	DMF[e] (1)	65	40 min	-	83	-
2[d]	K_2CO_3 (2)	DMF[e] (1)	65	0.5	-	85	-
1[c]	K_2CO_3 (1)	DMF[e] (1)	65	24	-	86	-
1[d]	K_2CO_3 (1)	DMF[e] (1)	65	70 min	-	81	-
1[c]	K_2CO_3 (0.5)	DMF[e] (1)	65	70 min	-	53	-
1[d]	K_2CO_3 (0.5)	DMF[e] (1)	65	2	-	42	-
1[c]	K_2CO_3 (0.25)	DMF[e] (1)	65	3	50[a]	45	-
1[d]	K_2CO_3 (0.25)	DMF[e] (1)	65	6	80[a]	10	-

[a] Recovered Starting Material; [b] Two colourless compounds were obtained; [c] The reaction took place in a microwave reactor (T = 122 °C, P = 12 psi); [d] The rxn took place in a sealed tube; [e] Dry and distilled DMF.

The problem of using excess chloroacetonitrile **244** was overcome by running the reaction either in a sealed tube or in a microwave reactor. In both cases when K_2CO_3 (1 and 2 equiv.) was used as base the desired product was obtained in 81-86% yield. Attempts to decrease the equivalents of base to 0.5 equiv. led to a drop in yield (42-53%) while the use of 0.25 equiv. of base gave incomplete reaction and recovered starting material.

Surprisingly when Cs_2CO_3 (2 equiv.) was used instead of K_2CO_3 in EtOH, the reaction gave two isomeric trimers of chloroacetonitrile, 2,4,6-(trichloromethyl)-1,3,5-triazine **247** and 4-amino-5-chloro-2,6-dichloromethylpyrimidine **248** in low yields. Pure chloroacetonitrile **244** treated with Cs_2CO_3 (2 equiv.) in EtOH at *ca.* 65 °C gave the triazine **247** and pyrimidine **248** in 12 and 4% yields, respectively (Table 32). No reaction was observed when EtOH was replaced by dry THF or when Cs_2CO_3 was replaced by K_2CO_3 in dry THF.

Table 32. Reaction of chloroacetonitrile **244** (1 mL, 15.78 mmol) with base (0.045 equiv.) in different solvents (1 mL) at 100 °C (oil bath).



244 **247** **248**

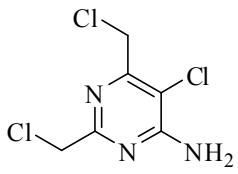
Base	Solvent	Products	
		247	**248**
Cs_2CO_3	EtOH	12	4
Cs_2CO_3	EtOH[a]	15	8
Cs_2CO_3	THF	18	-
Cs_2CO_3	THF[b]	-	-
K_2CO_3	THF[b]	-	-
K_2CO_3	EtOH	-	4
$CsHCO_3$	EtOH	17	4

[a] The concetration of chloroacetonitrile and cesium carbonate was 1:1; [b] Distilled THF

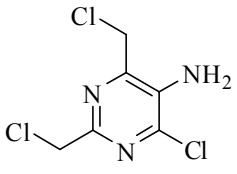
2,4,6-(Trichloromethyl)-1,3,5-triazine **247** was obtained as light yellow prisms, mp 72-73 °C (lit.,[387] 78-79 °C) (from cyclohexane); Mass spectroscopy supported the formula $C_6H_6Cl_3N_3$ [*m/z* (EI) 225 Da (M^+, 78%)]. UV/vis showed a λ_{max} at 271 nm (log ε 2.80). ^{13}C NMR spectroscopy showed only two peaks (175.5 and 45.2 ppm) where the high field one was a

CH_2 absorbtion as supported by DEPT studies. ^{1}H NMR spectroscopy showed only one peak at 4.68 ppm (two hydrogens) supporting the CH_2 group and the symmetry of the compound. IR spectroscopy showed no nitrile stretching frequency. A comparison with the literature data[388] confirmed the structure. Worthy of note was that this compound so far had been prepared *via* the acid catalysed trimerization of imidates[380,382] and this is the first time that the compound formed in the presence of base.

4-Amino-5-chloro-2,6-dichloromethylpyrimidine **248** was obtained as yellow prisms, mp 123-124 ^{o}C. Microanalysis and mass spectrometry supported the same formula as before $C_6H_6Cl_3N_3$ [*m/z* (EI) 225 Da (M^+ 100%)]. UV/vis spectroscopy showed a λ_{max} at 288 nm (log ε 3.76). The ^{13}C NMR spectroscopy showed six separate carbon resonances of which two (46.7 and 43.4 ppm) represented two CH_2 peaks as supported by DEPT studies. ^{1}H NMR spectroscopy identified one D_2O exchangeable broad resonance intergrating two at 5.71 ppm indicating the presence of 2^o amino group and this was supported by IR band at $\nu(NH_2)$ 3381 cm^{-1}. Two structures were possible to represent this compound: 4-Amino-5-chloro-2,6-dichloromethylpyrimidine **248** and 5-amino-4-chloro-2,6-dichloromethyl-pyrimidine **249**. If the compound was 5-amino-4-chloro-2,6-dichloromethyl-pyrimidine **249** then the NH_2 peak could have been appeared as a triplet with a small *J* value because of the presence of the CH_2 in the neighbouring carbon. The ^{1}H NMR spectrum however, showed a broad single peak for the NH_2 peak tentatively indicating that the compound was the 4-amino-5-chloro-2,6-dichloromethylpyrimidine **248**, which does not have any protons near the NH_2. This assumption was further supported with mechanistic rationale and literature data.



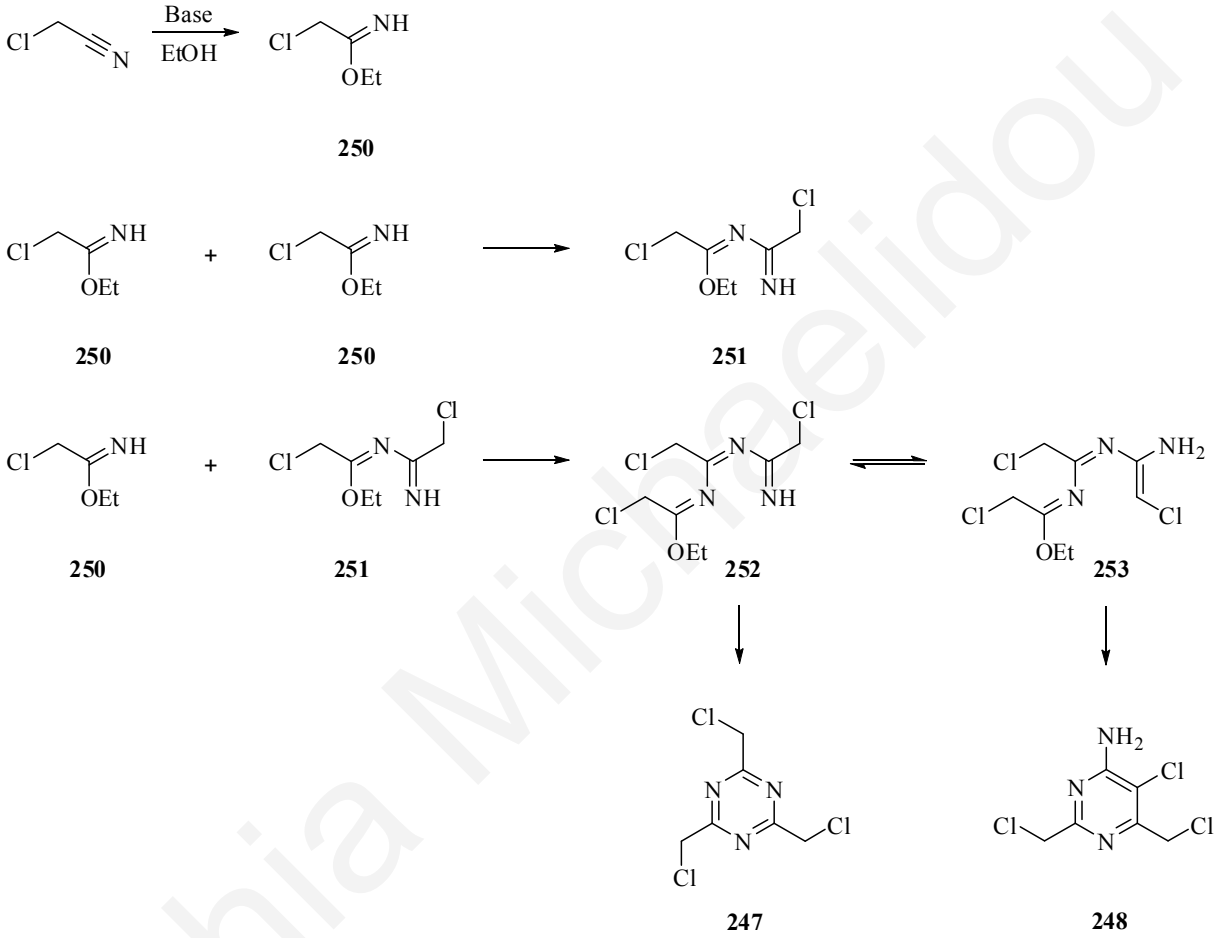
248



249

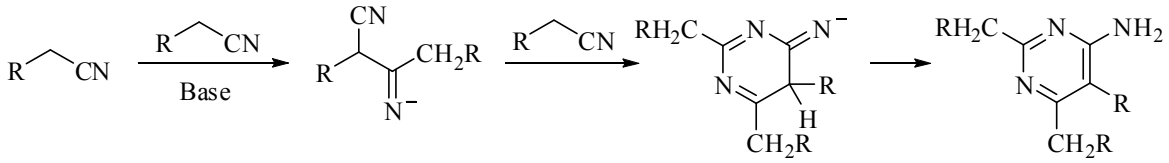
Possible mechanisms for the formation of the two compounds are presented below (Scheme 133). In the first case the base catalysed addition of EtOH to the acetonitrile could afford the imidate **250** which subsequently trimerises to 2,4,6-(trichloromethyl)-1,3,5-triazine **247**. This

reaction could be assisted by the known Lewis acidity of the cesium cations.[383] In THF and in the absence of either water or EtOH neither the triazine **247** nor the pyrimidine **248** were observed. In the second case tautomerization of imidate **251** to afford the enamine **253** leads to formation of 4-amino-5-chloro-2,6-dichloromethylpyrimidine **248** (Scheme 133).



Scheme 133

In the literature examples of similar pyrimidine systems exist and all of them have the amino group in the C4 position, supporting the proposed structure for our compound. For example, under basic conditions nitriles with *a*-hydrogens can self condensate forming *β*-iminonitriles **254** and pyrimidines **255** (Scheme 134).[384]



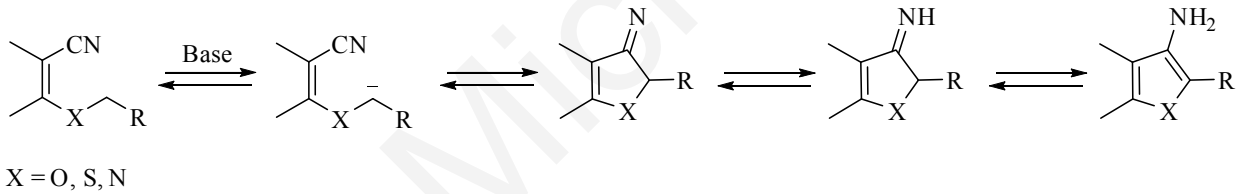
254 **255**

Scheme 134

The above literature data in comparison with the experimental data and the mechanistic rationale support the proposed structure **248** for the pyrimidine system.

7.2.3 Thorpe-Zeigler Cyclization

The base catalysed intramolecular ring closure reaction of *N*-(2-cyanophenyl)-*N*-(*p*-tosyl) aminoacetonitrile **246** to give 3-amino-1-tosylindole-2-carbonitrile **242**, is an example of a Thorpe-Ziegler cyclization (Scheme 135).[385-388]

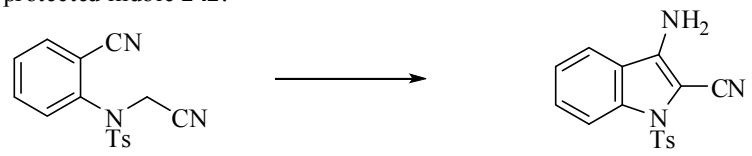


X = O, S, N

Scheme 135

In our hands the cyclization of *N*-(2-cyanophenyl)-*N*-(*p*-tosyl)aminoacetonitrile **246** into 3-amino-1-tosylindole-2-carbonitrile **242** worked well in both DCM and EtOH and was dependant on the nature of the base. Weak amine bases such as pyridine (pK_b = 8.8) and Et_3N (pK_b = 3.2) failed to cyclize *N*-(2-cyanophenyl)-*N*-(*p*-tosyl)aminoacetonitrile **246**, while DBU (0.5 equiv.) (pK_b = 2.0) in EtOH at *ca.* 20 ^oC for 1 h gave the indole **242** in high yield (98%). The use of less DBU (0.25 equiv.) in EtOH at *ca.* 20 ^oC for 4 d however, led to incomplete reaction. In EtOH inorganic bases were superior; alkali metal bicarbonates, carbonates and hydroxide bases worked well, the stronger the base the faster the reaction. The use of only a catalytic quantity of K_2CO_3 (1 mol %) in EtOH at *ca.* 20 ^oC led to a nearly quantitative cyclization in 26 h while, the use of either NaOH or Cs_2CO_3 (2 equiv.) led to a quantitative conversion in *ca.* 1 min (Table 33).

Table 33. Treatment of *N*-(2-cyanophenyl)-*N*-(p-tosyl)aminoacetonitrile **246** (0.16 mmol) with base in different solvents (2 mL) at rt gives as product the *N*-protected indole **242**.



246 **242**

Base (equiv.)	Solvent	Time (h)	Yields (%)
DBN (2)	DCM	7	84
DBN (2)	EtOH	0.5	98
DBU (2)	DCM	144	97
DBU (2)	EtOH	20 min	94
DBU (1)	EtOH	25 min	95
DBU (0.5)	EtOH	1	98
DBU (0.25)	EtOH	96	ir[a]
$NaHCO_3$ (2)	EtOH	27	92
$KHCO_3$ (2)	EtOH	20 min	96
$CsHCO_3$ (2)	EtOH	6	86
K_2CO_3 (2)	EtOH	15 min	96
K_2CO_3 (1)	EtOH	15 min	93
K_2CO_3 (0.5)	EtOH	1	93
K_2CO_3 (0.25)	EtOH	12	92
K_2CO_3 (0.1)	EtOH	18	98
K_2CO_3 (0.05)	EtOH	21	96
K_2CO_3 (0.02)	EtOH	24	97
K_2CO_3 (0.01)	EtOH	26	96
Cs_2CO_3 (2)	EtOH	1 min	91
Cs_2CO_3 (1.5)	EtOH	5 min	78
Cs_2CO_3 (1)	EtOH	10 min	33
NaOH (2)	EtOH	1 min	98
KOH (2)	EtOH	5 min	81
$Cs(OH)_2$ (2)	EtOH	1 min	85

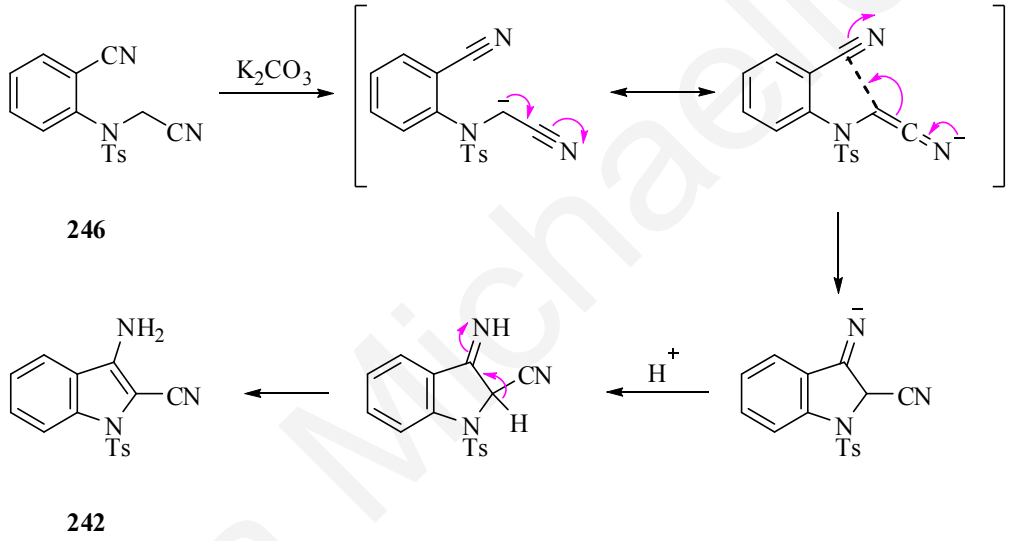
[a] Incomplete reaction.

This was in agreement with the literature were the Thorpe-Ziegler cyclization usually proceeds in the presence of a catalytic amount of an inorganic base.[386] Also, according to the literature *N*-protection of 2-(cyanomethylamino)benzonitrile **221** was necessary for the Thorpe–Ziegler cyclization to work.[371] Similar Thorpe–Ziegler cyclizations of (*Z*)-3-(cyanomethylamino)-

acrylonitriles to afford 3-aminopyrrole-2-carbonitriles also required protection of the amino group since the anion formed by the base abstraction of the NH proton would be more stable than its methylene analogue preventing the cyclization (Scheme 132, Section 7.1).[369,370]

Mechanistic rationale

Base catalysed deprotonation of the acidic methylene, was followed by intramolecular cyclization onto the nitrile to afford the pyrrole ring, which on tautomerization aromatises to give 3-amino-1-tosylindole-2-carbonitrile **242** (Scheme 136).



Scheme 136

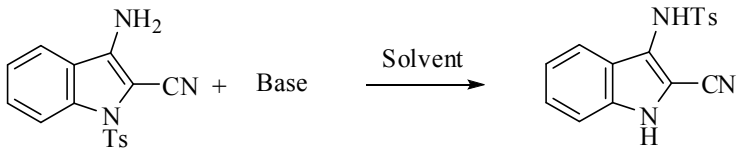
7.2.4 Deprotection Reaction - Mechanistic Rationale

In the literature, a wide range of reagents for detosylation reactions exist, including dissolving metal reductants (Li or Na) in NH_3 (l),[389-393] alcohol or HMPA; LiOH and mercaptoacetic acid in DMF[394] single electron transfer reagents such as sodium napthalenide and the related arenides.[395-405] Na–Hg, n-Bu_3SnH; reducing agents L-Selectride, Red-Al; photolysis.[406,407] Other reagents used for this deprotection are highly nucleophilic, Gilman's reagent $PhMe_2SiLi$,[406] highly basic NaOH (or KOH) in alcohol solvents at high temperatures,[394,408] KF on alumina under microwaves,[409,410] *n*-Bu_4NF in refluxing THF,[411] Mg/MeOH,[412,413] polymer-supported potassium thiophenolate,[414] $HSCH_2CO_2H$/LiOH,[415] strong acids,[389,395,415-419] and

sodium amalgam.[420-422] More specifically, 1-tosylpyrroles have been detosylated using stage I Na_2K-5G catalyst and benzoyl chloride in THF,[423] by using Mg/MeOH in a sonicator,[406] *t*-BuOK in THF,[424] KOH in EtOH,[425] $PhMe_2SiLi$ in THF at 0 ^oC (Gilman's reagent),[394,426] KF/Al_2O_3 in a microwave reactor,[415] thioglycolate in DMF,[394] $TMSC(Li)N_2$ in THF at -78 ^oC,[427] or Cs_2CO_3 in MeOH/THF,[428] or *t*-BuOK in THF.[424] A recent method for detosylation involves constant current electrolysis in DMF containing 0.1 M Et_4NBr as a supporting electrolyte by using a test tube-like undivided cell equipped with a platinum plate cathode and a magnesium rod anode giving quantitative yields of detosylated compounds.[429] *N*-tosylcarbazoles have been detosylated by using strong bases in alkaline solutions[304] or by using photochemical reactions in PhH or MeOH.[430]

In our case acid treatment of the 1-tosylindole **242** with either sulfuric acid (95%), or conc. HCl, or with HBr (48%) in the presence of phenol, or even glacial AcOH or PTSA gave at first no reaction, while prolonged heating led to highly coloured mixtures from which indigo (intense blue colour) could be tentatively identified by TLC against an authentic sample or MS (*m/z* M^+ 262 Da). Reductive cleavage using $NaBH_4$ in MeOH, or $LiAlH_4$ in THF, or treatment with Li dust in THF or Na metal in liquid NH_3/THF also failed to provide the detosylated indole **222a**. Heating 3-amino-1-tosylindole-2-carbonitriles **242** (0.06 mmol) in EtOH (1 mL) in the presence of NaOH or KOH gave 3-(*N*-tosylamino)indole-2-carbonitrile **256a** in low to moderate yields. In contrast K_2CO_3 (1 equiv.) at reflux for 24 h gave only recovered starting material but at *ca.* 100 ^oC (sealed tube), 3-(*N*-tosylamino)indole-2-carbonitrile **256a** was isolated in good yields. In the absence of K_2CO_3, heating the reactions in EtOH at 100 ^oC (sealed tube) led to the recovery of unreacted 1-tosylindole **242** (Table 34).

Table 34. Treatment of 3-amino-1-tosyl-1*H*-indole-2-carbonitrile **242** (20 mg, 1 equiv.) with base (2 equiv.) in different solvents (1 mL).

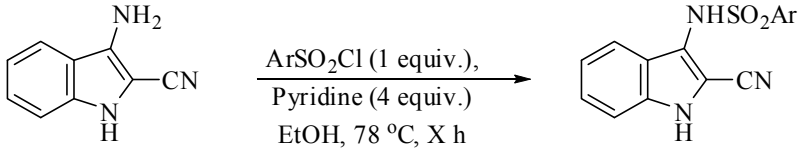


242 **256a**

Base (equiv.)	Solvent	Temperature (^oC)	Time (h)	Yield (%) **256a**
KOH (1.1)	EtOH	60	48	23
KOH (1.1)	MeOH	50	48	45
KOH (2)	EtOH	rt	6 d	62
KOH (2)	EtOH	60	24	44
KOH (3)	EtOH	rt	2	-
KOH (4)	EtOH	rt	1.5	-
NaOH (2)	EtOH	rt	7 d	44
NaOH (3)	EtOH	rt	2.5	-
NaOH (4)	EtOH	rt	1.5	-
LiOH (1.1)	THF	rt	24	56
K_2CO_3 (1)	EtOH	60[a]	5	65
-	EtOH	60[a]	24	-[b]

[a] The rxn took place in a sealed tube; [b] No reaction, recovered SM (95%).

The isomerization could also be achieved when 3-amino-1-tosylindole-2-carbonitrile **242** was treated with DBU (0.2 equiv., 24 h, to 3 equiv., 1 h) in PhH at *ca.* 80 ^oC. However, during these reactions the mixtures became notably green in colour prior to affording 3-(*N*-tosylamino)-indole-2-carbonitrile **256a** in 76–80% yields. The isomerization could not be achieved when DBU was replaced by either pyridine, Et_3N or DMAP (1 equiv.). Furthermore, sulfonylation of 3-aminoindoles with TsCl[431] or 4-aminobenzenesulfonyl chlorides[104] was reported to occur regioselectively on the exocyclic 3-amino to afford the 3-(*N*-sulfonylamino)indoles. Not surprisingly, treating pure sample of 3-aminoindole-2-carbo-nitrile **222a** with TsCl (1 equiv.) and pyridine (4 equiv.) in refluxing EtOH gave the 3-(*N*-tosylamino)indole-2-carbonitrile **256a** in 85% yield, while similar treatment of 3-aminoindole-2-carbonitrile **222a** with $PhSO_2Cl$ gave 3-(*N*-benzenesulfonylamino)indole-2-carbonitrile **256i** in 88% yield (Scheme 137).

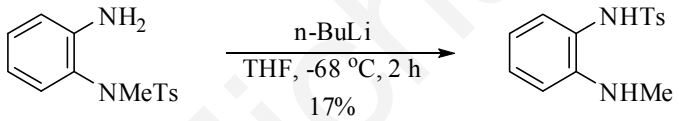


222a

256a, Ar = Tol, R = H (85%), X = 5 h
256i, Ar = Ph, R = H (88%), X = 12 h

Scheme 137

A pure sample of 3-(*N*-tosylamino)indole-2-carbonitrile **256a** treated with DBU in PhH at reflux or with K_2CO_3 in EtOH at reflux was stable, suffering neither isomerization nor detosylation. Only one example of a similar *N* to *N* tosyl migration has been reported on treating N^1-methyl-N^1-tosylbenzene-1,2-diamine **257** with BuLi to afford N^1-methyl-N^2-tosylbenzene-1,2-diamine **258** in low yield (Scheme 138).[433]



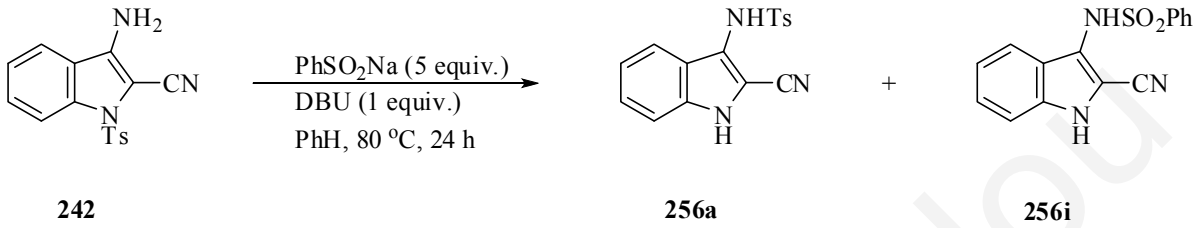
257 **258**

Scheme 138

The indole C2 nitrile was expected to activate the C3 amine towards deprotonation. In the presence of base, a direct tosyl metathesis could occur between the indole nitrogen at N1 and the C3 amine *via* presumably an intermolecular route. However, when the 1-tosylindole **242** was treated with primary aromatic amines or with the strongly nucleophilic secondary amine pyrrolidine (2 equiv.) in EtOH or PhH at reflux no tosyl metathesis was observed and the starting 1-tosyindole **242** could be recovered.

In light of this, it was postulated that the migration involved a base catalyzed elimination of *p*-toluenesulfinate anion to afford 2-cyano-3*H*-indol-3-imine **259**, which then trapped the sulfinate side-product (Scheme 140). DBU is known to promote elimination reactions.[118] The elimination of toluenesulfinate was partially supported when the reaction was repeated in the presence of sodium benzenesulfinate (5 fold excess) since a mixture of 3-(*N*-tosylamino)- and

3-(*N*-benzenesulfonylamino)indole-2-carbonitriles **256a** and **256i** (*ca.* 2:1 ratio by ^{1}H NMR) was obtained. Despite the 5-fold excess of sodium benzenesulfinate, the major isomer was clearly the 3-tosyl-aminoindole **256a** suggesting a possible tight ion pairing (Scheme 139).



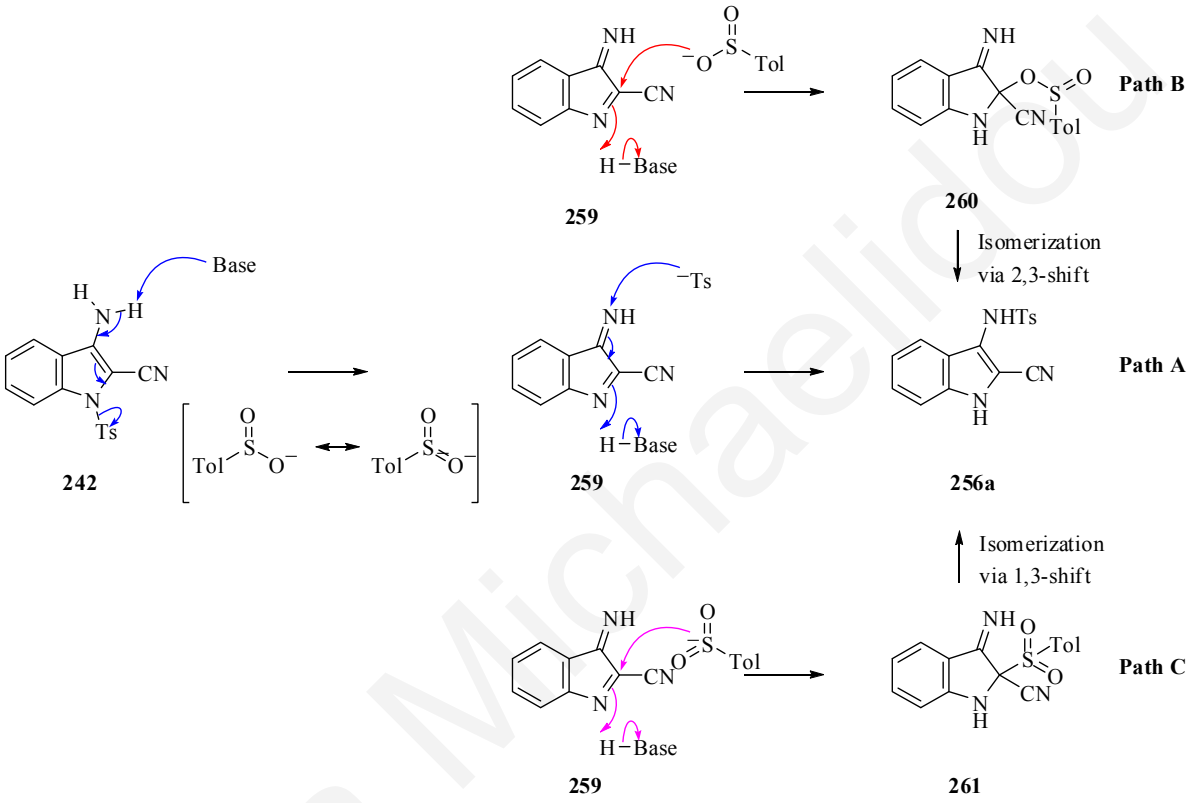
242 **256a** **256i**

Scheme 139

Furthermore, under the reaction conditions both 3-aminoindole-2-carbonitrile **222a** and 3-(*N*-tosylamino)indole-2-carbonitrile **256a** were inert to sodium benzenesulfinate. The reaction supported that base treatment of 3-amino-1-tosylindole-2-carbonitrile **242** released an intermediate, presumed to be the indolimine **259** that reacted rapidly *via* an intermolecular fashion with the arylsulfinate anion formed.

The possibility of recombination of the *p*-toluenesulfinate with the proposed intermediate 2-cyano-3*H*-indol-3-imine **259** was also considered. Since *p*-toluenesulfinates can be nucleophilic *via* oxygen or sulfur[434-438] several possibilities needed to be considered: The simplest (Path A) involved the direct addition of *p*-toluenesulfinate to the indolimine **259** in a manner that mimicked the Michael-type addition of nucleophiles to gramine derived 3-methylene-3*H*-indoles.[439] However, the conflicting local dipole of the exocyclic imine and lone pair repulsion from the imine nitrogen argued against this path. Path B, involved the addition of *p*-toluenesulfinate to the highly electrophilic indole C2 position. Isomerization of the sulfinate ester **260** *via* either a concerted 2,3-sigmatropic rearrangement or *via* a stepwise ion pair process could give the 3-(*N*-tosylamino)indole **256a**. Examples of the rearrangement of allylic sulfinate esters to the allylic sulfones are known[440-448] tentatively supporting the proposed mechanism; however no examples of an analogous rearrangement of iminoethyl sulfinate esters were found. Finally, Path C involved the addition of toluenesulfinate *via* its sulfur to the indole C2 position to afford intermediate **261**, followed by a 1,3-shift to the exocyclic imine. Examples of these types of shifts have also been frequently reported.[449-451]

Despite the prevalence of arylsulfinates to attack *via* sulfur, Path B was advantageous over Path C for two reasons: First a 2,3-shift would require a 5-membered transition state while a 1,3-shift would required a less favourable 4-membered transition state; and second, adduct **260** was less sterically crowded at the indole C-2 position than adduct **261** (Scheme 140).

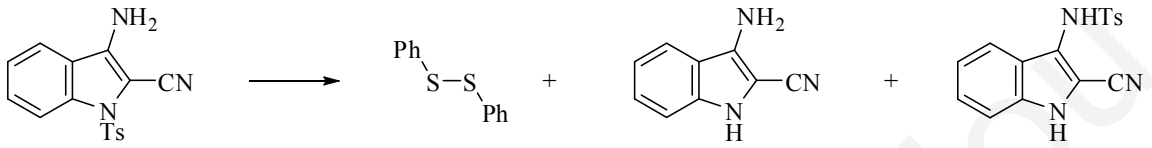


Scheme 140

While the true nature of this migration requires further study, the above studies indicated that the base catalysed deprotection would require reductive conditions. The related 2-aryl-3*H*-indol-3-oximes have previously been reduced using Zn/HCl,[452-453] Pd/H_2,[454] Pt/H_2,[455] sodium hydrosulfite,[456] or ammonium sulfide,[457] and there have been two base catalysed detosylations reported that used thiophenol,[458-459] however, despite the known reducing powers of thiophenol,[460] the authors did not mention the role of the mercaptans. Thiophenol facilitates the denosylation of 1-(*o*-, *p*-nitro substituted arylsulfonyl)indoles *via ipso* nucleophilic aromatic substitution on the nitroarenesulfonamide followed by elimination of the free indole, sulfur dioxide and a (phenyl)(nitrophenyl)sulfide.[461-463] In addition, thioglycolate has been used to detosylate indoles[394] but no support for a mechanism was presented.

Finally, the deprotection of 3-amino-1-tosylindole-2-carbonitrile **242** was achieved in the presence of thiophenol and DBU (Table 35).

Table 35. Deprotection of the 3-amino-1-tosylindole-2-carbonitrile **242** (0.06 mmol) using DBU and PhSH in PhH (2 mL) at 80 °C.



242 **222a** **256a**

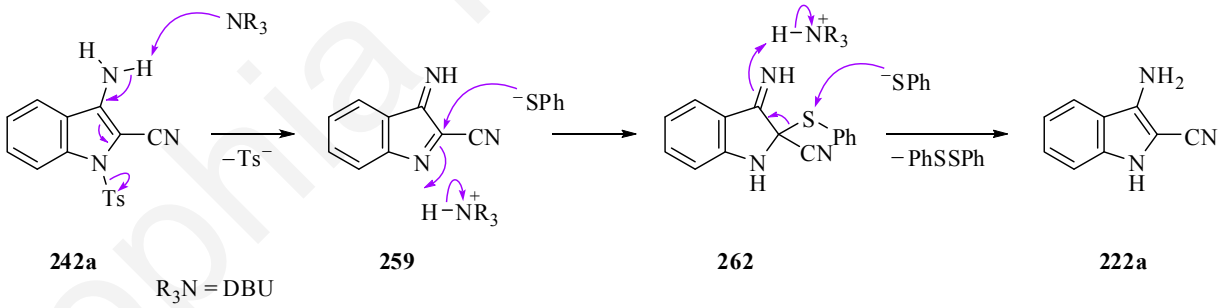
DBU (equiv.)	PhSH (equiv.)	Time (h)	Yields (%) PhSSPhb	**222a**	**256a**
1	1	26	62	27	71
1	2	24	95	40	57
1	3	18	144	60	39
1	4	14	183	85	8
1	5	12	248	92	-
1	5[a]	24	104	88	-
1	2[a]	17	85	89	6
1	2.5[a]	14	93	88	trace
0.5	5	24	183	80	-
0.2	5	32	243	90	-

[a]Dry and degassed PhH was used, and the rxn took place under Argon.
[b]Yield calculated based on the need for 2 x PhSH for the deprotection of 1 x tosylindole.

Treatment of 3-amino-1-tosylindole-2-carbonitrile **242** (0.06 mmol) with DBU and PhSH (1-5 equiv.) in an air atmosphere led to the isolation of detosylated 3-aminoindole-2-carbonitrile **222a** and the 3-(*N*-tosylamino)indole-2-carbonitrile **256a** together with a large quantity of diphenyl disulfide. Increasing the equivalents of PhSH (up to 5 equiv.) led to formation of detosylated indole **222a** in high yield, however, a pure sample of 3-(*N*-tosylamino)indole-2-carbonitrile **256a** was stable to the reaction conditions suggesting the increased yield of detosylated indole **222a** did not arise from detosylation of the 3-(*N*-tosylamino)indole-2-carbonitrile **256a**. Oxidation of the thiophenol could have occurred owing to oxygen in the reaction mixture or in the air atmosphere. When the reaction was repeated under anaerobic conditions (degassed PhH under an argon atmosphere) the quantity of diphenyl disulfide recovered became nearly equimolar with respect to the free indole. This tentatively supported

that thiophenol was reducing the 2-cyano-3*H*-indol-3-imine intermediate **259** to afford the desired 3-aminoindole-2-carbonitrile **222a**. On this basis the reaction was repeated with only 2-2.5 equiv. of PhSH under argon and the reaction also came to completion with only traces of the migrated product (Table 36).

Under these reaction conditions there was no trace of the possible diarylsulfide side product phenyl(*p*-tolyl)sulfide. This was not surprising since in the absence of nitro substitution the tosylamide was not activated toward nucleophilic aromatic substitution. The possibility that the mercaptan attacked directly the sulfonamide sulfur to eliminate *S*-phenyl *p*-tolylthio-sulfonate was also unlikely, since no trace of *S*-phenyl *p*-tolylthiosulfonate could be identified in the reaction mixture. A pure sample of *S*-phenyl *p*-tolylthiosulfonate was stable to the reaction conditions and also inert towards 3-aminoindole-2-carbonitrile **222a**. Having in mind the inability to detect either phenyl(*p*-tolyl)sulfide or *S*-phenyl *p*-tolylthiosulfonate in the reaction mixtures addition of thiophenol to the 2-cyano-3*H*-indol-3-imine **259** at the highly electrophilic indole C2 position to afford intermediate **262** was proposed. Attack of a second mercaptan at the phenyl sulfide could eliminate the observed diphenyl disulfide and the 3-aminoindole-2-carbonitrile **222a** that was shown earlier to be inert to the toluenesulfinate side product (Scheme 141).



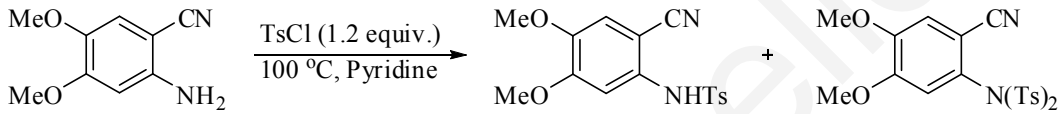
Scheme 141

7.2.5 Synthesis of Derivatives

Having completed successfully the optimization for the synthesis of 3-aminoindole-2-carbonitrile **222a** in 4 steps (protection of the NH_2 group with TsCl, alkylation, cyclization and deprotection using DBU/PhSH) the next target was to check the generality of the specific synthetic route by preparing electron poor and electron rich analogues. For this purpose, the

5,6-dimethoxy-3-aminoindole-2-carbonitrile **222h** and 5-nitro-3-aminoindole-2-carbonitrile **222b** were synthesized.

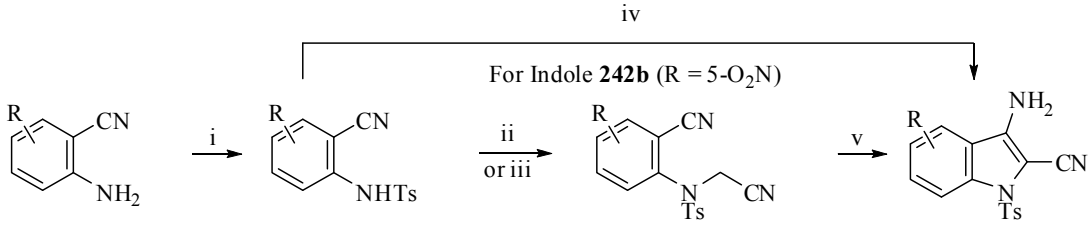
The 4,5-dimethoxy-2-aminobenzonitrile **219h** reacted readily with TsCl (1 equiv.) to give 4,5-dimethoxy-2-(tosylamino)benzonitrile **245h** in high yield (80%). If more than one equivalent of TsCl was used then two products were obtained. The first one was the expected 4,5-dimethoxy-2-(tosylamino)benzonitrile **245h** (78%) and the second one was the bistosylated compound **263** (15%) (Scheme 142). The second step of the alkylation and the third step of the cyclization proceeded without any difficulties or unexpected results.



219g **245h** (78%) **263** (15%)

Scheme 142

Mono-*N*-tosylation of 2-amino-5-nitrobenzonitrile **219b** occurred without any difficulties giving the desired 5-nitro-2-(tosylamino)benzonitrile **245b** in 81% yield. Cyanomethylation of this compound, however, could not readily be controlled and heating 5-nitro-2-(tosylamino)-benzonitrile **245b** in an excess of chloroacetonitrile **244** at 100 °C in the presence of K_2CO_3 (2 equiv.) for 1 d gave in moderate yield the cyclized 5-nitro-3-(tosylamino)indole-2-carbo-nitrile **242b** (40%) together with detosylated 2-amino-5-nitrobenzonitrile **219b** (46%). The procedures for the synthesis of 5,6-dimethoxy(tosylamino)indole-2-carbonitrile **237h** and 5-nitro-3-(tosylamino)-indole-2-carbonitrile **242b** are summarized below (Scheme 143).



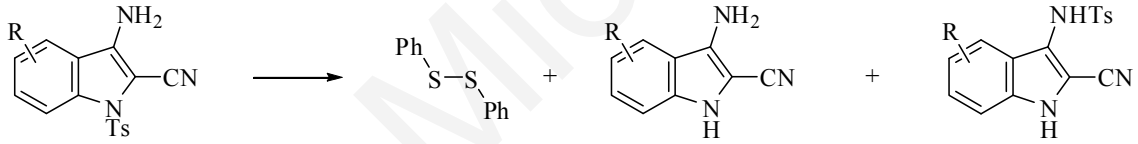
219h R = 4,5-$(MeO)_2$ **245h** R = 4,5-$(MeO)_2$ **246h** R = 4,5-$(MeO)_2$ **242h** R = 5,6-$(MeO)_2$
219b R = 5-O_2N **245b** R = 5-O_2N **242b** R = 5-O_2N

Reagents and conditions: (i) TsCl (1 equiv.), C_5H_5N, 100 °C, 5 h, **245h** (7 h, 80%), **245b** (36 h, 81%); (ii) $ClCH_2CN$ (1 equiv.), K_2CO_3 (1 equiv.), dry DMF, 100 °C, 70 min, (sealed tube) **246h** (2 h, 73%); (iii) $ClCH_2CN$ (1 equiv.), K_2CO_3 (1 equiv.), dry DMF, MW, 12 PSI, **246h** (100 °C, 10 min, 81%); (iv) $ClCH_2CN$ (1 mL), K_2CO_3 (2 equiv.), 100 °C, **242b** (1 d, 40%), **219b** (1 d, 46%); (v) K_2CO_3 (0.01 equiv.), EtOH, **242h** (78 °C, 30 h, 93%).

Scheme 143

Detosylation of the two indoles was achieved with DBU (1 equiv.) and PhSH (2 or 5 equiv.) in dry PhH giving the desired 3-aminoindole-2-carbonitriles **222b,h** in high yields (Table 36).

Table 36. Deprotection of the 3-amino-1-tosylindole-2-carbonitriles **242b,h** (0.06 mmol) using DBU and PhSH in PhH (2 mL) at 80 °C.

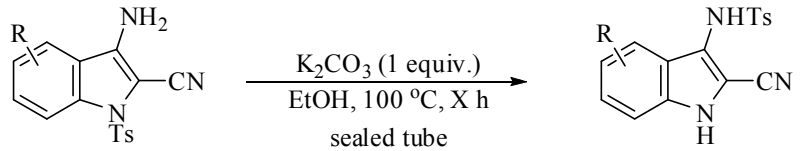


242b,h **222b,h** **256b,h**

R	DBU (equiv.)	PhSH (equiv.)	Time (h)	Yields (%) PhSSPh[b]	**222**	**256**
5,6-$(MeO)_2$	1	5	24	230	**222h** (88)	-
5-O_2N	1	5	1	240	**222b** (90)	-
5,6-$(MeO)_2$	1	2[a]	25	91	**222h** (86)	-
5-O_2N	1	2[a]	3	95	**222b** (89)	-

[a] Dry and degassed PhH was used, and the rxn took place under Argon.
[b] Yield calculated based on the need for 2 x PhSH for the deprotection of 1 x tosylindole.

Heating 5,6-dimethoxy(tosylamino)indole-2-carbonitrile **242h** and 5-nitro-3-(tosylamino)-indole-2-carbonitrile **242b** (0.06 mmol) in EtOH (1 mL) in the presence of K_2CO_3 (1 equiv.) at *ca.* 100 °C (sealed tube), 3-(*N*-tosylamino)indole-2-carbonitriles **256b,h** were isolated in good yields (Scheme 144).

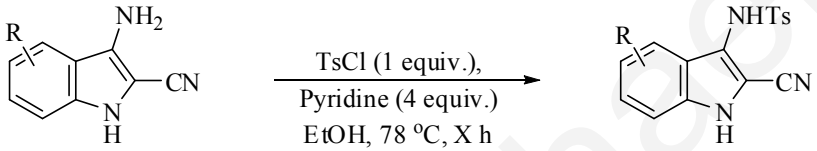


242h, R = 5,6-$(MeO)_2$
242b, R = 5-O_2N

256h, R = 5,6-$(MeO)_2$ (79%), X = 3 h
256b, R = 5-O_2N (85%), X = 1 h

Scheme 144

Interestingly, treatment of the 3-aminoindole-2-carbonitriles **222b,h** with TsCl (1 equiv.) and pyridine (4 equiv.) in refluxing EtOH gave the 3-(*N*-tosylamino)indole-2-carbonitriles **256b,h** in 86 and 82% yields, respectively (Scheme 145).



222h, R = 5,6-$(MeO)_2$
222b, R = 5-O_2N

256h, R = 5,6-$(MeO)_2$ (86%), X = 2 h
256b, R = 5-O_2N (82%), X = 48 h

Scheme 145

The above results indicate that this synthetic route was general and was applicable for electron rich and electron poor systems. Furthermore 5,6-dimethoxy-3-aminoindole-2-carbonitrile **222h** which could not be obtained from the reaction of the analogous dithiazolimine **142h** with Ph_3P (Chapter 6) was shown to be stable.

7.3 Synthesis of 3-Aminoindole-2-carbonitriles from Anthranilonitriles *via* *N*-unprotected 2-(cyanomethylamino)benzonitriles

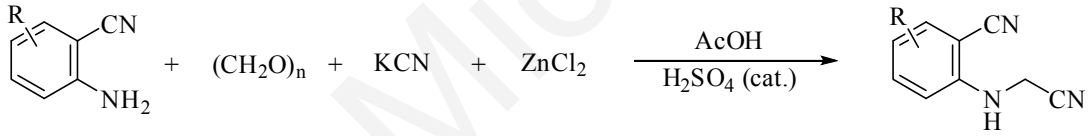
Having completed successfully the synthesis of three 3-aminoindole-2-carbonitriles **222a,b,h** using *N*-tosyl protected cyanomethylamines, the next target was to try to develop a shorter route that overcame the need for protection. According to the literature *N*-protection of 2-(cyanomethylamino)benzonitrile **142** was necessary for the Thorpe–Ziegler cyclization to work.[397] Similar Thorpe–Ziegler cyclizations of (*Z*)-3-(cyanomethylamino)acrylonitriles to afford 3-amino-pyrrole-2-carbonitriles also required protection of the amino group since the

anion formed by the base abstraction of the NH proton was more stable than its methylene analogue (Scheme 132, Section 7.1).[369,370]

Both *N*-methylation using diazomethane,[464,465] bromomethane[466] and *N*-carboalkoxylation using benzyl,[467] methyl[468] or ethyl chloroformate[370,469-474] have been used to enhance the formation of the required carbanion intermediate in the cyclization to afford pyrroles.

Direct cyanomethylation of 2-aminobenzonitriles **219a,b,h** using chloroacetonitrile **244** could not readily be achieved, however, an alternative route that made use of paraformaldehyde, KCN and $ZnCl_2$ in acetic acid catalyzed by H_2SO_4 worked well.[474-476] A partial optimization indicated that performing the reaction in a sealed tube allowed the use of fewer equivalents of reagents, in particular for the more electron rich aminobenzonitriles **219a** and **219h**. The 2-amino-5-nitrobenzo-nitrile **219b** required the use of excess reagents (Table 37).

Table 37. Reaction of 2-aminobenzonitriles **219a,b,h** with paraformaldehyde, KCN, $ZnCl_2$ and catalytic H_2SO_4 (1 drop) in AcOH.



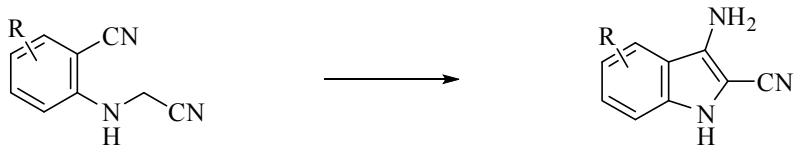
219a,b,h **221a,b,h**

R	$(CH_2O)_n$ (equiv.)	KCN (equiv.)	$ZnCl_2$ (equiv.)	Temp.[a] (°C)	Time (h)	Yields (%)
H	3	3	8	55	3 min	**221a** (85)
H	1.5	1.5	4	25	6	**221a** (97)
H	1.1	1.1	2	55[b]	3	**221a** (96)
H	1.1	1.1	1.1	25 to 55[b]	48	ir[c]
4,5-$(MeO)_2$	1.5	1.5	4	25	2	**221h** (83)
4,5-$(MeO)_2$	1.1	1.1	2	55[b]	1	**221h** (86)
5-NO_2	3	3	8	55[b]	48	ir[c]
5-NO_2	5	5	10	55	48	ir[c]
5-NO_2	5	5	10	55[b]	11	**221b** (57)

[a] Preheated oil bath temperature.
[b] The reaction took place in a sealed tube.
[c] ir = Incomplete reaction.

Having achieved high yielding synthesis of 2-(cyanomethylamino)benzonitriles **221a,b,h** the next step was the Thorpe-Zeigler cyclization. Treating 2-(cyanomethylamino)benzonitrile **221a**,**b**,**h** with a variety of bases (2 equiv.) (K_2CO_3, Cs_2CO_3, NaOH, DBU, Et_3N, Hünig's base) in different solvents (DCM, EtOH, PhMe) at room temperature gave no reaction while at 60 ^oC complex mixtures were obtained. Nevertheless, repeating the reaction using K_2CO_3 (2 equiv.) in EtOH, DMF or DMSO and heating in a CEM microwave reactor at *ca.* 120 ^oC at 180, 80 and 50 PSI, respectively gave the desired 3-aminoindole-2-carbonitrile **222a**,**b**,**h** in moderate yields (38-50%). Of the solvents screened, EtOH gave the highest product yields (50%) and the fastest reaction times (5 min), presumably due to the higher reaction vessel pressures. As such, EtOH was selected as the solvent for further optimizations. Indeed, in EtOH the reactions proceeded readily using only a catalytic amount of K_2CO_3 (0.5 equiv.). Furthermore, by using a sealed tube and preheated Wood's metal baths the cyclizations could be achieved using conventional heating (hot plate stirrers), although product yields were somewhat lower and the reaction times longer (Table 38).

Table 38. Transformation of 2-(cyanomethylamino)benzonitriles **221a**,**b,h** into 3-amino-indole-2-carbonitriles **222a**,**b,h** in EtOH (1 mL).



221a,b,h **222a,b,h**

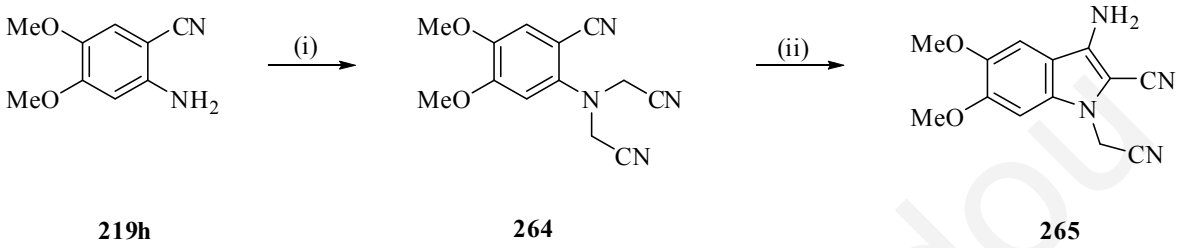
R	K_2CO_3 (equiv.)	Temp. (^oC)	Time (min)	Yields (%)
H	1	120[a]	5	**222a** (60)
H	0.5	120[a]	8	**222a** (78)
H	0.1	120[a]	20	**222a** (71)
4,5-$(MeO)_2$	0.5	120[a]	45	**222h** (88)
5-O_2N	0.5	120[a]	5	**222b** (87)
H	0.5	140[b]	90	**222a** (57)
H	0.5	180[b]	25	**222a** (55)
4,5-$(MeO)_2$	0.5	140[b]	90	**222h** (88)
4,5-$(MeO)_2$	0.5	180[b]	66	**222h** (66)[c]
5-O_2N	0.5	140[b]	60	**222b** (37)
5-O_2N	0.5	180[b]	15	**222b** (56)

[a] MW 300 W, 180 PSI (max).
[b] Sealed tube in preheated Woods metal bath.
[c] 2-Amino-5-nitrobenzonitrile **219b** was also isolated in 25% yield.

The observed differences between the microwave and the conventional heating were tentatively ascribed to the difficulty in accurately recording the internal temperature and pressure of the reactions performed in the microwave reactor using only the available external temperature and pressure probes. Nevertheless, at these elevated temperatures and pressures the formation of sufficient quantities of the required cyanomethylene carbanion allowed the desired Thorpe–Ziegler cyclization to proceed without the need for *N*-protection. By using this method a rapid two-step synthesis of 3-aminoindole-2-carbonitriles **222a,b,h** that tolerated both electron withdrawing NO_2 and electron releasing MeO substituents on the benzo ring was achieved.

As a cautionary note, treatment of 4,5-dimethoxy-2-aminobenzonitrile **219h** with $(CH_2O)_n$ (3 equiv.), KCN (3 equiv.) and $ZnCl_2$ (8 equiv.) led to the formation of the dialkylated compound

264 in 68% yield, cyclization of which could also be achieved in either a CEM microwave reactor at *ca.* 120 ^{o}C or either in a sealed tube giving the analogous alkylated indole compound **265** in 71% yield (Scheme 146).



219h **264** **265**

Reagents and Conditions: (i) $(CH_2O)_n$ (3 equiv.), KCN (3 equiv.), $ZnCl_2$ (8 equiv.), AcOH (2 mL), H_2SO_4 (1 drop), 55 ^{o}C, 1 h, (68%); (ii) K_2CO_3 (0.5 equiv.), EtOH (1 mL), 120 ^{o}C, sealed tube or MW (250 W, 180-160 psi), 5 min (71%)

Scheme 146

7.4 Summary

To summarise, two new synthetic routes toward the formation of 3-aminoindole-2-carbonitriles **222** were developed. The first one is an improvement of a literature procedure involving 4 synthetic steps. The first step was the protection of the NH_2 group using TsCl. The second step involved an alkylation reaction by using chloroacetonitrile **244**. The third step was a Thorpe-Ziegler base catalyst cyclization and the final step was deprotection of the TsCl using DBU/PhSH. In the deprotection reaction a migration of the Ts group from the N1 atom on the indole ring to the N3 position was observed. The N3 tosylated compound **256** was much more stable than the N1 tosylated compound **242**. Three 3-aminoindole-2-carbonitrile derivatives were synthesized, indicating the generality of the synthetic procedure and the stability of the 5,6-dimethoxy-3-aminoindole-2-carbonitrile **222h**. Moreover, we observed a trimerization of the chloroacetonitrile under basic conditions. The second synthetic route involved only two synthetic steps. The first one was a direct cyanomethylation of the analogous 2-aminobenzonitrile. This cyanomethylation occurred by using $(CH_2O)_n$, KCN, $ZnCl_2$ in glacial acetic acid in the presence of 1 drop of sulfuric acid. The second step was a Thorpe-Ziegler base catalyst cyclization. In order for the cyclization to occur pressure was found to be necessary and so the reactions occur in a microwave reactor or in a sealed tube in dry DMF. The same three derivatives as before were synthesized successfully in moderate yields also indicating the generality of this synthetic procedure. In both synthetic routes,

chromatography was not necessary for the isolation of the products in scales 1-2 g. As such use of MW conditions overcomes the need for protection of the amino group during the procedure synthesis of indoles. As future work, more derivatives can be synthesized in order to build up a complete library of compounds.

CHAPTER 8

Biological Activities of 1,2,3-Dithiazoles

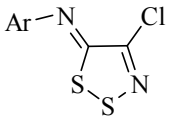
Sections

8.1 Introduction

The biological activities of (4-chloro-5*H*-1,2,3-dithiazolylideneamine)arenes were first studied in the 1976 by J. Moore *et al*.,[46] who found that 4-chloro substituted dithiazolylidenes **266** were useful as fungicides, ovicides, insecticides and herbicides.[1] Since then several biological studies have also indicated antifungal[48,49,50,76,478] and antibacterial activity.[67]

All the dithiazolylidenes that were synthesized and tested for their biological activities are presented below (Table 39).[46,48,49,50,76,478]

Table 39: Dithiazole derivatives



Ar = Phenyl, naphthyl, phenyl or naphthyl substituted

266

Compound number	Ar	Compound number	Ar
266a	C_6H_6	**266x**	4-FC_6H_5
266b	4-ClC_6H_5	**266y**	4-$H_3CC_6H_5$
266c	3,5-$Cl_2C_6H_4$	**266z**	3,5-Cl_2-4-HOC_6H_3
266d	2-H_3C-4-ClC_6H_4	**266aa**	4-benzoyl-C_6H_5
266e	3,4-$Cl_2C_6H_4$	**266ab**	2-H_3C-5-ClC_6H_4
266f	2,4-$Cl_2C_6H_4$	**266ac**	2-CNC_6H_5
266g	2-$H_3CC_6H_5$	**266ad**	3-(2-NC-4-F_3C-PhO)C_6H_5
266h	3-$O_2NC_6H_5$	**266ae**	2-$MeO_2CC_6H_5$
266i	2-H_3C-4-$Br_2C_6H_4$	**266af**	4-$MeOC_6H_5$
266j	2,6-$(H_3C)_2C_6H_4$	**266ag**	2-$MeOC_6H_5$
266k	2,4,6-$(H_3C)_3C_6H_3$	**266ah**	3,4-$(MeO)_2C_6H_4$
266l	3-BrC_6H_5	**266ai**	2-NC-4,5-$(MeO)_2C_6H_3$
266m	2,4-$(H_3C)_2C_6H_4$	**266aj**	2-MeO_2C-4,5-$(MeO)_2C_6H_3$
266n	2-ClC_6H_5	**266ak**	4,5-$OCH_2CH_2OC_6H_4$
266o	3-ClC_6H_5	**266al**	3,4,5-$(MeO)_3C_6H_3$
266p	naphth-2-yl	**266am**	2-$H_2OCC_6H_5$
266q	3-(2-F_3C-4-O_2N-PhO)C_6H_5	**266an**	2-H_2OC-4,5-$(MeO)_2C_6H_3$
266r	3-(4-O_2N-PhO)C_6H_5	**266ao**	2-H_2OC-5-ClC_6H_4
266s	4-(4-O_2N-PhO)C_6H_5	**266ap**	quinolin-8-yl
266t	2-(4-O_2N-PhO)C_6H_5	**266aq**	quinolin-5-yl
266u	2-H_3C-3-ClC_6H_4	**266ar**	quinolin-6-yl
266v	2-FC_6H_5	**266as**	2-H_3C-quinolin-8-yl
266w	4-NCC_6H_5	**266at**	naphth-1-yl
		266au	1-HO-naphth-5-yl

8.1.1 Herbicidal Activity

4-Chloro substituted dithiazolylidenes **266** are known to be herbicidal in post-emerged applications. They are effective against weed grasses as well as broadleaved weeds (Table 40).[46]

Table 40. Herbicidal Effectiveness.

Compound number	O	W	C	M	P	L
266a	0	10	20	85	70	80
266b	15	85	20	100	95	95
266c	35	85	55	100	100	100
266d	20	30	20	70	85	70
266e	35	55	30	100	100	100
266f	30	55	35	100	95	100
266g	0	0	0	70	70	60
266h	0	0	0	30	40	35
266i	0	0	0	30	30	25
266j	0	0	0	60	30	75
266l	30	30	30	85	55	100
266m	0	0	0	35	35	100
266n	0	40	30	93	100	50
266o	30	45	10	85	80	98
266p	0	90	20	85	70	100
266u	0	15	0	50	20	45
266v	0	20	0	70	70	85
266x	40	60	60	70	70	100
266y	30	55	35	90	45	100
266ab	45	65	20	100	95	100

O = Wild Oats (*Arena Fatua*)
W = Watergrass (*Echinochloa crusgalli*)
C = Crabgrass (*Digitaria Sanguinalis*)
L = Mustard (*Brassica arvensis*)
M = Pigweed (*Amaranthus retroflexus*)
P = Lambsquarter (*Chenopodium album*)

Then they were tested for the control mites and mite eggs (Table 41).[46]

Table 41. Mite and Mite eggs control tests.

Compound number	Mite Control (%)	Mite Eggs Control (%)
266c	90	85
266d	94	100
266e	99	100
266f	100	0
266i	70	100
266l	-	78
266m	0	30
266n	70	0
266s	0	78
266u	90	99
266v	0	39
266ab	85	85

8.1.2 Antifungal

4-Chloro-1,2,3-dithiazolylidenes **266** that were presented previously (see, Table 40), they were also found to be useful for controlling fungi, particularly plant fungal infections caused by *Botrytis cinerea*, leaf blights caused by organisms such as *Pythrium ultimum*, *Helminthosporum sativum*, *Fusarium moniliforme*, *Rhizoctonia solani*, *Monolinia fructicola and Uromyces phaseoli typical*.[52,80,486] More specifically the dithiazolylidenes were tested for the control of the Tomato Late Blight organism *Phytiphthora infestans conidia*, tomato Early Blight organism, *Alternaria solani conidia*, Celery Late Blight organism *septoria apii* and of the pathogen powdery mildew *Erysiphe polygoni* (Table 42).[46]

Table 42. Fungicidal activity.

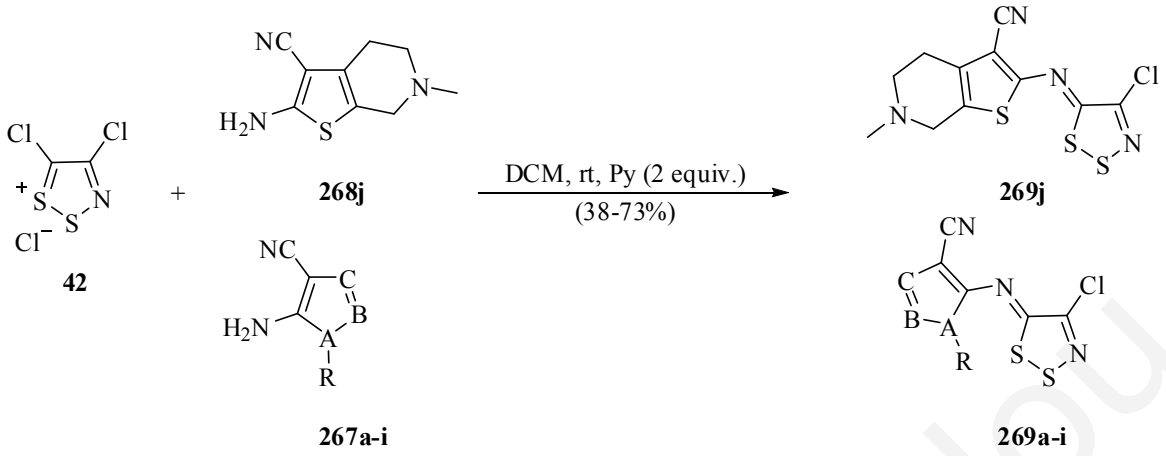
Compound number	Tomato Late Blight % Control	Tomato Early Blight % Control	Celery Late Blight % Control	Powdery Mildew % Control
266c	-	-	-	76
266d	-	-	-	100
266f	-	56	-	-
266h	44	-	-	-
266n	-	-	-	99
266m	63	44	-	-
266o	68	-	-	-
266p	73	-	-	-
266q	62	-	**56**	-
266r	-	44	-	-
266s	51	-	-	-
266t	80	-	-	-
266o	63	44	-	100
266v	-	50	-	-
266w	97	90	-	-
266ab	-	-	-	90

Moreover dithiazolylidenes **266a**, **266ab**, **266ap-266au** were also tested for their antifungal activity against the fungi *C. albicans*, *C. glabrata*, *C. tropicalis*, *I. orientalis* (Table 43).[50] Amphotericin B (AMB), fluconazole (FLU) and flucytosine (5-FC) were used as reference products for inhibitory activity against fungi. All the compounds showed significant fungicidal activity against tested strains, however, compounds **266a** and **266ab** were the most active. The results are similar to those generally observed with amphotericin and flucytocin.

Table 43. Fungicidal activities

Compound number	Fungi Tested			
	C. albicans (MIC)	*C. glabrata*	*C. tropicalis*	*I. orientalis*
266a	16	16	16	16
266ag	16	16	16	16
266ap	16	16	16	16
266aq	32	32	48	48
266ar	16	16	32	32
266as	32	32	48	48
266at	16	32	32	32
266au	16	32	48	48
AMP	0.25	1	1	0.5
FLU	2	4	4	16
5-FC	0.13	0.05	0.1	16

Dithiazolylidenes **269a-j** (Scheme 147) were tested for their *in vitro* antifungal activity against yeasts (*Candida albicans* ATCC 10231, *Candida utilis* ATCC 9950, *Candida lipolytica* CBS 6124, *Saccharomyces cerevisiae* ATCC 26785, *Pichia stipitis* CBS 5776) and moulds (*Aspergillus niger* L32 and *Penicillium sp*.) and exhibit high antifungal activity (Table 44).[10] Compounds **269d-i** exhibited the highest antifungal activity, showing good MIC values included in the range of 10-50 μg/mL. Particularly, the efficacy of these products against the moulds can be compared with that showed of amphotericin B, used as reference compound for inhibitory activity against fungi. Compounds **269a-c** appeared to be scarely active only against some microorganisms such as *Penicillium* and *C. utilis*, whereas **269c** and **269j** presented the lowest antifungal activities against all the fungi tested. It is interesting to note that compounds **269a-f** that were obtained from *o*-amino nitriles **267a-f** which possess the same heterocyclic ring, the biological activity is affected by substituents on the N1-position of the pyrazole ring (Table 44). These compounds could be implicated in inhibitory activity against fungi acting as a potent inhibitor of some enzymes like serine proteases.[48,49,93]



267a: R = Me, A=B=N, C =CH
267b: R = Ph, A=B=N, C=CH
267c: R = Bn, A=B=N, C=CH
267d: R = $Ph(CH_2)_2$, A=B=N, C=CH
267e: R = $Ph(CH_2)_3$, A=B=N, C=CH
267f: R = $C(CH_3)_3$, A=B=N, C=CH
267g: R = $Ph(CH_2)_2$, A=C=N, B=CH
267h: R = $(2,4\text{-}Cl_2\text{-}C_6H_3)CH_2CH_2$, A=C=N, B=CH
267i: R = R = *o*-xylyl, A=B=C=N

Scheme 147

Table 44. Minimum Inhibitory Concentration (MIC) against some fungi.

Compound	Fungi tested						
	Candida albicans ATCC 10231	*Candida utilis* ATCC 9950	*Candida lipolytica* CBS 6124	*Saccharomyces cerevisiae* ATCC 26785	Pichia stipitis CBS 5776	*Aspergillus niger*	*Penicilliumsp*
269a	50	50	25	25	25	25	100
269b	50	>100	25	25	50	25	100
269c	>100	>100	100	50	>100	25	100
269d	25	100	25	25	25	25	25
269e	25	50	25	25	25	10	25
269f	25	25	25	25	25	25	50
269g	25	25	25	25	25	10	25
269h	25	50	25	25	25	50	50
269i	50	25	25	25	50	25	50
269j	100	100	100	100	100	100	100
Amphotericin B	2.5	2.5	20	10	2.5	20	20

8.1.3 Antibacterial Activity

Dithiazolylidenes **266ae-266au** were also tested for their antibacterial activities.[48,49,50,76] It seemed to be evident that the aromatic portion of the molecule does not interfere with the

antibacterial activity which probably depends on the 1,2,3-dithiazole ring acting as a potent inhibitor or some enzymes like serine proteases.[50]

All these compounds were tested for their *in vitro* antibacterial activity against the following bacterial strains: Gram-negative bacteria, *Escherichia Coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Klebsiella pneumoniae* Lab. Coll., and Gram-positive bacteria, *staphylococcus aureus* ATCC 9144, *Streptococcus pyogenes* ATCC 19165, *Listeria monocytogenes* CIP 82110T, *Enterococcus faecallis* ATCC 29212. All the dithiazolimines did not show any affect on Gram-negative bacteria but they showed significant antibacterial activity against the Gram-positive bacteria (Table 45).[49,50] The minimum inhibitory concentrations (MICs) were determined by the broth dilution method (Table 46).[480]

Table 45. Antibacterial activities by the agar disk diffusion method.

	Zone diameter limit (mm)[a]			
Compound (30 µg)	*S. aureus*	*E. faecalis*	*S.pyogenes*	*L. monocytigenes*
266a	29	19	26	27
266w	11	11	15	11
266ae	18	16	18	17
266af	17	14	15	15
266ag	20	17	22	21
266ah	13	13	16	12
266ai	10	10	13	10
266aj	17	14	14	17
266ak	12	10	11	10
266al	13	10	16	17
266am	-	-	-	-
266an	-	-	-	-
266ao	-	-	-	-
266ap	14	19	14	14
266aq	8	17	9	7
266ar	13	14.5	11	11
266as	13	-	13.5	8
266at	11	12	12	10
266au	11.5	13	13	12

[a] The average diameter of clear zone (mm), measured in triplicate

Table 46. Minimum Inhibitory Concentration (μg/ml)[a]

Compound	Bacterial Tested			
	S. aureus	*E.faecalis*	*S.pyogenes*	*L. monocytigenes*
266a	16	16	*32*	16
266w	32	32	32	32
266ae	32	32	32	32
266af	32	32	32	32
266ag	32	16	32	16
266ah	32	32	32	32
266ai	32	32	32	32
266aj	32	32	32	32
266ak	32	32	32	32
266al	32	32	32	32
266am	-	-	-	-
266an	-	-	-	-
266ao	-	-	-	-
266ap	32	48	32	32
266aq	32	32	32	32
266ar	32	32	32	32
266as	32	48	32	32
266at	16	16	16	16
266au	16	16	16	16

[a] Measured in triplicate

Furthermore dithiazolylidenes **269a-j** (see, Scheme 147) were tested for their *in vitro* antibacterial activity against several pathogenic representative Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 9027, *Escherichia coli* ATCC 11105 and *Proteus mirabilis* MB81) and Gram-positive bacteria (*Enterococcus faecalis* ATCC 8043 and *Staphylococcus aureus* ATCC 29213). However, none of the compounds showed any antimicrobial activity (Table 47).[93]

Table 47. Minimum Inhibitory Concentration (MIC) against some strains of Gram-positive and negative bacterial

Compound	Bacteria tested				
	Pseudonomous aeruginosa ATCC 9027	*Escherichia coli* ATCC 11105	*Proteus mirabilis* MB	*Enterococcusfaecalis* ATCC 8043	Staphylococcus aureus ATCC 29213
269a	>100	>100	>100	>100	100
269b	>100	>100	>100	>100	100
269c	>100	>100	>100	>100	100
269d	>100	>100	>100	>100	75
269e	>100	>100	>100	>100	100
269f	>100	>100	>100	>100	75
269g	>100	>100	>100	>100	100
269h	>100	>100	>100	>100	100
269i	>100	>100	>100	>100	75
269j	>100	>100	>100	>100	100
Ampicillin	>100	5	10	2.5	0.5

8.1.4 Antiproliferative

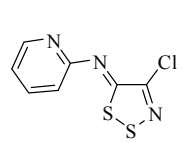
Dithiazolylidenes **269a-269j** were also tested for their *in vitro* antiproliferative activity on human myeloid leukemia K562 and L1210 murine leukemia cell lines and compared to the antiproliferative effects of the natural product distamycin A. All the dithiazolylidenes were active at a concentration ranging from 3 to 10 μM and they retained antiproliferative activities comparable to those exhibited by distamycin A (Table 48).[93]

Table 48. In vitro biological effects on L1210 and K562 cell lines

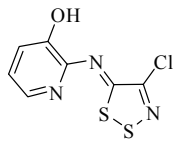
Compound	IC_{50} (μM)	
	L1210	K562
269a	5	5
269b	7.5	5
269c	8	5
269d	5	3
269e	3	5
269f	5	5
269g	3	4
269h	5	8
269i	7	8
269j	8	7
Distamycin A	10	20

8.2 Biological Studies on Dithiazolylidenes Prepared During this Thesis

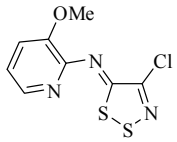
During this thesis a wide range of dithiazolylidenes were synthesized and tested for their biological activity. The structures of the compounds are presented below.



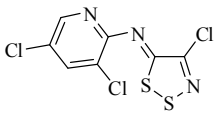
70a



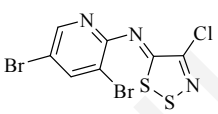
70b



70c



70d



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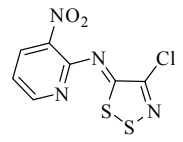

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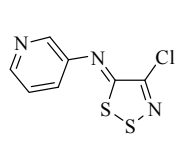

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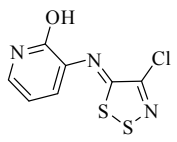

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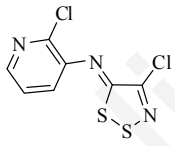

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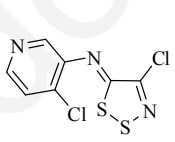

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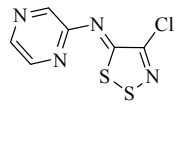

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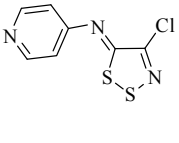

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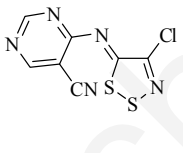

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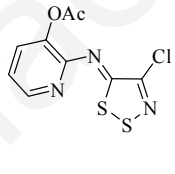

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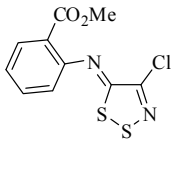

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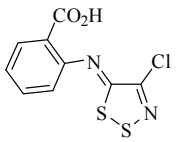

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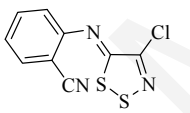

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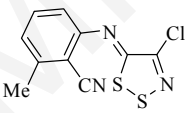

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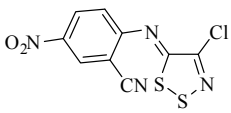

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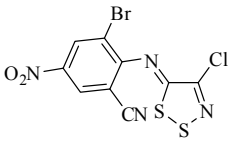

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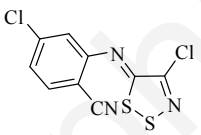

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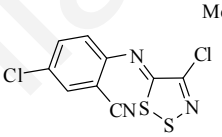

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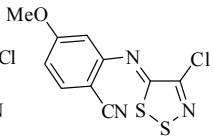

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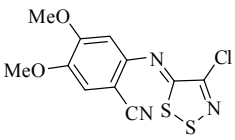

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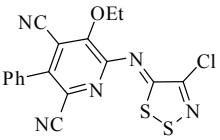

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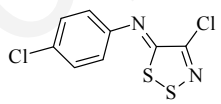

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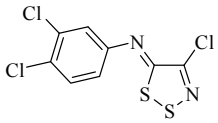

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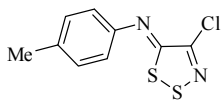

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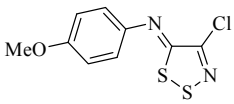

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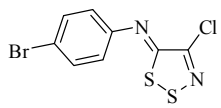

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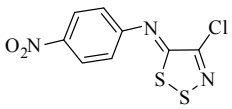

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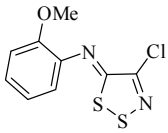

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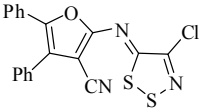


266ax

8.2.1 Cytotoxicity against Cancer cells

All the dithiazolylidenes were sent to the A*STAR Institute of Chemical and Engineering Sciences in Singapore in order to be tested against breast (MCF-7), lung (NCI-H460) and brain (SF268) cancer cell lines. The GI_{50} values were also determined. All the compounds were solubilized in neat DMSO at 10 mM stock concentration and kept frozen at -80 ^{o}C before use.

All the results obtained are summarized in the table below (Table 49). The GI50 determination for the compounds that exhibit % of net growth <50% in the prescreen assay are also summarized below (Table 50).

Table 49. Percentage of net cell growth administered with compounds against three different cancer cell lines (MCF-7, NCI-H460 and SF268).

Compound Code	Cell lines Percentage of cell growth (%)		
	MCF7	NCI-H460	SF268
70a	-50.35	91.38	99.86
70b	98.43	106.07	100.35
70d	62.24	102.20	101.77
70f	-14.86	89.35	97.11
70h	94.70	93.62	98.79
70j	93.63	99.14	101.48
70o	10.99	97.91	98.31
142a	95.33	101.11	101.32
142b	80.17	104.69	98.31
142c	99.62	100.67	105.86
142d	77.80	91.81	102.56
142e	97.64	95.58	101.09
142f	88.37	102.74	98.84
142g	93.56	100.58	101.88
142h	94.79	98.63	103.91
266b	73.92	98.28	86.51
266e	61.07	78.91	90.87
266y	82.48	101.92	100.12
266af	94.22	95.94	98.59
266au	74.82	84.75	81.82
266av	81.12	96.69	98.57

Table 50. GI50 values of the compounds tested against MCF-7 cell line

Compound code	% of net growth					
	10 μM	1 μM	0.1 μM	0.01 μM	0.001 μM	G150 (μM)
70a	-55.63	101.33	99.00	106.37	103.50	3.94
70f	-31.11	100.40	102.83	98.88	103.08	4.45
70o	0.27	98.01	102.40	101.33	103.86	5.42
Paclitaxel	14.53	20.03	20.12	26.63	99.54	0.007

8.2.2 Antifungal activity

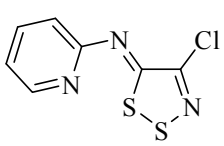
Dithiazolylidenes were also sent to l'Université de La Rochelle in France in order to be tested for their antifungal activity against (LV0004 *Candida albicans* ATCC10231, LV0006 *Candida glabrata* DSM6425, LV007 *Candida tropicalis* DSM1346, LV0008 *Issatchenkia orientalis* DSM6128). All the dithiazolylidenes that showed some antifungal activity are presented below. None of them showed any activity against LV008 (Table 51).

Table 51: Antifungal activity on dithiazolimines

Compounds 50 μg in DMSO 80%	LV0004	LV0006	LV0007
70a	+++	+	++
70c	+	-	-
70h	+	-	-
70i	+	-	-
70k	+++	-	-
70n	+++	-	++
70o	+++	++	+
108	++	++	++
139a	-	++	+
139c	+	-	-
139g	+	-	-
266e	+	-	+
266y	++	+	-
266af	++	+	+
266aw	+	+	-

-: inactive; +: inhibition zone 6-9mm; ++ inhibition zone 9-12mm; +++: inhibition zone >12mm

Almost all of the active compounds showed significant antimicrobial activity against the fungi LV004. In general the most active compounds were (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-amine **70a**, (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine **70k**, 4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyrimidine-5-carbonitrile **70n**, (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-pyridin-3-yl acetate **70o** and (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methoxyaniline **266af**.



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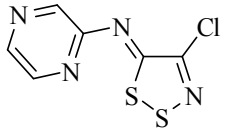

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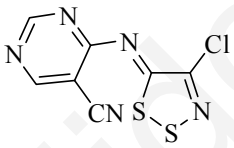

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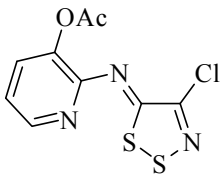

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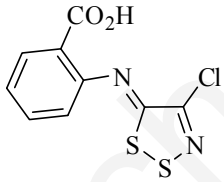

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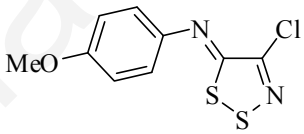


266aw

In the table below the minimum inhibitory concentration and minimum fungicidal concentration (μg/mL) is presented (Table 52).

Table 52: minimum inhibitory concentration and minimum fungicidal concentration (μg/mL)

Compound	Fungi Tested								
	C. albicans (LV004)			*C. glabrata* (LV006)			*C. tropicalis* (LV007)		
	MIC	MFC	MFC/MIC	MIC	MFC	MFC/MIC	MIC	MFC	MFC/MIC
70a	<2	4	>2	8	8	1	4	8	2
70k	2	8	>1.5	-	-	-	-	-	-
70n	<1	4	2	4	8	2	8	16	2
70o	32	>48	4	>48	>48	-	>48	>48	-
108	4	8	>4	16	16	1	16	32	2
Amphotericin B	0.25	0.5	2	2	2	2	1	2	2
Fluconazole	2	>128	>64	4	>128	>32	4	>128	>32

8.2.3 Antibacterial Activity

Dithiazolylidenes were also tested for their putative antibiotic activity against a panel of pathogenic bacteria and some yeast. More specifically the dithiazolylidenes were tested for their antimicrobial activity in Gram-negative bacteria (BM0022 *Escherichia coli* ATCC25922, BM0023 *Pseudomonas aeruginosa* ATCC27853, BM0029 *Klebsiella pneumonia* CIP 53153, BM0040 *salmonella Typhymurium* CIP5858, CP0013 *Enterococcus faecalis* CIP103214), Gram-positive bacteria (CP0016 *Staphylococcus aureus* ATCC25923, BP0001 *Bacillus cereus*, BP0056 *Listeria inocua*). All the dithiazolylidenes that showed some activity are presented below (Table 53). None of them showed any activity against BM0023.

Table 53: Antibacterial activity on dithiazolimines

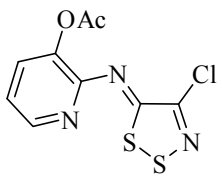
Compounds 50 μg in DMSO 80%	BM0022	BM0029	BM0040	CP0013	CP0016	BP0001	BP0056
70i	-	-	-	+	+	+	-
70n	-	-	-	-	+	+	-
70o	-	-	-	-	+	++	++
103	-	-	-	-	-	-	++
108	-	+	+	++	+	++	+
142a	+	-	-	+	-	+	+
142c	-	-	-	+	-	+	+
142d	-	-	-	-	++	-	-
160	-	-	+	++	+	-	++
266e	-	-	+	++	++	+	-
266y	-	-	-	++	-	+	+
266af	+	-	-	++	-	+	+
266aw	+	-	-	+	-	+	+

-: inactive; +: inhibition zone 6-9mm; ++ inhibition zone 9-12mm; +++: inhibition zone >12mm

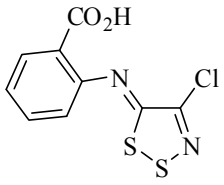
Almost all of the active compounds showed significant antimicrobial activity against the Gram-negative bacteria CP0013 and Gram-positive bacteria BP0001.

In general the most active compounds were 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-yl acetate **70o**, 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-benzoic acid **108** and 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene-amino)-6-ethoxy-4-

phenylpyridine-3,5-dicarbonitrile **160**, 3,4-dichloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)aniline **266e** and *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methoxyaniline **266af**.



70o



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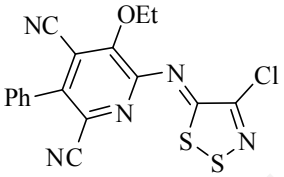

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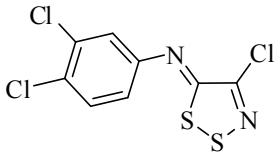
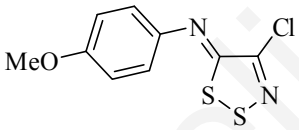
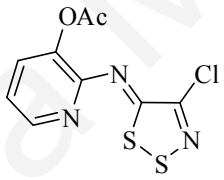


266e

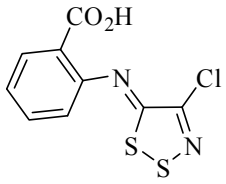


266af

The most active dithiazolylidenes that showed antifungal and antibacterial activities were 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-yl acetate **70o** and 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoic acid **108**.



70o



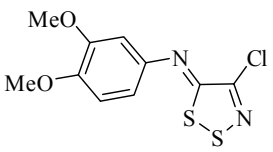
108

8.2.4 Fetax Toxicity Screen

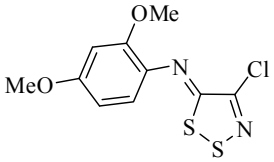
All the dithiazolylidenes were given to collaborators in the Biology Department of the University of Cyprus in order to be tested for their toxicity against XENOPUS embryos.

The FETAX (Frog Embryo Teratogenesis Assay - Xenopus) assay is widely used for toxicity evaluation. The method was established following the approved FETAX protocol (see Chapter 9.9).

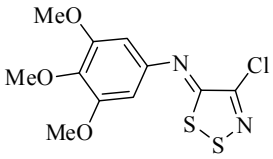
In general it was found that the 4-methoxy dithiazolylidene **266af** showed some interesting results and for this reason more methoxy analogues were synthesized and tested. All the biological results are summarized below (Table 54).



266ay



266az



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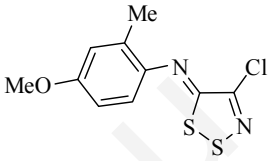

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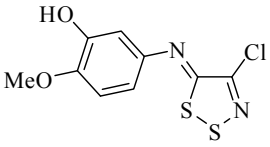

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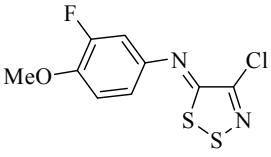

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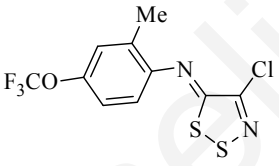

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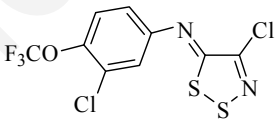

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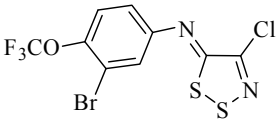

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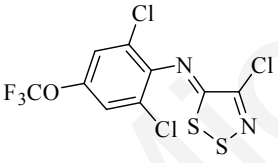

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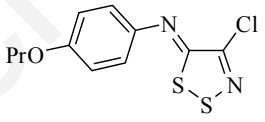

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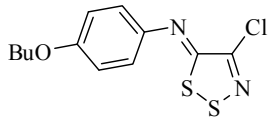

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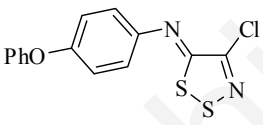
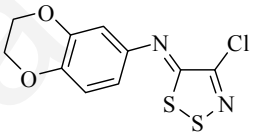
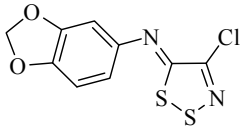


266aak



266aal



266aam

Table 54. Results on xenopus.

Compound code	MG	TI	EC50	LC50	Toxicity
70c	3.4	2.2	7.5	16.25	toxic
118	3.6	1.5	12.5	18.75	non toxic
142g	3.4	1.5	12.5	18.75	non toxic
142h	3.2	1.5	12.5	18.75	non toxic
266af	3.3	1.3	15.0	20.0	non toxic
266aw	3.9	1.3	15.0	20.0	non toxic
266ay	3.2	2.2	7.5	16.25	toxic
266az	3.4	10.0	1.25	12.5	toxic
266aaa	3.4	5.5	2.5	13.75	toxic
266aab	4.2	5.5	2.5	13.75	toxic
266aac	3.1	10.0	1.25	12.5	very toxic
266aad	3.4	15.0	1.25	18.75	very toxic
266aae	3.6	10.0	1.25	12.5	very toxic
266aaf	3.0	5.5	2.5	13.75	very toxic
266aag	3.9	1.5	12.5	18.75	non toxic
266aar	4.1	1.3	7.5	10.0	non toxic
266aai	3.5	1.4	13.75	18.75	non toxic
266aaj	3.0	10.0	1.25	12.5	very toxic
266aak	4.5	1.3	15.0	20.0	non toxic
266aal	3.5	2.6	6.25	16.25	toxic

The most reactive dithiazolylidene was the 4-methoxy derivative **266af**. This compound when tested on XENOPUS fetus made the fetus embryos transparent (Figure 10). All the methoxy derivatives had similar results but in much lower effect.

Figure 10 Picture of transparent XENOPUS embryos, after treatment with dithiazolylidene **266af**

8.3 Summary

All the dithiazolylidenes that were synthesized during this thesis were tested for cytotoxicity against cancer cells, for antifungal and antibacterial activities. The most active compounds for cytotoxicity against cancer cells were (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine **70a**, (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-3-nitropyridin-2-amine **70f** and (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-yl acetate **70o**. The most active compounds for their antifungal activity were (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine **70a**, (*Z*)-4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyrimidine-5-carbonitrile **70n**, (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-yl acetate **70o**, (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoic acid **108** and (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methoxyaniline **266af**. The most active compounds for their antibacterial activity were (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-pyridin-3-yl acetate **70o**, (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoic acid **108**, (*Z*)-6-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-5-ethoxy-3-phenylpyridine-2,4-dicarbo-nitrile **160**, (*Z*)-3,4-dichloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)aniline **266e**, (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methoxyaniline **266af** and (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-methoxyaniline **266aw**. In conclusion it was found that the most reactive compounds were the dithiazolylidenes (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylid-eneamino)pyridin-3-yl acetate **70o** and (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene-amino)benzoic acid **108**. Moreover all the dithiazolylidenes were tested for toxicity against XENOPUS fetus. It was found that the methoxy analogue (*Z*)-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-methoxyaniline **266af** made the fetus transparent.

CHAPTER 9

Experimental

Sections

9.1 Introduction

DCM, MeOH, EtOH, PhH, PhMe and PhCl were freshly distilled from CaH_2 under argon. DMF was azeotropically distilled with PhH then distilled under vacuum from anhydrous $MgSO_4$ and stored over 4Å molecular sieves. THF was freshly distilled from potassium under argon. Anhydrous $BnEt_3NX$ (where X = Cl and I) and Et_4NBr (for cyclization reactions, Chapters 3 and 4) were freshly powdered using an agate pestle and mortar before use and stored in a vacuum oven (P = 12 psi and T = 40 ^oC). Reactions were protected by $CaCl_2$ drying tubes or performed under an argon atm1osphere. All volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial thin layer chromatography (TLC) plates (Merck Kieselgel 60 F_{254}). The plates were observed under UV light at 254 and 365 nm. The technique of dry flash chromatography was used throughout for all non-TLC scale chromatographic separations using Merck Silica Gel 60 (less than 0.063 mm). Microwave mediated chemistry was performed with a CEM Discovery Microwave Reactor and reaction temperatures were controlled using standard IR thermometry. Melting points were determined using a PolyTherm-A, Wagner & Munz, Koefler-Hoststage Microscope apparatus or where noted using a TA Instruments DSC Q1000 with samples hermetically sealed in aluminium pans under an argon atmosphere; using heating rates of 5 ^oC/min. Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a Perkin-Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation "inf". IR spectra were recorder on a Shimidazu FTIR-NIR Prestige-21 spectrometer with Pike *Miracle* Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w, respectively. ^1H and ^{13}C NMR spectra were recorder on a Bruker Avance 300 machine (at 300 and 75 MHz respectively). *C*H and CH_2 assignments were supported by ^{13}C NMR DEPT 1354 experiments. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GCMS with direct inlet probe whilst high resolution spectra were recorded on a VG Autospec "Q" mass spectrometer. Petrol refers to light petroleum, bp 40-60 ^oC. 4,5-Dichloro-1,2,3-dithiazolium chloride **42**,[42] 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66**,[75] benzo[*d*]oxazole-2-carbonitrile **67**,[258] (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoic acid **108**,[84] benzo[*b*][1,2,3]dithiazolo[5,4-*c*][1,4]oxazine **114**,[258] 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino) benzonitriles **142a-h**,[111] 2-amino-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **159**,[281]

2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **227**,[98] 2-chloro-6,7-dimethoxyquinazoline **228**,[308] *N*-(2-cyanophenyl)formamide **233**,[329] 3-amino-1(*p*-tosyl)indole-2-carbonitrile **242a**[304] 2-(*p*-tosylamino)benzonitrile **245a**,[304] *N*-(2-cyanophenyl)-*N*-(*p*-tosyl)aminoacetonitrile **246a**,[304] *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methoxyaniline **266af**,[42] *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-3,4-dimethoxyaniline **266ay**,[84] *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,4-dimethoxyaniline **266az**[92] and *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,4,5-trimethoxyaniline **266aaa**[481] were prepared according to literature procedures.

9.2 Compounds Related to Chapter 2

N-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine 70a (typical procedure: see Table 2)

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (454.2 mg, 2.18 mmol) in DCM (4 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added 2-aminopyridine (500 mg, 2.18 mmol). After 1 h, to the reaction mixture was added, dropwise, Hünig's base (741 μL, 4.36 mmol) and left to stir at *ca*. 20 °C for additional 2 h. The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (traces), followed by 4-chloro-5*H*-1,2,3-dithiazole-5-thione (hexane/DCM, 4:1) and then (hexane/DCM, 1:4) the title compound **70a** (180.5 mg, 73%) as yellow-green needles, mp 149-150 °C (lit.[75] 154-155 °C) (cyclohexane); (found: C, 36.6; H, 1.7; N, 18.3. $C_7H_4ClN_3S_2$ requires C, 36.6; H, 1.8; N, 18.3%); λ_{max}(DCM)/nm 246 (log ε 2.83), 294 (2.48), 388 (2.84), 405 (2.96), 427 (2.76); ν_{max}/cm^{-1} 1589w, 1560w, 1512m, 1491m, 1449m, 1431m, 1296w, 1267w, 1258w, 1175m, 1142m, 1092w, 1042w, 999w, 891m, 862m, 787s, 742m, 704m; δ_H(300 MHz; $CDCl_3$) 8.60 (1H, d, *J* 4.2, Py *H*-3 or 6), 7.90 (1H, ddd, 7.7, 7.7, 1.7, Py *H*-4 or 5), 7.67 (1H, d, *J* 8.1, Py *H*-3 or 6), 7.28 (1H, ddd, *J* 7.2, 5.1, 1.0, Py *H*-4 or 5); δ_C(75 MHz; $CDCl_3$) 157.9, 153.9, 148.9, 143.3 (*C*H), 138.4 (*C*H), 122.4 (*C*H), 121.6 (*C*H); *m/z* (EI) 231 (M^++2, 8%), 229 (M^+, 19), 194 (85), 168 (5), 162 (5), 125 (3), 104 (3), 78 (100), 64 (20), 51 (43).

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol 70b

Similar treatment of 2-amino-3-hydroxypyridine (240 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using 2,6-lutidine (505.0 μL, 4.36 mmol) as base gave the *title compound* **70b** (123 mg, 11%) as orange cotton fibers, mp 142-143 °C (from

cyclohexane/EtOH); (found C, 34.1; H, 1.6; N, 17.0. $C_7H_4ClN_3OS_2$ requires C, 34.2; H, 1.6; N, 17.1%); λ_{max}(DCM)/nm 228 (log ε 2.79), 247 (2.74), 265 inf (2.40), 304 (2.47), 387 inf (2.66), 407 (2.90), 428 (2.96), 454 (2.71); ν_{max}/cm^{-1} 3466w (OH), 3366w, 1599w, 1572m, 1516s, 1491s, 1462m, 1433s, 1403w, 1337m, 1287m, 1271m, 1231s, 1186s, 1153s, 1105m, 1053m, 964w, 908m, 878s, 826m, 795s, 779s, 764s; δ_H(300 MHz; DMSO-d_6) 8.12 (1H, d, *J* 1.5, Py *H*-4), 7.45 (1H, d, *J* 7.9, Py *H*-6), 7.33-7.29 (1H, m, Py *H*-5); δ_C(75 MHz; DMSO-d_6) 156.1, 149.3, 148.3, 143.4, 133.7 (Py *C*H), 123.7 (Py *C*H), 123.6 (Py *C*H); δ_C(75 MHz; DEPT-135, DMSO-d_6), 133.7 (Py *C*H), 123.7 (Py *C*H), 123.6 (Py *C*H); *m/z* (EI) 247 (M^++2, 14%), 245 (M^+, 34), 210 (14), 146 (100), 120 (9), 94 (41), 70 (12), 64 (38); (found M^+, 244.9484 $C_7H_4ClN_3OS_2$ requires *M*, 244.9484). Further elution (DCM) gave *4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-[(*E*)-4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino]-pyridin-3(4*H*)-one* **74** (52 mg, 3%) as blue dust, mp 288-289 °C (from DCE); (found: C; 28.4, H; 0.5, N; 14.6. $C_9H_2Cl_2N_4OS_4$ requires C; 28.4; H, 0.5; N, 14.7%); λ_{max}(DCM)/nm 231 (log ε 2.39), 260 (2.34), 268 (2.32), 331 (1.81), 418 (1.74), 615 (2.09); ν_{max}/cm^{-1} 2922w, 2847w, 1570w, 1503m , 1485m, 1447m, 1424m, 1367w, 1360w, 1325s, 1288m, 1246s, 1209m, 1105w, 1047m, 941w, 914w, 883m, 851w, 824m, 808w, 789m, 779m; δ_H(500 MHz; TFA-d_1) 9.23 (1H, *J* 6.0, Py *H*), 8.08 (1H, *J* 5.5, Py *H*); δ_C(125 MHz; TFA-d_1) 164.4 (s), 162.9 (s), 155.5 (s), 146.3 (s), 141.0 (s), 129.6 (d), 129.3 (s), 119.9 (d); *m/z* (EI) 384 (M^++4, 7%), 382 (M^++2, 22), 380 (M^+, 25), 347 (13), 345 M^+ -Cl, 25), 310 (4), 283 (39), 281 (100), 253 (5), 231 (14), 229 (33), 220 (4), 214 (4), 192 (3), 166 (10), 160 (7), 142 (8), 140 (14), 137 (7), 134 (11), 102 (14), 99 (11), 96 (16), 85 (11), 82 (17), 76 (18), 70 (21), 64 (80), 57 (14); Further elution (DCM/*t*-BuOMe, 4:1) gave *2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-6-methylpyridin-3(2*H*)-one* **76** as lusterous bronze coloured, mp > 300 °C (from DCE); (found: C; 34.3, H; 1.6; N; 17.0. $C_7H_4ClN_3OS_2$ requires C; 34.2, H; 1.6; N, 17.1%); λ_{max}(DCM)/nm 232 (log ε 3.76), 281 (3.73), 298 (3.66), 549 (4.19); ν_{max}/cm^{-1} 3486w, 3300m (NH_2), 3215w, 1612w, 1554m, 1541s, 1511s, 1449m, 1428s, 1407s, 1365s, 1333w, 1318m, 1235s, 1206m, 1139m, 1079m, 960w, 875m, 831m, 812s, 753w; δ_H(500 MHz; DMSO-d_6) 8.51 (1H, *J* 9.5, Py *H*), 7.27 (2H, br d, N*H*$_2$), 6.34 (1H, *J* 9.0, Py *H*); δ_C(125 MHz; DMSO-d_6) 173.9 (s), 154.2 (s), 147.4 (s), 141.4 (s), 135.6 (s), 127.9 (d), 121.0 (d); *m/z* (EI) 247 (M^++2, 28%), 245 (M^+, 64), 210 (14), 182 (13), 178 (28), 175 (35), 140 (14), 110 (16), 104 (35), 96 (31), 93 (31), 82 (80), 76 (84), 70 (60), 64 (100), 53 (37).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-3-methoxypyridin-2-amine 70c**

Similar treatment of 2-amino-3-methoxypyridine (270 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using pyridine (353 μL, 4.36 mmol) as base gave the *title compound* **70c** (70.1 mg, 71%) as yellow fibers, mp 190-191 ^{o}C (cyclohexane/EtOH); (found: C, 36.9; H, 2.1; N, 16.3. $C_8H_6ClN_3OS_2$ requires C, 37.0; H, 2.3; N, 16.2%); λ_{max}(DCM) 228 (log ε 3.69), 249 (3.70), 304 (3.42), 361 inf (3.05), 374 inf (3.33), 386 inf (3.53), 403 (3.78), 425 (3.85), 449 (3.61); ν_{max}/cm^{-1} 3075w, 2970w, 2936w, 2837w, 1572m, 1508m, 1487m, 1464m, 1449w, 1431s, 1425s, 1308s, 1294m, 1279s, 1263w, 1209w, 1182m, 1171m, 1155w, 1125s, 1076w, 1013s, 951w, 893m, 868s, 808s, 783s, 764s; δ_H(300 MHz; DMSO-d_6) 8.22 (1H, d, *J* 4.2, Py *H*-4 or 6), 7.63 (1H, d, *J* 7.8, Py *H*-4 or 6), 7.43 (1H, dd, *J* 8.1, 4.8, Py *H*-5), 3.95 (3H, s, C*H*$_3$O); δ_C(75 MHz; DMSO-d_6) 156.9, 150.6, 148.3, 144.3, 134.3 (*C*H), 123.3 (*C*H), 119.8 (*C*H), 55.9 (*C*H$_3$O); *m/z* (EI); 261 (M$^+$+2, 8%), 259 (M$^+$, 19), 226 (8), 224 (37), 195 (5), 160 (36), 134 (7), 123 (8), 108 (13), 93 (14), 78 (100), 70 (12), 64 (30), 51 (20).

3,5-Dichloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine 70d

Similar treatment of 2-amino-3,5-dichloropyridine (355.3 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using 2,6-lutidine (505 μL, 4.36 mmol) as base gave the *title compound* **70d** (127.5 mg, 70%) as yellow cotton fibers, mp 145-146 ^{o}C (from cyclohexane); (found: C, 28.2; H, 0.6; N, 13.9. $C_7H_2Cl_3N_3S_2$ requires C, 28.2; H, 0.7; N, 14.1%); λ_{max}(DCM) 227 (log ε 2.93), 255 (3.09), 262 (3.08), 303 (2.65), 397 (3.06), 417 (3.17), 440 (2.97); ν_{max}/cm^{-1} 3067w, 3049w (Ar CH), 1846w, 1823w, 1564m, 1539m, 1524m, 1491m, 1412s, 1377m, 1279m, 1240m, 1225w, 1171m, 1142w, 1121m, 924w, 901m, 880s, 810m, 764m, 756m; δ_H(300 MHz; DMSO-d_6) 8.64 (1H, d, *J* 2.2, Py *H*-4 or 6), 8.37 (1H, d, *J* 2.2, Py *H*-4 or 6); δ_C(75 MHz; DMSO-d_6) 160.3, 150.1, 148.6, 141.6 (*C*H), 138.4 (*C*H), 127.6, 127.5; *m/z* (EI); 301 (M$^+$+4, 3%) 299 (M$^+$+2, 6), 297 (M$^+$, 6), 266 (4), 264 (18), 262 (24), 236 (3), 172 (3), 146 (10), 137 (4), 125 (4), 110 (29), 102 (5), 98 (5), 93 (8), 85 (8), 75 (15), 70 (16), 64 (100), 50 (5).

3,5-Dibromo-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-2-amine 70e

Similar treatment of 2-amino-3,5-dibromopyridine (549.4 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using 2,6-Lutidine (505 μL, 4.36 mmol) as base gave the *title compound* **70e** (108.4 mg, 70%) as yellow cubes, mp 174-175 ^{o}C (from cyclohexane); (found:

C, 21.8; H, 0.5; N, 10.8. $C_7H_2Br_2ClN_3S_2$ requires C, 21.7; H, 0.5; N, 10.8%); λ_{max}(DCM) 227 (log ε 3.86), 256 (3.93), 265 (3.91), 398 (3.86), 419 (3.97), 443 (3.75); ν_{max}/cm^{-1} 1802w, 1539m, 1514s, 1485s, 1454w, 1414s, 1364m, 1314w, 1275m, 1244w, 1231w, 1167m, 1123w, 1098m, 1045m, 914w, 897m, 891s, 876s, 795s, 754m, 737s; δ_H(300 MHz; DMSO-d_6) 8.75 (1H, s, Py *H*-4 or 6), 8.59 (1H, s, Py *H*-4 or 6); δ_C(75 MHz; DMSO-d_6) 160.3, 151.1, 148.55, 144.25 (*C*H), 143.9 (*C*H), 118.4, 115.8; *m/z* (EI); 389 (M^++4, 18%), 387 (M^++2, 21), 385 (M^+, 9), 354 (25), 352 (37), 350 (20), 310 (10), 308 (28), 306 (23), 262 (5), 247 (11), 245 (11), 236 (17), 183 (6), 181 (6), 156 (21), 154 (19), 125 (7), 102 (12), 93 (9), 76 (41), 64 (100), 50 (15).

_N_-(4-Chloro-5_H_-1,2,3-dithiazol-5-ylidene)-3-nitropyridin-2-amine 70f

Similar treatment of 2-amino-3-nitropyridine (303.0 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using 2,6-Lutidine (505 μL, 4.36 mmol) as base gave the *title compound* **70f** (122.8 mg, 62%) as yellow cotton fibers, mp 188-189 ^oC (from cyclohexane); (found: C, 30.7; H, 1.0; N, 20.4. $C_7H_3ClN_4O_2S_2$ requires C, 30.6; H, 1.1; N, 20.4%); λ_{max}(DCM)/nm 230 (log ε 2.93), 278 (2.49), 395 (2.90), 411 (3.03), 432 (2.88); ν_{max}/cm^{-1} 1597m, 1560m, 1526s, 1479m, 1427s, 1362m, 1344s, 1279w, 1261w, 1244w, 1169m, 1086w, 901s, 878m, 847s, 808s, 770s, 706m; δ_H(300 MHz; DMSO-d_6) 8.87 (1H, dd, *J* 5.0, 1.5, Py *H*-6), 8.53 (1H, dd, *J* 7.9, 1.5, Py *H*-4), 7.59 (1H, dd, *J* 7.9, 5.0, Py *H*-5); δ_C(75 MHz; DMSO-d_6) 161.9, 148.6, 148.3 (*C*H), 146.8, 141.6, 133.5 (*C*H), 121.8 (*C*H); *m/z* (EI); 276 (M^++2, 16%), 274 (M^+, 37), 239 (18), 228 (41), 226 (99), 210 (4), 191 (6), 155 (12), 149 (35), 137 (13), 119 (78), 102 (18), 91 (63), 76 (38), 70 (29), 64 (100), 50 (22).

_N_-(4-Chloro-5_H_-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70g

Similar treatment of 3-amino-pyridine (500 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using Hünig's base (741 μL, 4.36 mmol) as base gave the *title compound* **70g** (140.9 mg, 57%) as yellow cotton fibers, mp 126-127 ^oC (from cyclohexane/EtOH); (found: C, 36.7; H, 1.7; N, 18.2. $C_7H_4ClN_3S_2$ requires C, 36.6; H, 1.8; N, 18.3%); λ_{max}(DCM) 230 (log ε 2.86), 280 (2.33), 374 (2.65); ν_{max}/cm^{-1} 3051w, 3042w, 1570s, 1539w, 1504m, 1474m, 1410s, 1327w, 1229s, 1192m, 1150s, 1121w, 1099m, 1042m, 1022m, 943m, 914m, 870s, 851m, 812m, 773s, 706s; δ_H(300 MHz; DMSO-d_6) 8.47-8.43 (2H, m, Py *H*-2 and 6), 7.65 (1H, ddd, *J* 8.3, 2.6, 1.5, Py *H*-4), 7.51 (1H, dd, *J* 8.1, 4.8, Py *H*-5); δ_C(75 MHz; DMSO-d_6) 161.9, 147.3, 146.8 (*C*H), 146.6, 141.5 (*C*H), 126.25 (*C*H), 124.6 (*C*H); *m/z* (EI) 231 (M^++2, 17%),

229 (M^+, 42), 168 (23), 130 (6), 125 (8), 104 (9), 93 (6), 78 (38), 70 (11), 64 (S_2, 100), 51 (47).

3-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol 70h

Similar treatment of 3-amino-2-hydroxypyridine (240.0 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using pyridine (351.2 μL, 4.36 mmol) as base gave the *title compound* **70h** (590.8 mg, 53%) as orange dust, mp 151-152 ^oC (from Pentane/DCM in the fridge); (found C, 34.3; H, 1.7; N, 17.0 $C_7H_4ClN_3OS_2$ requires C, 34.2; H, 1.6; N, 17.1%); λ_{max}(DCM)/nm 228 (log ε 2.75), 251 (2.67), 326 (2.64), 347 (2.64), 409 (2.77); ν_{max}/cm^{-1} 3125w (OH), 2922w, 2853w, 1703w, 1638s, 1612m, 1572m, 1547m, 1524w, 1472m, 1433w, 1358w, 1346w, 1323w, 1310w, 1245m, 1236m, 1175w, 1144m, 1057w, 1020w, 959w, 943m, 910m, 893w, 856s, 826w, 797w, 779w, 770s; δ_H(300 MHz; DMSO-d_6) 12.07 (1H, br s, O*H*), 7.35(2H, dd, *J* 4.85, Py *H*), 6.33 (1h, dd, *J* 6.7, Py *H*); δ_C(75 MHz; DMSO-d_6) 157.5, 155.1, 147.0, 137.9, 132.7 (Py *C*H), 131.2 (Py *C*H), 105.6 (Py *C*H), 91.1; δ_C(75 MHz; DEPT-135, DMSO-d_6), 132.7 (Py *C*H), 131.2 (Py *C*H), 105.6 (Py *C*H); *m/z* (EI) 247 (M^++2, 9%), 245 (M^+, 21), 210 (32), 146 (100), 120 (13), 117 (10), 102 (12), 96 (10), 92 (40), 76 (11), 70 (33), 64 (77), 52 (19); (found M^+, 244.9484 $C_7H_4ClN_3OS_2$ requires *M*, 244.9484).

2-Chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70i

Similar treatment of 2-amino-2-chloropyridine (281.2 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using DABCO (489 mg, 4.36 mmol) as base gave the *title compound* **70i** (175 mg, 85%) as yellow-orange needles, mp 133-134 ^oC (from cyclohexane); (found: C, 31.9; H, 1.0; N, 15.9. $C_7H_3Cl_2N_3S_2$ requires C, 31.8; H, 1.1; N, 15.9%); λ_{max}(DCM) 232 (log ε 2.87), 281 (2.46), 363 (2.63); ν_{max}/cm^{-1} 3051w, 1722w, 1703w, 1657w, 1584s, 1566w, 1557w, 1506m, 1443w, 1400s, 1267w, 1250w, 1240w, 1221w, 1207m, 1157m, 1082s, 1067w, 972w, 926w, 903w, 870s, 797m, 779s, 743s, 710s; δ_H(300 MHz; $CDCl_3$) 8.26 (1H, d, *J* 3.6, Py *H*-6), 7.45 (1H, dd, *J* 7.7, 1.3, Py *H*-4), 7.33 (1H, dd, *J* 7.8, 4.7, Py *H*-5); δ_C(75 MHz; $CDCl_3$) 162.8, 147.3, 146.35 (*C*H), 145.0, 142.45, 127.3 (*C*H), 123.4 (*C*H); *m/z* (EI); 267 (M^++4, 4%), 265 (M^++2, 21), 263 (M^+, 30), 204 (14), 202 (34), 164 (9), 135 (6), 125 (7), 112 (13), 103 (14), 93 (7), 76 (30), 64 (100), 50 (14).

4-Chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70j

Similar treatment of 3-amino-4-chloropyridine (281.2 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol)using 2,6-Lutidine (505 μL, 4.36 mmol) as base gave the *title compound* **70j** (156.5 mg, 76%) as yellow prisms, mp 160-161 ^{o}C (from cyclohexane/EtOH); (found: C, 31.9; H, 1.1; N, 15.8 $C_7H_3Cl_2N_3S_2$ requires C, 31.8; H, 1.1; N, 15.9%); λ_{max}(DCM) 231 (log ε 2.80), 279 (2.32), 364 (2.59); ν_{max}/cm^{-1} 3080w, 3057w, 1591s, 1557m, 1547w, 1506m, 1485w, 1466m, 1402m, 1283m, 1242m, 1225w, 1215w, 1146m, 1092s, 1053w, 966w, 912m, 862s, 831s, 783s, 739w, 708s; δ_H(300 MHz; DMSO-d_6) 8.48 (1H, s, Py *H*-2), 8.40 (1H, d, *J* 5.4, Py *H*-5 or 6), 7.70 (1H, d, *J* 5.4, Py *H*-5 or 6); δ_C(75 MHz; DMSO-d_6) 164.45, 147.4 (*C*H), 145.7, 145.55. 140.6 (*C*H), 133.4, 125.1 (*C*H); *m/z* (EI) 267 (M$^+$+4, 6%), 265 (M$^+$+2, 24), 263 (M$^+$, 33), 204 (10), 202 (25), 170 (7), 164 (5), 125 (9), 112 (12), 103 (9), 93 (5), 86 (18), 84 (26), 76 (18), 70 (10), 64 (100), 57 (10).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyrazin-2-amine 70k**

Similar treatment of 3-amino-pyrazine (207.1 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using pyridine (353 μL, 4.36 mmol) as base gave the *title compound* **70k** (157.7 mg, 65%) as yellow-orange needles, mp 208-209 ^{o}C (from cyclohexane/EtOH); (found: C, 31.2; H, 1.2; N, 24.2. $C_6H_3ClN_4S_2$ requires C, 31.2; H, 1.3; N, 24.3%); λ_{max}(DCM) 227 (log ε 2.96), 244 (2.91), 293 (2.69), 328 (2.46), 393 (2.98), 409 (3.09), 429 (2.92); ν_{max}/cm^{-1} 1526s, 1501m, 1476s, 1452s, 1406s, 1298m, 1281m, 1179s, 1146m, 1061m, 1016m, 903s, 868s, 845s, 793s, 750w, 714m; δ_H(300 MHz; DMSO-d_6) 8.95 (1H, d, *J* 1.2, pyrazine *H*-3), 8.72 (1H, dd, *J* 2.7, 1.5, pyrazine *H*-5), 8.59 (1H, d, *J* 2.7, pyrazine *H*-6); δ_C(75 MHz; DMSO-d_6) 160.6, 150.6, 148.5, 144.7 (*C*H), 141.0 (*C*H), 139.3 (*C*H); *m/z* (EI) 232 (M$^+$+2, 14%), 230 (M$^+$, 32), 195 (100), 169 (11), 125 (12), 102 (8), 79 (70), 70 (16), 64 (68), 52 (66).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine 70l**

Similar treatment of 4-amino-pyridine (500 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using triethylamine (604 μL, 4.36 mmol) as base gave the *title compound* **70l** (59.2 mg, 24%) as yellow prisms, mp 166-167 ^{o}C (from cyclohexane/EtOH); (found: C, 36.5; H, 1.8; N, 18.1. $C_7H_4ClN_3S_2$ requires C, 36.6; H, 1.8; N, 18.3%); λ_{max}(DCM) 230 (log ε 2.82), 374 (2.63); ν_{max}/cm^{-1} 1593m, 1568s, 1549m, 1501m, 1485w, 1418m, 1246w, 1207m, 1152m, 1090w, 1053w, 999m, 872s, 858s, 827m, 779m, 735w; δ_H(300 MHz; DMSO-d_6) 8.63 (2H, d,

J 5.1, Py *H*-2 and 6), 7.15 (2H, dd, *J* 4.7, 1.4, Py *H*-3 and 5); δ_C(75 MHz; DMSO-d_6) 162.5, 158.1, 151.6 (*C*H), 146.4, 113.9 (*C*H); *m/z* (EI) 231 (M^++2, 34%), 229 (M^+, 87), 194 (25), 168 (57), 162 (24), 130 (14), 127 (13), 125 (31), 104 (14), 93 (11), 78 (55), 64 (100), 51 (70).

_N_-(4-Chloro-5_H_-1,2,3-dithiazol-5-ylidene)-2,6-dimethylpyridin-4-amine 70m

Similar treatment of 4-amino-2,6-dimethylpyridine (266.0 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using triethylamine (604 μL, 4.36 mmol) as base gave the *title compound* **70m** (46.5 mg, 22%) as yellow prisms, mp 127-128 ^oC (from cyclohexane/EtOH); (found: C, 42.0; H, 3.1; N, 16.3. $C_9H_8ClN_3S_2$ requires C, 41.9; H, 3.1; N, 16.3%); λ_{max}(DCM) 331 (log ε 3.01), 248 inf (2.72), 317 inf (2.28), 370 (2.75); ν_{max}/cm^{-1} 2920w, 2077w, 1645w, 1584s, 1557m, 1508m, 1454w, 1410w, 1373w, 1319m, 1292w, 1269w, 1238w. 1207w, 1171s, 1123w, 1024w, 995w, 939m, 905w, 887s, 864w, 839m, 779s, 756w, 733m; δ_H(300 MHz; $CDCl_3$) 6.65 (2H, s, Py *H*-2 and 6), 2.50 (6H, s, 2×CH_3); δ_C(75 MHz; $CDCl_3$) 160.8, 160.0, 159.0, 147.4, 109.8 (*C*H), 24.5 (*C*H$_3$); *m/z* (EI) 259 (M^++2, 36%), 257 (M^+, 84), 244 (5), 242 (20), 224 (12), 222 (38), 196 (14), 190 (31), 132 (100), 125 (13), 106 (25), 91 (6), 77 (7), 64 (51), 51 (6).

4-(4-Chloro-5_H_-1,2,3-dithiazol-5-ylideneamino)pyrimidine-5-carbonitrile 70n

Similar treatment of 4-amino-5-cyanopyrimidine (261.6 mg, 2.18 mmol) with Appel salt **42** (454.2 mg, 2.18 mmol) using pyridine (353 μL, 4.36 mmol) as base gave the *title compound* **70n** (129.1 mg, 61%) as orange prisms, mp 205-206 ^oC (from EtOH); (found: C, 32.9; H, 0.8; N, 27.3. $C_7H_2ClN_5S_2$ requires C, 32.9; H, 0.8; N, 27.4%); λ_{max}(DCM) 230 (log ε 2.70), 268 (2.57), 318 (2.06), 376 inf (2.50), 395 (2.88), 414 (3.08), 435 (2.99); ν_{max}/cm^{-1} 2239w and 2230w (C≡N), 1565w, 1560w, 1537m, 1507m, 1459s, 1424s, 1412s, 1391s, 1282w, 1192m, 1178w, 1162w, 1106w, 950w, 923s, 876s, 823w, 816m, 787m, 774m; δ_H(300 MHz; acetone-d_6) 9.45 (1H, s, Pyrimidine *H*-2 or 6), 9.28 (1H, s, Pyrimidine *H*-2 or 6); δ_C(75 MHz; acetone-d_6) 166.4, 163.05 (Pyrimidine *C*H), 162.3, 159.2 (Pyrimidine *C*H), 150.9, 114.6 (*C*≡N), 105.6 (*C*C≡N); *m/z* (EI) 257 (M^++2, 12%), 255 (M^+, 27), 220 (87), 194 (9), 125 (10), 104 (11), 102 (8), 93 (8), 77 (55), 64 (100), 51 (17).

Reaction of 3-hydroxypyridines with Appel salt 42 (see Scheme 53)

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (1.10 g, 5.26 mmol) in DCM (4 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was added 3-hydroxypyridine (500 mg, 5.26 mmol). After 1 h, to the reaction mixture was added, dropwise, pyridine (1.12 mL, 10.52 mmol) and left to stir at *ca*. 20 ^{o}C for additional 2 h. The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (traces), followed by 4-chloro-5*H*-1,2,3-dithiazole-5-thione (hexane/DCM, 4:1) and then (hexane/DCM, 1:9) *4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3(4*H*)-one* **78** (14.5 mg, 6%) as red needles mp>300°C (from cyclohexane/DCE); (found: C; 36.6, H; 1.2, N; 12.0. $C_7H_3ClN_2OS_2$ requires C; 36.4, H; 1.3, N; 12.1%); λ_{max}(DCM)/nm 229 (log ε 3.35), 247 (3.31), 297 (2.85), 354 (2.77), 519 (3.34); ν_{max}/cm^{-1} 3059w, 1593w, 1506s, 1422w, 1375m, 1364m, 1312w, 1273s, 1248s, 1204w, 1142s, 1117m ,1024m, 989w, 891m, 851s, 814s, 768m; δ_H(500 MHz; $CDCl_3$) 8.48 (1H, dd, *J* 3.5, 1.5, Py *H*), 7.60 (1H, dd, *J* 9.0, 1.0, Py *H*), 7.52 (1H, dd, *J* 9.0, 4.0, Py *H*); δ_C(125 MHz; $CDCl_3$) 169.9 (s), 155.9 (s), 150.8 (s), 142.3 (d), 141.7 (s), 130.5 (d), 128.1 (d); *m/z* (EI) 232 (M^+ +2, 25), 230 (M^+, 59), 204 (11), 202 (28), 197 (10), 196 (10), 195 (100), 167 (16), 163 (6), 141 (29), 137 (5), 114 (7), 109 (13), 103 (9), 102 (22), 97 (6), 93 (7), 82 (15), 79 (26), 77 (16), 70 (26), 64 (15).

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-6-methylpyridin-3(2*H*)-one 81

Similar treatment of 2-methyl-5-hydroxypyridine (573.3 mg, 5.26 mmol) with Appel salt **42** (1.10 g, 5.26 mmol) using pyridine (1.12 mL, 10.52 mmol) as base gave the *title compound* **81** (24.8 mg, 11%) as purple dust, mp > 300 ^{o}C (from cyclohexane/DCE); (found C, 39.4; H, 2.0; N, 11.4 $C_8H_5ClN_2OS_2$ requires C, 39.3; H, 2.1; N, 11.45%) λ_{max}(DCM)/nm 231 (log ε 3.10), 308 (2.99), 367 inf (2.43), 536 (2.48); ν_{max}/cm^{-1} 3065w, 2916w, 2847w, 1520s, 1371s, 1319m, 1267m, 1256m, 1233m, 1150s, 1115m, 1032w, 976w, 964w, 891m, 860s, 833s, 822s, 777w, 770w; δ_H(300 MHz; CD_2Cl_2) 7.63 (1h, d, *J* 8.4, Py *H*), 7.47 (1H, d, *J* 9.0, Py *H*), 2.72 (3H, s, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 170.2 (*C*=O), 154.25, 151.6, 150.6, 141.0, 132.6 (Py *C*H), 128.4 (Py *C*H), 25.0 (*C*H$_3$); δ_C(75 MHz; DEPT-135, CD_2Cl_2) 132.6 (Py *C*H), 128.4 (Py *C*H), 25.0 (*C*H$_3$); *m/z* (EI) 246 (M^++2, 22%), 244 (M^+, 53), 216 (16), 209 (100), 181 (21), 122 (9), 91 (6), 70 (10), 53 (45).

Purple 2 compound 84

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (219.5 mg, 1.05 mmol) in DCE (4 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was added 3-hydroxypyridine (100 mg, 1.05 mmol). The mixture was left to heat at reflux temperature for 4 h until no more 4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3(4*H*)-one **78**remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (traces). Further elution (hexane/DCM, 4:1) gave 4-chloro-5*H*-1,2,3-dithiazole-5-thione (10 mg, 6%) and further elution (hexane/DCM, 7:2) gave the *title compound* **84** (14.5 mg, 10%) as purple dust, mp 160-161 ^{o}C (from cyclohexane/DCE); ν_{max}/cm^{-1} 3061w, 1512s, 1385w, 1366s, 1319m, 1265m, 1248m, 1153s, 1132w, 1074m, 1018w, 889m, 858m, 843m, 826m, 783m, 754w; δ_H(300 MHz; DMSO-d_6) 7.79 (1H, d, *J* 9.0, Py *H*), 7.57 (1H, d, *J* 8.4, Py *H*); δ_C(75 MHz; CD_2Cl_2) 170.1, 154.8, 151.4, 145.1, 140.8, 130.3 (Py *C*H), 128.6 (Py *C*H), 114.1, 99.05; δ_C(75 MHz; DEPT-135, CD_2Cl_2) 130.3 (Py *C*H), 128.6 (Py *C*H); *m/z* (EI) 232 (M^++2, 37%), 230 (M^+, 90).

9.3 Compounds Related to Chapter 3

Thermolysis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70g (typical procedure: see Scheme 63)

Thermolysis of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridine **70g** (50.4 mg, 0.22 mmol) at *ca.* 150 ^{o}C in argon atmosphere gave after 8 min 3 products (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (5.1 mg, 36%). Further elution (DCM) gave *thiazolo[5,4-*b*]pyridine-2-carbonitrile* **97** (7.8 mg, 22%) as colourless cotton fibers, mp 124-125 ^{o}C (from cyclohexane); (found: C, 52.1; H, 2.0; N, 25.9. $C_7H_3N_3S$ requires C, 52.2; H, 1.9; N, 26.1%); λ_{max}(DCM) 242 inf (log ε 2.75), 247 (2.66), 274 (2.85), 302 (2.75); ν_{max}/cm^{-1} 3107w, 3069w (Ar CH), 2234w (C≡N), 1574w, 1551m, 1462m, 1441s, 1375s, 1279m, 1248m, 1221w, 1167m, 1155m, 1115w, 1090w, 1042w, 880w, 810s, 748s, 704m; δ_H(300 MHz; $CDCl_3$) 8.83 (1H, br s, Ar *H*-5 or 7), 8.49 (1H, dd, *J* 8.4, 1.4, Ar *H*-5 or 7), 7.63 (1H, dd, *J* 8.3, 4.5, Ar *H*-6); δ_C(75 MHz; $CDCl_3$) 157.4, 150.8 (*C*H), 145.1, 137.5, 132.5 (*C*H), 122.8 (*C*H), 112.5 (*C*≡N); *m/z* (EI) 161 (M^+, 100%), 109 (26), 103 (12), 82 (24), 70 (18), 64 (6), 51 (6). Further elution (DCM/*t*-butyl methyl ether, 9:1) gave *thiazolo[4,5-*c*]pyridine-2-carbonitrile* **99** (8.5 mg, 24%) as colourless needles, mp 162-163 ^{o}C

(from cyclohexane); (Found: C, 52.2; H, 1.8; N, 26.0. $C_7H_3N_3S$ requires C, 52.2; H, 1.9; N, 26.1%); λ_{max}(DCM) 241 (log ε 3.24), 278 (3.12), 315 inf (2.35); ν_{max}/cm^{-1} 3094w and 3065w (Ar CH), 2232w (C≡N), 1576m, 1526w, 1460m, 1437m, 1416m, 1273w, 1233m, 1196s, 1157s, 1121w, 1084m, 1036m, 922w, 881m, 856w, 822s, 743m, 725m, 704s; δ_H(300 MHz; $CDCl_3$) 9.56 (1H, s, Ar *H*-4), 8.75 (1H, d, *J* 5.6, Ar *H*-6 or 7), 7.97 (1H, d, *J* 5.6, Ar *H*-6 or 7); δ_C(75 MHz; $CDCl_3$) 148.5, 147.8 (*C*H), 146.4 (*C*H), 142.8, 137.9, 116.5 (*C*H), 112.2 (*C*≡N); *m/z* (EI) 161 (M^+, 100%), 134 (7), 109 (25), 82 (61), 69 (16), 52 (5), 45 (7).

Thermolysis of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine 70l

Similar treatment of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine **70l** at *ca*. 180 ^oC gave S_8 (3.2 mg, 23%) and *thiazolo[5,4-c]pyridine-2-carbonitrile* **98** (10.6 mg, 30%) as colourless needles, mp 162-163 ^oC (from cyclohexane); (found C, 52.2; H, 1.8; N, 26.0. $C_7H_3N_3S$ requires C, 52.2; H, 1.9; N, 26.1%); λ_{max}(DCM); ν_{max}/cm^{-1} 1574m, 1535w, 1458m, 1429w, 1402s, 1269m, 1250m, 1234w, 1155m, 1092w, 1078, 1020m, 1005w, 910w, 885m, 868w, 831m, 822m; δ_H(500 MHz; $CDCl_3$) 9.38 (1H, s, Ar *H*-2), 8.83 (1H, d, *J* 5.5, Ar *H*-5 or 6), 8.12 (1H, d, *J* 5.5, Ar *H*-6 or 5); δ_C(125 MHz; $CDCl_3$) 156.7 (s), 147.0 (*C*H), 145.1 (*C*H), 141.7 (s), 131.6 (s), 118.9 (*C*H), 112.3 (*C*≡N); *m/z* (EI) 161 (M^+, 100%), 134 (7), 109 (25), 82 (61), 69 (16), 52 (5), 45 (7).

Treatment of N-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70g with $BnEt_3NI$ (typical procedure: see Table 3)

To a mixture of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70g** (50.4 mg, 0.22 mmol) with $BnEt_3NI$ (3.5 mg, 0.01 mmol, 0.05 equiv.) under argon atmosphere was added dry and degassed PhCl (2 mL) and the mixture was put into a preheated woods metal bath at 140 ^oC and left to stirr until no more starting material remained (TLC). The reaction mixture was adsorbed onto silica and chromatography gave sulfur (11.7mg, 83%), *thiazolo [5,4-b]pyridine-2-carbonitrile* **97** (14.2 mg, 40%) as colourless cotton fibers, mp 124-125 ^oC (from cyclohexane) identical to that described previously and *thiazolo[4,5-*c*]pyridine-2-carbonitrile* **97** (13.1 mg, 37%) as colourless needles, mp 162-163 ^oC (from cyclohexane) identical to that described previously.

Treatment of N-(4-chloro-5H-1,2,3-dithiazol-5-ylidene)pyridin-4-amine 70l with $BnEt_3NI$ (see Table 4)

Similar treatment of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-4-amine **70l** (50.4 mg, 0.22 mmol) with $BnEt_3NI$ (3.5 mg, 0.01 mmol, 0.05 equiv.) gave sulfur (12.2mg, 85%) and *thiazolo[5,4-c]pyridine-2-carbonitrile* **98** (13.8 mg, 39%) as colourless needles, mp 124-125 ^oC (from cyclohexane) identical to that described previously.

Reaction of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70a with Ph_3P (typical procedure: see Table 5)

To a stirred solution of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70a** (50.4 mg, 0.22 mmol) in DCM (2 mL) at 20 ^oC and protected with a $CaCl_2$ drying tube, was added Ph_3P (230.6 mg, 0.88 mmol, 4 equiv.). The mixtures were then allowed to stir at ca. 20 ^oC until no starting material remained (TLC). The reaction mixtures were adsorbed onto silica and chromatography (hexane–DCM, 50:50) gave unreacted Ph_3P (55.3 mg, 24%) as colourless needles, mp 80 ^oC (from cyclohexane) identical to an authentic sample. Further elution (Hexane/DCM, 4:1) gave $Ph_3P{=}S$ (88.0 mg, 68%) as colourless needles, mp 161-162 ^oC (from cyclohexane) identical to an authentic sample. Further elution (DCM) gave *thiazolo[5,4-*b*] pyridine-2-carbonitrile* **97** (6.0 mg, 17%) as colourless cotton fibers, mp 124-125 ^oC (from cyclohexane) identical to that described previously. Further elution (DCM/*t*-butyl methyl ether, 9:1) gave *thiazolo[4,5-*c*]pyridine-2-carbonitrile* **99** (6.7 mg, 19%) as colourless needles, mp 162-163 ^oC (from cyclohexane) identical to that described previously. Further elution (DCM/*t*-butyl ether, 7:3) gave triphenylphosphine oxide (26.9 mg, 22%) as colourless needles, mp 154-155 ^oC (from cyclohexane) identical to an authentic sample.

Reaction with Polymer bound Ph_3P (general procedure: see Table 5):

To a stirred solution of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-X-amine (0.22 mmol) in DCM (2 mL) at 20 ^oC and protected with a $CaCl_2$ drying tube, was added polymer bound Ph_3P. The mixtures were then allowed to stir at ca. 20 ^oC. The reaction mixtures were then filtered to remove the polymer bound Ph_3P, giving the analogous compounds.

Thermolysis of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70i (see Scheme 65)

Thermolysis of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** (58.1 mg, 0.22 mmol) at *ca.* 180 ^{o}C in argon atmosphere gave after 10 min 3 products (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane) gave sulfur (4.9 mg, 35%). Further elution (hexane/DCM, 1:1) gave *(Z)-(2-chloropyridin-3-yl)carbono-cyanidimidic chloride* **100** (33.9 mg, 77%) as colourless cotton fibers, mp 216-217 ^{o}C (from cyclohexane); (found: C, 42.1; H, 1.5; N, 20.5. $C_7H_3Cl_2N_3$ requires C, 42.0; H, 1.5; N, 21.0%); λ_{max}(DCM) 272 (log ε 2.82), 284 inf (2.87); ν_{max}/cm^{-1} 3258w and 3069w (Py CH), 2957w, 2922w, 2851w, 2243w (C≡N), 1639s, 1558w, 1445w, 1404s, 1236w, 1204m, 1130m, 1080m, 1059m, 1047s, 1011w, 943w, 843m, 810s, 741s, 712s; δ_H(300 MHz; $CDCl_3$) 8.74 (1H, dd, *J* 8.25, 1.65, Py *H*-4 or 6), 8.21 (1H, dd, *J* 4.95, 1.65, Py *H*-4 or 6), 7.32 (1H, dd, *J* 8.1, 4.8, Py *H*-5); δ_C(75 MHz; $CDCl_3$) 148.3 (Py *C*H), 141.9, 138.1, 128.6 (Py *C*H), 122.7 (Py *C*H), 120.65, 111.5 (*C*≡N); *m/z* (EI) 203 (M^++4, 6%), 201 (M^++2, 40), 199 (M^+, 60), 166 (38), 164 (100). 154 (8), 146 (8), 114 (32), 112 (95), 103 (4), 87 (6), 85 (12), 76 (44), 57 (8), 50 (22). Further elution (DCM) gave *thiazolo[5,4-*b*]pyridine-2-carbonitrile* **97** (3.5 mg, 10%) as colourless cotton fibers, mp 124-125 ^{o}C (from cyclohexane) identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 9:1) gave *4-chlorothiazolo[4,5-*c*]pyridine-2-carbonitrile* **101** (6.5 mg, 15%) as colourless needles, mp 161-162 ^{o}C (from cyclohexane); (found: C, 42.8; H, 1.2; N, 21.6. $C_7H_2ClN_3S$ requires C, 43.0; H, 1.0; N, 21.5%); λ_{max}(DCM) 241 inf (log ε 2.73), 246 (2.76), 273 (2.96), 302 (2.84); ν_{max}/cm^{-1} 3086w (Ar CH), 2241w (C≡N), 1923w, 1697w, 1566s, 1514m, 1460m, 1423s, 1383m, 1287m, 1234m, 1215m, 1159m, 1119s, 1105m, 1069w, 835s, 822s; δ_H(300 MHz; $CDCl_3$) 8.52 (1H, d, *J* 5.5, Ar *H*-5 or 6), 7.90 (1H, d, *J* 5.6, Ar *H*-5 or 6); δ_C(75 MHz; $CDCl_3$) 148.0, 145.8 (*C*H), 144.6, 138.1, 115.8 (*C*H), 111.8 (*C*≡N); *m/z* (EI) 197 (M^++2, 40%), 195 (M^+, 100), 160 (78), 108 (10), 98 (2), 86 (4), 82 (18), 69 (8), 64 (10).

Thermolysis of 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70j (see Scheme 66)

Thermolysis of 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70j** (58.1 mg, 0.22 mmol) at 180 ^{o}C gave sulfur (4.2 mg, 30%), *7-chlorothiazolo[5,4-*b*]pyridine-2-carbonitrile* **102** (9.5 mg, 22%) as colourless cotton fibers, mp 177-178 ^{o}C (from

cyclohexane); (found: C, 42.9; H, 1.0; N, 21.6. $C_7H_2ClN_3S$ requires C, 43.0; H, 1.0; N, 21.5%); λ_{max}(DCM) 228 (log ε 2.85), 240 (2.73), 247 (2.73), 282 (3.02), 303 inf (2.79); ν_{max}/cm^{-1} 2957w, 2922m, 2851m, 2234w (C≡N), 1935w, 1730w, 1694w, 1566m, 1537m, 1530m, 1495w, 1462m, 1439m, 1377w, 1364w, 1340m, 1306w, 1288m, 1271w, 1252m, 1209w, 1184w, 1167m, 1121s, 1080w, 957w, 935w, 891w, 864w, 841s, 833w, 816w, 793w, 735w;δ_H(300 MHz; $CDCl_3$) 8.70 (1H, d, *J* 5.0 Ar *H*), 7.66 (1H, d, *J* 5.0, Ar *H*); δ_C(75 MHz; $CDCl_3$) 158.3, 151.1 (*C*H), 143.3, 140.3, 138.2, 123.4 (*C*H), 112.1 (*C*≡N); *m/z* (EI) 197 (M^++2, 37%), 195 (M^+, 100%), 160 (18), 143 (10), 137 (7), 108 (8), 83 (13), 81 (14), 70 (17), 64 (9), 50 (5) and *thiazolo[4,5-*c*]pyridine-2-carbonitrile* **99** (15.6 mg, 44%) as colourless needles, mp 162-163 ^oC (from cyclohexane) identical to an authentic sample.

Treatment of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70i with $BnEt_3NI$ (see Table 6)

To a mixture of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** (58.1 mg, 0.22 mmol) and $BnEt_3NI$ (3.5 mg, 0.01 mmol, 0.05 equiv.) under argon atmosphere was added dry and degassed PhCl (2 mL) and the mixture was put into a preheated woods metal bath at 140 ^oC and left to stirr for 24 h until no more starting material remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane) gave sulfur (11.6 mg, 83%). Further elution (DCM) gave *thiazolo[5,4-*b*]pyridine-2-carbonitrile* **97** (34.7 mg, 98%) as colourless cotton fibers, mp 124-125 ^oC (from cyclohexane) identical that described above.

Treatment of 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70j with $BnEt_3NI$ (see Table 7)

Similar treatment of 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70j** (58.1 mg, 0.22 mmol) and $BnEt_3NI$ (3.5 mg, 0.01 mmol, 0.05 equiv.) gave *thiazolo[4,5-*c*]pyridine-2-carbonitrile* **99** (35.1 mg, 99%) as colourless needles, mp 162-163 ^oC (from cyclohexane) identical that described above.

Reaction of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70i with Ph_3P (typical procedure: see Table 8)

To a stirred solution of 2-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70i** (58.1 mg, 0.22 mmol) in DCM (2 mL) at 20 ^oC and protected with a $CaCl_2$ drying tube,

was added Ph_3P (230.6 mg, 0.88 mmol, 4 equiv.). The mixtures were then allowed to stir at ca. 20 ^oC for 120 min until no starting material remained (TLC). The reaction mixtures were adsorbed onto silica and chromatography (hexane/DCM, 4:1) gave $Ph_3P{=}S$ (103.5 mg, 80%) as colourless needles, mp 161-162 ^oC (from cyclohexane) identical to an authentic sample. Further elution (DCM/*t*-butyl methyl ether, 9:1) gave *thiazolo[4,5-*c*]pyridine-2-carbonitrile* **99** (10.0 mg, 28%) as colourless needles, mp 162-163 ^oC (from cyclohexane) identical to that described previously. Further elution (DCM/*t*-butyl ether, 7:3) gave $Ph_3P{=}O$ (73.4 mg, 60%) as colourless needles, mp 154-155 ^oC (from cyclohexane) identical to an authentic sample.

Reaction of 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine 70j with Ph_3P (see Table 8)

Treatment of 4-chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)pyridin-3-amine **70j** (58.1 mg, 0.22 mmol) with Ph_3P (230.6 mg, 0.88 mmol, 4 equiv.) gave *thiazolo[4,5-*c*]pyridine-2-carbonitrile* **99** (10.0 mg, 28%) as colourless needles, mp 162-163 ^oC (from cyclohexane) identical that described above.

Synthesis of (*Z*)-methyl-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate 103 (see Scheme 67)

To a stirred solution of Appel salt **42** (1.075 mmol, 1 equiv) in DCM (4 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added methyl 2-aminobenzoate (1.075 mmol). After 1 h, to the reaction mixture was added, dropwise, pyridine (173.9 μL, 2.15 mmol, 2 equiv.) and left to stir at *ca*. 20 ^oC for additional 2 h. The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (traces), followed by 4-chloro-5*H*-1,2,3-dithiazole-5-thione (hexane/DCM, 4:1). Further elution (hexane/DCM, 7:3) gave the title compound **103** (328 mg, 79%) as yellow oil; δ_H(300 MHz; $CDCl_3$) 7.93 (1H, d, *J* 7.9, Ph *H*-3/6), 7.49 (1H, dd, *J* 7.65, Ph *H*4/5), 7.16 (1H, dd, *J* 7.6, Ph *H*5/4), 6.90 (1H, d, *J* 7.9 Ph *H*6/3); δ_C(75 MHz; $CDCl_3$) 165.3, 159.9, 152.3, 146.5, 134.0 (Ph *C*H), 131.4 (Ph *C*H), 125.1 (Ph *C*H), 118.0 (Ph *C*H), 51.8 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$); 134.0 (Ph *C*H), 131.4 (Ph *C*H), 125.1 (Ph *C*H), 118.0 (Ph *C*H), 51.8 (*C*H_3) identical to an authentic sample.

Thermolysis of (*Z*)-methyl-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate 103 (see Scheme 68)

Thermolysis of **(***Z*)-methyl-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate **103** (100 mg, 0.35 mmol) at *ca.* 200 ^{o}C in argon atmosphere gave after 10 min 3 products (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (12.5 mg, 56%). Further elution (hexane/DCM 7:3) gave 4-oxo-4*H*-benzo[*d*][1,3]thiazine-2-carbonitrile **104** (16.5 mg, 25%) as colourless needles, mp 122-123 ^{o}C (lit.,[226] 122 ^{o}C) (from cyclohexane); ν_{max}/cm^{-1} 1697w, 1682w, 1584w, 1510w, 1479m, 1450w, 1433s, 1391w, 1308m, 1273w, 1244w, 1182w, 1159w, 1159w, 1103s, 1069m, 1026m, 997m; δ_H(300 MHz; $CDCl_3$) 8.28 (1H, d, *J* 7.8, Ph *H*), 7.98-7.93 (1H, m, Ph *H*), 7.77-7.71 (2H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) 155.9, 144.3, 137.5 (Ph *C*H), 134.6, 131.8 (Ph *C*H), 129.3 (Ph *C*H), 128.4 (Ph *C*H), 118.7 (*C*≡N), 110.1; δ_C(75 MHz; DEPT-135, $CDCl_3$); 137.5 (Ph *C*H), 134.6, 131.8 (Ph *C*H), 129.3 (Ph *C*H), 128.4 (Ph *C*H) identical to an authentic sample. Further elution (DCM) gave *methyl 2-cyano-benzo[*d*]thiazole-4-carboxylate* **105** (26.7 mg, 35%) as colourless needles, mp 123-124 ^{o}C (from cyclohexane); (found C, 55.0; H, 2.8; N, 13.0. $C_{10}H_6N_2O_2S$ requires C, 55.0; H, 2.8; N, 12.8); λ_{max}(DCM) 234 (log ε 2.86), 248 inf (282), 294 (2.88), 319 inf (2.66); ν_{max}/cm^{-1} 3071w, 2232w (C≡N), 1767w, 1726s, 1587w, 1726s, 1587w, 1562m, 1460m, 1425m, 1396m, 1362w, 1325m, 1277s, 1211m, 1155m, 1103s, 1072m, 1022w, 982w, 854m, 820w, 764s, 731m; δ_H(300 MHz; $CDCl_3$) 8.25 (1h, d, *J* 7.5, Ph H), 8.19 (1H, d, *J* 8.2, Ph H), 7.71 (1h, dd, *J* 7.8, 8.1, Ph *H*), 4.06 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 165.9, 150.3, 138.7, 131.0 (Ph *C*H), 128.5 (Ph *C*H), 127.7, 126.3 (Ph *C*H), 113.1 (*C*≡N), 53.4 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$); 131.0 (Ph *C*H), 128.5 (Ph *C*H), 126.3 (Ph *C*H), 53.4 (*C*H_3); *m/z* (EI) 218 (M^+, 29%), 187 (100), 160 (28), 107 (10), 81 (4), 63 (10).

Reaction of (*Z*)-methyl-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate 103 with $BnEt_3NI$ (see Table 9)

To a mixture of **(***Z*)-methyl-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate **103** (100 mg, 0.35 mmol) and $BnEt_3NI$ (11.7 mg, 0.35 mmol, 1 equiv.) under argon atmosphere was added dry and degassed PhCl (2 mL) and the mixture was put into a preheated woods metal bath at 140 ^{o}C and left to stirr for 20 min until no more starting material remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (8.1 mg, 36%). Further elution (Hexane/DCM 4:1) gave methyl 2-isothiocyanatobenzoate **106** (25.7

mg, 38%) as colourless oil; ν_{max}/cm^{-1} 2951w, 2924w, 2851w, 2183w, 2100s, 1722s, 1597m, 1483m, 1450m, 1433m, 1298s, 1281m, 1258s, 1190w, 1163w, 1130m, 1086s, 1043w, 964w, 934m, 876w, 824m, 793w, 752.24s; δ_H(300 MHz; $CDCl_3$) 7.97 (1h, dd, *J* 1.5, 7.9, Ph *H*), 7.50 (1H, ddd, *J* 1.4, 7.65, Ph *H*), 7.37-7.29 (2H, m, Ph *H*), 3.95 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 165.0, 135.5, 133.2 (Ph *C*H), 131.7 (Ph *C*H), 130.4, 127.6 (Ph *C*H), 126.8 (Ph *C*H), 126.2, 52.7 (*C*H$_3$); δ_C(75 MHz; DEPT-135, $CDCl_3$); 133.2 (Ph *C*H), 131.7 (Ph *C*H), 127.6 (Ph *C*H), 126.8 (Ph *C*H), 52.7 (*C*H$_3$); *m/z* (EI) 193 (M$^+$, 67%), 178 (30), 162 (100), 146 (60), 134 (22), 124 (17), 91 (85), 63 (17) identical to an authentic sample. Further elution (Hexane-DCM 50:50) gave *methyl* (Z)-methyl-2-(cyanothioformanilido)benzoate **107** (23.9 mg, 31%) as orange cotton, mp 119-120 ^{o}C (lit.,[226] 122-123 ^{o}C) (from cyclohexane); ν_{max}/cm^{-1} 2982w, 2953w, 2229w (C≡N), 1684m, 1597m, 1589m, 1530s, 1449m, 1439m, 1383s, 1312m, 1294m, 1275s, 1211m, 1196w, 1159w, 1136m, 1103s, 1087m, 959m, 862w, 820m, 795m, 756s, 745m, 694m; δ_H(300 MHz; $CDCl_3$) 13.52 (1H, br s, N*H*), 9.36 (1h, d, *J* 8.4, Ph *H*), 8.17 (1h, dd, *J* 1.3, 7.9, Ph *H*), 7.67-7.61(1H, m, Ph *H*), 7.37 (1H, dd, *J* 7.65, 7.7, Ph *H*), 4.00 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 168.5, 161.9, 140.0, 134.4 (Ph *C*H), 131.4 (Ph *C*H), 126.6 (Ph *C*H), 120.6 (Ph *C*H), 116.8, 113.7, 53.1 (*C*H$_3$); δ_C(75 MHz; DEPT-135, $CDCl_3$); 134.4 (Ph *C*H), 131.4 (Ph *C*H), 126.6 (Ph *C*H), 120.6 (Ph *C*H), 53.1 (*C*H$_3$); *m/z* (EI) 220 (M$^+$, 20%), 193 (30), 187 (15), 161 (100), 146 (10), 134 (30), 90 (15), 63 (10).

Treatment of (*Z*)-methyl-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate 103 with DBU (see Scheme 70)

To a mixture of (*Z*)-methyl-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzoate **103** (100 mg, 0.35 mmol) in distilled DCM (2 mL) cooled to *ca*. -86 ^{o}C and protected with a $CaCl_2$ drying tube, was added in one portion, DBU (14.7 μL, 0.70 mmol, 2 equiv.). After 10 min at *ca*. -86 ^{o}C no starting material remained (TLC) and the reaction mixture was adsorbed onto silica. Chromatography (hexane/DCM 1:1) gave *methyl 2-(cyanocarbonothioylamino)-benzoate* **107** (50.1 mg, 65%) as orange cotton, mp 119-120 ^{o}C (lit.,[232] 122-123 ^{o}C) (from cyclohexane) identical to an authentic sample.

9.4 Compounds Related to Chapter 4

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol 66

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (956.4 mg, 4.59 mmol) in DCM (10 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added 2-aminophenol (500 mg, 4.59 mmol). After 1 h, to the reaction mixture was added, dropwise, pyridine (742.5 μL, 9.18 mmol) and left to stir at *ca*. 20 °C for additional 2 h. The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (traces). Further elution (hexane/DCM, 4:1) gave 4-chloro-5*H*-1,2,3-dithiazole-5-thione (10 mg, 6%) and further elution (hexane/DCM, 3:7) gave the *title compound* **66** (1.07 g, 95%) as orange prisms, mp 160-161 °C (lit.,[75] 95-96 °C) (from pentane/DCM in the fridge); λ_{max}(DCM)/nm 230 inf (log ε 2.86), 257 (2.98), 265 inf (2.94), 303 inf (2.26), 383 inf (2.89), 394 inf (2.96), 414 (3.02), 440 inf (2.85); ν_{max}/cm^{-1} 3391m (OH), 1605m, 1594m, 1562m, 1531m, 1499m, 1477s, 1462w, 1418w, 1362w, 1346w, 1290m, 1254s, 1234m, 1221m, 1190m, 1157m, 1142s, 1096w, 1059w, 1032m, 959w, 930w, 914w, 862s, 841w, 806m, 762s; δ_H(300 MHz; CD_2Cl_2) 7.52 (1H, dd, *J* 1.2, 7.8, Ph *H*), 7.30-7.25 (1H, m, Ph *H*), 7.08-7.07 (1H, m, Ph *H*), 7.05-7.00 (1H, m, Ph *H*); δ_C(75 MHz; CD_2Cl_2) 153.9, 152.8, 149.9, 132.7, 130.15 (Ph *C*H), 120.1 (Ph *C*H), 116.9 (Ph *C*H), 115.2 (Ph *C*H); δ_C(75 MHz; DEPT-135, CD_2Cl_2), 130.15 (Ph *C*H), 120.1 (Ph *C*H), 116.9 (Ph *C*H), 115.2 (Ph *C*H); *m/z* (EI) 246 (M^++2, 9%), 244 (M^+, 22), 180 (3), 145 (100), 119 (26), 93 (12), 64 (53), 51 (12).

Thermolysis of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol 66

Neat 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** (50.0 mg, 0.20 mmol) in argon atmosphere was heated at *ca.* 200 °C for 1 min. On cooling to *ca.* 20 °C the reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (4.7 mg, 60%). Further elution (hexane/DCM, 6:4) gave benzo[*d*]oxazole-2-carbonitrile **67** (25.9 mg, 90%) as colourless needles, mp 99-100 °C (lit.,[258] 100-102 °C) (from cyclohexane); λ_{max}(DCM)/nm 273 inf (log ε 3.19); ν_{max}/cm^{-1} 2251m (C≡N), 1794w, 1611m, 1603m, 1530m, 1476m, 1445s, 1429w, 1371w, 1341s, 1287w, 1275w, 1258m, 1233w, 1219w, 1171s, 1163w, 1136w, 1105m, 993m, 953s, 895m, 953s, 895m, 854w, 837w, 818s, 760s; δ_H(300 MHz; $CDCl_3$) 7.90-7.86 (1H, m, Ph *H*), 7.67-7.49 (3H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) 150.3, 139.4, 137.2, 129.1 (Ph *C*H), 126.5 (Ph *C*H), 121.9 (Ph *C*H), 111.5 (Ph *C*H), 109.1; δ_C(75 MHz; DEPT-135, $CDCl_3$), 129.1 (Ph

*C*H), 126.5 (Ph *C*H), 121.9 (Ph *C*H), 111.5 (Ph *C*H); *m/z* (EI) 144 (M^+, 100%), 116 (8), 92 (120, 64 (35).

Stability test of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol 70h (see Table 11)

3-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** (50 mg, 0.20 mmol) was left to stirr in xylene at *ca.* 139 ^oC until no more 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-pyridin-2-ol **70h** remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane/DCM, 1:1) gave oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** (24.4 mg, 84%) as colourless needles, mp 105-106 ^oC (from cyclohexane); (found C, 57.8; H, 2.0; N, 29.0. $C_7H_3N_3O$ requires C, 57.9; H, 2.1; N, 29.0%); λ_{max}(DCM)/nm 247 inf (log ε 2.63), 327 (2.57), 418 (2.68); ν_{max}/cm^{-1} 2257w (C≡N), 1609m, 1599m, 1524m, 1476w, 1400s, 1362w, 1333s, 1279m, 1231s, 1167w, 1153m, 1117w, 1032w, 1005w, 993w, 953m, 901m, 845w, 829s, 816s, 806s, 773s; δ_H(300 MHz; $CDCl_3$) 8.63 (1H, dd, *J* 1.5, 4.8, Py *H*-4 or 6), 8.26 (1H, dd, *J* 1.65, 7.95, Py *H*-6 or 4), 7.56 (1H, dd, *J* 4.8, 8.1, Py *H*-5); δ_C(75 MHz; $CDCl_3$) 158.3, 149.3 (Py *C*H), 137.5, 131.2, 131.1 (Py *C*H), 122.9 (Py *C*H), 108.6; δ_C(75 MHz; DEPT-135, $CDCl_3$), 149.3 (Py *C*H), 131.1 (Py *C*H), 122.9 (Py *C*H); *m/z* (EI) 145 (M^+, 100%), 117 (82), 65 (35), 64 (20), 54 (8), 51 (4). Further elution (DCM) gave *[1,2,3]dithiazolo[5,4-*e*] pyrido[2,3-*b*][1,4]oxazine* **119** (traces) as orange fibers, mp 217-218 ^oC (from cyclohexane/EtOH); (found C, 40.3; H, 1.4; N, 20.1. $C_7H_3N_3OS_2$ requires C, 40.2; H, 1.45; N, 20.1%) λ_{max}(DCM)/nm 272 inf (log ε 2.45), 308 (2.35), 383 inf (3.02), 411 (3.17), 434 inf (3.04); ν_{max}/cm^{-1} 3044w, 3007w, 1582m, 1562s, 1501s, 1423s, 1287m, 1269w, 1234s, 1192m, 1123m, 1076m, 1045m, 982w, 932m, 856w, 806s, 756s, 727m; δ_H(300 MHz; DMSO-d_6) 7.92 (1H, d, *J* 4.1, Py *H*), 7.52 (1H, d, *J* 7.3, Py *H*), 7.14 (1H, dd, *J* 5.0, 7.0, Py *H*); δ_C(75 MHz; DMSO-d_6) 166.2, 152.4, 150.5, 144.3 (Py *C*H), 133.4 (Py *C*H), 127.8, 122.4 (Py *C*H); δ_C(75 MHz; DEPT-135, DMSO-d_6) 144.3 (Py *C*H), 133.4 (Py *C*H), 122.4 (Py *C*H); *m/z* (EI) 209 (M^+, 100%), 135 (54), 108 (17), 103 (10), 76 (13), 70 (16), 64 (24); (found M^+, 208.9718 $C_7H_3N_3OS_2$ requires *M*, 208.9718).

Thermolysis of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol 70h (typical procedure: see Table 12)

Neat 3-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** (50 mg, 0.20 mmol) in argon atmosphere was heated at *ca.* 200 ^{o}C for 2 min. On cooling to *ca.* 20 ^{o}C the reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (11.5 mg, 90%). Further elution (hexane/DCM, 4:6) gave *oxazolo[5,4-*b*]pyridine* **118** (19.1 mg, 66%) as colourless needles, mp 105-106 ^{o}C (from cyclohexane), identical to the one described previously. Further elution (DCM) gave *[1,2,3]dithiazolo[5,4-*e*]pyrido[3,2-*b*][1,4]oxazine* **119** (0.4 mg, 1%) as orange fibers, mp 217-218 ^{o}C (from cyclohexane/EtOH) identical to the one described previously.

Thermolysis of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol 70b

Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene-amino)pyridin-3-ol **70b** (50 mg, 0.20 mmol) at *ca.* 200 ^{o}C for 5 min gave S_8 (11.5 mg, 90%) and oxazolo[4,5-*b*]pyridine-2-carbonitrile **120** (24.4 mg, 84%) as colourless needles, mp 49-50 ^{o}C (from cyclohexane); (found C, 57.9; H, 2.1; N, 28.9. $C_7H_3N_3O$ requires C, 57.9; H, 2.1; N, 29.0%); λ_{max}(DCM)/nm 245 (log ε 2.63), 292 (3.09), 304 inf (2.89); ν_{max}/cm^{-1} 3043w, 2259w (C≡N), 1715w, 1700w, 1684w, 1653w, 1611m, 1537m, 1506w, 1403s, 1321m, 1293w, 1260m, 1251w, 1223m, 1212w, 1171m, 1111w, 1030m, 954m, 844m, 828m, 795s, 780s; δ_H(300 MHz; $CDCl_3$) 8.80 (1H, d, *J* 4.45, Py *H*-4 or 6), 8.04 (1h, dd, *J* 1.4, 8.4, Py *H*-6 or 4), 7.59 (1H, dd, *J* 4.7, 8.4, Py *H*-5); δ_C(75 MHz; $CDCl_3$) 152.4, 149.6 (Py *C*H), 143.2, 139.6, 123.8 (Py *C*H), 120.0 (Py *C*H), 108.5; δ_C(75 MHz; DEPT-135, $CDCl_3$) 149.6 (Py *C*H), 123.8 (Py *C*H), 120.0 (Py *C*H); *m/z* (EI) 145 (M^+, 98%), 94 (6), 93 (100), 65 (49), 64 (23).

Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol 66 with NaH (typical procedure: see Table 12)

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** (50.0 mg, 0.20 mmol) in dry THF (2 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was added NaH (9.6 mg, 0.4 mmol) and the mixture was then heated at *ca.* 66 ^{o}C for 2 until no more starting material remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (7.0 mg, 55%). Further elution (hexane/DCM, 6:4) gave

benzo[*d*]oxazole-2-carbonitrile **67** (18.7 mg, 65%) as colourless needles, mp 99-100 ^{o}C (from cyclohexane) identical to an authentic sample.

Reaction of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol 70h with NaH

Similar treatment of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** (49.2 mg, 0.20 mmol) with NaH (9.6 mg, 0.4 mmol) gave *oxazolo[5,4-*b*]pyridine* **118** (traces) as colourless needles, mp 105-106 ^{o}C (from cyclohexane), identical to the one described previously.

Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol 70b with NaH

Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** (49.2 mg, 0.20 mmol) with NaH (9.6 mg, 0.4 mmol) gave *oxazolo[4,5-*b*]pyridine-2-carbonitrile* **120** (25.5 mg, 88%) as colourless needles, mp 49-50 ^{o}C (from cyclohexane) identical to the that described previously.

Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol 66 with base (typical procedure: see Table 13)

To a stirr solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** (50.0 mg, 0.20 mmol) in DCM (2 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was added lutidine (92.6 μL, 0.80 mmol) and the mixture was left to stirr 5 d until no more starting material remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (traces). Further elution (hexane/DCM, 6:4) gave benzo[*d*]oxazole-2-carbonitrile **67** (1.4 mg, 5%) as colourless needles, mp 99-100 ^{o}C (from cyclohexane) identical to an authentic sample. Further elution (hexane/DCM, 3:7) gave *benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine* **114** (39.5 mg, 95%) as orange fibers, mp 183-184 ^{o}C (from cyclohexane/EtOH) (lit.,[258] 184-186 ^{o}C); (found C, 46.2; H, 2.0; N, 13.4. $C_8H_4N_2OS_2$ requires C, 46.1; H, 1.9; N, 13.5%); λ_{max}(DCM)/nm 272 inf (log ε 2.45), 308 (2.35), 383 inf (3.02), 411 (3.17), 434 inf (3.04); ν_{max}/cm^{-1} 2259w (C≡N), 1584w, 1570w, 1560s, 1499w, 1491m, 1476m, 1458m, 1437w, 1371w, 1302m, 1285w, 1273w, 1236m, 1207m, 1190w, 1113m, 1049s, 974w, 939m, 926s, 856w, 841w; δ_H(300 MHz; DMSO-d_6) 7.12-7.10 (3H, m, Ph *H*), 7.01-6.99 (1H, m, Ph *H*); δ_C(75 MHz; DMSO-d_6) 165.1, 150.5, 143.9, 131.9, 127.6 (Ph *C*H), 125.5 (Ph *C*H), 125.3 (Ph *C*H), 115.15 (Ph *C*H); δ_C(75 MHz; DEPT-135, DMSO-d_6), 127.6 (Ph *C*H), 125.5 (Ph

*C*H), 125.3 (Ph *C*H), 115.15 (Ph *C*H); *m/z* (EI) 208 (M^+, 100%), 144 (17), 122 (12), 104 (91), 90 (22), 78 (10), 76 (13), 70 (21), 64 (78), 51 (29), identical to an authentic sample.

Reaction of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol 70h with base

Similar treatment of 3-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-2-ol **70h** (49.2 mg, 0.20 mmol) with Et_3N (30.7 μL, 0.22 mmol) gave [1,2,3]dithiazolo[5,4-*e*]pyrido[3,2-*b*][1,4]oxazine **119** (26.3 mg, 63%) as orange fibers, mp 217-218 ^oC (from cyclohexane/EtOH) identical to the one described previously.

Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol 70b with base

Similar treatment of 2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** 49.2 mg, 0.20 mmol) with Et_3N (30.7 μL, 0.22 mmol) gave *oxazolo[4,5-*b*]pyridine-2-carbonitrile* **120** (22.0 mg, 76%) as colourless needles, mp 49-50 ^oC (from cyclohexane) identical to the that described previously.

Treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol 66 with polymer bound Ph_3P (typical procedure: see Table 14)

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenol **66** (50.0 mg, 0.20 mmol) in DCM (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added polymer bound Ph_3P (104.8 mg, 0.40 mmol). The mixture was then allowed to stir at *ca*. 20 °C for 48 h, until no starting materials remained (TLC). Filtration of the reaction to remove the polymer, gave benzo[*d*]oxazole-2-carbonitrile **67** (15.8 mg, 55%) as colourless needles, mp 99-100 ^oC (from cyclohexane) identical to an authentic sample.

Thermolysis reaction of benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine 114 (typical procedure: see Table 15)

Neat benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114** (50.0 mg, 0.24 mmol) in argon atmosphere was heated at *ca.* 275 ^oC for 7 min. On cooling to *ca.* 20 ^oC the reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (8.4 mg, 55%). Further elution (hexane/DCM, 6:4) gave the benzo[*d*]oxazole-2-carbonitrile **67** (9.3 mg, 27%) as colourless needles, mp 99-100 ^oC (from cyclohexane) identical to an authentic sample.

Thermolysis of [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine 119

Similar treatment of [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** (50.2 mg, 0.24 mmol) at *ca.* 230 ^{o}C for 10 min gave S_8 (14.9 mg, 97%) and oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** (32.6 mg, 65%) as colourless needles, mp 105-106 ^{o}C (from cyclohexane) identical to that described previously.

Reaction of benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine 114 with base (typical procedure: see Table 15)

To a stirred solution of benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114** (50 mg, 0.24 mmol) in PhCl (2 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was added Et_3N (33.5 μL, 0.24 mmol, 1 equiv.). The mixture was then heated at *ca*. 132 °C for 24 h, until no starting materials remained (TLC). Chromatography (hexane) gave S_8 (13.1 mg, 85%) and further elution gave benzo[*d*]oxazole-2-carbonitrile **67** (15.5 mg, 45%) as colourless needles, mp 99-100 ^{o}C (from cyclohexane) identical to an authentic sample.

Reaction of [1,2,3]dithiazolo[5,4-*e*]pyrido-[2,3-*b*][1,4]oxazine 119 with base

Similar treatment of [1,2,3]dithiazolo[5,4-*e*]pyrido-[2,3-*b*][1,4]oxazine **119** (50.0 mg, 0.24 mmol) with Et_3N (33.5 μL, 0.24 mmol) gave oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** (13.9 mg, 40%) as colourless needles, mp 105-106 ^{o}C (from cyclohexane) identical to that described previously.

Reaction of [1,2,3]dithiazolo[5,4-e]pyrido[2,3-b][1,4]oxazine 119 with TsOH.H_2O

To a stirred solution of [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** (50.0 mg, 0.24 mmol) in PhCl (2 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was added TsOH.H_2O (2.3 mg, 0.012 mmol). The mixture was then heated at *ca*. 132 °C for 20 h, until no starting materials remained (TLC). Chromatography (hexane) gave S_8 (13.4 mg, 86%) and further elution gave oxazolo[5,4-*b*]pyridine-2-carbonitrile **118** (17.4 mg, 50%) as colourless needles, mp 105-106 ^{o}C (from cyclohexane) identical to that described previously.

Reaction of benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine 114 with $BnEt_3NCl$ (typical procedure: see Table 15)

To a stirred solution of benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114** (50.0 mg, 0.24 mmol) in PhCl (2 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added $BnEt_3NCl$ (54.5 mg, 0.24 mmol). The mixture was then heated at *ca*. 132 °C for 12 h, until no starting materials remained (TLC). Chromatography (hexane) gave S_8 (10.9 mg, 71%) and further elution (hexane/DCM, 6:4) gave benzo[*d*]oxazole-2-carbonitrile **67** (12.1 mg, 35%) as colourless needles, mp 99-100 °C (from cyclohexane) identical to an authentic sample.

Reaction of [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine 119 with $BnEt_3NCl$

Similar treatment of [1,2,3]dithiazolo[5,4-*e*]pyrido[2,3-*b*][1,4]oxazine **119** (50.0 mg, 0.24 mmol) with $BnEt_3NCl$ (54.5 mg, 0.24 mmol) gave S_8 (5.8 mg, 38%) and oxazolo[5,4-*b*] pyridine-2-carbonitrile **118** (14.6 mg, 42%) as colourless needles, mp 105-106 °C (from cyclohexane) identical to that described previously.

Reaction of benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine 114 with $BnEt_3NCl$ and 2,3-dimethylbuta-1,3-diene 130 (see Scheme 80)

A stirred mixture of benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine **114** (50.0 mg, 0.24 mmol), $BnEt_3NCl$ (54.5 mg, 0.24 mmol), 2,3-dimethylbuta-1,3-diene **130** (131.8 mg, 1.6 mmol) and PhCl (2 mL) in a sealed tube was heated to *ca*. 132 °C (a preheated Wood's metal bath was used) for 24 h. The reaction mixture was allowed to cool to *ca*. 20 °C and diluted with DCM. Chromatography (hexane/DCM, 9:1) gave 4,5-dimethyl-3,6-dihydro-1,2-dithiine **129** (12.3 mg, 35%) as light yellow oil (lit.,[260] bp 203 °C). Further elution (hexane/DCM, 6:4) gave benzo[*d*]oxazole-2-carbonitrile **67** (15.5 mg, 45%) as colourless needles, mp 99-100 °C (from cyclohexane) identical to an authentic sample.

Reaction of benzo[*b*][1,2,3]dithiazolo[5,4-*e*][1,4]oxazine 114 with $BnEt_3NCl$ and 2-norbornene 131 (see Scheme 80)

A stirred mixture of benzo[*b*][1,2,3]dithiazolo-[5,4-*e*][1,4]-oxazine **114** (50 mg, 0.24 mmol), $BnEt_3NCl$ (54.5 mg, 0.24 mmol), norbornene **131** (150.4 mg, 1.6 mmol) and PhCl (2 mL) in a sealed tube was heated to *ca.* 132 °C (a preheated Wood's metal bath was used) for 24 h. The reaction mixture was allowed to cool to *ca.* 20 °C and diluted with DCM. Chromatography

(hexane) gave 1,2,3-trithiole **128** (18.2 mg, 40%) as yellow oil (lit.,[251] bp 279.9 °C). Further elution (hexane/DCM, 6:4) gave benzo[*d*]oxazole-2-carbonitrile **67** (15.8 mg, 46%) as colourless needles, mp 99-100 °C (from cyclohexane) identical to an authentic sample.

Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol 70b with $BnEt_3NCl$ and 2-norbornene 131 (see Scheme 81)

A stirred mixture of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-ol **70b** (50 mg, 0.20 mmol), Et_3N (111.6 μL, 0.80 mmol, 4 equiv.), norbornene **131** (126.0 mg, 1.34 mmol, 6.7 equiv.) and PhCl (2 mL) in a sealed tube was heated to *ca*. 132 °C (a preheated Wood's metal bath was used) for 4 d. The reaction mixture was allowed to cool to *ca*. 20 °C and diluted with DCM. Chromatography (hexane) gave sulfur (8.3 mg, 65%). Further elution (hexane/DCM, 4:1) gave 1,2,3-trithiole **128** (7.6 mg, 20%) as yellow oil (lit.,[251] bp. 279.9 °C). Further elution (DCM) gave oxazolo[4,5-*b*]pyridine-2-carbonitrile **120** (22.6 mg, 78%) as colourless needles, mp 49-50 °C (from cyclohexane) identical to that described previously.

9.5 Compounds Related to Chapter 5

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine 160

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (79.0 mg, 0.38 mmol) in DCM (4 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added 2-amino-3,5-dicyano-4-phenyl-6-ethoxypyridine **159** (100 mg, 0.38 mmol). After 1 h, to the reaction mixture was added, dropwise, pyridine (61.5 μL, 0.76 mmol) and left to stir at *ca*. 20 °C for additional 2 h. The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (traces). Further elution (hexane/DCM, 4:1) gave 4-chloro-5*H*-1,2,3-dithiazole-5-thione (8.3 mg, 8%) and further elution (hexane/DCM, 7:3) gave the *title compound* **160** (133.4 mg, 88%) as yellow-orange cotton, mp 264-265 °C (from toluene); (found C, 51.2; H, 2.4; N, 17.5. $C_{17}H_{10}ClN_5OS_2$ requires C, 51.1; H, 2.5; N, 17.5%); λ_{max}(DCM) 229 (log ε 4.53), 264 (4.50), 279 inf (4.39), 301 inf (4.19), 329 inf (3.98), 403 inf (4.21), 424 (4.45), 447 (4.51), 472 (4.24); ν_{max}/cm^{-1} 3061w, 2976w, 2224m (C≡N), 1580w, 1553s, 1518m, 1508s, 1468s, 1443m, 1429m, 1412m, 1373s, 1339s, 1287w, 1269w, 1237w, 1186m, 1165m, 1078w, 1022w, 91/8w, 883m, 849w, 804m, 785w, 760w, 745m, 710s; δ_H(300 MHz; DMSO-d_6) 7.64

(5H, s, Ph *H*), 4.71 (2H, q, *J* 6.75, OC*H*$_2$), 1.48 (3h, t, *J* 6.9, OCH$_2$C*H*$_3$); δ_C(75 MHz; DMSO-d_6) 164.9, 164.7, 160.5, 158.7, 149.3, 133.1, 130.75 (Ph *C*H), 128.75 (Ph *C*H), 128.7 (Ph *C*H), 114.4 (*C*≡N), 113.85 (*C*≡N), 98.6, 92.05, 67.0 (*C*H$_2$), 14.3 (*C*H$_3$); δ_C(75 MHz; DEPT-135, $CDCl_3$) 130.75 (Ph *C*H), 128.75 (Ph *C*H), 128.7 (Ph *C*H), 67.0 (*C*H$_2$), 14.3 (*C*H$_3$); *m/z* (EI); 401 (M^++2, 40%), 399 (M^+, 100), 398 (88), 372 (25), 371 (17), 364 (9), 337 (16), 336 (80), 306 (8), 305 (11), 278 (11), 277 (7), 273 (11), 272 (16), 246 (41), 245 (14), 220 (19), 219 (22), 218 (37), 191 (21), 190 (15), 166 (11), 165 (58), 164 (25), 139 (16), 138 (22), 127 (12), 126 (7), 125 (12), 102 (9), 100 (8), 91 (12), 77 (20), 70 (10), 64 (91), 51 (19).

1,3-Di-*n*-butyl-2-(3,5-dicyano-6-ethoxy-4-phenylpyridin-2-yl)guanidine 161a (typical procedure: see Table 16)

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine **160** (50.0 mg, 0.13 mmol) in DCM (2 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added *n*-butylamine (54.8 μL, 0.52 mmol) and the mixture was heated at reflux for 4 h. On cooling to *ca.* 20 °C the reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (7.8 mg, 94%). Further elution (DCM/*t*-BuOMe, 4:1) gave the *title compound* **161a** (17.4 mg, 32%) as colourless needles, mp 204-205 °C (from EtOH); (found: C, 68.9; H, 7.4; N, 20.0. $C_{24}H_{30}N_6O$ requires C, 68.9; H, 7.2; N, 20.1%); λ_{max}(DCM)/nm 231 (log ε 3.35), 249 inf (3.25), 315 (3.61), 347 (3.55); ν_{max}/cm^{-1} 3337m (NH), 2222m (C≡N), 1599w, 1578m, 1526s, 1493s, 1464m, 1447w, 1423s, 1381w, 1335m, 1315w, 1308w, 1296w, 1271w, 1246w, 1231w, 1207w, 1184m, 1148w, 1090w, 1076w, 1013w, 934w, 912w, 851w, 835w, 822w, 810w, 785m; δ_H(300 MHz, $CDCl_3$) 7.52-7.47 (5h, m, Ph *H*), 4.34 (2H, q, *J* 7.1, C*H*$_2$O), 3.34 (3H, s, C*H*$_3$), 1.68-1.36 (12H, m, C*H*$_2$), 0.94 (6H, t, *J* 7.3, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 164.7, 163.8, 160.0, 156.4, 134.3, 130.0 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H), 128.3 (Ph *C*H), 116.7 (*C*≡N), 115.6 (*C*≡N), 95.5 (*C*C≡N), 84.0 (*C*C≡N), 63.2 (*C*H$_2$O), 41.3 (*C*H$_2$N), 31.4 (*C*H$_2$), 20.0 (*C*H$_2$), 14.4 (*C*H$_3$), 13.7 (*C*H$_3$); δ_C(75 MHz; DEPT-135, $CDCl_3$) 130.0 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H), 128.3 (Ph *C*H), 63.2 (*C*H$_2$O), 41.3 (*C*H$_2$N), 31.4 (*C*H$_2$), 20.0 (*C*H$_2$), 14.4 (*C*H$_3$), 13.7 (*C*H$_3$); *m/z* (EI) 418 (M^+, 100%), 403 (11), 389 (46), 376 (37), 361 (25), 347 (39), 333 (25), 320 (33), 305 (35), 291 (14), 288 (12), 278 (17), 262 (44), 236 (45), 220 (43), 208 (9), 192 (9), 165 (31), 155 (12), 128 (9), 115 (18), 99 (15), 72 (34), 57 (19); (found M^+, 418.2481 $C_{24}H_{30}N_6O$ requires *M*, 418.2481).

1,3-Dibenzyl-2-(3,5-dicyano-6-ethoxy-4-phenylpyridin-2-yl)guanidine 161b.

Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine **160** (50.0 mg, 0.13 mmol) with benzylamine (56.9 μL, 0.52 mmol) heated at reflux for 7 h gave on chromatography (hexane) S_8 (8.2 mg, 98%) and on further elution (DCM) gave the *title compound* **161b** (50.3 mg, 82%) as colourless prisms, mp 230-231 ^{o}C (from EtOH); (found: C, 74.2; H, 5.5; N, 17.6. $C_{30}H_{26}N_6O$ requires C, 76.3; H, 5.5; N, 17.8%); λ_{max}(DCM)/nm 230 (log ε 4.59), 250 inf (4.46), 313 (4.58), 348 (4.58); ν_{max}/cm^{-1} 3335m (NH), 2222m (C≡N), 1599w, 1578m, 1530s, 1493s, 1466m, 1447w, 1423s, 1381w, 1337m, 1315w, 1296w, 1269m, 1246w, 1231w, 1207w, 1184m, 1148m, 1090w, 1076w, 1014m, 932w, 910w, 841w, 822w, 785m; δ_H(300 MHz, DMSO-d_6) 9.31 (1H, br s, N*H*), 8.25 (1H, br s, N*H*), 7.33-7.53 (15H, m, Ph *H*), 4.58 (4H, s, CH_2Ph), 3.76 (2H, dd, *J* 6.8, 6.9, CH_2O)1.03 (3H, t, *J* 7.0, CH_3); δ_C(75 MHz, DMSO-d_6) 164.1, 162.9, 159.6, 156.2, 134.4 (Ph *C*H), 130.0 (Ph *C*H), 128.5 (Ph *C*H), 128.3 (Ph *C*H), 128.1 (Ph *C*H), 116.7 (*C*≡N), 115.3 (*C*≡N), 94.0 (*C*C≡N), 82.8, 79.4, 63.0 (*C*H$_2$O), 54.9, 13.8 (CH_3); δ_C(75 MHz; DEPT-135, DMSO-d_6) 134.4 (Ph *C*H), 130.0 (Ph *C*H), 128.5 (Ph *C*H), 128.3 (Ph *C*H), 128.1 (Ph *C*H), 63.0 (*C*H$_2$O), 13.8 (CH_3); *m/z* (EI) 486 (M$^+$, 3%), 414 (11), 395 (6), 385 (6), 345 (7), 316 (33), 288 (4), 220 (5), 165 (7), 106 (16), 91 (29), 70 (100), 55 (38); (found M$^+$, 486.2168 $C_{30}H_{26}N_6O$ requires *M*, 486.2168).

4-(Diethylamino)-7-ethoxy-5-phenylpyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile 167c (typical procedure: see Table 17)

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine **160** (50.0 mg, 0.13 mmol) in DCM (2 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was added diethylamine (53.6 μL, 0.52 mmol) and the mixture was heated at reflux. After 3.5 h TLC showed the presence of 5 main products and the reaction mixture was allowed to cool to *ca.* 20 ^{o}C, adsorbed onto silica and chromatography (hexane) gave S_8 (7.2 mg, 86%). Further elution (hexane/DCM, 1:1) gave the *title compound* **167c** (40.6 mg, 84%) as yellow prisms, mp 158-159 ^{o}C (from cyclohexane/EtOH); (found: C, 68.7; H, 5.3; N, 22.5. $C_{21}H_{20}N_6O$ requires C, 67.7; H, 5.4; N, 22.6%); λ_{max}(DCM)/nm 223 (log ε 3.10), 242 (3.08), 274 (2.96), 318 (2.96), 363 (3.24); ν_{max}/cm^{-1} 2997w, 2982w, 2941w, 2220m (C≡N), 1589m, 1578m, 1531s, 1497m, 1485s, 1468w, 1437w, 1422m, 1383m, 1371w, 1360m, 1344m, 1308w, 1267m, 1238w, 1213m, 1163m, 1138w, 1096w, 1076m, 1067w, 1026w, 1001w, 974w, 953w, 934w, 918w, 870w, 853w, 804w, 787m, 752s, 733w, 706m; δ_H(300

MHz, $CDCl_3$) 7.54 (5H, s, Ph *H*), 4.64 (2H, q, *J* 7.1, C*H*$_2$O), 3.82-3.71 (4H, m, C*H*$_2$N), 1.48 (3H, t, *J* 7.1, C*H*$_3$), 1.40 (3H, t, *J* 7.2, C*H*$_3$), 1.32 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.1, 161.4, 160.7, 135.3, 133.3, 130.6 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 115.3 (*C*≡N), 114.2 (*C*≡N), 108.9, 96.1 (*C*C≡N), 91.3 (*C*C≡N), 65.1 (*C*H$_2$O), 46.2 (*C*H$_2$N), 44.2 (*C*H$_2$N), 14.4 (*C*H$_3$), 14.3 (*C*H$_3$), 11.8 (*C*H$_3$); δ_C(75 MHz; DEPT-135, $CDCl_3$) , 130.6 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 65.1 (*C*H$_2$O), 46.2 (*C*H$_2$N), 44.2 (*C*H$_2$N), 14.4 (*C*H$_3$), 14.3 (*C*H$_3$), 11.8 (*C*H$_3$); *m/z* (EI) 372 (M^+, 100%), 343 (59), 318 (100, 315 (30), 290 (18), 288 (30), 274 (130, 262 (10), 247 (8), 220 (20), 192 (6), 165 (46), 138 (5), 109 (72), 96 (21), 81 (29), 79 (10), 72 (28), 69 (13), 56 (22), (found M^+, 372.1699 $C_{21}H_{20}N_6O$ requires *M*, 372.1699). Further elution (hexane/DCM, 1:4) gave 2-amino-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **159** (2.1 mg, 6%) as colourless prisms, mp 238-239 °C (lit.,[281] 233-234 °C) (from $CHCl_3$), identical to an authentic sample. Further elution (hexane/*t*-BuOMe, 7:3) gave *2-[4-(diethylamino)-5*H*-1,2,3-dithiazol-5-ylideneamino]-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile* **168** (2.8 mg, 5%) as red prisms, mp 174-175 °C (from cyclohexane/EtOH); (found: C, 57.9; H, 4.7; N, 19.3. $C_{21}H_{20}N_6OS_2$ requires C, 57.8; H, 4.6; N, 19.3%); λ_{max}(DCM)/nm 286 (log ε 3.28), 401 inf (2.99), 452 inf (2.97), 497 (3.12), 531 (3.07); ν_{max}/cm^{-1} 3057w, 2980w, 2932w, 2224m (C≡N), 1632w, 1584w, 1547s, 1520m, 1497w, 1474s, 1454m, 1431s, 1412m, 1398w, 1379m, 1335s, 1279w, 1267m, 1234m, 1199w, 1167m, 1142w, 1103w, 1078w, 1063w, 1045w, 1024m, 982w, 949w, 936w, 922w, 907w, 893w, 841w, 814w, 789m, 773m, 748s, 729w, 706s; δ_H(300 MHz, $CDCl_3$) 7.57 (5H, m, Ph *H*), 4.81 (2H, q, *J* 7.1, C*H*$_2$O), 3.93 (4H, q, *J* 7.0, C*H*$_2$N), 1.59 (3H, t, *J* 7.1, C*H*$_3$), 1.27 (6H, t, *J* 7.0, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.6, 162.1, 160.8, 160.3, 160.0, 133.1, 130.9 (Ph *C*H), 129.0 (Ph *C*H), 128.6 (Ph *C*H), 115.1 (*C*≡N), 114.1 (*C*≡N), 99.0 (*C*C≡N), 91.9 (*C*C≡N), 66.8 (*C*H$_2$O), 45.9 (*C*H$_2$N), 14.6 (*C*H$_3$), 13.7 (*C*H$_3$); δ_C(75 MHz; DEPT-135, $CDCl_3$) 130.9 (Ph *C*H), 129.0 (Ph *C*H), 128.6 (Ph *C*H), 66.8 (*C*H$_2$O), 45.9 (*C*H$_2$N), 14.6 (*C*H$_3$), 13.7 (*C*H$_3$); *m/z* (EI) 436 (M^+, 83%), 421 (18), 407 (16), 403 (49), 390 (9), 376 (47), 357 (8), 348 (9), 344 (12), 306 (9), 279 (12), 247 (7), 220 (15), 204 (5), 165 (25), 98 (47), 83 (74), 70 (100), 64 (12), 55 (31) (found M^+, 436.1140 $C_{21}H_{20}N_6OS_2$ requires *M*, 436.1140). Further elution (*t*-BuOMe) gave the *quinoidal 2,2'-bithiazole* **169** (2.2 mg, 2%) as green needles, mp > 300 °C (from DCE); (found, C, 63.3; H, 4.8; N, 20.1. $C_{44}H_{42}N_{12}O_2S_2$ requires C, 63.4; H, 4.8; N, 20.2%); ν_{max}/cm^{-1} 2986w, 2938w, 2872w, 2228m (C≡N), 1584w, 1543m, 1464s, 1441m, 1433w, 1400m, 1352s, 1337m, 1325m, 1298m, 1263s, 1233m, 1165m, 1153w, 1126m, 1080m, 1015w, 1003w, 891w,

843w, 816w, 797w, 772w, 748m, 708m, 698w, 644w, 633m; δ_H(300 MHz, $CDCl_3$) 7.59-7.58 (5H, m, Ph *H*), 4.90 (4H, q, *J* 7.3, 7.5, CH_2O), 3.75 (6H, t, *J* 6.6, CH_3), 1.87-1.83 (8H, m, CH_2N), 1.40-1.32 (12H, m, CH_3).

4-(Di-*n*-propylamino)-7-ethoxy-5-phenylpyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile 167d. Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine **160** (50.0 mg, 0.13 mmol) with dipropylamine (71.1 μL, 0.52 mmol) gave the *title compound* **167d** (31.7 mg, 61%) as yellow prisms, mp 170-171 ^oC (from cyclohexane/EtOH); (found: C, 68.9; H, 6.0; N, 20.9. $C_{23}H_{24}N_6O$ requires C, 69.0; H, 6.0; N, 21.0%); λ_{max}(DCM)/nm 243 (log ε 3.05), 265 inf (3.01), 275 (3.03), 319 (2.92), 365 (3.22); ν_{max}/cm^{-1} 2965w, 2226m (C≡N), 1591m, 1578m, 1530s, 1497m, 1443m, 1429w, 1416w, 1371m, 1342m, 1267w, 1248m, 1207w, 1159m, 1103w, 1024w, 1013w, 980w, 922w, 868w, 802w, 787w, 727w; δ_H(300 MHz, $CDCl_3$) 7.54 (5h, s, Ph *H*), 4.64 (2H, m, CH_2O), 3.67 (4H, m, CH_2N), 1.78 (4H, m, CH_2), 1.48 (3H, t, *J* 6.2, 6.7, CH_3), 0.9 (6H, m, CH_3); δ_C(75 MHz, $CDCl_3$) 165.1, 161.25, 160.7, 135.8, 133.3, 130.6 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 115.3 (*C*≡N), 114.3 (*C*≡N), 109.1, 96.2 (*C*C≡N), 91.2 (*C*C≡N), 65.1 (*C*H_2O), 53.2 (*C*H_2N), 51.2 (*C*H_2N), 22.4 (*C*H_2), 20.0 (*C*H_2), 14.4 (*C*H_3), 11.3 (*C*H_3), 11.0 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$) 130.6 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 65.1 (*C*H_2O), 53.2 (*C*H_2N), 51.2 (*C*H_2N), 22.4 (*C*H_2), 20.0 (*C*H_2), 14.4 (*C*H_3), 11.3 (*C*H_3), 11.0 (*C*H_3); *m/z* (EI) 400 (M^+, 15%), 371 (8), 357 (14), 315 (9), 272 (7), 220 (8), 165 (29), 137 (16), 124 (60), 56 (13); (found M^+, 400.2012 $C_{23}H_{24}N_6O$ requires *M*, 400.2012).

4-(Dibenzylamino)-7-ethoxy-5-phenylpyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile 167e. Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine **160** (50.0 mg, 0.13 mmol) with dibenzylamine (526.3 μL, 2.6 mmol) gave the *title compound* **167e** (47.7 mg, 74%) as yellow needles, mp 185-186 ^oC (from EtOH); (found: C, 75.2; H, 5.0; N, 17.0. $C_{31}H_{24}N_6O$ requires C, 75.0; H, 4.9; N, 17.0%); λ_{max}(DCM)/nm 230 (log ε 4.53), 242 (4.53), 270 (4.50), 315 (4.30), 364 (4.55); ν_{max}/cm^{-1} 3063w, 3034w, 2994w, 2982w, 2940w, 2226m (C≡N), 1593m, 1578m, 1530s, 1497w, 1483w, 1454w, 1445m, 1429m, 1381m, 1366m, 1340m, 1314w, 1296w, 1285w, 1267w, 1233m, 1206w, 1180m, 1157w, 1121w, 1105w, 1082w, 1020w, 1003w, 943m, 934w, 918w, 910w, 885w, 853w, 827w; δ_H(300 MHz, $CDCl_3$) 7.45 (15H, m, Ph *H*), 4.90 (4H, s, PhCH_2), 4.70 (2H, q, *J* 7.1,

CH_2O), 1.52 (3H, t, *J* 7.1, CH_3); δ_C(75 MHz, $CDCl_3$) 165.6, 161.6, 161.4, 137.3 (Ph *C*H), 134.8 (Ph *C*H), 134.3 (Ph *C*H), 133.7 (Ph *C*H), 131.2 (Ph *C*H), 129.8 (Ph *C*H), 129.5 (Ph *C*H), 129.0 (Ph *C*H), 128.9 (Ph *C*H), 128.2 (Ph *C*H), 115.8 (*C*≡N), 114.6 (*C*≡N), 109.8, 97.0 (*C*C≡N), 92.6 (*C*C≡N), 65.8 (*C*H_2O), 53.7 (Ph*C*H_2), 50.9 (Ph*C*H_2), 14.9 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$) 137.3 (Ph *C*H), 134.8 (Ph *C*H), 134.3 (Ph *C*H), 133.7 (Ph *C*H), 131.2 (Ph *C*H), 129.8 (Ph *C*H), 129.5 (Ph *C*H), 129.0 (Ph *C*H), 128.9 (Ph *C*H), 128.2 (Ph *C*H), 65.8 (*C*H_2O), 53.7 (Ph*C*H_2), 50.9 (Ph*C*H_2), 14.9 (*C*H_3); *m/z* (EI) 496 (M^+, 10%), 405 (11), 264 (4), 165 (7), 91 (100), 65 (24); (found: M^+, 496.2012 $C_{31}H_{24}N_6O$ requires *M*, 496.2012).

7-Ethoxy-5-phenyl-4-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile 167f (typical procedure: see table 18)

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine **160** (50.0 mg, 0.13 mmol) in DCM (2 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added pyrrolidine (21.3 μL, 0.26 mmol) and the mixture was heated at reflux temperature. After 22 h TLC showed the presence of 4 main products. The reaction mixture was allowed to cool to *ca.* 20 °C, adsorbed onto silica and chromatography (hexane) gave S_8 (7.8 mg, 94%). Further elution (hexane/DCM, 1:1) gave the *title compound* **167f** (36.6 mg, 76%) as yellow-green needles, mp 217-218 °C (from EtOH); (found: C, 67.9; H, 4.8; N, 22.5. $C_{21}H_{18}N_6O$ requires C, 68.1; H, 4.9; N, 22.7%); λ_{max}(DCM)/nm 238 (log ε 4.44), 274 (4.40), 318 (4.24), 365 (4.49); ν_{max}/cm^{-1} 2997w, 2984w, 2941w, 2916w, 2870w, 2226m (C≡N), 1591s, 1578m, 1530s, 1499w, 1474m, 1445m, 1431w, 1412m, 1379m, 1362m, 1343w, 1327s, 1296w, 1269m, 1236w, 1227w, 1194w, 1179w, 1155w, 1125w, 1109w, 1078w, 1018w, 989w, 961w, 914w, 881w, 868w, 853w, 833w, 791w; δ_H(300 MHz, $CDCl_3$) 7.54 (5H, m, Ph *H*), 4.63 (2H, q, *J* 7.1, CH_2O), 3.93 (2H, t, *J* 6.3, CH_2N), 3.80 (2H, t, *J* 6.9, CH_2N), 2.08 (4H, m, CH_2C), 1.48 (3H, t, *J* 7.1, CH_3); δ_C(75 MHz, $CDCl_3$) 165.1, 161.2, 160.8, 133.8 (Ph *C*H), 133.3 (Ph *C*H), 130.6 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 115.4 (*C*≡N), 114.3 (*C*≡N), 110.0, 96.0 (*C*C≡N), 91.2 (*C*C≡N), 65.2 (*C*H_2O), 50.1 (*C*H_2N), 49.5 (*C*H_2N), 25.2 (*C*H_2C), 24.4 (*C*H_2C), 14.4 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$) 133.8 (Ph *C*H), 133.3 (Ph *C*H), 130.6 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 65.2 (*C*H_2O), 50.1 (*C*H_2N), 49.5 (*C*H_2N), 25.2 (*C*H_2C), 24.4 (*C*H_2C), 14.4 (*C*H_3); *m/z* (EI) 370 (M^+, 48%), 341 (36), 313 (14), 272 (12), 245 (4), 220 (6), 193 (7) 165 (32), 138 (9), 122 (11), 95 (12), 79 (20), 70 (100), 68 (22), 55 (27), 42 (43); (found M^+, 370.1542 $C_{21}H_{18}N_6O$ requires *M*, 370.1542). Further elution

(hexane/DCM, 3:7) gave 2-amino-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **159** (171.6 mg, 5%) as colourless prisms, mp 238-239 ^{o}C (from $CHCl_3$), identical to an authentic sample. Further elution (DCM) gave *2-(dipyrrolidin-1-ylmethyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile* **161f** (11.8 mg, 22%) as colourless prisms, mp 190-191 ^{o}C (from EtOH); (found C, 70.5; N, 20.1; H, 6.2. $C_{24}H_{26}N_6O$ requires C, 69.5; N, 20.3; H, 6.3%); λ_{max}(DCM)/nm 228 (log ε 4.50), 248 inf (4.38), 308 (4.48), 346 (4.16); ν_{max}/cm^{-1} 2980w, 2955w, 2880w, 2212m (C≡N), 1585m, 1566m, 1510s, 1474m, 1441s, 1422w, 1398m, 1377m, 1360m, 1331s, 1277m, 1258w, 1236w, 1215w, 1184w, 1169w, 1149w, 1121w, 1105w, 1090w, 1024m, 1003w, 968w, 934w, 920w, 887w, 876w, 862w, 841w, 808w, 779m, 766m; δ_H(300 MHz, $CDCl_3$) 7.26-7.52 (5H, m, Ph *H*), 4.30 (2H, q, *J* 7.1, C*H*$_2$O), 3.47 (8H, s, C*H*$_2$N), 1.90 (8H, s, C*H*$_2$C), 1.35 (3H, t, *J* 7.0, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.5, 161.9, 131.7, 160.4, 134.7 (Ph *C*H), 129.7 (Ph *C*H), 128.4 (Ph *C*H), 128.4 (Ph *C*H), 118.1 (*C*≡N), 116.6 (*C*≡N), 88.5 (*C*C≡N), 81.1 (*C*C≡N), 62.3 (*C*H$_2$O), 58.2 (*C*H$_2$N), 53.4 (*C*H$_2$N), 49.5 (*C*H$_2$), 25.3 (*C*H$_2$), 14.4 (*C*H$_3$); δ_C(75 MHz; DEPT-135, $CDCl_3$) 134.7 (Ph *C*H), 129.7 (Ph *C*H), 128.4 (Ph *C*H), 128.4 (Ph *C*H), 62.3 (*C*H$_2$O), 58.2 (*C*H$_2$N), 53.4 (*C*H$_2$N), 49.5 (*C*H$_2$), 25.3 (*C*H$_2$), 14.4 (*C*H$_3$); *m/z* (EI) 414 (M$^+$, 12%), 386 (16), 357 (12), 344 (11), 316 (37), 288 (10), 220 (14), 165 (38), 138 (10), 124 (48), 98 (9), 85 (9), 70 (100), 55 (36); (found M$^+$, 414.2168 $C_{24}H_{26}N_6O$ requires *M*, 414.5090).

7-Ethoxy-5-phenyl-4-(piperidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile 167g

Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine **160** (50.0 mg, 0.13 mmol) with piperidine (51.4 μL, 0.52 mmol) gave the *title compound* **167g** (36.9 mg, 74%) as yellow needles, mp 190-191 ^{o}C (from EtOH); (found: C, 69.0; N, 21.8; H, 5.1. $C_{22}H_{20}N_6O$ requires C, 68.8; N, 21.9; H, 5.2%); λ_{max}(DCM)/nm 241 (log ε 4.50), 274 (4.40), 319 (4.30), 365 (4.50); ν_{max}/cm^{-1} 2949w, 2224m (C≡N), 1587m, 1576m, 1529s, 1518s, 1504w, 1474m, 1443m, 1429w, 1412m, 1366m, 1342m, 1287w, 1258m, 1236m, 1229m, 1194w, 1161w, 1136w, 1111w, 1101w, 1074w, 1053w, 1018m, 991w, 953w, 932w, 916w, 879w, 851w, 831w, 799w; δ_H(300 MHz, $CDCl_3$) 7.54 (5H, m, Ph *H*), 4.64 (2H, q, *J* 7.1, C*H*$_2$O), 3.96 (2H, d, *J* 5.2, C*H*$_2$N), 3.89 (2H, d, *J* 5.1, C*H*$_2$N), 1.77 (6H, s, C*H*$_2$C), 1.47 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.1, 161.4, 160.7, 135.1 (Ph *C*H), 133.3 (Ph *C*H), 130.1 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 115.3 (*C*≡N), 114.3 (*C*≡N), 108.7, 96.0 (*C*C≡N), 91.3 (*C*C≡N), 65.1 (*C*H$_2$O), 50.2 (*C*H$_2$N), 46.7 (*C*H$_2$N), 26.6 (*C*H$_2$C), 25.1 (*C*H$_2$C),

23.9 (*C*H_2C), 14.4 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$) 135.1 (Ph *C*H), 133.3 (Ph *C*H), 130.1 (Ph *C*H), 128.8 (Ph *C*H), 128.5 (Ph *C*H), 65.1 (*C*H_2O), 50.2 (*C*H_2N), 46.7 (*C*H_2N), 26.6 (*C*H_2C), 25.1 (*C*H_2C), 23.9 (*C*H_2C), 14.4 (*C*H_3); *m/z* (EI) 384 (M^+, 33%), 355 (31), 316 (6), 300 (5), 288 (5), 276 (9), 272 (5), 248 (18), 220 (8), 192 (5), 165 (37), 136 (12), 121 (13), 109 (14), 84 (50), 70 (29), 55 (62); (found: M^+, 384.1699 $C_{22}H_{20}N_6O$ requires *M*, 384.4373) and *2-(dipiperidin-1-ylmethyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile* **161g** (6.3 mg, 11%) as colourless needles, mp 186-187 °C (from EtOH); (found C, 70.6; H, 6.9; N, 19.1 $C_{26}H_{30}N_6O$ requires C, 70.6; H, 6.8; N, 19.0%); λ_{max}(DCM)/nm 280 (log ε 3.36), 299 (3.39), 321 inf (3.25), 342 inf (2.95), 364 inf (2.68); ν_{max}/cm^{-1} 2978w, 2945w, 2924w, 2857w, 2214m (C≡N), 1582w, 1564w, 1533m, 1512m, 1483s, 1476s, 1437s, 1408m, 1381m, 1358w, 1331m, 1317s, 1258m, 1225m, 1190m, 1153m, 1139w, 1121w, 1105w, 1082w, 1072w, 1022m, 982w, 955w, 935w, 920w, 878w, 860w, 853w, 841w, 804w, 779m, 765m; δ_H(300 MHz, $CDCl_3$) 7.54-7.46 (5H, m, Ph *H*), 4.42 (2H, q, *J* 7.1, C*H*$_2$O), 3.25 (8H, s, C*H*$_2$N), 1.61 (12H, s, C*H*$_2$C), 1.41 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 166.1, 164.6, 161.0, 134.7, 130.6 (Ph *C*H), 129.1 (Ph *C*H), 127.0 (Ph *C*H), 117.8 (*C*≡N), 116.2 (*C*≡N), 92.1 (*C*C≡N), 85.2 (*C*C≡N), 63.6 (*C*H_2O), 50.3 (*C*H_2N), 27.3, 25.6 (*C*H_2C), 24.8 (*C*H_2C), 14.9 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$) 130.6 (Ph *C*H), 129.1 (Ph *C*H), 127.0 (Ph *C*H), 63.6 (*C*H_2O), 50.3 (*C*H_2N), 27.3, 25.6 (*C*H_2C), 24.8 (*C*H_2C), 14.9 (*C*H_3); *m/z* (EI) 442 (M^+, 8%), 359 (12), 330 (28), 220 (5), 165 (7), 84 (100), 69 (14), 56 (21); (found: M^+, 442.2481 $C_{26}H_{30}N_6O$ requires *M*, 442.2481).

7-Ethoxy-4-morpholino-5-phenylpyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile 167h

Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-3,5-dicyano-4-phenyl-6-ethoxypyridine **160** (50.0 mg, 0.13 mmol) with morpholine (45.0 μL, 0.52 mmol) gave the *title compound* **167h** (38.6 mg, 77%) as orange dust, mp 165-166 °C (from EtOH); (found: C, 66.4; H, 4.8; N, 21.9. $C_{21}H_{18}N_6O_2$ requires C, 65.2; H, 4.7; N, 21.8%); λ_{max}(DCM)/nm 230 (log ε 4.43), 277 (4.37), 315 (4.18), 365 (4.40); ν_{max}/cm^{-1} 3325w, 3067w, 2963w, 2845w, 2226m (C≡N), 1626w, 1589m, 1578m, 1530s, 1520s, 1503w, 1474m, 1439m, 1412m, 1381m, 1368m, 1356w, 1344m, 1331w, 1321w, 1298w, 1275w, 1250s, 1238w, 1196w, 1157w, 1119m, 1070w, 1040w, 1032w, 1016w, 962m, 885m, 853w, 843w, 799w; δ_H(300 MHz, $CDCl_3$) 7.55 (5H, m, Ph *H*), 4.65 (2H, q, *J* 7.1, C*H*$_2$O), 4.03 (2H, t, *J* 4.8, C*H*$_2$O), 3.95 (2H, t, *J* 4.2, C*H*$_2$O), 3.87 (2H, t, *J* 4.7, C*H*$_2$N), 3.82 (2H, t, *J* 4.8, C*H*$_2$N), 1.49 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.1, 160.9, 160.8, 135.4, 133.2, 130.8, (Ph *C*H), 128.9 (Ph *C*H), 128.6

(Ph *C*H), 115.1 (*C*≡N), 114.0 (*C*≡N), 108.5, 96.5 (*C*C≡N), 92.3 (*C*C≡N), 66.5 (*C*H_2O), 65.9 (*C*H_2O), 65.4 (*C*H_2O), 48.9 (*C*H_2N), 45.8 (*C*H_2N), 14.4 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$) 130.8, (Ph *C*H), 128.9 (Ph *C*H), 128.6 (Ph *C*H), 66.5 (*C*H_2O), 65.9 (*C*H_2O), 65.4 (*C*H_2O), 48.9 (*C*H_2N), 45.8 (*C*H_2N), 14.4 (*C*H_3); *m/z* (EI) 386 (M^+, 100%), 357 (54), 340 (5), 330 (8), 315 (5), 300 (11), 288 (14), 274 (15), 272 (16), 261 (9), 248 (14), 220 (17), 193 (11), 165 (60), 138 (17), 124 (13), 108 (6), 96 (7), 85 (45), 77 (12), 66 (28), 56 (16); (found: M^+, 386.1491 $C_{21}H_{18}N_6O_2$ requires *M*, 386.1491) and *2-(dimorpholinomethyleneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile* **161h** (1.15 mg, 2%) as colourless prisms, mp 216-217 °C (from EtOH); (found: C, 64.7; N, 18.9; H, 5.9. $C_{24}H_{26}N_6O_3$ requires C, 64.6; N, 18.8; H, 5.8%); λ_{max}(DCM)/nm 230 (log ε 4.51), 248 inf (4.42), 312 (4.46), 338 (4.42); ν_{max}/cm^{-1} 2970w, 2926w, 2914w, 2893w, 2855w, 2218m (C≡N), 1585w, 1570w, 1530w, 1510w, 1483s, 1452w, 1439s, 1412m, 1363m, 1337w, 1317m, 1296w, 1265m, 1244w, 1213w, 1179m, 1155m, 1111s, 1092m, 1067w, 1036m, 1022m, 989m, 932w, 907w, 878m, 854w, 849w, 831w; δ_H(300 MHz, $CDCl_3$) 7.51 (5H, m, Ph *H*), 7.51 (5H, m, Ph *H*), 4.46 (2H, q, *J* 7.1, C*H*$_2$O), 3.72 (8H, t, *J* 4.6, C*H*$_2$O), 3.33 (8H, t, *J* 4.6, C*H*$_2$N), 1.44 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz, $CDCl_3$) 165.8, 165.2, 162.2, 160.7, 133.8, 130.4 (Ph *C*H), 128.7 (Ph *C*H), 128.5 (Ph *C*H), 116.7 (*C*≡N), 115.0 (*C*≡N), 92.5 (*C*C≡N), 86.8 (*C*C≡N), 66.2 (*C*H_2O), 63.6 (*C*H_2O), 49.0 (*C*H_2N), 14.4 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$) 130.4 (Ph *C*H), 128.7 (Ph *C*H), 128.5 (Ph *C*H), 66.2 (*C*H_2O), 63.6 (*C*H_2O), 49.0 (*C*H_2N), 14.4 (*C*H_3); *m/z* (EI) 446 (M^+, 18%), 360 (10), 332 (55), 303 (14), 288 (11), 275 (19), 220 (13), 192 (5), 165 (29), 138 (4), 112 (13), 86 (100), 69 (28), 56 (54); (found: M^+, 446.2066 $C_{24}H_{26}N_6O_3$ requires *M*, 446.4916).

Treatment of 7-ethoxy-5-phenyl-4-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-di-carbonitrile 167f with pyrrolidine (typical procedure: see Table 19)

To a stirred solution of 7-ethoxy-5-phenyl-4-(pyrrolidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-di-carbonitrile **167f** (30.0 mg, 0.08 mmol) in DCM (2 mL) at 20 °C and protected with $CaCl_2$ drying tube, was added pyrrolidine (131.4 μL, 1.6 mmol) and the mixture was heated at reflux for 5 h until no starting materials remained (TLC). The reaction mixture was allowed to cool to *ca.* 20 °C, adsorbed onto silica and chromatography (DCM) gave 2-(dipyrrolidin-1-yl-methyleneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **161f** (21.5 mg, 65%) as colourless prisms, mp 190-191 °C (from EtOH) identical to that described above.

Treatment of 7-ethoxy-5-phenyl-4-(piperidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile 167g with piperidine

Similar treatment of 7-ethoxy-5-phenyl-4-(piperidin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile **167g** (30.7 mg, 0.08 mmol) with piperidine (316.1 μL, 3.2 mmol) in PhMe at reflux gave the 2-(dipiperidin-1-yl-methyleneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **161g** (7.4 mg, 21%) as colourless needles, mp 186-187 ^{o}C (from EtOH) identical to that described above.

Treatment of 7-ethoxy-5-phenyl-4-(morpholin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile 167h with morpholine

Similar treatment of 7-ethoxy-5-phenyl-4-(morpholin-1-yl)pyrido[2,3-*d*]pyrimidine-2,6-dicarbonitrile **167h** (30.7 mg, 0.08 mmol) with morpholine (138.4 μL, 1.6 mmol) gave 2-(dimorpholin-1-yl-methyleneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **161h** (27.8 mg, 78%) as colourless prisms, mp 216-217 ^{o}C (from EtOH) identical to that described above.

3-Amino-6-ethoxy-4-phenyl-2-(4-chloro-1,2,5-thiadiazol-2-amino)-3,5-dicarbonitrile 182

A stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **160** (100 mg, 0.25 mmol) in THF (4 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was purged with NH_3 (g) (excess) the whole time and the mixture was left to heat at reflux temperature for 1 h, until no starting materials remained (TLC). On cooling to *ca.* 20 ^{o}C the reaction mixture was adsorbed onto silica and chromatography (hexane/DCM, 1:4) gave 2-amino-6-ethoxy-4-phenylpyrido-3,5-dicarbonitrile **159** (14.4 mg, 35%) as colourless needles, mp 235-236 ^{o}C (from $CHCl_3$) identical to an authentic sample. Further elution (hexane/DCM, 1:9) gave the *title compound* **182** (26.7 mg, 28%) as colourles cotton fibers, mp 178-179 ^{o}C (from cyclohexane/EtOH); (found: C, 53.4; H, 2.75; N, 22.2. $C_{17}H_{11}ClN_6OS$ requires C, 53.3; H, 2.9; N, 22.0%); λ_{max}(DCM)/nm 228 (log ε 3.00), 322 (3.13), 313 (3.13), 277 inf (2.98), 261 (3.07); ν_{max}/cm^{-1} 3387m (NH), 2978w, 2224m (C≡N), 2214 (C≡N), 1599s, 1578s, 1562s, 1514s, 1494w, 1477m, 1458m, 1445m, 1420m, 1396w, 1383m, 1346m, 1321w, 1298m, 1263m, 1240w, 1175m, 1155w, 1107w, 1092m, 1078w, 1014m, 928m, 916m, 858w, 833w, 812m, 787m, 772m, 733s, 721w, 700m; δ_H(300 MHz; $CDCl_3$) 8.07 (1H, br s, N*H*), 7.58 (5H, s, Ph *H*), 4.54 (2H, q, *J* 7.1, CH_2O), 1.45 (3H, t, *J* 7.1, CH_3); δ_C(75 MHz, $CDCl_3$) 166.1, 160.8, 155.5, 147.2, 137.6, 132.9, 131.2 (Ph *C*H), 129.2 (Ph

*C*H), 128.5 (Ph *C*H), 114.6 (*C*≡N), 113.7 (*C*≡N), 89.95 (*C*C≡N), 87.2 (*C*C≡N), 65.5 (*C*H_2), 14.2 (*C*H_3); *m/z* (EI) 382 (M^+, 100%), 381 (M^+-1, 80), 353 (84), 319 (70), 287 (14), 264 (8), 236 (10), 220 (8), 180 (8), 165 (30), 153 (8), 127 (10), 77 (10), 57 (10).

3-Amino-6-ethoxy-4-phenyl-2-azidonicotino-3,5-dicarbonitrile 188

To stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **160** (100 mg, 0.25 mmol) in THF (4 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added NaN_3 (65.0 mg, 1 mmol.) and 18-crown-6 (13.2 mg, 5 mol%). The mixtures were then allowed to heat at reflux temperature for 9 h, until no starting materials remained (TLC). The mixture was then adsorbed onto silica and chromatography (hexane/DCM, 1:4) gave traces of 2-amino-6-ethoxy-4-phenylpyrido-3,5-dicarbonitrile **159**. Further elution (DCM, 100%) gave the *title compound* **188** (66 mg, 91%) as light orange cubes, mp 145-146 °C (from cyclohexane/EtOH); (found: C, 62.0; H, 3.5; N, 29.1. $C_{15}H_{10}N_6O$ requires C, 62.1; H, 3.5; N, 29.0%); λ_{max}(DCM)/nm 238 (log ε 3.05), 268 (3.36), 325 (3.02); ν_{max}/cm^{-1} 2230w (C≡N), 1555s, 1497w, 1477w, 1452m, 1441m, 1416w, 1377s, 1344s, 1275w, 1240m, 1217m, 1163m, 1086w, 1065w, 1015m, 920w, 785m, 741s, 696m; δ_H(300 MHz; $CDCl_3$) 7.58-7.50 (5H, m, Ph *H*), 4.62 (2H, q, *J* 7.1, CH_2O), 1.51 (3H, t, *J* 7.1, CH_3); δ_C(75 MHz, $CDCl_3$) 165.4, 161.65, 159.5, 132.3, 131.3 (Ph *C*H), 129.1 (Ph *C*H), 128.5 (Ph *C*H), 113.1 (*C*≡N), 113.0 (*C*≡N), 93.2 (*C*C≡N), 91.8 (*C*C≡N), 65.5 (*C*H_2), 14.1 (*C*H_3); *m/z* (EI) 290 (M^+, 72%), 264 (12), 262 (16), 236 (18), 234 (100), 207 (58), 179 (85), 165 (18), 152 (22), 139 (8), 127 (68), 100 (6), 77 (16), 51 (17).

9.6 Compounds Related to Chapter 6

Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile 160 with Ph_3P (see Table 21)

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **160** (100 mg, 0.25 mmol) in dry DCM (4 mL) at *ca*. 20 °C and protected with a $CaCl_2$ drying tube was added H_2O (9.0 μL, 0.50 mmol) and Ph_3P (262.0 mg, 1 mmol). The mixture was then allowed to stir at *ca*. 20 °C for 3 h, until no starting materials remained (TLC). The reaction mixture was then adsorbed onto silica and chromatography (hexane/DCM, 1:1) gave Ph_3P=S (137.2 mg, 94%) as colourless needles, mp 161–162 °C

(from cyclohexane), identical to an authentic sample. Further elution (hexane/DCM, 4:6) gave 2-amino-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile **159** (11.2 mg, 17%) as colourless prisms, mp 238-239 °C (from $CHCl_3$), identical to an authentic sample. Further elution (hexane/DCM, 1:4) gave *3-amino-6-ethoxy-4-phenyl-1*H-*pyrrolo[2,3-*b*]pyridine-2,5-dicarbonitrile* **212** (53.0 mg, 70%) as yellow prisms, mp 191–192 °C (from cyclohexane/EtOH); (found: C, 67.2; H, 4.4; N, 23.0. $C_{17}H_{13}N_5O$ requires C, 67.3; H, 4.3; N, 23.1%); λ_{max} (DCM)/nm 243 (log ε 3.21), 276 (3.46), 314 inf (2.80), 328 (2.93), 372 inf (3.39); ν_{max}/cm^{-1} 3345m (NH), 3231m (NH_2), 2234m (C≡N), 2203s (C≡N), 1587s, 1580s, 1516m, 1489m, 1472m, 1381s, 1315s, 1180m, 1159m, 1024m, 924m, 868m, 793m, 772m, 741s, 702s; δ_H (300 MHz; $CDCl_3$) 8.31 (1H, br s, N*H*), 7.59-7.56 (3H, m, Ph *H*), 7.52–7.48 (2H, m, Ph *H*), 4.51 (2H, q, *J* 7.1, CH_2), 3.74 (2H, br s, NH_2), 1.47 (3H, t, *J* 7.1, CH_3); δ_C (75 MHz, $CDCl_3$) 163.7, 152.6, 146.0, 138.2, 133.1, 130.4 (Ph *C*H), 129.2 (Ph *C*H), 128.3 (Ph *C*H), 115.2 (*C*≡N), 113.8 (*C*≡N), 103.1, 91.2, 87.2, 63.8 (*C*H_2), 14.3 (*C*H_3); *m/z* (EI) 303 (M+, 84%), 275 (100), 247 (11), 219 (12), 194 (9), 165 (12), 140 (70), 51 (5). Further elution (DCM) gave *3-aminophosphorane-6-ethoxy-4-phenyl-1*H-*pyrrolo[2,3-*b*]pyridine-2,5-dicarbonitrile* **213** (23.9 mg, 17%) as colourless cubes, mp 285-286 °C (from cyclohexane/EtOH); (found C, 74.5; H, 4.6; N, 12.4. $C_{35}H_{26}N_5OP$ requires C, 74.6; H, 4.7; N, 12.4%); λ_{max} (DCM)/nm 240 (log ε 3.97), 265 (3.97), 274 inf (3.94), 295 (3.92), 301 inf (3.90), 351 (3.88); ν_{max}/cm^{-1} 3379w (NH), 3259w, 3092w, 3060w, 2929w, 2229m (C≡N), 2219m (C≡N), 1683s, 1651m, 1604m, 1549w, 1537m, 1516w, 1490s, 1456w, 1441s, 1410s, 1383w, 1369m, 1340s, 1320w, 1278w, 1253m, 1239w, 1192w, 1170m, 1123w, 1101w, 1079w, 1018w, 1003w, 986w, 936w, 922w, 852w, 826w, 806w, 793w, 778w, 753m, 743m; δ_H (300 MHz; $CDCl_3$) 7.83-7.76 (6H, m, Ph_3P *H*), 7.73-7.57 (4H, m, Ph_3P *H*), 7.56-7.42 (5H, m, Ph_3P *H*), 7.39-7.36 (2H, m, Ph *H*), 7.35-7.22 (3H, m, Ph *H*), 3.72 (2H, q, *J* 6.9, 7.1, 7.2, CH_2O), 1.24 (3H, t, *J* 6.9 CH_3); δ_C(75 MHz; DMSO-d_6) 159.1, 152.2, 142.2 (d, J_{PC} 22.5, Ph_3P *C*-1), 136.1, 134.0 (d, J_{PC} 10.5, Ph_3P *C*-2), 132.8, 131.6 (d, J_{PC} 10.5, Ph_3P *C*-2), 131.1 (Ph *C*H), 129.5 (d, J_{PC} 12.75, Ph_3P *C*-4), 128.9 (Ph *C*H), 128.3 (Ph *C*H), 128.1 (, J_{PC} 24.0, Ph_3P *C*-3), 120.9, 119.7, 119.0 (*C*≡N), 1147.2 (*C*≡N), 56.0 (*C*H_2O), 18.5 (*C*H_3); δ_C(75 MHz; DEPT-135, DMSO-d_6) 134.0 (d, J_{PC} 10.5, Ph_3P *C*-2), 131.6 (d, J_{PC} 10.5, Ph_3P *C*-2), 131.1 (Ph *C*H), 129.5 (d, J_{PC} 12.75, Ph_3P *C*-4), 128.9 (Ph *C*H), 128.3 (Ph *C*H), 128.1 (, J_{PC} 24.0, Ph_3P *C*-3); δ_P(121.5 MHz; DMSO-d_6) 10.5; *m/z* (EI) 563 (M+, 100%), 534 (7), 378 (7), 323 (13), 277 (10), 268 (7), 262 (9), 183 (72), 152 (10), 108 (20). Further elution (DCM/*t*-BuOMe, 4:1) gave *6-cyano-5-oxo-7-phenyl-2,5-bis-*

*(triphenylphosphino)imidazo[1,2-*a*]pyridin-4-ium-1-ide* **214** as yellow prisms, mp 316-318 °C (from EtOH); (found C, 77.0; H, 4.5; N, 8.8. $C_{51}H_{35}N_5OP2$ requires C, 77.0; H, 4.4; N, 8.8%); λ_{max} (DCM)/nm 268 (log ε 4.07), 274 (4.07), 290 (4.05), 398 (3.68); ν_{max}/cm^{-1} 3082w, 3056w, 2205m (C≡N), 1639s (C=O), 1577w, 1563s, 1508m, 1486m, 1438s, 1370w, 1343w, 1310w, 1255m, 1215w, 1190w, 1167w, 1109s, 1072w, 1049w, 1027w, 999w, 978m, 916w, 876w, 829w, 767w, 744m, 726w, 716s; δ_H(300 MHz; DMSO-d_6) 7.83-7.31 (5H, m, Ph *H*), 7.63-7.58 (6H, m, Ph_3P *H*), 7.49-7.41 (6H, m, Ph_3P *H*), 7.33-7.31 (6H, m, Ph_3P *H*), 7.25-7.18 (6H, m, Ph_3P *H*); δ_C(75 MHz; DMSO-d_6) 206.5 (*C*=O), 159.1, 152.2, 136.12, 134.0 (d, J_{PC} 10.5, Ph_3P *C*-2), 131.4 (d, J_{PC} 9.75, Ph_3P *C*-3), 131.1 (Ph *C*H), 129.5 (d, J_{PC} 12.75, Ph_3P *C*-4), 128.9 (Ph *C*H), 128.3 (Ph *C*H), 128.1 (d, J_{PC} 12.75, Ph_3P *C*-4), 120.3 (d, J_{PC} 92.25, Ph_3P *C*-1), 119.0 (*C*≡N), 117.3 (*C*≡N), 79.89 (*C*C≡N), 76.6 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 134.0 (d, J_{PC} 10.5, Ph_3P *C*-2), 131.4 (d, J_{PC} 9.75, Ph_3P *C*-3), 131.1 (Ph *C*H), 129.5 (d, J_{PC} 12.75, Ph_3P *C*-4), 128.9 (Ph *C*H), 128.3 (Ph *C*H), 128.1 (d, J_{PC} 12.75, Ph_3P *C*-4); δ_P(121.5 MHz; DMSO-d_6) 13.9, 8.0; *m/z* (EI) 795 (M+, 47%), 536 (10), 534 (27), 476 (35), 445 (33), 304 (29), 284 (33), 267 (29), 162 (25), 149 (100), 118 (9), 48 (9). Further elution (DCM/*t*-BuOMe, 7:3) gave Ph_3P=O as colourless needles, (104.25 mg, 75%), mp 154-155 °C (from cyclohexane), identical to an authentic sample.

Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenylpyridine-3,5-dicarbonitrile 160 with Ph_3P polymer bound (see Table 22)

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-ethoxy-4-phenyl-pyridine-3,5-dicarbonitrile **160** (100 mg, 0.25 mmol) in DCM (4 mL) at *ca*. 20 °C and protected with a $CaCl_2$ drying tube, was added polymer bound Ph_3P (328 mg, 1.25 mmol). The mixture was then allowed to stir at *ca*. 20 °C for 3 d, until no starting materials remained (TLC). Filtration of the reaction to remove the polymer, gave 3-amino-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-2,5-dicarbonitrile **212** (47 mg, 62%) as yellow prisms mp 191–192 °C (from cyclohexane/EtOH), identical to that described above.

3-Aminophosphorane-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-2,5-dicarbonitrile 213 from 3-amino-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-2,5-dicarbonitrile 212

A. From Ph_3P and Br_2

To a stirred solution of Ph_3P (89.1 mg, 0.34 mmol) and Br_2 (8.66 μL, 0.34 mmol) in distilled DCM (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added 3-aminoindole -2-carbonitrile **212** (50.0 mg, 0.17 mmol). The mixture was left to stirr for 25 h, until no starting materials remained (TLC). The reaction mixture was directly adsorbed onto silica and chromatography (DCM/*t*-BuOMe, 7:3) gave the title compound **213** (65.1 mg, 68%) as colourless cubes, mp 285-286 ^oC (from cyclohexane/EtOH) identical to that described above.

B. From Ph_3P and hexachloroethane

To a stirred solution of 3-aminoindole-2-carbonitrile **212** (50.0 mg, 0.17 mmol) in distilled PhH (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added triethylamine (94.25 μL, 0.68 mmol), Ph_3P (89.8 mg, 0.34 mmol) and then hexachloroethane (79.6 mg, 0.34 mmol). The mixture was then heated to *ca.* 80 ^oC for 4 h, until no starting material remained (TLC). The reaction mixture was directly adsorbed onto silica and chromatography (DCM/*t*-BuOMe, 7:3) gave the title compound **213** (81.4 mg, 85%) as colourless cubes, mp 285-286 ^oC (from cyclohexane/EtOH) identical to that described above.

3-Amino-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-b]pyridine-2,5-dicarbonitrile 212 from 3-amino-phosphorane-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-2,5-dicarbonitrile 208

A. Using HCl (0.5 N)

To a stirred solution of 3-aminophosphorane-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-2,5-dicarbonitrile **213** (50.0 mg, 0.09 mmol) in MeOH (1 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added 0.5 N HCl (1 mL) and the mixture was then heated to *ca.* 80 ^oC for 5 h, until no starting material remained (TLC). The reaction mixture was then extracted (DCM), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (hexane/DCM, 1:4) gave 3-amino-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-2,5-dicarbonitrile **212** (24.5mg, 90%) as yellow prisms, mp 191–192 °C (from cyclohexane/EtOH) identical to that described above.

B. Using AcOH (80%)

To a stirred solution of 80% acetic acid (2 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added 3-amino-phosphorane-6-ethoxy-4-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine-2,5-di-carbonitrile **213** (50.0 mg, 0.09 mmol) and the mixture was heated to *ca.* 80 °C for 6.5 h, until no starting material remained (TLC). The reaction mixture was then extracted (DCM), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (hexane/DCM, 1:4) gave the *title compound* **212**(25.1 mg, 92%) as yellow prisms, mp 191–192 °C (from cyclohexane/EtOH) identical to that described above.

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile 142a: (typical procedure) (see Table 23)

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (352.4 mg, 1.69 mmol) in DCM (4 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added 2-amino-benzonitrile **219a** (200 mg, 1.69 mmol). After 1 h, to the reaction mixture was added, dropwise, pyridine (273.4 μL, 3.38 mmol) and left to stir at *ca*. 20 °C for additional 2 h. The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (traces). Further elution (hexane/DCM, 4:1) gave 4-chloro-5*H*-1,2,3-dithiazole-5-thione (10 mg, 6%) and further elution (hexane/DCM, 1:4) gave the *title compound* **142a** (395.0 mg, 92%) as yellow crystals, mp 125-126 °C (lit.,[111] 128 °C) (from cyclohexane/DCM); λ_{max}(DCM)/nm 231 (log ε 3.33), 268 inf (2.79), 302 (2.65), 379 (2.92), 398 inf (2.85), 423 inf (2.56); ν_{max}/cm^{-1} 3088w, 3056w and 3025w (Ph CH), 2238m (C≡N), 1593s, 1562s, 1524w, 1505w, 1479s, 1442m, 1286w, 1233m, 1186w, 1165w, 1145s, 1099m, 1045m, 1000w, 879m, 857s, 771s, 737m; δ_H(300 MHz; $CDCl_3$) 7.76-7.65 (2H, m, Ph *H*), 7.35-7.29 (2H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) 161.5, 153.2, 148.0, 134.4 (Ph *C*H), 134.0 (Ph *C*H), 126.3 (Ph *C*H), 117.4 (Ph *C*H), 116.3 (*C*≡N), 106.0 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 134.4 (Ph *C*H), 134.0 (Ph *C*H), 125.3 (Ph *C*H), 117.4 (Ph *C*H); *m/z* (EI) 255 (M^++2, 35%), 253 (M^+, 84), 192 (99), 160 (12), 154 (18), 128 (11), 125 (10), 116 (4), 102 (71), 93 (13), 75 (53), 64 (100), 51 (31) identical to an authentic sample.

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-5-nitrobenzonitrile 142b

Similar treatment of 2-amino-5-nitrobenzonitrile **219b** (200 mg, 1.36 mmol), 4,5-dichloro-1,2,3-dithiazolium chloride **42** (283.6 mg, 1.36 mmol) and pyridine (220 μL, 2.72 mmol) in

DCM (4 mL) gave the *title compound* **142b** (324.2 mg, 80%) as a red powder, mp 181-182 ^{o}C (from EtOH); (found: C, 36.2; H, 1.0; N, 18.6. $C_9H_3Cl_2N_4O_2S_2$ requires C, 36.2; H, 1.0; N, 18.8%); λ_{max}(DCM)/nm 490 (log ε 2.83), 305 (2.77), 265 (2.81), 231 (3.07); ν_{max}/cm^{-1} 3099w and 3077 (Ph CH), 2234w (C≡N), 1601w, 1586m, 1569s, 1515s, 1506m, 1471w, 1345s, 1259m, 1235m, 1164w, 1153w, 1129w, 1080m, 914s, 873s, 837w, 796s, 768w, 752m, 730m; δ_H(300 MHz; DMSO-d_6) 8.83 (1H, d, *J* 2.5, Ph *H*-6), 8.59 (1H, dd, *J* 9.0, 2.6, Ph *H*-4), 7.72 (1H, d, *J* 9.0, Ph *H*-3); δ_C(75 MHz; DMSO-d_6) 165.1, 158.2, 146.7, 144.1, 130.6 (Ph *C*H), 130.1 (Ph *C*H), 119.2 (Ph *C*H), 115.0 (*C*≡N), 106.0 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 130.6 (Ph *C*H), 130.1 (Ph *C*H), 119.2 (Ph *C*H); *m/z* (EI) 300 (M^++2, 6%), 298 (M^+, 14), 237 (15), 205 (1), 175 (3), 157 (6), 127 (8), 125 (8), 115 (6), 100 (13), 93 (10), 88 (7), 75 (15), 70 (8), 64 (100), 50 (13).

3-Bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-5-nitrobenzonitrile 142c

Similar treatment of 2-amino-3-bromo-5-nitrobenzonitrile **219c** (200 mg, 0.83 mmol), 4,5-dichloro-1,2,3-dithiazolium chloride **42** (173.1 mg, 0.83 mmol) and pyridine (134 μL, 1.66 mmol) in DCM (4 mL) gave the *title compound* **142c** (168.4 mg, 73%) as yellow crystals, mp 171-172 ^{o}C (from EtOH); (found: C, 28.6; H, 0.5; N, 15.0. $C_9H_2BrCl_2N_4O_2S_2$ requires C, 28.6; H, 0.5; N, 14.8%); λ_{max}(DCM)/nm 236 (log ε 3.10), 284 (2.93), 371 (2.76); ν_{max}/cm^{-1} 3080w (Ph CH), 2240w (C≡N), 1591s, 1559s, 1525s, 1514w, 1497w, 1424m, 1343s, 1238m, 1212w, 1174w, 1153m, 1082m, 931w, 918w, 901m, 870m, 845w, 830m, 782s, 742s, 727m; δ_H(300 MHz; DMSO-d_6) 8.90 (1H, d, *J* 2.4, Ph *H*-4 or 6), 8.87 (1H, d, *J* 2.4, Ph *H*-4 or 6); δ_C(75 MHz; DMSO-d_6) 165.9, 157.3, 145.1, 144.4, 133.6 (Ph *C*H), 129.4 (Ph *C*H), 114.2, 113.9, 104.0; δ_C(75 MHz; DEPT-135, DMSO-d_6) 133.6 (Ph *C*H), 129.4 (Ph *C*H); *m/z* (EI) 380 (M^++4, 56%), 378 (M^++2, 100), 376 (M^+, 99), 317 (94), 315 (93), 287 (5), 285 (8), 279 (6), 253 (7), 237 (14), 235 (13), 233 (10), 231 (11), 227 (5), 225 (5), 207 (5), 193 (6), 190 (8), 181 (4), 158 (28), 152 (5), 125 (45), 107 (9), 100 (64), 95 (15), 93 (36), 88 (18), 75 (28), 70 (21), 64 (100), 50 (8), 46 (6).

4-Chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile 142d

Similar treatment of 2-amino-4-chlorobenzonitrile **219d** (200 mg, 1.31 mmol), 4,5-dichloro-1,2,3-dithiazolium chloride **42** (273.1 mg, 1.31 mmol) and pyridine (212 μL, 2.62 mmol) in DCM (4 mL) gave the *title compound* **142d** (327.1 mg, 87%) as a yellow powder, mp 177-178

^{o}C (from cyclohexane/DCM); (found: C, 37.6; H, 1.1; N, 14.7. $C_9H_3Cl_2N_3S_2$ requires C, 37.5; H, 1.1; N, 14.6%); λ_{max}(DCM)/nm 233 (log ε 3.25), 272 inf (2.76), 337 (2.78); ν_{max}/cm^{-1} 3069w (Ph CH), 2237m (C≡N), 1587s, 1581w, 1552s, 1506m, 1498m, 1464m, 1392w, 1377w, 1262w, 1231m, 1148s, 1117m, 1089m, 919s, 875s, 858s, 832s, 799s, 753s; δ_H(300 MHz; DMSO-d_6) 7.98 (1H, d, *J* 8.4, Ph *H*-6), 7.60 (1H, d, *J* 1.9, Ph *H*-3), 7.47 (1H, dd, *J* 8.4, 2.0, Ph *H*-5); δ_C(75 MHz; DMSO-d_6) 164.7, 155.0, 146.3, 139.8, 135.8 (Ph *C*H), 126.3 (Ph *C*H), 118.3 (Ph *C*H), 115.9 (*C*≡N), 103.3 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 135.8 (Ph *C*H), 126.3 (Ph *C*H), 118.3 (Ph *C*H); *m/z* (EI) 291 (M^++4, 5%), 289 (M^++2, 26), 287 (M^+, 35), 228 (36), 226 (76), 194 (5), 188 (6), 162 (6), 136 (10), 127 (9), 125 (7), 100 (30), 93 (10), 84 (8), 75 (13), 64 (100), 50 (9).

5-Chloro-2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile 142e

Similar treatment of 2-amino-5-chlorobenzonitrile **219e** (200 mg, 1.31 mmol), 4,5-dichloro-1,2,3-dithiazolium chloride **42** (273.1 mg, 1.31 mmol) and pyridine (212 μL, 2.62 mmol) in DCM (4 mL) gave the *title compound* **142e** (323.3 mg, 86%) as yellow cotton fibers, mp 147-148 ^{o}C (from cyclohexane/DCM); (found: C, 37.6; H, 1.1; N, 14.7. $C_9H_3Cl_2N_3S_2$ requires C, 37.5; H, 1.1; N, 14.6%); λ_{max}(DCM)/nm 430 inf (log ε 2.39), 383 (2.78), 313 (2.39), 247 (2.96), 229 (3.03); ν_{max}/cm^{-1} 3071w (Ph CH), 2237w (C≡N), 1587m, 1568s, 1551m, 1492s, 1478m, 1464m, 1395w, 1266w, 1234w, 1185m, 1152m, 1130m, 1083m, 876s, 865s, 816s, 800w, 769s; δ_H(300 MHz; DMSO-d_6) 8.09 (1H, d, *J* 2.4, Ph *H*-6), 7.85 (1H, dd, *J* 8.8, 2.4, Ph *H*-4), 7.51 (1H, d, *J* 8.8, Ph *H*-3); δ_C(75 MHz; DMSO-d_6) 163.5, 152.0, 146.7, 135.3 (Ph *C*H), 133.5 (Ph *C*H), 129.9, 119.7 (Ph *C*H), 115.4 (*C*≡N), 106.9 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 135.3 (Ph CH), 133.5 (Ph CH), 119.7 (Ph CH); *m/z* (EI) 291 (M^++4, 8%), 289 (M^++2, 28), 287 (M^+, 37), 228 (21), 226 (47), 194 (9), 188 (7), 162 (9), 136 (12), 127 (7), 125 (6), 109 (5), 100 (31), 93 (8), 75 (10), 70 (8), 64 (100), 50 (8).

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-methylbenzonitrile 142f

Similar treatment of 2-amino-6-methylbenzonitrile **219f** (200 mg, 1.52 mmol), 4,5-dichloro-1,2,3-dithiazolium chloride **42** (315.9 mg, 1.52 mmol) and pyridine (245.9 μL, 3.04 mmol) in DCM (4 mL) gave the *title compound* **142f** (369.3 mg, 91%) as yellow cotton fibers, mp 109-110 ^{o}C (from cyclohexane/EtOH); (found: C, 44.9; H, 2.3; N, 15.7. $C_{10}H_6ClN_3S_2$ requires C, 44.9; H, 2.3; N, 15.7%); λ_{max}(DCM)/nm 232 (log ε 3.04), 271 inf (2.47), 378 (2.63); ν_{max}/cm^{-1}

2232w (C≡N), 1653w, 1601m, 1582s, 1569w, 1559w, 1506w, 1461m, 1383w, 1289w, 1262w, 1245w, 1188w, 1172w, 1149s, 1084w, 1034w, 989w, 897w, 961s, 800m, 790s, 779s, 739m, 703m; δ_H(300 MHz; CD_2Cl_2) 7.56 (1H, dd, *J* 7.8, 7.8, Ph *H*-4), 7.20 (1H, d, *J* 7.8, Ph *H*-3 or 5), 7.16 (1H, d, *J* 8.1, Ph *H*-3 or 5), 2.57 (3H, s, CH_3); δ_C(75 MHz; CD_2Cl_2) 161.6, 153.8, 148.35, 144.55, 134.1 (Ph *C*H), 127.85 (Ph *C*H), 115.75 (*C*≡N), 114.5 (Ph *C*H), 107.1 (*C*C≡N), 20.8 (*C*H_3); δ_C(75 MHz; DEPT-135, CD_2Cl_2) 134.1 (Ph *C*H), 127.85 (Ph *C*H), 114.5 (Ph *C*H), 20.8 (*C*H_3); *m/z* (EI) 269 (M^++2, 27%), 267 (M^+, 65), 206 (87), 174 (5), 168 (13), 142 (12), 116 (22), 115 (21), 102 (4), 89 (28), 76 (6), 70 (6), 64 (100), 51 (5).

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-4-methoxybenzonitrile 142g

Similar treatment of 2-amino-4-methoxybenzonitrile **219g** (200 mg, 1.35 mmol), 4,5-dichloro-1,2,3-dithiazolium chloride **42** (281.8 mg, 1.35 mmol) and pyridine (218 μL, 2.70 mmol) in DCM (4 mL) gave the *title compound* **142g** (282.7 mg, 74%) as orange needles, mp 163-164 ^oC (from cyclohexane/DCM); (found: C, 42.4; H, 2.0; N, 14.8. $C_{10}H_5ClN_3OS_2$ requires C, 42.3; H, 2.1; N, 14.8%); λ_{max}(DCM)/nm 234 (log ε 3.30), 256 inf (3.17), 272 inf (2.88), 302 (2.53), 367 (2.75), 411 inf (2.51); ν_{max}/cm^{-1} 2965w, 2937w and 2835w, (CH_3), 2221s (C≡N), 1589s, 1562m, 1521w, 1495s, 1458w, 1437m, 1408w, 1328m, 1277m, 1249s, 1199m, 1191m, 1171m, 1154m, 1095s, 1022s, 953m, 871s, 840w, 821s, 801m, 756s, 735m, 719m; δ_H(300 MHz; $CDCl_3$) 7.66 (1H, d, *J* 8.7, Ph *H*-6), 6.81 (1H, dd, *J* 8.7, 2.4, Ph *H*-5), 6.75 (1H, d, *J* 2.4, Ph *H*-3), 3.88 (3H, s, C*H*$_3$); δ_C(75 MHz; DMSO-d_6) 164.3, 163.6, 156.0, 146.3, 135.7 (Ph *C*H), 116.9 (*C*≡N), 112.4 (Ph *C*H), 103.4 (Ph *C*H), 95.7 (*C*C≡N), 56.1 (*C*H_3); δ_C(75 MHz; DEPT-135, DMSO-d_6) 135.7 (Ph *C*H), 112.4 (Ph *C*H), 103.3 (Ph *C*H), 56.1 (*C*H_3); *m/z* (EI) 285 (M^++2, 19%), 283 (M^+, 47), 222 (42), 190 (4), 184 (7), 158 (100), 147 (11), 128 (24), 117 (15), 115 (19), 102 (15), 93 (8), 89 (18), 76 (11), 64 (55), 50 (7).

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-4,5-dimethoxybenzonitrile 142h

Similar treatment of 2-amino-4,5-dimethoxybenzonitrile **219h** (200 mg, 1.12 mmol), 4,5-dichloro-1,2,3-dithiazolium chloride **42** (233.5 mg, 1.12 mmol) and pyridine (181.0 μL, 2.24 mmol) in DCM (4 mL) gave the title compound **142h** (266.4 mg, 76%) as orange crystals, mp 156-157 ^oC (from cyclohexane/EtOH); (found: C, 42.3; H, 2.6; N, 13.3. $C_{11}H_8ClN_3O_2S_2$ requires C, 42.1; H, 2.6; N, 13.4%); λ_{max}(DCM)/nm 350 inf (log ε 2.59), 379 inf (2.68), 398 (2.72), 418 inf (2.69), 443 inf (2.48); ν_{max}/cm^{-1} 3002w (Ph CH), 2961w, 2933w, 2912w,

2849w and 2829w (CH_3), 2224m (C≡N), 1591s, 1549m, 1515m, 1498s, 1464m, 1445m, 1394w, 1348m, 1281s, 1222s, 1205m, 1191w, 1150m, 1103s, 1026w, 990m, 931w, 902s, 876m, 862m, 849m, 805w, 763s; δ_H(300 MHz; $CDCl_3$) 7.12 (1H, s, Ph *H*-6), 6.81 (1H, s, Ph *H*-3), 3.93 (3H, s, CH_3O), 3.93 (3H, s, CH_3O); δ_C(75 MHz; DMSO-d_6) 162.6, 153.9, 148.8, 146.6, 146.5, 117.0 (*C*≡N), 115.0 (Ph *C*H), 101.55 (Ph *C*H), 95.1 (*C*C≡N), 56.3 (*C*H_3O), 56.2 (*C*H_3O); δ_C(75 MHz; DEPT-135, DMSO-d_6) 115.0 (Ph *C*H), 101.6 (Ph *C*H), 56.3 (*C*H_3O), 56.2 (*C*H_3O); *m/z* (EI) 315 (M^++2, 26%), 313 (M^+, 63), 300 (7), 298 (16), 220 (11), 214 (6), 205 (8), 188 (100), 177 (9), 173 (20), 162 (8), 145 (18), 134 (8), 119 (11), 117 (22), 104 (15), 102 (16), 90 (20), 83 (8), 76 (21), 70 (7), 64 (33), 51 (7).

Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazolylideneamino)benzonitrile 142a with Ph_3P (see Table 24)

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitriles **142a** (50.8 mg, 0.20 mmol) in distilled DCM (2 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added water (7.2 μL, 0.4 mmol) and then Ph_3P (210 mg, 0.8 mmol). The mixtures were then allowed to stir at *ca*. 20 °C1 for 5 min, until no starting materials remained (TLC). The reaction mixtures were adsorbed onto silica and chromatography (hexane/DCM, 1:1) gave Ph_3P=S (90.6 mg, 77%) as colourless needles, mp 161-162 °C (from cyclohexane) identical to an authentic sample. Further elution (hexane/DCM, 1:4) gave 2-aminobenzocarbonitrile **219a** (3.1 mg, 13%) as colourless needles, mp 146-147 °C. Further elution gave *2-(cyano-methyleneamino)benzonitrile* **220** (1.9 mg, 6%) as colourless cotton fibers, mp 75-76 °C (from cyclohexane); (found: C, 69.7; H, 3.3; N, 27.0. $C_9H_5N_3$ requires C, 69.7; H, 3.3; N, 27.1%); λ_{max}(DCM)/nm 229 inf (log ε 3.03), 237 inf (3.08), 243 (3.12), 253 inf (2.96), 321 (2.54); ν_{max}/cm^{-1} 3096w, 3067w and 3032w (Ar CH), 2926w, 2234m (C≡N), 1599w, 1587w, 1570w, 1485m, 1447w, 1337m, 1283w, 1213w, 1188w, 1045w, 1005m, 932m, 874w, 853w, 762s, 733w; δ_H(300 MHz; $CDCl_3$) 7.78 (1H, dd, *J* 7.7, 1.5, Ph *H*-2 or 6), 7.68 (1H, ddd, *J* 7.9, 7.9, 1.4, Ph *H*-4 or 5), 7.62 (1H, s, C*H*=N), 7.50 (1H, ddd, *J* 7.7, 7.7, 0.9, Ph *H*-4 or 5), 7.18 (1H, d, *J* 8.1, Ph *H*-2 or 6); δ_C(75 MHz, $CDCl_3$) 150.6, 137.1 (Ph *C*H), 134.4 (Ph *C*H), 134.3 (Ph *C*H), 130.05 (*C*H), 118.3 (Ph *C*H), 116.2 (*C*≡N), 114.8 (*C*≡N), 109.25 (*C*C≡N); *m/z* (EI) 155 (M^+, 28%), 129 (M^+-CN, 8), 103 [M^+-2(CN), 100], 102 (26), 76 ($C_6H_4^+$, 30), 75 (27), 63 (7), 51 (17) and *2-(cyanomethylamino)benzonitrile* **221a** (1.9 mg, 6%) as colourless cotton fibers, mp 95-96 °C (lit.,[98] 95-96 °C) (from cyclohexane/EtOH); (found: C, 68.7; H, 4.4; N, 26.7.

$C_9H_7N_3$ requires C, 68.8; H, 4.5; N, 26.7%); λ_{max}(DCM)/nm 228 inf (log ε 3.84), 244 (4.06), 318 (3.79); ν_{max}/cm^{-1} 3379m (NH), 2218m (C≡N), 1603s, 1582m, 1522s, 1460m, 1427w, 1317m, 1273m, 1256w, 1165m, 1134w, 1076m, 986w, 880w, 845w, 818w, 752s; δ_H(300 MHz; DMSO-d_6) 7.55-7.51 (2H, m, Ph *H*-4 and 6), 6.91 (1H, d, *J* 8.7, Ph *H*-3), 6.83 (1H, dd, *J* 7.7, 7.7, Ph *H*-5), 6.78 (1H, br m, N*H*), 4.36 (2H, d, *J* 6.0, CH_2); δ_C(75 MHz; DMSO-d_6) 148.5, 134.6 (Ph *C*H), 133.4 (Ph *C*H), 118.05 (Ph *C*H), 117.8 (*C*≡N), 117.4 (*C*≡N), 111.7 (Ph *C*H), 96.2 (*C*C≡N), 31.2 (*C*H_2); δ_C(75 MHz; DEPT-135, DMSO-d_6) 134.6 (Ph *C*H), 133.4 (Ph *C*H), 118.1 (Ph *C*H), 111.7 (Ph *C*H), 31.2 (*C*H_2); *m/z* (EI) 157 (M^+, 90%), 130 (M^+-HCN, 49), 117 (M^+-C_2H_2N, 13), 103 (M^+-$C_2H_2N_2$, 100), 90 (39), 76 (17), 63 (17), 51 (13). Further elution (DCM, 100%) gave *3-aminoindole-2-carbonitrile* **222a** (12.2 mg, 39%) as light yellow cotton fibers, mp 172-173 ^oC (from cyclohexane/EtOH); (found: C, 68.7; H, 4.5; N, 26.7. $C_9H_7N_3$ requires C, 68.8; H, 4.5; N, 26.7%); λ_{max}(DCM)/nm 233 (log ε 3.36), 245 (3.39), 290 (3.14), 299 inf (3.08), 323 inf (2.85); ν_{max}/cm^{-1} 3356m (NH), 3309 (NH_2), 3231w, 3059 (Ar CH), 2924w, 2212s (C≡N), 1628m, 1597w, 1584w, 1557m, 1493w, 1450w, 1344s, 1310s, 1292w, 1248w, 1182m, 1159s, 1105w, 1090w, 1042w, 1016w, 1009w, 932w, 891w, 814m, 746s, 739s, 727s; δ_H(300 MHz; DMSO-d_6) 10.67 (1H, br s, N*H*), 7.73 (1H, d, *J* 8.1, Ph *H*-4), 7.24 (1H, ddd, 1.1, 7.5, 7.5, Ph *H*-5), 7.18 (1H, d, *J* 7.8, Ph *H*-7), 6.94 (1H, ddd, 1.2, 7.5, 7.5, Ph *H*-6), 5.71 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 139.0, 136.8, 126.1 (Ph *C*H), 120.2 (Ph *C*H), 118.2, 118.0 (Ph *C*H), 116.2 (*C*≡N), 111.6 (Ph *C*H), 86.6 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 126.1 (Ph *C*H), 120.2 (Ph *C*H), 118.0 (Ph *C*H), 111.6 (Ph *C*H); *m/z* (EI) 157 (M^+, 100%), 129 (31), 105 (23), 104 (40), 103 (48), 102 (32), 77 (12), 76 (26), 75 (14), 65 (5), 51 (16), 50 (13). Further elution (DCM/*t*-BuOMe, 4:1) gave (*2-cyanoindol-3-yl) iminotriphenylphosphorane* **223a** (13.3 mg, 16%) as colourless crystals, mp 183-184 ^oC (from PhH); (found: C, 77.6; H, 4.9; N, 10.1. $C_{27}H_{20}N_3P$ requires C, 77.7; H, 4.8; N, 10.1%); λ_{max}(DCM)/nm 231 (log ε 4.52), 253 inf (4.36), 293 (3.92), 303 inf (3.87), 345 (3.87); ν_{max}/cm^{-1} 3076w, 3059w, 2203m (C≡N), 1614w, 1574w, 1520s, 1464w, 1450w, 1437m, 1383w, 1333m, 1315w, 1265m, 1252m, 1202w, 1188w, 1165w, 1115s, 1103m, 1018w, 993m, 924w, 845w, 746s, 733s, 719s; δ_H(300 MHz; DMSO-d_6) 10.75 (1H, br s, N*H*), 7.80-7.73 (6H, m, Ph_3P *H*), 7.66-7.53 (9H, m, Ph_3P *H*), 7.18-7.11 (3H, m, indole *H*), 6.74 (1H, ddd, 1.8, 6.7, 6.7, indole *H*-5 or 6); δ_C(75 MHz; CD_2Cl_2) 141.7, 137.6, 133.0 (d, J_{PC} 9.75, Ph_3P *C*-3), 132.3 (d, J_{PC} 3.0, Ph_3P *C*-4), 131.85 (d, J_{PC} 101.2, Ph_3P *C*-1), 129.0 (d, J_{PC} 12.0, Ph_3P *C*-2), 126.25 (indole *C*H), 125.5 (d, J_{PC} 11.25, indole *C*-3), 121.5 (indole *C*H), 119.3 (indole *C*H), 117.4

(*C*≡N), 111.8 (indole *C*H), 95.9 (d, J_{PC} 13.5, indole *C*-2, *C*C≡N); δ_C(75 MHz; DEPT-135, CD_2Cl_2) 133.0 (d, J_{PC} 9.75, Ph_3P *C*-3), 132.3 (d, J_{PC} 3.0, Ph_3P *C*-4), 129.0 (d, J_{PC} 12.0, Ph_3P *C*-2), 126.25 (indole *C*H), 121.5 (indole *C*H), 119.3 (indole *C*H), 111.8 (indole *C*H); δ_P(121.5 MHz; CD_2Cl_2) 5.48; *m/z* (EI) 417 (M^+, 100%), 390 (14), 340 (5), 313 (7), 262 (11), 232 (14), 209 (12), 205 (23), 183 (84), 170 (3), 152 (9), 141 (6), 115 (4), 108 (17), 89 (3), 77 (17), 51 (7). Further elution (DCM/*t*-BuOMe, 7:3) gave Ph_3P=O (103.2 mg, 69%) as colourless needles, mp 154-155 ^oC (from cyclohexane), identical to an authentic sample.

3-Amino-1*H*-indole-2-carbonitrile 222a from (2-cyanoindol-3-yl)iminotriphenyl-phosphorane 223a

A. Using HCl (0.5 N)

To a stirred solution of (2-cyanoindol-3-yl)iminotriphenylphosphorane **223a** (20.0 mg, 0.05 mmol) in MeOH (1 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added 0.5 N HCl (1 mL) and the mixture was then heated to *ca.* 80 ^oC for 32 h, until no starting material remained (TLC). The reaction mixture was then extracted (DCM), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (DCM, 100%) gave the *title compound* **222a** (7.3 mg, 93%) as light yellow cotton fibers, mp 172-173 ^oC (from cyclohexane/EtOH), identical to that described above.

B. Using AcOH (80%)

To a stirred solution of 80% acetic acid (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added (2-cyanoindol-3-yl)iminotriphenylphosphorane **223a** (20.0 mg, 0.05 mmol) and the mixture was heated to *ca.* 80 ^oC for 6.5 h, until no starting material remained (TLC). The reaction mixture was then extracted (DCM), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (DCM, 100%) gave the *title compound* **222a** (7.2 mg, 92%) as light yellow cotton fibers, mp 172-173 ^oC (from cyclohexane/EtOH), identical to that described above.

(2-Cyanoindol-3-yl)iminotriphenylphosphorane 223a from 3-amino-1*H*-indole-2-carbo-nitrile 222a

To a stirred solution of 3-aminoindole-2-carbonitrile **222a** (20.0 mg, 0.13 mmol) in distilled PhH (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, was added Et_3N (72.1 μL, 0.52 mmol), Ph_3P (68.2 mg, 0.26 mmol) and then hexachloroethane (61.6 mg, 0.26 mmol). The

mixture was then heated to *ca.* 80 ^{o}C for 6 h, until no starting material remained (TLC). The reaction mixture was directly adsorbed onto silica and chromatography (DCM/*t*-BuOMe, 4:1) gave the *title compound* **223a** (49.3 mg, 91%) as colourless crystals, mp 183-184 ^{o}C (from PhH), identical to that described above.

Reaction of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-5-nitrobenzonitrile 142b with Ph_3P (typical procedure: see Table 25)

To stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-5-nitrobenzonitrile **142b** (59.6 mg, 0.20 mmol) in distilled DCM (2 mL) at *ca*. 20 ^{o}C and protected with $CaCl_2$ drying tube, was added water (7.2 μL, 0.40 mmol) and then Ph_3P (210 mg, 0.80 mmol). The mixtures were then allowed to stir at *ca*. 20 ^{o}C for 5 min, until no starting materials remained (TLC). The reaction mixtures were adsorbed onto silica and chromatography (hexane/DCM, 1:1) gave traces of unreacted Ph_3P. Further elusion (hexane/DCM, 4:1) gave Ph_3P=S (116.4 mg, 99%) as colourless needles, mp 161-132 ^{o}C (from cyclohexane) identical to an authentic sample. Further elusion (hexane/DCM, 1:4) gave 2-amino-5-nitrobenzonitrile **219b** (2.6 mg, 8%) as pale yellow powder, mp 199-201 ^{o}C (from cyclohexane/EtOH) identical to an authentic sample. Further elusion (DCM, 100%) gave *3-amino-5-nitroindole-2-carbonitrile* **222b** (30.3 mg, 75%) as red cotton fibers, mp 310-311 ^{o}C (from PhH); (found: C, 53.4; H, 2.9; N, 27.6. $C_9H_6N_4O_2$ requires C, 53.5; H, 3.0; N, 27.7%); λ_{max}(DCM)/nm 225 (log ε 4.14), 237 inf (3.17), 265 (3.19), 268 (3.18), 272 (3.23), 299 (3.49); ν_{max}/cm^{-1} 3463w (NH_2), 3376m and 3279m (NH), 3065w, 2204s (C≡N), 1635m, 1614m, 1588m, 1533m, 1521w, 1476s, 1398w, 1327s, 1244w, 1190m, 1132w, 1064m, 942w, 914w, 846w, 814m, 778w, 755m; δ_H(300 MHz; DMSO-d_6) 11.62 (1H, br s, N*H*), 8.95 (1H, d, *J* 2.4, Ph *H*-4), 8.07 (1H, dd, *J* 2.3, 9.2, Ph *H*-6), 7.33 (1H, d, *J* 9.3, Ph *H*-7), 6.29 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 141.0, 139.4, 138.5, 120.8 (Ph *C*H), 118.9 (Ph *C*H), 117.2, 115.0 (*C*≡N), 112.1 (Ph *C*H), 87.4 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 120.8 (Ph *C*H), 118.9 (Ph *C*H), 112.1 (Ph *C*H); *m/z* (EI) 202 (M^+, 100%), 183 (2), 172 (5), 156 (75), 144 (10), 129 (69), 117 (5), 102 (48), 94 (10), 75 (22), 63 (9), 51 (12), 50 (12). Further elusion (DCM/*t*-BuOMe, 7:3) gave Ph_3P=O (105.6 mg, 95%) as colourless needles, mp 154-155 ^{o}C (from cyclohexane), identical to an authentic sample.

3-Amino-7-bromo-5-nitroindole-2-carbonitrile 222c

Similar treatment of 3-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-5-nitrobenzonitrile **142c** (75.6 mg, 0.20 mmol), water (7.2 μL, 0.40 mmol) and Ph_3P (210 mg, 0.80 mmol) in distilled DCM (2 mL) gave the *title compound* **222c** (14.9 mg, 41%) as orange cotton fibers, mp 290-291 ^oC (from PhH); (found: C, 38.4; H, 1.8; N, 19.8. $C_9H_5BrN_4O_2$ requires C, 38.5; H, 1.8; N, 19.9%); λ_{max}(DCM)/nm 238 inf (log ε 3.25), 265 (3.24), 269 (3.27), 273 (3.29), 294 (3.39), 360 inf (2.73), 414 inf (2.28); ν_{max}/cm^{-1} 3434w (NH_2), 3356w (NH), 3254w, 3090w (Ar CH), 2206s (C≡N), 1647m, 1610w, 1587m, 1560w, 1526s, 1476s, 1424w, 1327s, 1239w, 1207w, 1190s, 1072w, 1045w, 1022m, 990m, 902m, 886w, 870w, 848w, 828w, 787w; δ_H(300 MHz; DMSO-d_6) 11.91 (1H, br s, N*H*), 8.99 (1H, d, *J* 1.8, Ph *H*-4), 8.27 (1H, d, *J* 1.8, Ph *H*-6), 6.41 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 141.8, 139.6, 136.75, 122.7 (Ph *C*H), 118.2 (Ph *C*H), 117.9, 114.4, 104.3, 89.4 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 122.7 (Ph *C*H), 118.2 (Ph *C*H); *m/z* (EI) 282 (M^++2, 100%), 280 (M^+, 92), 252 (3), 236 (75), 235 (13), 234 (84), 224 (9), 222 (9), 209 (42), 207 (46), 180 (7), 182 (7), 155 (83), 143 (15), 128 (66), 116 (14), 102 (42), 101 (75), 100 (73), 99 (22), 88 (12), 77 (24), 76 (46), 75 (67), 74 (69), 73 (14), 64 (19), 63 (20), 62 (23), 54 (11), 53 (45), 52 (44), 50 (30) and *(7-Bromo-2-cyano-5-nitroindol-3-yl)iminotriphenylphosphorane* **223c** (10.5 mg, 15%) as red cotton fibers, mp 120-121 ^oC (from PhH); (found: C, 60.0; H, 3.2; N, 10.2. $C_{27}H_{18}BrN_4O_2P$ requires C, 59.9; H, 3.4; N, 10.4%); λ_{max}(DCM)/nm 221 (log ε 4.07), 225 (3.81), 264 (3.40), 272 (3.39), 300 (3.51), 365 inf (2.93); ν_{max}/cm^{-1} 3330w (NH), 2923w, 2847w, 2199m (C≡N), 1607w, 1570w, 1533s, 1483m, 1449w, 1445w, 1436m, 1421w, 1325s, 1271s, 1236m, 1209m, 1188w, 1112s, 1074m, 1010w, 1000w, 909w, 887w, 873w, 846w, 742s, 719s; δ_H(300 MHz; DMSO-d_6) 11.99 (1H, br s, N*H*), 8.19 (1H, d, *J* 2.1, indole *H*-4 or 6), 8.04 (1H, d, *J* 2.1, indole *H*-4 or 6), 7.81-7.74 (6H, m, Ph_3P *H*), 7.70-7.56 (9H, m, Ph_3P *H*); δ_C(75 MHz; DMSO-d_6) 143.0, 139.8, 136.65, 132.5 (d, J_{PC} 3.0, Ph_3P *C*-4), 132.1 (d, J_{PC} 10.5, Ph_3P *C*-3), 130.1 (d, J_{PC} 100.5, Ph_3P *C*-1), 129.1 (d, J_{PC} 12.0, Ph_3P *C*-2), 123.7 (d, J_{PC} 12.1, indole *C*-3), 122.0 (Ph *C*H), 117.5 (Ph *C*H), 115.4 (d, J_{PC} 2.3, *C*≡N), 104.7, 98.7 (d, J_{PC} 14.3, indole *C*-2, *C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 132.5 (d, J_{PC} 3.0, Ph_3P *C*-4), 132.1 (d, J_{PC} 10.5, Ph_3P *C*-3), 129.1 (d, J_{PC} 12.0, Ph_3P *C*-2), 122.0 (Ph *C*H), 117.5 (Ph *C*H); δ_P(121.5 MHz; DMSO-d_6) 7.24; *m/z* (EI) 542 (M^++2, 100%), 540 (M^+, 100), 515 (8), 495 (9), 494 (8), 493 (8), 462 (9), 415 (4), 389 (2), 336 (2), 311 (3), 282 (3), 278 (7), 277 (17), 262 (10), 247 (4), 234 (3), 207 (5), 201(7), 185 (15), 184 (15), 183 (88), 152 (13), 132 (7), 108 (14), 77 (12).

3-Amino-6-chloroindole-2-carbonitrile 222d

Similar treatment of 4-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142d** (57.6 mg, 0.20 mmol), water (7.2 μL, 0.40 mmol) and Ph_3P (210 mg, 0.80 mmol) in distilled DCM (2 mL) gave the *title compound* **222d** (27.1 mg, 71%) as red powder, mp 210-211 ^oC (from EtOH); (found: C, 56.4; H, 3.04; N, 21.8. $C_9H_6ClN_3$ requires C, 56.4; H, 3.2; N, 21.9%); λ_{max}(DCM)/nm 253 (log ε 3.64), 298 (3.17), 309 inf (3.08), 336 (2.88); ν_{max}/cm^{-1} 3411w, 3386w, 3354w (NH), 3335w, 3298w, 3228w, 2221s and 2212s (C≡N), 1617m, 1581m, 1551m, 1507w, 1490w, 1465w, 1458w, 1444w, 1338s, 1290w, 1245w, 1221w, 1188m, 1113w, 1061s, 922m, 859w, 843m, 799s; δ_H(300 MHz; DMSO-d_6) 10.88 (1H, br s, N*H*), 7.75 (1H, d. *J* 8.7, Ph *H*-4), 7.23 (1H, d, *J* 1.8, Ph *H*-7), 6.97 (1H, dd, *J* 1.8, 8.7, Ph *H*-5) 5.83 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 139.0, 136.8, 131.0, 121.8 (Ph *C*H), 118.5 (Ph *C*H), 117.0, 115.7 (*C*≡N), 111.05 (Ph *C*H), 87.3 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 121.80 (Ph *C*H), 118.5 (Ph *C*H), 111.05 (Ph *C*H); *m/z* (EI) 193 (M^++2, 32%), 191 (M^+, 100), 165 (7), 163 (15), 156 (M^+-Cl, 19), 137 (19), 129 (11), 110 (3), 102 (12), 100 (9), 95 (5), 75 (12), 63 (2), 50 (4).

3-Amino-5-chloroindole-2-carbonitrile 222e

Similar treatment of 5-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142e** (57.6 mg, 0.20 mmol), water (7.2 μL, 0.40 mmol) and Ph_3P (210 mg, 0.80 mmol) in distilled DCM (2 mL) gave the *title compound* **222d** (12.2 mg, 32%) as light red powder, mp 190-191 ^oC (from EtOH); (found: C, 56.4; H, 3.2; N, 21.9. $C_9H_6ClN_3$ requires C, 56.4; H, 3.2; N, 21.9%); λ_{max}(DCM)/nm 221 (log ε 3.65), 223 (3.56), 253 (3.46), 256 (3.43), 299 (3.03), 307 inf (2.98), 341 (2.80); ν_{max}/cm^{-1} 3458w (NH_2), 3371w and 3329m (NH), 2202s (C≡N), 1627m, 1581w, 1554m, 1473m, 1447w, 1374w, 1321m, 1292s, 1235w, 1188w, 1140m, 1123m, 1055m, 1025w, 1000w, 924w, 847m, 800s, 782w; δ_H(300 MHz; DMSO-d_6) 10.92 (1H, br s, N*H*), 7.85 (1H, s, Ph *H*), 7.22-7.21 (2H, m, Ph *H*), 5.76 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 138.3, 135.0, 126.1 (Ph *C*H), 122.4, 119.45 (Ph *C*H), 119.0, 115.6 (*C*≡N), 113.4 (Ph *C*H), 88.1 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 126.1 (Ph *C*H), 119.45 (Ph *C*H), 113.4 (Ph *C*H); *m/z* (EI) 193 (M^++2, 32%), 191 (M^+, 100), 165 (6), 163 (15), 156 (M^+-Cl, 33), 138 (17), 137 (16), 136 (11), 129 (14), 112 (2), 102 (14), 100 (11), 95 (4), 75 (13), 62 (2), 50 (6).

3-Amino-4-methylindole-2-carbonitrile 222f

Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-methylbenzonitrile **142f** (53.6 mg, 0.20 mmol), water (7.2 μL, 0.40 mmol) and Ph_3P (210 mg, 0.80 mmol) in distilled DCM (2 mL) gave the *title compound* **222f** (2.1 mg, 6%) as yellow cotton fibers, mp 156-157 ^oC (from cyclohexane/EtOH); (found: C, 70.3; H, 5.3; N, 24.55. $C_{10}H_9N_3$ requires C, 70.2; H, 5.3; N, 24.5%); λ_{max}(DCM)/nm 230 inf (log ε 3.35), 242 (3.41), 273 (1.95), 297 (2.85), 331 (2.87); ν_{max}/cm^{-1} 3423w and 3330s (NH_2), 3049w and 3018w (Ar CH), 2977w, 2927w, 2202s, (C≡N), 1615m, 1586m, 1546m, 1516w, 1470w, 1439w, 1419w, 1376w, 1358m, 1318m, 1262m, 1245m, 1185m, 1165w, 1133w, 1077w, 1050w, 1030w, 967w, 948w, 864w, 789w, 772s; δ_H(300 MHz; DMSO-d_6) 10.81 (1H, br s, N*H*), 7.07 (1H, dd, *J* 7.5, 7.5, Ph *H*-5), 6.99 (1H, d, *J* 8.1, Ph *H*-7), 6.64 (1H, d, *J* 6.6, Ph *H*-6), 5.16 (2H, br s, NH_2), 3.39 (3H, s, CH_3); δ_C(75 MHz; DMSO-d_6) 139.6, 137.3, 132.1, 126.1 (Ph *C*H), 119.6 (Ph *C*H), 117.3 (*C*-7), 115.95 (*C*≡N), 109.7 (Ph *C*H), 88.3 (*C*C≡N), 19.5 (*C*H_3); δ_C(75 MHz; DEPT-135, DMSO-d_6) 126.1 (Ph *C*H), 119.6 (Ph *C*H), 109.7 (Ph *C*H), 19.5 (*C*H_3); *m/z* (EI) 171 (M^+, 100%), 156 (7), 143 (16), 116 (15), 89 (15), 76 (3), 63 (6), 51 (3).

3-Amino-6-methoxyindole-2-carbonitrile 222g

Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-4-methoxybenzonitrile **142g** (56.8 mg, 0.20 mmol), water (7.2 μL, 0.40 mmol) and Ph_3P (210 mg, 0.80 mmol) in distilled DCM (2 mL) gave the *title compound* **222g** (2.6 mg, 7%) as red crystals, mp 179-180 ^oC (from cyclohexane/EtOH); (found: C, 64.2; H, 4.7; N, 22.4. $C_{10}H_9N_3O$ requires C, 64.2; H, 4.9; N, 22.5%); λ_{max}(DCM)/nm 230 inf (log ε 4.18), 254 (4.37), 305 inf (4.12), 312 (4.16); ν_{max}/cm^{-1} 3440w (NH_2), 3378w and 3348w (NH), 3234w, 2971w, 2936w, 2843w, 2207s (C≡N), 1623s, 1586s, 1556m, 1506m, 1455s, 1441w, 1338m, 1315s, 1251w, 1225s, 1207w, 1185w, 1167s, 1103s, 1021s, 951w, 941w, 823s, 808s; δ_H(300 MHz; DMSO-d_6) 10.46 (1H, br s, N*H*), 7.60 (1H, d, *J* 8.7, Ph *H*-4), 6.61-6.57 (2H, m, Ph *H*-5 and 7), 5.64 (2H, br s, NH_2), 3.76 (3H, s, CH_3O); δ_C(75 MHz; DMSO-d_6) 159.1, 139.4, 137.9, 121.0 (Ph *C*H), 116.55, 112.5, 109.3 (Ph *C*H), 93.3 (Ph *C*H), 85.3 (*C*C≡N), 55.0 (CH_3O); δ_C(75 MHz; DEPT-135, DMSO-d_6) 121.0 (Ph *C*H), 109.35 (Ph *C*H), 93.3 (Ph *C*H), 55.0 (*C*H_3O); *m/z* (EI) 187 (M^+, 100%), 186 (7), 172 (72), 159 (8), 144 (42), 129 (3), 117 (18), 90 (11), 76 (4), 63 (13), 52 (3).

2-(Cyanomethyleneamino)-4,5-dimethoxybenzonitrile 225

Similar treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)4,5-dimethoxy benzonitrile **142h** (62.6 mg, 0.20 mmol), water (7.2 μL, 0.40 mmol) and Ph_3P (210 mg, 0.80 mmol) in distilled DCM (2 mL) gave the *title compound* **225** (5.2 mg, 15%) as yellow cotton fibers, mp 170-171 ^oC (from cyclohexane); (found: C, 61.4; H, 4.2; N, 19.5. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%); λ_{max}(DCM)/nm 228 (log ε 3.02), 235 (3.21), 261 (3.35), 285 inf (2.88), 363 (3.02); ν_{max}/cm^{-1} 2974w, 2920w, 2851w, 2230m (C≡N), 1597m, 1547w, 1537w, 1516s, 1464m, 1441w, 1396w, 1368m, 1339w, 1287s, 1231s, 1198w, 1109s, 1026w, 993s, 908w, 876m, 837m; δ_H(300 MHz; DMSO-d_6) 8.17 (1H, s, Ph *H*-4), 7.51 (1H, s, Ph *H*-5), 7.31 (1H, s, Ph *H*-8) 3.87 (3H, s, CH_3O), 3.86 (3H, s, CH_3O); δ_C(75 MHz; DMSO-d_6) 152.9, 150.2, 143.85, 137.4 (Ph *C*H), 116.8, 116.0, 114.5 (Ph *C*H), 102.2, 101.8 (Ph *C*H), 56.3 (*C*H_3O), 56.25 (*C*H_3O); δ_C(75 MHz; DEPT-135, DMSO-d_6) 137.4 (Ph *C*H), 114.5 (Ph *C*H), 101.8 (Ph *C*H), 56.3 (*C*H_3O), 56.25 (*C*H_3O); *m/z* (EI) 215 (M^+, 100%), 200 (72), 188 (2), 172 (33), 157 (5), 145 (74), 129 (11), 117 (25), 115 (12), 106 (8), 104 (29), 102 (49), 90 (39), 88 (23), 78 (57), 76 (58), 64 (33), 53 (30) and *2-(cyanothioformamido)-4,5-dimethoxybenzonitrile* **144h** (17.8 mg, 35%) as orange crystals, mp 145-146 ^oC (lit.,[48] 146-147 ^oC) (from cyclohexane/EtOH); (found: C, 53.4; H, 3.8; N, 16.9. $C_{11}H_9N_3O_2S$ requires C, 53.4; H, 3.7; N, 17.0%); λ_{max}(DCM)/nm 230 (log ε 3.56), 265 (3.48), 277 inf (3.51), 287 (3.56), 331 inf (3.07), 346 (3.11), 375 (3.16), 395 inf (3.07); ν_{max}/cm^{-1} 3198w, 3169w, 3103w (NH), 3015w, 2976w, 2922w, 2230m (C≡N), 1603m, 1516s, 1470m, 1439m, 1395m, 1354s, 1271s, 1236s, 1204w, 1136m, 1099m, 1028w, 993s, 866s, 779s, 748m; δ_H(300 MHz; CD_2Cl_2) (NH missing), 7.83 (1H, s, Ph *H*-3), 7.16 (1H, s, Ph *H*-5), 3.97 (3H, s, CH_3O), 3.96 (3H, CH_3O); δ_C(75 MHz; DMSO-d_6) 165.3 (*C*=S), 153.0 (Ph *C*), 148.4 (Ph *C*), 133.5 (Ph *C*), 116.1 (*C*≡N), 114.6 (Ph *C*H), 113.5 (*C*≡N), 110.4 (Ph *C*H), 100.5 (*C*C≡N), 56.3 (*C*H_3O), 56.2 (*C*H_3O); δ_C(75 MHz; DEPT-135, DMSO-d_6) 114.65 (Ph *C*H), 110.4 (Ph *C*H), 56.3 (*C*H_3O), 56.2 (*C*H_3O); *m/z* (EI) 247 (M^+, 100%), 232 (7), 220 (50), 214 (15), 205 (27), 195 (35), 180 (21), 177 (28), 162 (13), 150 (10), 134 (13), 119 (17), 104 (13), 90 (7), 83 (7), 76 (15), 70 (23), 50 (11).

2-(Cyanomethyleneamino)-4,5-dimethoxybenzonitrile 225 *via* oxidation of 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile 227 (see Scheme 119)

A. Using NBS

To a stirred solution of NBS (26.7 mg, 0.20 mmol) in CCl_4 (1 mL) at *ca.* 55 ^oC, was added a solution of 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **227** (35.6 mg, 0.20 mmol) in CCl_4 (1 mL). The mixture was left to stir at *ca.* 55 ^oC for 5 min and then $Ca(OH)_2$ (31.1 mg, 0.42 mmol) and $CaCl_2$ (11.1 mg, 0.1 mmol) were added to the solution. The mixture was left to stir at this temperature for 2 d until no starting material remained (TLC) and the mixture was then adsorbed onto silica. Chromatography (DCM, 100%) gave 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **225** (13.8 mg, 32%) as yellow cotton fibers, mp 170-171 ^oC (from cyclohexane) (DSC: onset 175.4 ^oC, peak 177.0 ^oC); (found: C, 61.4; H, 4.2; N, 19.5. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%); λ_{max}(DCM)/nm 228 (log ε 3.02), 235 (3.21), 261 (3.35), 285 inf (2.88), 363 (3.02); ν_{max}/cm^{-1} 2920w, 2230m (C≡N), 1597m, 1547m, 1537m, 1516s, 1464m, 1368m, 1287s, 1231s, 1198m, 1109s, 1026m, 993s, 908w, 876m, 837m; δ_H(300 MHz; DMSO-d_6) 8.17 (1H, s, N=C*H*), 7.51 (1H, s, Ph *H*), 7.31 (1H, s, Ph *H*) 3.87 (3H, s, CH_3O), 3.86 (3H, s, CH_3O); δ_C(75 MHz; DMSO-d_6) 152.9, 150.2, 143.9, 137.4 (Ar *C*H), 116.8, 116.0, 114.5 (Ar *C*H), 102.2, 101.8 (Ar *C*H), 56.4 (*C*H_3O), 56.3 (*C*H_3O); *m/z* (EI) 215 (M^+, 100%), 200 (72), 172 (33), 157 (5), 145 (74), 129 (11), 117 (25), 104 (29), 102 (49), 90 (39), 88 (23), 78 (57), 76 (58), 64 (33), 53 (30).

B. Using calcium hypochlorite

To a stirred solution of 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **227** (35.6 mg, 0.20 mmol) in DCM (2 mL) was added CaOCl (42.9 mg, 0.30 mmol) and $CaCl_2$ (11.1 mg, 0.10 mmol). The mixture was left to stir at *ca.* 20 ^oC for 5 min and then $Ca(OH)_2$ (29.6 mg, 0.40 mmol) was added to the solution. The mixture was left to stir at this temperature for 4 d until no starting material remained (TLC) and then adsorbed onto silica. Chromatography (DCM, 100%) gave 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **225** (21.5 mg, 50%) as yellow cotton fibers, mp 170-171 ^oC (from cyclohexane) identical to that described above.

2-(Cyanomethylamino)-4,5-dimethoxybenzonitrile 227 *via* reduction of 2-(cyanomethyl-eneamino)-4,5-dimethoxybenzonitrile 225

To a stirred solution of 2-(cyanomethyleneamino)-4,5-dimethoxybenzonitrile **225** (20 mg, 0.09 mmol) in dry MeOH (2 mL) at *ca*. 20 °C, was added $NaBH_4$ (4.1 mg, 0.11 mmol). The mixture was then left to stirr at *ca* 20 °C for 10 min until no starting material remained (TLC). The mixture was then extracted with DCM (20 mL). The combined organic layers were dried (Na_2SO_4) and filtered to afford the *title compound* **227** (17.7 mg, 91%) as colourless cotton fibers, mp 143-144 °C (lit.,[98] 143-144 °C) (from cyclohexane/EtOH) identical to an authentic sample.

6,7-Dimethoxyquinazoline-2-carbonitrile 226

To a stirred solution of 2-chloro-6,7-dimethoxyquinazoline **228** (30 mg, 0.134 mmol) in DMSO (2 mL) at *ca*. 20 °C, was added DABCO (15 mg, 0.134 mmol) and NaCN (13.1 mg, 0.268 mmol). The mixture was left to warm at 80 °C for 10 h until no starting material remained (TLC). On cooling to rt the mixture was diluted with water (20 mL) and extracted with DCM (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give a pale yellow solid reside. Chromatography (DCM, 100%) gave the *title compound* **226** (10.9 mg, 38%) as a colourless powder, mp 300-301 °C (from EtOH) (DSC: onset 301.3 °C, peak 303.4 °C); (found: C, 61.3; H, 4.1; N, 19.5. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%); λ_{max}(DCM)/nm 230 (log ε 2.96), 255 (3.35), 299 inf (2.44), 324 (2.58), 338 (2.71); ν_{max}/cm^{-1} 3059w, 2986w, 2955w, 2239w (C≡N), 1611m, 1568m, 1560w, 1501s, 1476w, 1445m, 1427s, 1412m, 1389w, 1342m, 1288m, 1256s, 1240m, 1219m, 1167s, 1096w, 1022m, 997s, 951m, 870s, 841m, 789m; δ_H(300 MHz; DMSO-d_6) 9.43 (1H, s, *H*-4), 7.65 (1H, s, *H*-5 or 8), 7.53 (1H, s, *H*-5 or 8), 4.02 (3H, s, CH_3O), 3.99 (3H, s, CH_3O); δ_C(75 MHz; DMSO-d_6) 157.9 (*C*-4), 157.4, 152.5, 147.4, 138.5, 121.7, 117.1 (*C*≡N), 106.2 (Ar *C*-5 or 8), 105.1 (Ar *C*-5 or 8), 56.7 (*C*H$_3$O), 56.4 (*C*H$_3$O); *m/z* (EI) 215 (M$^+$, 100%), 200 (19), 172 (19), 145 (13), 120 (23), 117 (8), 102 (6), 92 (13), 90 (11), 77 (10), 65 (12).

3-Aminoindole-2-carbonitriles 222a-h from polymer bound Ph_3P (general procedure: see Table 26)

To stirred solutions of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitriles **142a-h** (0.20 mmol) in distilled DCM (2 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was

added water (7.2 μL, 0.4 mmol) and then polymer bound Ph_3P (333.3 mg, 1.0 mmol). The mixtures were then allowed to stir at *ca*. 20 ^oC for 24 h. The reaction mixtures were then filtered to remove the polymer bound Ph_3P, and adsorbed onto silica. Chromatography gave anthranilonitriles **219a-h** (hexane/DCM, 1:1) and 3-aminoindole-2-carbonitriles **222a-h** (DCM, 100%) identical to those described above.

2-(Cyanothioformamido)benzonitrile 144a (typical procedure: see Table 27)

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142a** (100 mg, 0.39 mmol) in distilled DCM (2 mL) cooled to *ca*. -5 ^oC and protected with a $CaCl_2$ drying tube, was added in one portion, DBU (175 μL, 1.17 mmol). After 5 min at *ca*. -5 ^oC no starting material remained (TLC) and the reaction mixture was adsorbed onto silica. Chromatography (DCM) gave the title compound **144a** (67.8 mg, 93%) as an orange powder, mp 100-101 ^oC (lit.,[111] 104-105 ^oC) (from pentane/DCM); λ_{max}(DCM)/nm 228 (log ε 3.60), 250 (3.45), 333 (3.57); ν_{max}/cm^{-1} 3200w, 3181w, 3113w, 3036w, 3003w, 2241m, 1653w, 1605w, 1585w, 1547m, 1477m, 1450m, 1364s, 1298m, 1231w, 1167w, 1115m, 1040w, 949w, 860w, 752s, 706m; δ_H(300 MHz; $CDCl_3$) 9.79 (1H, br s, NH), 8.23 (1H, d, *J* 7.8, Ph *H*), 7.81 (1H, d, *J* 7.8, Ph *H*), 7.73 (1H, dd, *J* 8.0, 7.95, Ph *H*), 7.50 (1H, dd, *J* 7.1, 7.1, Ph *H*); δ_C(75 MHz; $CDCl_3$) 164.6 (*C*=S), 138.3 (Ph *C*-2), 134.0 (Ph *C*H), 133.8 (Ph *C*H), 128.6 (Ph *C*H), 125.9 (Ph *C*H), 115.5 (*C*≡N), 113.0 (*C*≡N), 107.8 (Ph *C*-1 *C*C≡N); δ_C(75 MHz; DEPT-135, $CDCl_3$) 134.0 (Ph *C*H), 133.8 (Ph *C*H), 128.6 (Ph *C*H), 125.9 (Ph *C*H); *m/z* (EI) 187 (M^+, 100%), 186 (91), 160 (19), 135 (37), 117 (3), 108 (9), 102 (33), 70 (24), 61 (3), 51 (2) identical to an authentic sample.

2-(Cyanothioformamido)-5-nitrobenzonitrile 144b

Similarly treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-5-nitrobenzonitrile **142b** (100 mg, 0.34 mmol) cooled to *ca*. -78 ^oC, with DBU gave after chromatography (DCM/*t*-BuOMe, 1:1) the *title compound* **144b** (74.9 mg, 95%) as a red powder, mp > 300 ^oC (from pentane/DCM); (found: C, 46.5; H, 1.8; N, 24.1. $C_9H_4N_4O_2S$ requires C, 46.6; H, 1.7; N, 24.1%); λ_{max}(DCM)/nm 228 (log ε 3.10), 254 (2.97), 283 (2.75), 332 (2.79), 348 (2.85); ν_{max}/cm^{-1} 3611w, 3399w (NH), 3053w (Ar CH), 2236w (C≡N), 1639w, 1597m, 1566w, 1483s, 1443s, 1346s, 1317w, 1261m, 1233w, 1177m, 1138w, 1096w, 1082w, 1069w, 924w, 899w, 843m, 800w, 758w, 733m; δ_H(300 MHz; DMSO-d_6) (NH missing), 8.58 (1H, d, *J* 2.7, Ph *H*-

6), 8.33 (1H, dd, *J* 2.7, 9.0, Ph *H*-4), 7.64 (1H, d, *J* 9.0, Ph *H*-3); δ_C(75 MHz; DMSO-d_6) 162.7, 160.75, 141.5, 128.85 (Ph *C*H), 128.0 (Ph *C*H), 122.85 (Ph *C*H), 117.7 (*C*≡N), 116.1 (*C*≡N), 105.7 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 128.9 (Ph *C*H), 128.0 (Ph *C*H), 122.85 (Ph *C*H); *m/z* (EI) 232 (M^+, 19%), 205 (100), 199 (8), 186 (6), 175 (36), 159 (37), 147 (24), 132 (14), 115 (26), 99 (7), 94 (14), 88 (17), 75 (21), 70 (16), 64 (21), 57 (14), 50 (13).

4-Chloro-2-(cyanothioformamido)benzonitrile 144d

Similarly treatment of 4-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142d** (100 mg, 0.35 mmol) cooled to *ca*. -78 °C with DBU gave after chromatography (DCM) the *title compound* **144d** (69.6 mg, 90%) as a yellow powder, mp 85-86 °C (from pentane/DCM); (found: C, 48.9; H, 1.9; N, 19.0. $C_9H_4ClN_3S$ requires C, 48.8; H, 1.8; N, 19.0%); λ_{max}(DCM)/nm 230 (log ε 3.05), 259 inf (2.84), 264 inf (2.80), 327 (2.61), 340 (2.62), 380 inf (2.23); ν_{max}/cm^{-1} 3568w, 3374m (NH), 3096w (Ar CH), 2922w, 2232m & 2216w (C≡N), 1632m, 1580m, 1553w, 1474s, 1456s, 1366m, 1288w, 1209w, 1117w, 1086w, 1059m, 908m, 881m, 866w, 812s, 779w; δ_H(300 MHz; CD_2Cl_2) 8.19 (1H, br s, N*H*), 7.75-7.72 (2H, m, Ph *H*-3 & 6), 7.59 (1H, dd, *J* 2.1, 8.7, Ph *H*-5); δ_C(75 MHz; DMSO-d_6) 162.4 (*C*=S), 154.6 (Ph *C*), 137.4 (Ph *C*), 134.2 (Ph *C*H), 123.4 (Ph *C*H), 122.3 (Ph *C*H), 117.6 (*C*≡N), 117.1 (*C*≡N), 104.7 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 134.2 (Ph *C*H), 123.4 (Ph *C*H), 122.3 (Ph *C*H); *m/z* (EI) 223 (M^++2, 13%), 221 (M^+, 34), 196 (39), 194 (100), 190 (5), 188 (17), 186 (9), 169 (9), 159 (10), 136 (22), 124 (5), 100 (30), 88 (8), 75 (19), 70 (24), 63 (7), 50 (13).

5-Chloro-2-(cyanothioformamido)benzonitrile 144e

Similarly treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-5-chlorobenzonitrile **142e** (100 mg, 0.35 mmol) cooled to *ca*. -5 °C with DBU gave after chromatography (DCM) the *title compound* **144e** (89.4 mg, 89%) as dark red crystals, mp 131-132 °C (from cyclohexane); (found: C, 48.8; H, 1.8; N, 18.8. $C_9H_4ClN_3S$ requires C, 48.8; H, 1.8; N, 19.0%); λ_{max}(DCM)/nm 232 (log ε 4.10), 274 (3.43), 346 (3.50); ν_{max}/cm^{-1} 3271m (NH), 3082w & 3024w (Ar CH), 2228w (C≡N), 1587m, 1553w, 1541w, 1468m, 1406m, 1302s, 1269m, 1258w, 1236s, 1219m, 1163s, 1123m, 1076s, 1059m, 972w, 926m, 856m, 841s, 739m, 702m; δ_H(300 MHz; DMSO-d_6) (NH missing), 8.18 (1H, s, Ph *H*-6), 7.90 (1H, dd, *J* 1.5, 7.5, Ph *H*-4), 7.68 (1H, d, *J* 8.7, Ph *H*-3); δ_C(75 MHz; DMSO-d_6) 165.4 (*C*=S), 138.9 (Ph

C), 134.6 (Ph *C*H), 133.3 (Ph *C*H), 132.9 (Ph *C*), 128.9 (Ph *C*H), 114.7 (*C*≡N), 113.7 (*C*≡N), 110.9 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d_6) 134.6 (Ph *C*H), 133.3 (Ph *C*H), 128.9 (Ph *C*H); *m/z* (EI) 223 (M^++2, 37%), 221 (M^+, 82), 196 (37), 194 (100), 190 (18), 188 (53), 171 (18), 169 (48), 151 (7), 136 (37), 124 (15), 100 (38), 84 (34), 75 (29), 70 (25), 56 (45).

2-(Cyanothioformamido)-6-methylbenzonitrile 144f

Similarly treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-6-methylbenzonitrile **142f** (100 mg, 0.37 mmol) cooled to *ca*. -5 °C, with DBU gave after chromatography (DCM) the *title compound* **144f** (71.4 mg, 96%) as yellow cotton fibers, mp 128-129 °C (from cyclohexane/EtOH); (found: C, 59.7; H, 3.5; N, 20.9. $C_{10}H_7N_3S$ requires C, 59.7; H, 3.5; N, 20.9%); λ_{max}(DCM)/nm 226 (log ε 3.71), 255 inf (3.38), 337 (3.65); ν_{max}/cm^{-1} 3229w, 3198w, 3146w, 3021w, 2986w, 2239m (C≡N), 1612w, 1566m, 1474s, 1435w, 1373s, 1296w, 1254w, 1179m, 1117m, 1026w, 980w, 789s, 748m, 725m; δ_H(300 MHz; CD_2Cl_2) 9.75 (1H, br s, N*H*), 7.90 (1H, d, *J* 8.1, Ph *H*-3 or 5), 7.63-7.55 (1H, m, Ph *H*-4), 7.43-7.36 (1H, m, Ph *H*-3 or 5), 2.61 (3H, s, CH_3); δ_C(75 MHz; DMSO-d_6) 165.4 (*C*=S), 143.5 (Ph *C*), 139.3 (Ph *C*), 133.9 (Ph *C*H), 130.0 (Ph *C*H), 124.6 (Ph *C*H), 114.8 (*C*≡N), 113.5 (*C*≡N), 109.7 (Ph *C*-1 *C*C≡N), 20.0 (*C*H_3); δ_C(75 MHz; DEPT-135, DMSO-d_6) 133.85 (Ph *C*H), 130.0 (Ph *C*H), 124.6 (Ph *C*H), 20.0 (*C*H_3); *m/z* (EI) 201 (M^+, 56%), 200 (31), 186 (14), 174 (100), 168 (15), 149 (14), 142 (17), 131 (6), 116 (87), 104 (16), 89 (43), 77 (25), 70 (24), 63 (25), 51 (15).

2-(Cyanothioformamido)-4-methoxybenzonitrile 144g

Similarly treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-4-methoxybenzonitrile **142g** (100 mg, 0.35 mmol) cooled to *ca*. 0 °C, with DBU gave after chromatography (DCM) the *title compound* **144g** (73.7 mg, 97%) as a yellow powder, mp 116-117 °C (from cyclohexane); (found: C, 55.3; H, 3.3; N, 19.3. $C_{10}H_7N_3OS$ requires C, 55.3; H, 3.3; N, 19.3%); λ_{max}(DCM)/nm 217 inf (log ε 2.99), 229 (3.21), 250 (3.22), 272 inf (2.88), 337 (2.95); ν_{max}/cm^{-1} 3205w & 3183w (NH), 3038w (Ar CH), 2997w, 2236m (C≡N), 1614s, 1580m, 1549m, 1487m, 1449m, 1435m, 1364s, 1325w, 1314m, 1296m, 1252s, 1213m, 1171w, 1117m, 1030m, 966w, 945w, 864m, 847m, 817s, 764w, 731w; δ_H(300 MHz; CD_2Cl_2) 9.80 (1H, br s, N*H*), 7.80 (1H, br s, Ph *H*-3), 7.71 (1H, d, *J* 8.7, Ph *H*-6), 7.05-6.95 (1H, m, Ph *H*-5), 3.88 (3H, s, CH_3O); δ_C(75 MHz; DMSO-d_6) 164.9, 163.3, 142.2 (Ph *C*), 135.1 (Ph *C*H), 116.3 (*C*≡N), 114.3 (Ph *C*H), 113.9 (*C*≡N), 112.6 (Ph *C*H), 100.5 (*C*C≡N), 56.1 (*C*H_3O);

δ_C(75 MHz; DEPT-135, DMSO-d_6) 135.1 (Ph *C*H), 114.3 (Ph *C*H), 112.6 (Ph *C*H), 56.1 (*C*H_3); *m/z* (EI) 217 (M^+, 100%), 201 (7), 190 (42), 186 (26), 184 (21), 175 (6), 165 (23), 160 (11), 147 (15), 132 (16), 120 (11), 117 (15), 102 (12), 89 (14), 77 (20), 70 (21), 63 (17), 50 (9).

2-(Cyanothioformamido)-4,5-dimethoxybenzonitrile 144h

Similarly treatment of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-4,5-dimethoxybenzonitrile **142h** (100 mg, 0.32 mmol) cooled to *ca*. -5 °C, with DBU gave after chromatography (DCM) the *title compound* **144h** (73.7 mg, 88%) as orange crystals, mp 145-146 °C (lit.,[48] 146-147 °C) (from cyclohexane/EtOH), identical to that described previously.

2-Isothiocyanatobenzonitrile 229 [from 2-(cyanothioformamido)benzonitrile 144a]

To a stirred solution of 2-(cyanothioformamido)benzonitrile **144a** (100 mg, 0.53 mmol) in distilled DCM (2 mL) at *ca*. 20 °C and protected with a $CaCl_2$ drying tube, was added dropwise, DBU (79.3 μL, 0.53 mmol). The mixture was then allowed to stir at *ca*. 20 °C, until no starting material remained (TLC). The reaction mixture was adsorbed onto silica. Chromatography (DCM/*t*-BuOMe, 9:1) gave the title compound **229** (81.4 mg, 96%) as colourless needles, mp 66-67 °C (lit.,[108] 64 °C) (from cyclohexane); ν_{max}/cm^{-1} 2926w, 2851w, 2232m (C≡N), 1624m, 1597m, 1493s, 1452m, 1377m, 1333m, 1319s, 1275w, 1221w, 1206w, 1188w, 1165w, 1099m, 1070w, 1037w, 932m, 903m, 752s, 706s; δ_H(300 MHz; $CDCl_3$) 8.26 (1H, d, *J* 7.8, Ph *H*), 7.80 (1H, d, *J* 7.8, Ph *H*), 7.73 (1H, dd, *J* 8.1, 7.5, 7.8, Ph *H*), 7.50 (1H, dd, *J* 7.2, 7.5, 7.35, Ph *H*); *m/z* (EI) 161 (M^++1, 12), 160 (M^+, 100), 133 (7), 116 (11), 102 (41), 91 (4), 76 (C_6H_4, 36), 75 (25), 70 (8), 64 (10), 51 (17), identical to an authentic sample.

2-Isothiocyanatobenzonitrile 229 [from 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-benzonitrile 142a]

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)benzonitrile **142a** (100 mg, 0.39 mmol) in distilled DCM (2 mL) cooled to *ca*. -5 °C and protected with a $CaCl_2$ drying tube, was added in one portion, DBU (233 μL, 1.56 mmol). The mixture was then allowed to warm to *ca*. 20 °C, until no starting material remained (TLC). The reaction mixture was adsorbed onto silica. Chromatography (DCM/*t*-BuOMe, 9:1) gave the title compound **229**

(59.3 mg, 95%) as colourless needles, mp 66-67 °C (lit.,[108] 64 °C) (from cyclohexane), identical to that described above.

Reaction of 2-cyano cyanothioformanilide 144a with Ph_3P (see Table 28)

To a stirred solution of 2-cyano cyanothioformanilide **144a** (50.0 mg, 0.27 mmol) in dry PhH (2 mL) at *ca*. 20 °C, was added Ph_3P (142 mg, 0.54 mmol). The reaction mixture was then allowed to stir at *ca*. 20 °C for 5 min, until no starting materials remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane/DCM, 1:1) gave Ph_3P=S (134 mg, 84%) as colourless needles, mp 161-162 °C (from cyclohexane), identical to an authentic sample. Further elution (hexane/DCM, 1:4) gave 2-(cyanomethyleneamino)benzonitrile **220a** (4.2 mg, 11%) as colourless cotton fibers, mp 75-76 °C (from cyclohexane), identical to the one described above and 2-(cyanomethylamino)benzonitrile **221a** (16.1 mg, 38%) as light yellow needles, mp 95-96 °C (from cyclohexane/EtOH) identical to an authentic sample. Further elution (DCM, 100%) gave 3-aminoindole-2-carbonitrile **222a** (1.3 mg, 3%) as light yellow cotton fibers, mp 172-173 °C (from cyclohexane/EtOH), identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 4:1) gave (2-cyanoindol-3-yl)iminotriphenyl-phosphorane **223a** (50.7 mg, 45%) as colourless prisms, mp 183-184 °C (from PhH), identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 7:3) gave Ph_3P=O (103.2 mg, 69%) as colourless needles, mp 154-155 °C (from cyclohexane) identical to an authentic sample.

Reaction of 2-(cyanomethyleneamino)benzonitrile 220a with Ph_3P, PTSA in MeOH

To a stirred solution of 2-(cyanomethyleneamino)benzonitrile **220a** (20.0 mg, 0.13 mmol) and PTSA (24.5 mg, 0.13 mmol) in MeOH (2 mL) at *ca*. 20 °C, was added in one portion Ph_3P (68.2 mg, 0.26 mmol). The mixture was left to stir at this temperature for 5 h, until no starting material remained (TLC) and then adsorbed onto silica. Chromatography (hexane/DCM, 1:1) gave unreacted Ph_3P (40.2 mg, 59%) as colourless crystals, mp 80-81 °C (from cyclohexane), identical to an authentic sample. Further elution (hexane/DCM, 1:4) gave anthranilonitrile **219a** (2.0 mg, 13%) as yellow prisms, identical to an authentic sample. Further elution (DCM, 100%) gave 3-aminoindole-2-carbonitrile **222a** (6.1 mg, 30%) as light yellow cotton fibers, mp 172-173 °C (from cyclohexane/EtOH), identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 9:1) gave *N*-(2-cyanophenyl)formamide **233** (10.1 mg, 53%) as yellow fibers, mp 121-122 °C (lit.,[329] 125-127 °C) (from Et_2O); ν_{max}/cm^{-1} 3260w (NH), 2220m (C≡N),

1711m, 1668s, 1585s, 1537s, 1450s, 1404s, 1358w, 1302s, 1258w, 1165m, 1038w, 947w, 864m; δ_H(300 MHz; DMSO-d_6) 10.39 (1H, br s, N*H*), 8.35 (1H, s, C*H*O), 7.91 (1H, d, *J* 8.1, Ph *H*-3 or 6), 7.82 (1H, d, *J* 7.5, Ph *H*-3 or 6), 7.69 (1H, dd, *J* 7.8, 7.7, Ph *H*-4 or 5), 7.33 (1H, dd, *J* 7.8, 7.7, Ph *H*-4 or 5); *m/z* (EI) 146 (M^+, 24%), 118 (100), 91 (50), 64 (19), 57 (13), identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 4:1) gave Ph_3P=O (12.6 mg, 35%) as colourless needles, mp 154-155 ^oC (from cyclohexane), identical to an authentic sample.

Reaction of 2-(cyanothioformamide)benzonitrile 144a with Ph_3P and PTSA in MeOH (typical procedure: see Table 29)

To stirred solution of 2-cyano cyanothioformanilide **144a** (50.0 mg, 0.27 mmol) in MeOH (2 mL) at *ca*. 20 ^oC, was added PTSA (46.4 mg, 0.27 mmol) and the mixture was left to stir *ca*. 20 ^oC for 5 min. Then Ph_3P (142 mg, 0.54 mmol) was added and the mixture was then allowed to stir at *ca*. 20 ^oC for 50 min, until no starting materials remained (TLC). The reaction mixture was adsorbed onto silica and chromatography (hexane/DCM, 1:1) gave Ph_3P=S (114.4 mg, 72%) as colourless needles, mp 161-162 ^oC (from cyclohexane), R_f (hexane/DCM, 1:1) 0.60, identical to an authentic sample. Further elution (hexane/DCM, 3:7) gave anthranilonitrile (2.5 mg, 8%) **219a** as yellow prisms, mp 50-51 ^oC (from cyclohexane/EtOH), identical to an authentic sample. Further elution (DCM, 100%) gave 3-aminoindole-2-carbonitrile **222a** (38.2 mg, 90%) as light yellow cotton fibers, mp 172-173 ^oC (from cyclohexane/EtOH), identical to an authentic sample. Further elution (DCM/*t*-BuOMe, 7:3) gave Ph_3P=O (119.7 mg, 80%) as colourless needles, mp 154-155 ^oC (from cyclohexane), identical to an authentic sample.

Reaction of 2-(cyanothioformamido)-5-nitrobenzonitrile 144b with Ph_3P and PTSA in MeOH

Similar treatment of 2-(cyanothioformamide)-5-nitrobenzonitrile **144b** (62.6 mg, 0.27 mmol), PTSA (46.4 mg, 0.27 mmol) and Ph_3P (142 mg, 0.54 mmol) in MeOH gave 3-amino-5-nitroindole-2-carbonitrile **222b** (35.5 mg, 65%) as red cotton fibers, mp 310-311 ^oC (from PhH), identical to an authentic sample and *N*-(2-cyano-5-nitroindol-3-yl)iminotriphenyl-phosphorane **223b** (21.3 mg, 21%) as red powder, mp > 300 ^oC (from PhH); (found: C, 70.1; H, 4.1; N, 12.2. $C_{27}H_{19}N_4O_2P$ requires C, 70.1; H, 4.1; N, 12.1%); λ_{max}(DCM)/nm 231 (log ε

4.31), 294 (4.51), 332 inf (4.07); ν_{max}/cm^{-1} 3248w (NH), 2210m (C≡N), 1612w, 1576m, 1537s, 1468s, 1437m, 1396w, 1329s, 1310s, 1258m, 1180w, 1134w, 1109s, 1070m, 1016m, 997m, 897w, 870w, 854w, 841w, 818m, 756m, 741m, 733m, 719s; δ_H(300 MHz; CD_2Cl_2) 8.29 (1H, d, *J* 2.1, indole *H*-4), 8.07 (1H, br s, N*H*), 8.05 (1H, dd, *J* 9.2, 2.3, indole *H*-6), 7.84-7.77 (6H, m, PPh_3 *H*), 7.62-7.57 (3H, m, Ph_3P *H*), 7.54-7.48 (6H, m, Ph_3P *H*), 7.20 (1H, d, *J* 9.3, indole *H*-7); δ_C(75 MHz; CD_2Cl_2) 143.5, 141.3, 139.2, 133.0 (d, J_{PC} 9.8, Ph_3P *C*-3), 132.6 (d, J_{PC} 3.0, Ph_3P *C*-4), 131.0 (d, J_{PC} 101.3, Ph_3P *C*-1), 129.2 (d, J_{PC} 12.7, Ph_3P *C*-2), 124.7 (d, J_{PC} 12.8, indole *C*-3), 121.2 (indole *C*H), 119.3 (indole *C*H), 116.2 (*C*≡N), 111.8 (indole *C*H), 97.6 (d, J_{PC} 12.8, indole *C*-2, *C*C≡N); δ_P(121.5 MHz; DMSO-d_6) 6.59; *m/z* (EI) 462 (M^+, 100%), 436 (M^+-CN, 8), 435 (8), 416 (5), 415 (9), 390 (3), 262 (Ph_3P^+, 6), 231 (5), 208 (6), 183 (47), 152 (6), 133 (2), 108 (8).

Reaction of 4-chloro-2-(cyanothioformamido)benzonitrile 144d with Ph_3P and PTSA in MeOH

Similar treatment of 4-chloro-2-(cyanothioformamido)benzonitrile **144d** (59.9 mg, 0.27 mmol), PTSA (46.4 mg, 0.27 mmol) and Ph_3P (142 mg, 0.54 mmol) in MeOH gave 3-amino-5-chloroindole-2-carbonitrile **222d** (37.1 mg, 72%) as light red powder, mp 190-191 ^oC (from EtOH), identical to an authentic sample.

Reaction of 5-chloro-2-(cyanothioformamido)benzonitrile 144e with Ph_3P and PTSA in MeOH

Similar treatment of 5-chloro-2-(cyanothioformamido)benzonitrile **144e** (59.9 mg, 0.27 mmol), PTSA (46.4 mg, 0.27 mmol) and Ph_3P (142 mg, 0.54 mmol) in MeOH gave 3-amino-5-chloroindole-2-carbonitrile **222e** (38.7 mg, 75%) as red powder, mp 210-211 ^oC (from EtOH), identical to an authentic sample and 6-Chloro-4-methoxy-quinazoline-2-carbonitrile **238e** (11.6 mg, 23%) as colourless fibers, mp 139-140 ^oC (from cyclohexane); (found: C, 54.7; H, 2.8; N, 19.2. $C_{10}H_6ClN_3O$ requires C, 54.7; H, 2.8; N, 19.1%); λ_{max}(DCM)/nm 237 (log ε 4.46), 309 inf (3.80), 322 inf (3.40); ν_{max}/cm^{-1} 3092w (Ar CH), 2963w, 2241w (C≡N), 1609w, 1570s, 1553m, 1499s, 1460m, 1499s, 1346w, 1294m, 1221w, 1190m, 1146w, 1130m, 1074m, 988m, 951s, 891m, 835s, 814m, 791m; δ_H(300 MHz; $CDCl_3$) 8.14 (1H, d, *J* 2.1, *H*-5), 7.93 (1H, d, *J* 9.0, *H*-8), 7.85 (1H, dd, *J* 8.9, 2.3, *H*-7), 4.23 (3H, br s, CH_3O); δ_C(75 MHz; $CDCl_3$) one peak missing 166.8, 148.8, 139.7, 135.7 (Ar *C*H), 129.9 (Ar *C*H), 122.9 (Ar *C*H),

117.5, 115.9, 55.7 (CH$_3$O); *m/z* (EI) 221 (M^++2, 35%), 219 (M^+, 100), 190 (41), 184 (83), 162 (15), 149 (16), 139 (32), 137 (80), 126 (18), 124 (28), 111 (23), 100 (29), 97 (31), 85 (41), 75 (27), 71 (53), 57 (94).

Reaction of 2-(cyanothioformamido)-6-methylbenzonitrile 144f with Ph$_3$P and PTSA in MeOH

Similar treatment of 2-(cyanothioformamido)-6-methylbenzonitrile **144f** (54.3 mg, 0.27 mmol), PTSA (46.4 mg, 0.27 mmol) and Ph$_3$P (142 mg, 0.54 mmol) in MeOH gave 3-amino-4-methylindole-2-carbonitrile **222f** (34.6 mg, 75%) as yellow cotton fibers, mp 156-157 ^{o}C (from cyclohexane/EtOH), identical to an authentic sample.

Reaction of 2-(cyanothioformamido)-4-methoxybenzonitrile 144g with Ph$_3$P and PTSA in MeOH

Similar treatment of 2-(cyanothioformamido)-4-methoxybenzonitrile **144g** (58.6 mg, 0.27 mmol), PTSA (46.4 mg, 0.27 mmol) and Ph$_3$P (142 mg, 0.54 mmol) in MeOH gave 3-amino-6-methoxyindole-2-carbonitrile **222g** (31.8 mg, 63%) as red crystals, mp 179-180 ^{o}C (from cyclohexane/EtOH), identical to an authentic sample.

Reaction of 2-(cyanothioformamido)-4,5-dimethoxybenzonitrile 144h with Ph$_3$P and PTSA in MeOH

Similar treatment of 2-(cyanothioformamido)-4,5-dimethoxybenzonitrile **144h** (66.7 mg, 0.27 mmol), PTSA (46.4 mg, 0.27 mmol) and Ph$_3$P (142 mg, 0.54 mmol) in MeOH gave 4,6,7-trimethoxyquinazoline-2-carbonitrile **238h** (9.3 mg, 19%) as yellow needles, mp 228-229 ^{o}C (lit.,[98] 238 ^{o}C) (from cyclohexane/EtOH); (found: C, 58.8; H, 4.6; N, 17.1. $C_{12}H_{11}N_3O_3$ requires C, 58.8; H, 4.5; N, 17.1%); λ_{max}(DCM)/nm 248 (log ε 4.65), 263 inf (4.32), 303 inf (4.05), 313 (4.12), 328 (4.05); ν_{max}/cm^{-1} 3011w (Ar CH), 2986w and 2943w, 2237w (C≡N), 1611m, 1578m, 1558w, 1504m, 1481s, 1454w, 1433m, 1420m, 1410m, 1375m, 1315w, 1267s, 1250s, 1223m, 1213m, 1182m, 1167m, 1105m, 1022m, 999s, 947m, 862m, 847m, 789m, 764w; δ_H(300 MHz; $CDCl_3$) 7.37 (1H, s, *H*-5 or 8), 7.29 (1H, s, *H*-5 or 8), 4.19 (3H, s, CH_3O), 4.04 (3H, s, CH_3O), 4.03 (3H, s, CH_3O); δ_C(75 MHz; $CDCl_3$) 165.7, 156.1, 151.7, 147.9, 138.1, 116.5, 111.6, 107.0 (Ar *C*H), 101.1 (Ar *C*H), 56.5 (CH$_3$O), 56.4 (CH$_3$O), 55.0

(CH$_3$O); *m/z* (EI) 245 (M^+, 100%), 230 (M^+-CH$_3$, 21), 216 (23), 202 (7), 174 (6), 159 (6), 145 (6), 131 (6), 97 (8), 77 (9), 67 (17), 57 (12).

Reaction of 2-(cyanothioformamido)-4,5-dimethoxybenzonitrile 144h with Ph$_3$P and PTSA in dry toluene

To a stirred solution of 2-(cyanothioformamido)-4,5-dimethoxybenzonitrile **144h** (66.7 mg, 0.27 mmol) in toluene (2 mL) at *ca*. 20 ^{o}C, was added Ph$_3$P (142 mg, 0.54 mmol) in one portion. The mixture was then heated to 110 ^{o}C for 1 h, until no starting material remained (TLC) and adsorbed onto silica. Chromatography (hexane/DCM, 5:5) gave Ph$_3$P=S (61 mg, 52%) as colourless needles, mp 161-162 ^{o}C (from cyclohexane), identical to an authentic sample. Further elution (DCM, 100%) gave 2-(cyanomethyleneamino)-4,5-dimethoxy-benzonitrile **225** (10 mg, 23%) as yellow cotton fibres, mp 170-171 ^{o}C (from cyclohexane); (found: C, 61.4; H, 4.2; N, 19.5. $C_{11}H_9N_3O_2$ requires C, 61.4; H, 4.2; N, 19.5%); λ_{max}(DCM)/nm 228 (log ε 3.02), 235 (3.21), 261 (3.35), 285 inf (2.88), 363 (3.02); ν_{max}/cm^{-1} 2920w, 2230m (C≡N), 1597m, 1547m, 1537m, 1516s, 1464m, 1368m, 1287s, 1231s, 1198m, 1109s, 1026m, 993s, 908w, 876m, 837m; δ_H(300 MHz; DMSO-d$_6$) 8.17 (1H, s, N=C*H*), 7.51 (1H, s, Ph *H*), 7.31 (1H, s, Ph *H*), 3.87 (3H, s, C*H*$_3$O), 3.86 (3H, s, C*H*$_3$O); δ_C(75 MHz; DMSO-d$_6$) 152.9, 150.2, 143.9, 137.4 (Ar *C*H), 116.8, 116.0, 114.5 (Ar *C*H), 102.2, 101.8 (Ar *C*H), 56.4 (*C*H$_3$O), 56.3 (*C*H$_3$O); *m/z* (EI) 215 (M^+, 100%), 200 (72), 172 (33), 157 (5), 145 (74), 129 (11), 117 (25), 104 (29), 102 (49), 90 (39), 88 (23), 78 (57), 76 (58), 64 (33), 53 (30). Further elution (DCM/*t*-BuOMe, 4:1) gave Ph$_3$P=O (55 mg, 50%) as colourless needles, mp 154-155 ^{o}C (from cyclohexane), identical to an authentic sample. Further elution (hexane/EtOH, 7:3) gave (2-cyano-5,6-dimethoxyindol-3-yl)iminotriphenylphosphorane **223h** (30 mg, 31%) as red prisms, mp 157-158 ^{o}C (from cyclohexane/EtOH); (found: C, 73.0; H, 5.1; N, 8.8. $C_{29}H_{24}N_3O_2P$ requires C, 73.0; H, 5.1; N, 8.8%); λ_{max}(DCM)/nm 230 (log ε 3.47), 256 (3.22), 318 (3.22), 351.5 inf (2.79); ν_{max}/cm^{-1} 3057w, 3015w, 2926w, 2193m (C≡N), 1630w, 1518s, 1477s, 1450w, 1437s, 1329m, 1294s, 1250m, 1227m, 1204w, 1194s, 1173m, 1144m, 1111s, 1016m, 993m, 988m, 932m, 841m, 802m, 750m, 745m, 718s; δ_H(300 MHz; CD_2Cl_2) 7.80-7.73 (6H, m, Ph$_3$P *H*), 7.65 (1H, br s, N*H*), 7.60-7.54 (3H, m, Ph$_3$P *H*), 7.50-7.45 (6H, m, Ph$_3$P *H*), 6.63 (1H, s, indole *H*-4 or 7), 6.54 (1H, s, indole *H*-4 or 7), 3.78 (3H, s, C*H*$_3$O), 3.45 (3H, s, C*H*$_3$O); δ_C(75 MHz; CD_2Cl_2) 150.7, 145.3, 141.5, 133.0 (d, J_{PC} 9.8, Ph$_3$P *C*-3), 132.7, 132.3 (d, J_{PC} 3.0, Ph$_3$P *C*-4), 132.0 (d, J_{PC} 100.5, Ph$_3$P *C*-1), 129.0 (d, J_{PC} 12.0,

Ph_3P C-2), 117.7 (d, J_{PC} 2.3, indole *C*≡N), 117.3 (d, J_{PC} 9.0 indole *C*-3), 102.3 (indole *C*H), 95.7 (d, J_{PC} 15.8, indole *C*-2, *C*C≡N), 94.5 (indole *C*H), 56.1 (*C*H_3O), 56.0 (*C*H_3O); δ_P (121.5 MHz; CD_2Cl_2) 4.0; *m/z* (EI) 477 (M^+, 100%), 462 (4), 435 (8), 292 (6), 265 (17), 262 (8), 239 (7.5), 183 (37), 108 (14), 77 (3).

9.7 Compounds Related to Chapter 7

Reaction of 2-aminobenzonitrile 219a with *p*-TsCl (see Table 31)

To a stirred solution of 2-aminobenzonitrile **219a** (1.0 g, 8.47 mmol) in pyridine (10 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added *p*-TsCl (1.61 g, 8.47 mmol). The mixture then was heated to *ca*. 100 °C for 5 h until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (20 mL) and washed with 5% HCl (4 × 20 mL). The organic layer was separated and dried to give the 2-(*p*-tosylamino)benzonitrile **245a** (2.0 g, 87%) as colourless plates, mp 133-134 °C (lit.,[304] 133-134 °C) (from cyclohexane/EtOH); λ_{max}(DCM)/nm 231 (log ε 4.21), 241 inf (4.07), 275 inf (3.21), 294 (3.39); ν_{max}/cm^{-1} 3472w, 3364w, 3212w (NH), 2230m (C≡N), 1597m, 1578m, 1495s, 1431m, 1335s, 1298m, 1290m, 1159s, 1094s, 916s, 822m, 806s, 762s, 719m; δ_H(300 MHz; $CDCl_3$) 7.73-7.69 (3H, m, Ar *H*), 7.55 (1H, dd, *J* 7.9, 7.9, 1.5, Ph *H*), 7.47 (1H, dd, *J* 7.8, 1.5, Ph *H*), 7.26 (2H, d, *J* 8.1, Tos *H*-3/5), 7.17 (1H, ddd, *J* 7.6, 7.6, 1.0, Ph *H*), 7.11 (1H, br s, N*H*), 2.39 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 144.6, 139.2, 135.4, 134.1 (*C*H), 132.8 (*C*H), 129.9 (*C*H), 127.3 (*C*H), 125.1 (*C*H), 121.8 (*C*H), 115.7 (*C*≡N), 104.3 (*C*C≡N), 21.5 (*C*H_3); *m/z* (EI) 272 (M^+, 32%), 207 (2), 155 (56), 139 (2), 91 ($C_7H_7^+$, 100), 77 (2), 65 (24), 51 (3) identical to an authentic sample.

Reaction of 2-(*p*-Tosylamino)benzonitrile 245a with chloroacetonitrile 244 (see Table 32)

To a stirred mixture of 2-(*p*-tosylamino)benzonitrile **245a** (50.0 mg, 0.18 mmol) in DMF (2 mL) and K_2CO_3 (25 mg, 0.18 mmol) at *ca*. 20 °C, chloroacetonitrile **244** was added (11 μL, 0.18 mmol). The reaction tube was then sealed and the mixture was heated to *ca*. 100 °C for 70 min, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (10 mL) and washed with water (4 × 10 mL). The organic layer was separated and dried to give N-*(2-Cyanophenyl)*-N-*(*p-*tosyl)aminoacetonitrile* **246** (48 mg, 81%) as colourless cotton-like fibers, mp 82-83 °C (lit.,[304] 81-82 °C) (from

cyclohexane/DCM); λ_{max}(DCM)/nm 220 inf (log ε 2.91), 231 (3.42), 275 inf (2.34), 282 inf (2.21); ν_{max}/cm^{-1} 2239w (C≡N), 1491m, 1449m, 1362s, 1169s, 1117m, 1086m, 856s, 814m, 785m, 766m, 741m; δ_H(300 MHz; $CDCl_3$) 7.72 (1H, dd, *J* 9.0, 1.8, Ph *H*), 7.68-7.62 (3H, m, Ar *H*), 7.54 (1H, ddd, *J* 7.5, 7.5, 1.2, Ph *H*), 7.44 (1H, dd, *J* 8.1, 0.6, Ph *H*), 7.34 (2H, d, *J* 8.1, Tos *H*-3/5), 4.62 (2H, s, CH_2), 2.45 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 145.5, 140.0, 134.3 (*C*H), 134.0 (*C*H), 134.0, 131.0 (*C*H), 130.2 (*C*H), 130.1 (*C*H), 128.1 (*C*H), 115.4, 114.5, 114.2, 39.1 (N*C*H$_2$), 21.7 (*C*H$_3$); *m/z* (EI) 311 (M$^+$, 12%), 284 (3), 155 (75), 129 (7), 103 (8), 102 (9), 91 ($C_7H_7^+$, 100), 76 (3), 65 (25), 51 (5) identical to an authentic sample.

Reaction of chloroacetonitrile 244 with base (see Table 33)

To a stirred mixture of chloroacetonitrile **244** (100 μL, 119.6 mg, 1.59 mmol) in EtOH (1 mL) at *ca*. 20 °C, was added cesium carbonate (518 mg, 1.59 mmol). The mixture was heated to *ca*. 65 °C, for 24 h. The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (10 mL) and extracted with water (4 × 10 mL). The organic layer was separated, dried and chromatographed (hexane/DCM, 1:1) to give 2,4,6-tris(chloromethyl)-1,3,5-triazine **247** (278 mg, 77%) as yellow crystals, mp 72-73 °C (lit.,[380] 78-79 °C) (from cyclohexane); λ_{max}(DCM)/nm 229 (log ε 2.82), 271 (2.80); ν_{max}/cm^{-1} 3038w, 2977w, 1539s, 1540s, 1432m, 1380m, 1260m, 1153w, 1146w, 844w, 732s; δ_H(300 MHz; $CDCl_3$) 4.68 (6H, s, CH_2); δ_C(75 MHz; $CDCl_3$) 175.5, 45.2 (*C*H$_2$); δ_C(75 MHz; DEPT-135, $CDCl_3$) 45.2 (*C*H$_2$); *m/z* (EI) 229 (M$^+$+4, 23%), 227 (M$^+$+2, 70), 225 (M$^+$, 78), 152 (25), 150 (39), 115 (8), 103 (5), 101 (17), 88 (12), 78 (30), 76 (100), 66 (14), 51 (21), identical to an authentic sample. Further elution (DCM) gave 4-amino-5-chloro-2,6-dichloromethylpyrimidine **248** (68.6 mg, 19%) as light yellow crystals, mp 123-124 °C (from cyclohexane); (found: C, 31.8; H, 2.6; N, 18.4. $C_6H_6N_3Cl_3$ requires C, 31.8; H, 2.7; N, 18.6%); λ_{max}(DCM)/nm 230 inf (log ε 3.89), 240 (3.99), 288 (3.76); ν_{max}/cm^{-1} 3381m (NH$_2$), 3181m, 1643s, 1614m, 1425m, 1402m, 1314w, 1265m, 1177w, 1099m, 930w, 891w, 806w, 766; δ_H(300 MHz; DMSO-d_6) 7.95 (H, br s, N*H*), 7.45 (H, br s, N*H*), 4.63 (2H, s, CH_2Cl), 4.51 (2H, s, CH_2Cl) and δ_H(300 MHz; $CDCl_3$) 5.71 (2H, s, NH_2), 4.60 (2H, s, CH_2Cl), 4.50 (2H, s, CH_2Cl); δ_C(75 MHz; DMSO-d_6) 162.4, 160.7, 158.5, 110.4, 46.7 (*C*H$_2$), 43.4 (*C*H$_2$); δ_C(75 MHz; DEPT-135, $CDCl_3$) 46.7 (*C*H$_2$), 43.4 (*C*H$_2$); *m/z* (EI) 229 (M$^+$+4, 30%), 227 (M$^+$+2, 80), 225 (M$^+$, 100), 190 (16), 189 (M$^+$-Cl, 11), 165 (5), 163 (8), 156 (9), 154 (M$^+$-2Cl, 29), 140 (4), 127 (7), 118 (5), 115 (31), 101 (15), 90 (12), 88 (37), 76 (23), 75 (31), 74 (12), 73 (28), 66 (16), 52 (23).

Synthesis of 3-amino-1-(*p*-tosyl)indole-2-carbonitrile 242a (see Table 34)

To a stirred solution of *N*-(2-cyanophenyl)-*N*-(*p*-tosyl)aminoacetonitrile **246a** (100 mg, 0.32 mmol) in EtOH (2 mL) at *ca*. 20 °C, was added K_2CO_3 (0.4 mg, 3.2×10^{-3} mmol). The reaction mixture was left to stir for 26 h until no starting material remained (TLC). The mixture was then diluted with DCM (15 mL) and washed with water (4 × 20 mL). The organic layer was separated and dried to give the *title compound* **242a** (96 mg, 96%) as light orange needles, mp (DSC) onset: 203 °C, peak max: 205 °C (lit.,[304] 195.5-196.5 °C) (from cyclohexane/EtOH); λ_{max}(DCM)/nm 231 (log ε 4.35), 247 inf (4.25), 270 inf (3.95), 277 inf (3.93), 297 (4.04), 319 (4.10); ν_{max}/cm^{-1} 3447m (NH_2), 3348m (NH), 3260w, 3240w, 2208s (C≡N), 1653s, 1597m, 1568m, 1364s, 1184m, 1169s, 1153m, 1115m, 1086s, 974m, 810m, 770s, 752s; δ_H(300 MHz; $CDCl_3$) 8.18 (1H, d, *J* 8.7, indole *H*-4), 7.72 (2H, d, *J* 8.4, Tos *H*-2/6), 7.54 (1H, ddd, *J* 7.8, 7.8, 1.2, indole *H*-5), 7.40 (1H, d, *J* 7.5, indole *H*-7), 7.31 (1H, ddd, *J* 7.5, 7.5, 0.9, indole *H*-6), 7.18 (2H, d, *J* 8.1, Tos *H*-3/5), 4.49 (2H, br s, N*H*$_2$), 2.33 (3H, s, C*H*$_3$); δ_C(75 MHz; DMSO-d_6) one peak overlapping 148.1, 145.5, 137.2, 131.4, 129.9 (*C*H), 126.7 (*C*H), 124.7 (indole *C*H), 123.7, 120.8 (indole *C*H), 115.9 (indole *C*H), 114.4 (*C*≡N), 84.3 (*C*C≡N), 20.95 (*C*H$_3$); *m/z* (EI) 311 (M^+, 11%), 156 (100), 129 (21), 102 (13), 91 ($C_7H_7^+$, 15), 76 (5), 65 (9), 51 (5) identical to an authentic sample.

Synthesis of 3-(*p*-Tosylamino)indole-2-carbonitrile 256a (see Table 35)

To a stirred solution of 3-amino-1-(*p*-tosyl)indole-2-carbonitrile **242a** (20.0 mg, 0.06 mmol) in EtOH (1 mL) at *ca*. 20 °C was added K_2CO_3 (9 mg, 0.06 mmol). The reaction vessel was sealed, and heated at 100 °C (bath temperature). The reaction mixture was left to stir for 5 h until no starting material remained (TLC). The mixture was diluted with DCM (15 mL) and washed with water (4 × 20 mL) to remove the K_2CO_3. The organic layer was separated and dried to give the *title compound* **256a** (25.7 mg, 65%) as colourless cotton-like fibers, mp 234-235 °C (from cyclohexane/EtOH); (found: C, 61.7; H, 4.2; N, 13.4. $C_{16}H_{13}N_3O_2S$ requires C, 61.7; H, 4.2; N, 13.5%); λ_{max}(DCM)/nm 231 (log ε 4.50), 289 (4.23), 313 inf (3.75); ν_{max}/cm^{-1} 3358m and 3310m (NH), 2228m (C≡N), 1366m, 1346s, 1310s, 1250m, 1182m, 1157s, 1090m, 893m, 814s, 748s; δ_H(300 MHz; DMSO-d_6) 12.33 (1H, br s, N*H*Ts), 10.19 (1H, br s, N*H*), 7.52 (2H, d, *J* 8.1, Tos *H*-2/6), 7.35 (1H, d, *J* 8.4, indole *H*-4), 7.29-7.22 (3H, m, Ar *H*), 7.12 (1H, d, *J* 8.1, indole *H*-7), 6.96 (1H, dd, *J* 7.5, 7.5, indole *H*-6), 2.33 (3H, s, C*H*$_3$); δ_C(75 MHz; DMSO-d_6) 143.2, 136.8, 135.3, 129.5 (*C*H), 126.8 (*C*H), 125.8 (indole *C*H), 122.4,

121.6, 120.7 (indole *C*H), 119.4 (indole *C*H), 112.9 (*C*≡N), 112.4 (indole *C*H), 103.9 (*C*C≡N), 20.9 (*C*H_3); *m/z* (EI) 311 (M^+, 23%), 156 (100), 129 (20), 102 (11), 91 ($C_7H_7^+$, 7), 76 (4), 65 (5).

Preparation of 3-(*p*-tosylamino)indole-2-carbonitrile 256a from 3-amino-1-(*p*-tosyl) indole-2-carbonitrile 242a using DBU

To a stirred solution of DBU (3 μL, 0.019 mmol, 0.2 equiv) in dry PhH at *ca*. 20 °C, was added 3-amino-1-tosylindole-2-carbonitrile **242a** (30 mg, 0.096 mmol). The reaction mixture was left to stir for 24 h at reflux until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 °C, adsorbed onto silica and chromatography (hexane – *t*-butyl ether, 1:1) gave 3-(*p*-tosylamino)indole-2-carbonitrile **256a** in (30 mg, 76%) as a colourless cotton-like fibers, mp 234-235 °C (from cyclohexane/EtOH) identical to that described above.

Preparation of 3-(*p*-tosylamino)indole-2-carbonitrile 256a from 3-amino-indole-2-carbonitrile 222a and *p*-TsCl

To a stirred solution of 3-aminoindole-2-carbonitrile **222a** (20.0 mg, 0.06 mmol) and pyridine (21 μL, 0.24 mmol) in EtOH (2 mL) at *ca*. 20 °C, was added *p*-TsCl (11 mg, 0.06 mmol). The reaction mixture was heated at reflux for 5 h until no starting material remained (TLC). The mixture was diluted with DCM (15 mL) and washed with 5% HCl (4 × 20 mL) to remove pyridine. The organic layer was separated and dried to give 3-(*p*-tosylamino)indole-2-carbonitrile **256a** (34 mg, 85%) identical to that described above.

3-(Benzesulfonylamino)indole-2-carbonitrile 256i

Similar treatment of 3-aminoindole-2-carbonitrile **222a** (20.0 mg, 0.06 mmol) gave after 12 h the *title compound* **256i** (16 mg, 88%) as a light yellow cotton-like fibers, mp 230-231 °C (from cyclohexane/EtOH); (found C, 60.6; H, 3.7; N, 14.1. $C_{15}H_{11}N_3O_2S$ requires C, 60.6; H, 3.7; N, 14.1%); λ_{max}(DCM)/nm 208 (log ε 3.50), 223 (3.61), 289 (3.29), 305 inf (3.02), 317 inf (2.76); ν_{max}/cm^{-1} 3360m and 3306m (NH), 2228m (C≡N), 1450m, 1366m, 1344m, 1308m, 1167s, 1159s, 1094m, 895m, 745s, 721m; δ_H(300 MHz; DMSO-d_6) 12.36 (1H, br s, N*H*SO_2Ph), 10.27 (1H, br s, N*H*), 7.66-7.58 (3H, m, Ph *H*), 7.51-7.45 (2H, m, Ph *H*), 7.36 (1H, d, *J* 8.4, indole *H*-4 or 7), 7.25 (1H, dd, *J* 7.5, 7.4, indole *H*-5 or 6), 7.07 (1H, d, *J* 8.1,

indole *H*-4 or 7), 6.95 (1H, dd, *J* 7.7, 7.35, indole *H*-5 or 6); δ_C(75 MHz; DMSO-d_6) 139.5, 135.3, 132.9 (*C*H), 129.1 (*C*H), 126.7 (*C*H), 125.8 (*C*H), 122.5, 121.4, 120.8 (*C*H), 119.3 (*C*H), 112.8 (*C*≡N), 112.4 (*C*H), 104.1 (*C*C≡N); *m/z* (EI) 297 (M^+, 16%), 287 (4), 156 ($PhSO_2N^+$, 100), 129 (30), 103 (25), 77 (19), 76 (14), 51 (17).

Reaction of 3-amino-1-(*p*-tosyl)indole-2-carbonitrile 242a with sodium phenylsulfinate

To a stirred solution of DBU (10 μL, 0.06 mmol) and sodium benzenesulfinate (49 mg, 0.3 mmol) in dry PhH (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, 3-amino-1-(*p*-tosyl)indole-2-carbonitrile **242a** (20.0 mg, 0.06 mmol) was added. The reaction mixture was then heated to *ca*. 80 ^oC for 1 d, until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 ^oC, adsorbed onto silica and chromatography (DCM/*t*-BuOMe, 1:1) gave a mixture of 3-(*N*-tosylamino)- and 3-(*N*-benzenesulfonyl-amino)indole-2-carbonitriles **256a** and **256i** (ratio by ^1H NMR *ca.* 2:1).

Synthesis of 3-aminoindole-2-carbonitrile 222a using aerobic conditions (see Table 36)

To a stirred solution of DBU (10 μL, 0.06 mmol) and thiophenol (31 μL, 0.30 mmol) in distilled PhH (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, 3-amino-1-(*p*-tosyl)indole-2-carbonitrile **242a** (20.0 mg, 0.06 mmol) was added. The reaction mixture was then heated to *ca*. 80 ^oC for 12 h, until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 ^oC, adsorbed onto silica and chromatography (hexane) gave diphenyl disulfide (32 mg, 248%) as colourless needles, mp 60-61 ^oC (from cyclohexane). Further elution (hexane/*t*-BuOMe, 1:1) gave the *title compound* **222a** (21 mg, 92%) as light yellow cotton-like fibers, mp 172-173 ^oC (from cyclohexane/EtOH) identical to an authentic sample.

Synthesis of 3-aminoindole-2-carbonitrile 222a using anaerobic conditions (see Table 36)

To a stirred solution of DBU (10 μL, 0.06 mmol) and thiophenol (31 μL, 0.30 mmol) in distilled and degassed PhH (2 mL) at *ca*. 20 ^oC under argon atmosphere, 3-amino-1-(*p*-tosyl) indole-2-carbonitrile **242a** (20.0 mg, 0.06 mmol) was added. The reaction mixture was then heated to *ca*. 80 ^oC for 24 h, until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 ^oC, adsorbed onto silica and chromatography (hexane) gave diphenyl disulfide (14 mg, 104%) as colourless needles, mp 60-61 ^oC (from cyclohexane).

Further elution (hexane/*t*-BuOMe, 1:1) gave the title compound **222a** (8 mg, 88%) as light yellow cotton-like fibers, mp 172-173 °C (from cyclohexane/EtOH) identical to an authentic sample.

Synthesis of 4,5-Dimethoxy-2-(p-tosylamino)benzonitrile 245h (typical procedure: see Scheme 142)

To a stirred solution of 4,5-dimethoxy-2-aminobenzonitrile **219h** (1.5 g, 8.47 mmol) in pyridine (10 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added *p*-TsCl (1.9 g, 10.1 mmol, 1.2 equiv.). The mixture then was heated to *ca*. 100 °C for 1 h until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (20 mL) and washed with 5% HCl (4 × 20 mL). The organic layer was separated and dried to give after chromatography (hexane/*t*-BuOMe, 7:3) the *title compound* **245h** (2.19 g, 78%) as colourless prisms, mp 192-193 °C (from cyclohexane/EtOH); (found: C, 57.9; H, 4.9; N, 8.4. $C_{16}H_{16}N_2O_4S$ requires C, 57.8; H, 4.85; N, 8.4%); λ_{max}(DCM)/nm 242 (log ε 2.87), 268 inf (2.80), 301 (2.57); ν_{max}/cm^{-1} 3254m (NH), 2224w (C≡N), 1514s, 1396m, 1354s, 1333m, 1275s, 1223s, 1202m, 1169s, 1110m, 1090m, 999s, 893s, 862s, 816s; δ_H(300 MHz; $CDCl_3$) 7.64 (2H, d, *J* 8.4, Tos *H*-2/6), 7.24 (2H, d, *J* 9.0, Tos *H*-3/5), 7.23 (1H, s, Ph *H*-3 or 6), 6.98 (1H, br s, N*H*), 6.80 (1H, s, Ph *H*-3 or 6), 3.93 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 2.39 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 153.5, 147.0, 144.6, 135.2, 134.2, 129.8 (*C*H), 127.3 (*C*H), 116.1 (*C*≡N), 112.9 (*C*H), 107.3 (*C*H), 96.7 (*C*C≡N), 56.4 (*C*H_3O), 56.2 (*C*H_3O), 21.6 (*C*H_3); *m/z* (EI) 332 (M^+, 45%), 177 ($C_7H_7SO_2^+$, 100), 150 (19), 135 (8), 120 (4), 107 (3), 104 (3), 91 ($C_7H_7^+$, 27), 77 (7), 68 (9), 65 (23), 53 (1). Further elution (hexane/*t*-BuOMe, 7:3) gave N-*(2-cyano-4,5-dimethoxyphenyl)-4-methylbenzenesulfonamide* **263** (0.617 g, 15%) as a colourless powder, mp 220-221 °C (from EtOH); (found: C, 56.75; H, 4.5; N, 5.7. $C_{23}H_{22}N_2O_6S_2$ requires C, 56.8; H, 4.6; N, 5.8%); λ_{max}(DCM)/nm 233 (log ε 4.67), 270 (4.11), 276 inf (4.09), 288 inf (3.87), 298 inf (3.57); ν_{max}/cm^{-1} 2224w (C≡N), 1597m, 1520m, 1474w, 1462w, 1450w, 1439w, 1395w, 1373m, 1352m, 1287m, 1227m, 1206m, 1188w, 1163s, 1115m, 1082m, 1028w, 1003m, 907s, 872w, 837m, 810m, 785w, 710m; δ_H(300 MHz; $CDCl_3$) 7.86 (4H, d, *J* 8.1, Tos *H*-2/6), 7.35 (4H, d, *J* 8.1, Tos *H*-3/5), 7.05 (1H, s, Ph *H*-3 or 6), 6.50 (1H, s, Ph *H*-3 or 6), 3.91 (3H, s, CH_3O), 3.81 (3H, s, CH_3O), 2.46 (6H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 152.15, 150.2, 145.7, 135.5, 130.0, 129.6 (Tos *C*H), 129.1 (Tos *C*H), 115.9 (*C*≡N), 115.4 (Ph *C*H), 114.4 (Ph *C*H), 108.2 (*C*C≡N), 56.4 (*C*H_3O), 56.2 (*C*H_3O), 21.7 (*C*H_3); δ_C(75 MHz; DEPT-

135, $CDCl_3$), 129.6 (Tos *C*H), 129.1 (Tos *C*H), 115.4 (Ph *C*H), 114.4 (Ph *C*H), 56.4 (CH_3O), 56.2 (CH_3O), 21.7 (CH_3); *m/z* (EI) 486 (M^+, 54%), 332 (15), 331 ($C_7H_7SO_2^+$, 76), 267 (97), 252 (11), 236 (20), 223 (4), 209 (4), 177 (11), 161 (11), 155 (12), 139 (8), 133 (15), 118 (7), 105 (4), 91 ($C_7H_7^+$, 100), 77 (6), 65 (37), 51 (4).

5-Nitro-2-(*p*-tosylamino)benzonitrile 245b

Similar treatment of 2-amino-5-nitrobenzonitrile **219b** (1.0 g, 6.17 mmol) with *p*-TsCl (1.18 g, 6.17 mmol) gave after 36 h the *title compound* **245b** (1.58 g, 81%) as light yellow cotton-like fibers, mp 159-160 °C (lit.,[477] 165.5-167 °C); λ_{max}(DCM)/nm 229 (log ε 3.31), 237 inf (3.25), 302 (3.10); ν_{max}/cm^{-1} 3217w (NH), 3188w, 3075w, 2239w (C≡N), 1585m, 1531m, 1493m, 1416m, 1344s, 1287m, 1169s, 1082m, 924m, 878s, 795m, 745m; δ_H(300 MHz; $CDCl_3$) 8.39 (1H, d, *J* 2.4, Ph *H*-6), 8.36 (1H, d, *J* 9.2, 2.6, Ph *H*-4), 7.86 (1H, d, *J* 9.0, Ph *H*-3), 7.82 (2H, d, *J* 8.4, Tos *H*-2/6), 7.68 (1H, br s, N*H*), 7.34 (2H, d, *J* 8.1, Tos *H*-3/5), 2.42 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 145.8, 144.8, 142.9, 134.8, 130.3 (*C*H), 129.3 (*C*H), 128.7 (*C*H), 127.4 (*C*H), 118.6 (*C*H), 113.9 (*C*≡N), 102.3 (*C*C≡N), 21.65 (CH_3); *m/z* (EI) 318 (M^++1, 2), 317 (M^+, 12%), 156 (5), 155 (57), 91 (100), 89 (7), 65 (26).

***N*-(2-Cyano-4,5-dimethoxyphenyl)-*N*-(*p*-tosyl)aminoacetonitrile 246h**

Similar treatment of 4,5-dimethoxy-2-[(*p*-tosylamino)]benzonitrile **245h** (50.0 mg, 0.15 mmol) with chloroacetonitrile **244** gave after 2 h the *title compound* **246h** (43 mg, 73%) as colourless needles, mp 191-192 °C (from cyclohexane/DCM); (found: C, 58.3; H, 4.6; N, 11.3. $C_{18}H_{17}N_3O_4S$ requires C, 58.2; H, 4.6; N, 11.3%); λ_{max}(DCM)/nm 242 (log ε 2.93), 261 (2.87), 269 (2.86), 274 inf (2.83), 297 inf (2.51); ν_{max}/cm^{-1} 2272w (C≡N), 1599m, 1522m, 1360s, 1275m, 1225m, 1164s, 1134m, 1090m, 1076m, 1015m, 968m, 876m, 860m, 816m, 781m; δ_H(300 MHz; $CDCl_3$) 7.68 (2H, d, *J* 8.4, Tos *H*-2/6), 7.34 (2H, d, *J* 8.1, Tos *H*-3/5), 7.02 (1H, s, Ph *H*-3 or 6), 6.90 (1H, s, Ph *H*-3 or 6), 4.61 (2H, s, CH_2), 3.91 (3H, s, CH_3O), 3.84 (3H, s, CH_3O) 2.45 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 153.0, 149.9, 145.4, 134.2, 134.1, 130.0 (*C*H), 128.2 (*C*H), 115.7 (*C*≡N), 114.6 (*C*≡N), 114.3 (*C*H), 113.8 (*C*H), 105.5 (*C*C≡N), 56.4 (CH_3O), 39.3 (CH_2), 21.7 (CH_3); *m/z* (EI) 371 (M^+, 18%), 216 ($C_7H_7SO_2^+$, 100), 200 (1), 189 (41), 174 (3), 155 (5), 147 (3), 119 (2), 104 (3), 91 ($C_7H_7^+$, 28), 77 (2), 65 (12).

3-Amino-5,6-dimethoxy-1-(*p*-tosyl)indole-2-carbonitrile 242h

Similar treatment of *N*-(2-cyano-4,5-dimethoxyphenyl)-*N*-(*p*-tosyl)aminoacetonitrile **246h** (100 mg, 0.27 mmol) gave after 30 h the *title compound* **242h** (93 mg, 93%) as light yellow needles, mp 209-210 °C (from cyclohexane/EtOH00); (found C, 58.3; H, 4.6; N, 11.2. $C_{18}H_{17}N_3O_4S$ requires C, 58.2; H, 4.6; N, 11.3%); λ_{max}(DCM)/nm 230 (log ε 2.34), 269 (2.23), 277 (2.23), 312 (2.28), 324 inf (2.22); ν_{max}/cm^{-1} 3466w (NH_2), 3372w, 3352m (NH), 3265w, 2185m (C≡N), 1649m, 1570m, 1485s, 1437m, 1364s, 1298s, 1229s, 1188m, 1176m, 1171m, 1159s, 1090m, 1013s, 918m, 849m, 816m, 770m; δ_H(300 MHz; DMSO-d_6) 7.58 (2H, d, *J* 8.1, Tos *H*-2/6), 7.51 (1H, s, indole *H*-4), 7.37 (1H, s, indole *H*-7), 7.32 (2H, d, *J* 8.1, Tos *H*-3/5), 6.79 (2H, br s, N*H*$_2$), 3.92 (3H, s, C*H*$_3$O), 3.73 (3H, s, C*H*$_3$O) 2.29 (3H, s, C*H*$_3$); δ_C(75 MHz; DMSO-d_6) 151.3, 148.7, 147.5, 145.3, 132.1, 131.2, 129.8 (*C*H), 126.9 (*C*H), 116.1, 114.9, 101.8 (*C*H), 99.0 (*C*H), 83.3 (*C*C≡N), 55.8 (*C*H$_3$O), 55.6 (*C*H$_3$O), 21.0 (*C*H$_3$); *m/z* (EI) 371 (M^+, 8%), 216 ($C_7H_8SO_2^+$, 100), 200 (2), 189 (2), 172 (6), 158 (4), 143 (2), 121 (3), 116 (3), 103 (3), 91 ($C_7H_7^+$, 14), 78 (3), 65 (13), 51 (4).

3-Amino-5-nitro-1-(*p*-tosyl)indole-2-carbonitrile 242b

To a stirred mixture of 5-nitro-2-(*p*-tosylamino)benzonitrile **245b** (100 mg, 0.315 mmol) in chloroacetonitrile (1 mL) at *ca*. 20 °C was added K_2CO_3 (87 mg, 0.63 mmol). The mixture heated to *ca*. 100 °C for 24 h, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (10 mL) and washed with water (4 × 10 mL). The organic layer was separated, dried, adsorbed onto silica and chromatography (hexane/DCM, 1:4) gave 2-amino-5-nitrobenzocarbonitrile **219b** (23.1 mg, 45%) as light yellow dust, mp 207-208 °C (lit.,[477] 210-211 °C) identical to an authentic sample. Further elution (DCM 100%) gave the *title compound* **242b** (45 mg, 40%) as yellow fibers, mp 236-237 °C (from cyclohexane/EtOH); R_f (DCM) 0.30; (found C, 53.8; H, 3.2; N, 15.65. $C_{16}H_{12}N_4O_4S$ requires C, 53.9; H, 3.4; N, 15.7%); λ_{max}(DCM)/nm 233 (log ε 3.43), 287 (3.50), 326 inf (3.04), 338 inf (2.91); ν_{max}/cm^{-1} 3458m (NH_2), 3375s, 3102w, 2207m (C≡N), 1632m, 1612m, 1593m, 1524s, 1477m, 1383s, 1342s, 1285m, 1256s, 1192s, 1175s, 1088m, 1070m, 982m, 903m, 891m, 837m, 822m, 810s, 739m, 702s; δ_H(300 MHz; $CDCl_3$) 8.41 (1H, s, indole *H*-4), 8.37 (1H, d, *J* 2.1, indole *H*-7), 8.30 (1H, dd, *J* 8.7, 1.2, indole *H*-6), 7.77 (2H, d, *J* 8.4, Tos *H*-2/6), 7.28 (2H, d, *J* 7.8, Tos *H*-3/5), 2.36 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 147.0, 144.4, 139.7, 136.2, 133.5, 130.6 (*C*H), 127.5 (*C*H), 124.4 (*C*H), 123.7, 122.6, 116.5 (*C*H),

116.2 (*C*H), 112.4 (*C*≡N), 21.8 (*C*H_3); *m/z* (EI) 356 (M^+, 21%), 202 (13), 201 ($C_7H_8SO_2^+$, 100), 156 (7), 155 (55), 128 (16), 116 (3), 102 (8), 101 (14), 92 (19), 91 (87), 77 (5), 76 (6), 75 (7), 65 (33).

Deprotection of 3-amino-5,6-dimethoxy-1-(*p*-tosyl)indole-2-carbonitrile 242h using DBU and PhSH (see Table 37)

To a stirred solution of DBU (10 μL, 0.06 mmol) and thiophenol (31 μL, 0.30 mmol) in distilled PhH (2 mL) at *ca*. 20 ^oC and protected with $CaCl_2$ drying tube, 3-amino-5,6-di-methoxy-1-(*p*-tosyl)indole-2-carbonitrile **242h** (22.3 mg, 0.06 mmol) was added. The reaction mixture was then heated to *ca*. 80 ^oC for 24 h, until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 ^oC, adsorbed onto silica and chromatography (hexane) gave diphenyl disulfide (30.8 mg, 230%) as colourless needles, mp 60-61 ^oC (from cyclohexane). Further elution (hexane/*t*-BuOMe, 1:1) gave *3-amino-5,6-dimethoxyindole-2-carbonitrile* **222h** (11.5 mg, 88%) as yellow needles mp 194–195 ^oC (from cyclohexane/EtOH); (found: C, 60.8; H, 5.0; N,19.3. $C_{11}H_{11}N_3O_2$ requires C, 60.8; H, 5.1; N, 19.3%); λ_{max}(DCM)/nm 232 (log ε 4.24), 248 (4.24), 311 (4.33); ν_{max}/cm^{-1} 3426w (NH), 3347m (NH_2), 3007w (Ar CH), 2949w, 2907w, 2839w, 2185s (C≡N), 1636m, 1591w, 1557s, 1485s, 1462m, 1439m, 1385w, 1331s, 1319s, 1240m, 1225s, 1204s, 1190s, 1169s, 1105m, 1032w, 1001m, 910w, 853m, 822w, 806m, 754m; δ_H(300 MHz; CD_2Cl_2) 7.46 (1H, br s, N*H*), 6.86 (1H, s, Ph *H*-4), 6.73 (1H, s, Ph *H*-7), 3.99 (2H, br s, NH_2), 3.86 (6H, s, CH_3O); δ_C(75 MHz; CD_2Cl_2) 151.8, 146.0, 138.0, 132.6, 115.3, 111.6, 99.65 (Ph *C*H), 94.5 (Ph *C*H), 89.0, 56.5 (O*C*H_3), 56.2 (O*C*H_3); *m/z* (EI) 218 (M^++1, 14), 217 (M^+, 100%), 216 (M^+-1, 7), 202 (M^+-CH_3, 28), 189 (5), 174 (12), 173 (8), 172 (6), 163 (12), 159 (23), 157 (8), 156 (10), 147 (23), 145 (4), 144 (9), 131 (7), 130 (5), 129 (7), 120 (6), 117 (6), 111 (5), 109 (6), 104 (10), 97 (8), 85 (6), 78 (6), 77 (11), 71 (9), 69 (9), 57 (16), 56 (5), 55 (11), 43 (12).

Deprotection of 3-amino-5-nitro-1-(*p*-tosyl)indole-2-carbonitrile 242b using DBU and PhSH

Similar treatment of 3-amino-5-nitro-1-(*p*-tosyl)indole-2-carbonitrile **242b** (21.4 mg, 0.06 mmol), DBU (10 μL, 0.06 mmol) and thiophenol (31 μL, 0.30 mmol) in distilled PhH (2 mL) gave *3-amino-5nitroindole-2-carbonitrile* **222b** (10.9 mg, 90%) as red cotton fibres mp 310-311 ^oC (from PhH); (found: C, 53.4; H, 2.9; N, 27.6. $C_9H_6N_4O_2$ requires C, 53.5; H, 3.0;

N, 27.7%); λ_{max}(DCM)/nm 225 (log ε 4.14), 237 inf (3.17), 265 (3.19), 268 (3.18), 272 (3.23), 299 (3.49); ν_{max}/cm^{-1} 3463w (NH_2), 3376m and 3279m (NH), 3065w, 2204s (C≡N), 1635m, 1614m, 1588m, 1533m, 1521w, 1476s, 1398w, 1327s, 1244w, 1190m, 1132w, 1064m, 942w, 914w, 846w, 814m, 778w, 755m; δ_H(300 MHz; DMSO-d_6) 11.62 (1H, br s, N*H*), 8.95 (1H, d, *J* 2.4, Ph *H*-4), 8.07 (1H, dd, *J* 2.3, 9.2, Ph *H*-6), 7.33 (1H, d, *J* 9.3, Ph *H*-7), 6.29 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 141.0, 139.4, 138.5, 120.8 (Ph *C*H), 118.9 (Ph *C*H), 117.2, 115.0 (*C*≡N), 112.1 (Ph *C*H), 87.4 (*C*C≡N); *m/z* (EI) 202 (M^+, 100%), 183 (2), 172 (5), 156 (75), 144 (10), 129 (69), 117 (5), 102 (48), 94 (10), 75 (22), 63 (9), 51 (12), 50 (12).

Synthesis of 5,6-dimethoxy-3-(*p*-tosylamino)indole-2-carbonitrile 256h from 5,6-dimethoxy(tosylamino)indole-2-carbonitrile 242h using K_2CO_3 (see Scheme 144)

To a stirred solution of 5,6-dimethoxy(tosylamino)indole-2-carbonitrile **242h** (22.3 mg, 0.06 mmol) in EtOH (1 mL) at *ca*. 20 °C was added K_2CO_3 (9 mg, 0.06 mmol). The reaction vessel was sealed, and heated at 100 °C (bath temperature). The reaction mixture was left to stir for 3 h until no starting material remained (TLC). The mixture was diluted with DCM (15 mL) and washed with water (4 × 20 mL) to remove the K_2CO_3. The organic layer was separated and dried to give the *title compound* **256h** as colourless cotton-like fibers, mp 214-215 °C (from cyclohexane/EtOH); (found: C, 58.3; H, 4.6; N, 11.3. $C_{18}H_{17}N_3O_4S$ requires C, 58.2; H, 4.6; N, 11.3%); λ_{max}(DCM)/nm 230 (log ε 4.45), 296 inf (4.23), 307 inf (4.27), 318 (4.31), 330 inf (4.22); ν_{max}/cm^{-1} 3362m and 3271m (NH), 2833, 2218m (C≡N), 1487m, 1379m, 1339s, 1319s, 1260s, 1246m, 1227m, 1204m, 1161s, 1117m, 1092s, 1016m, 947w, 887m, 849m, 816s, 758m, 750m; δ_H(300 MHz; DMSO-d_6) 12.02 (1H, br s, N*H*Ts), 9.97 (1H, br s, N*H*), 7.54 (2H, d, *J* 8.1, Tos *H*-2/6), 7.30 (2H, d, *J* 8.1, Tos *H*-3/5), 6.75 (1H, s, indole *H*-4 or 7), 6.20 (1H, s, indole *H*-4 or 7), 3.76 (3H, s, CH_3O), 3.46 (3H, s, CH_3O), 2.33 (3H, s, CH_3); δ_C(75 MHz; DMSO-d_6) 150.0, 145.8, 143.1, 137.1, 130.4, 129.5 (*C*H), 126.9 (*C*H), 121.4, 115.3, 113.5 (*C*≡N), 102.1 (*C*C≡N), 99.0 (indole *C*H), 94.1 (indole *C*H), 55.4 (O*C*H_3), 55.0 (O*C*H_3), 20.9 (*C*H_3); *m/z* (EI) 371 (M^+, 21%), 216 (M^+-$C_7H_7O_2S$, 100), 200 (3), 189 (7), 173 (4), 163 (4), 155 (4), 144 (3), 130 (2), 104 (3), 91 (14), 77 (4), 65 (9).

5-Nitro-3-(*p*-tosyl)aminoindole-2-carbonitrile 256b

Similar treatment of 3-amino-5-nitro-1-(*p*-tosyl)indole-2-carbonitrile **242b** (20.0 mg, 0.056 mmol) and K_2CO_3 (9 mg, 0.06 mmol) in EtOH (1 mL) gave after 1 h the *title compound* **256b**

(17 mg, 85%) as colourless plates, mp 264-265 ^{o}C (from cyclohexane/EtOH); (found C, 54.0; H, 3.4; N, 15.7. $C_{16}H_{12}N_4O_4S$ requires C, 53.9; H, 3.4; N, 15.72%); λ_{max}(DCM)/nm 226 (log ε 4.06), 263 inf (4.13), 265 (4.14), 268 (4.11), 272 (4.09); ν_{max}/cm^{-1} 3375m (NH), 3258, 2232 (C≡N), 1533m, 1485m, 1404m, 1339s, 1157s, 1088m, 897m, 814m, 777m, 735s; δ_H(300 MHz; DMSO-d_6) 13.13 (1H, br s, N*H*Ts), 10.42 (1H, br s, N*H*), 8.08 (1H, dd, *J* 6.6, 2.3, indole *H*-6), 7.86 (1H, d, *J* 2.1, indole *H*-4), 7.57 (1H, d, *J* 9.0, indole *H*-7), 7.51 (2H, d, *J* 8.4, Tos *H*-2/6), 7.28 (2H, d, *J* 8.1 Tos *H*-3/5), 2.29 (3H, s, C*H*$_3$); δ_C(75 MHz; DMSO-d_6) 143.7, 141.8, 137.6, 136.0, 129.6 (*C*H), 126.8 (*C*H), 123.9, 121.4, 120.3 (indole *C*H), 116.8 (indole *C*H), 113.7 (indole *C*H), 111.8 (*C*≡N), 107.5 (*C*C≡N), 20.8 (*C*H$_3$); *m/z* (EI) 356 (M$^+$, 28%), 201 (80), 155 (64), 148 (3), 128 (13), 116 (4), 101 (17), 91 (100), 75 (13), 65 (40), 51 (8).

Reaction of 5,6-dimethoxy-3-aminoindole-2-carbonitrile 222h with TsCl (see Scheme 145)

To a stirred solution of 5,6-dimethoxy-3-aminoindole-2-carbonitrile **222h** (13 mg, 0.06 mmol) and pyridine (21 μL, 0.24 mmol) in EtOH (2 mL) at *ca*. 20 ^{o}C, was added *p*-TsCl (11 mg, 0.06 mmol). The reaction mixture was heated at reflux for 2 h until no starting material remained (TLC). The mixture was diluted with DCM (15 mL) and washed with 5% HCl (4 × 20 mL) to remove pyridine. The organic layer was separated and dried to give 5,6-dimethoxy-3-(*p*-tosylamino)indole-2-carbonitrile **256h** (19.1 mg, 86%) identical to that described above.

5-Nitro-3-(*p*-tosyl)aminoindole-2-carbonitrile 256b

Similar treatment of 3-amino-5-nitroindole-2-carbonitrile **222b** (12.1, 0.06 mmol), *p*-TsCl (11 mg, 0.06 mmol) and pyridine (21 μL, 0.24 mmol) in EtOH (2 mL) gave after 48 h the *title compound* **256b** (17.5 mg, 82%) as colourless plates, mp 264-265 ^{o}C (from cyclohexane/EtOH) identical to that described above.

Reaction of 2-aminobenzonitrile 219a with paraformaldehyde, KCN, $ZnCl_2$ and catalytic H_2SO_4 in AcOH (typical prodedure: see Table 38)

To a stirred solution of 2-aminobenzonitrile **219a** (200 mg, 1.69 mmol) in acetic acid (5 mL), in a sealed tube at room temperature, were added paraformaldehyde (55.8 mg, 1.86 mmol), potassium cyanide (121.1 mg, 1.86 mmol), zinc chloride (461 mg, 3.38 mmol) and sulfuric acid (1 drop, *ca.* 16 mg). The mixture was then warmed to *ca.* 55 ^{o}C for 3 h until no starting

material remained (TLC). The reaction mixture was allowed to cool to rt, poured onto ice and made pH neutral (Na_2CO_3). Filtration of the precipitate gave *2-(Cyanomethyl-amino)benzonitrile* **221a** (255 mg, 96%) as colourless cotton, mp 95–96 ^oC (from cyclohexane/EtOH); (found: C, 68.7; H, 4.4; N, 26.7. $C_9H_7N_3$ requires C, 68.8; H, 4.5; N, 26.7%); λ_{max}(DCM)/nm 228 inf (log ε 3.84), 244 (4.06), 318 (3.79); ν_{max}/cm^{-1} 3379m (NH), 2218m (C≡N), 1603s, 1582m, 1522s, 1460m, 1427w, 1317m, 1273m, 1256w, 1165m, 1134w, 1076m, 986w, 880w, 845w, 818w, 752s; δ_H(300 MHz; DMSO-d_6) 7.55-7.51 (2H, m, Ph *H*-4 and 6), 6.91 (1H, d, *J* 8.7, Ph *H*-3), 6.83 (1H, dd, *J* 7.7, 7.7, Ph *H*-5), 6.78 (1H, br m, N*H*), 4.36 (2H, d, *J* 6.0, CH_2); δ_C(75 MHz; DMSO-d_6) 148.5, 134.6 (Ph *C*H), 133.4 (Ph *C*H), 118.05 (Ph *C*H), 117.8 (*C*≡N), 117.35 (*C*≡N), 111.7 (Ph *C*H), 96.2 (*C*C≡N), 31.2 (*C*H_2); δ_C(75 MHz; DEPT-135, DMSO-d_6) 134.6 (Ph *C*H), 133.4 (Ph *C*H), 118.05 (Ph *C*H), 111.7 (Ph *C*H), 31.2 (*C*H_2); *m/z* (EI) 157 (M^+, 90%), 130 (M^+-HCN, 49), 117 (M^+-C_2H_2N, 13), 103 (M^+-$C_2H_2N_2$, 100), 90 (39), 76 (17), 63 (17), 51 (13).

2-(Cyanomethylamino)-4,5-dimethoxybenzonitrile 221h.

Similar treatment of 2-amino-4,5-dimethoxybenzonitrile **219h** (300.9 mg, 1.69 mmol), paraformaldehyde (55.8 mg, 1.86 mmol), potassium cyanide (121.1 mg, 1.86 mmol), zinc chloride (461 mg, 3.38 mmol) and sulfuric acid (1 drop, *ca.* 16 mg) in acetic acid (5 mL) gave *2-(cyanomethylamino)-4,5-dimethoxybenzonitrile* **221h** (209 mg, 86%) as colourless cotton-like fibers, mp 143-144 ^oC (from cyclohexane/EtOH); (found: C, 60.8; H, 5.0; N, 19.3 $C_{11}H_{11}N_3O_2$ requires C, 60.8; H, 5.1; N, 19.3%); λ_{max}(DCM)/nm 232 (log ε 4.53), 260 (4.10), 324 (3.88); ν_{max}/cm^{-1} 3370m and 3358w (NH), 2986w, 2963w, 2934w, 2833w, 2205s (C≡N), 1618s, 1587m, 1531s, 1520s, 1477m, 1462w, 1450w, 1437w, 1414m, 1360w, 1341m, 1294w, 1283s, 1261m, 1250w, 1231s, 1215s, 1146m, 1078s, 1045w, 1011s, 966w, 872s, 839w, 833m, 822m; δ_H(300 MHz; CD_2Cl_2) 6.94 (1H, s, Ph *H*-3 or 6), 6.32 (1H, s, Ph *H*-6 or 3), 4.78 (1H, dd, *J* 6, 6.15, 6.3, N*H*), 4.22 (2H, d, *J* 6.6, CH_2), 3.92 (3H, s, CH_3), 3.78 (3H, s, CH_3); δ_C(75 MHz; CD_2Cl_2) 155.45, 144.6, 143.0, 117.8 (*C*≡N), 116.6 (*C*≡N), 115.4 (Ph *C*H), 96.6 (Ph *C*H), 88.3 (*C*C≡N), 56.9 (*C*H_3), 56.4 (*C*H_3), 32.9 (*C*H_2); δ_C(75 MHz; DEPT-135, CD_2Cl_2) 115.4 (Ph *C*H), 96.6 (Ph *C*H), 56.9 (*C*H_3), 56.4 (*C*H_3), 32.9 (*C*H_2); *m/z* (EI) 217 (M^+, 95%), 202 (100), 190 (5), 177 (22), 175 (16), 174 (15), 150 (12), 147 (83), 145 (13), 120 (10), 117 (12), 104 (18), 90 (7), 77 (20), 76 (18), 68 (15), 64 (12), 53 (13), 52 (13).

2-(Cyanomethylamino)-5-nitrobenzonitrile 216c

Similar treatment of 2-amino-5-nitrobenzonitrile **219b** (275.5 mg, 1.69 mmol), paraformaldehyde (253.5 mg, 8.45 mmol), potassium cyanide (549.3 mg, 8.45 mmol), zinc chloride (2.30 g, 16.9 mmol) and sulfuric acid (1 drop, *ca.* 16 mg) in acetic acid (10 mL) gave *2-(cyanomethylamino)-5-nitrobenzonitrile* **221b** (141.6 mg, 57%) as yellow cotton-like fibers, mp 138-139 ^{o}C (from cyclohexane/EtOH); (found: C, 53.5; H, 2.9; N, 27.7 $C_9H_6N_4O_2$ requires C, 53.5; H, 3.0; N, 27.7%); λ_{max}(DCM)/nm 228 (log ε 4.11), 243 inf (3.93), 327 (4.31); ν_{max}/cm^{-1} 3345m (NH), 3304w, 3096w, 2978w, 2226m (C≡N), 1611m, 1587s, 1537m, 1510s, 1449w, 1339s, 1312s, 1271w, 1256w, 1179m, 1159m, 1099s, 1070w, 989w, 924w, 914m, 903w, 833m, 808m, 748s, 725w; δ_H(300 MHz; DMSO-d_6) 8.55 (1H, d, *J* 2.7, Ph *H*-3), 8.39 (1H, dd, *J* 2.7, 9.3, Ph *H*-4), 7.94 (1H, br s, N*H*), 7.11 (1H, d, *J* 9.3, Ph *H*-6), 4.53 (2H, s, CH_2); δ_C(75 MHz; DMSO-d_6) 152.8, 137.6, 130.4 (Ph *C*H), 130.0 (Ph *C*H), 116.9 (*C*≡N), 115.4 (*C*≡N), 111.5 (Ph *C*H), 95.7 (*C*C≡N), 31.3 (*C*H$_2$); δ_C(75 MHz; DEPT-135, DMSO-d_6) 130.4 (Ph *C*H), 130.0 (Ph *C*H), 111.5 (Ph *C*H), 31.3 (*C*H$_2$); *m/z* (EI) 202 (M$^+$, 100%), 185 (10), 175 (M$^+$-HCN, 49), 172 (12), 158 (12), 156 (14), 148 (26), 145 (80), 130 (11), 129 (56), 128 (13), 117 (15), 116 (58), 103 (13), 102 (46), 101 (14), 90 (23), 89 (31), 88 (17), 77 (12), 76 (19), 75 (27), 65 (13), 64 (11), 63 (20), 62 (24), 52 (17), 51 (13), 50 (19).

3-Aminoindole-2-carbonitrile 222a: (typical microwave procedure: see Table 39)

To a stirred solution of 2-(cyanomethylamino)benzonitrile **221a** (50.0 mg, 0.32 mmol) in EtOH (1 mL) was added K_2CO_3 (22 mg, 0.16 mmol) and the mixture was sealed and heated to *ca.* 120 ^{o}C in a microwave reactor (250 W, 180-160 PSI), for 8 min until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 ^{o}C, added to water (50 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried (Na_2CO_3) and the volatiles removed under reduced pressure to give the title compound **222a** (39.2 mg, 78%) as light yellow cotton fibers, mp 172-173 ^{o}C (lit.,[306] 172-173 ^{o}C) (from cyclohexane/EtOH) identical to that described above.

3-Amino-5,6-dimethoxyindole-2-carbonitrile 222h

Similar treatment of 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **221h** (69.4 mg, 0.32 mmol) and K_2CO_3 (22 mg, 0.16 mmol) in EtOH (1 mL) gave the title compound **222h** (25.1

mg, 89%) as yellow needles, mp 194-195 ^{o}C (from cyclohexane/EtOH) identical to that described above.

3-Amino-5-nitroindole-2-carbonitrile 222b

Similar treatment of 2-(cyanomethylamino)-5-nitrobenzonitrile **221b** (64.6 mg, 0.32 mmol) and K_2CO_3 (22 mg, 0.16 mmol) in EtOH (1 mL) gave the title compound **222b** (56 mg, 87%) as red cotton fibers, mp 310-311 ^{o}C (lit.,[306] 310-311 ^{o}C) (from PhH) identical to that described above.

3-Aminoindole-2-carbonitrile 222a: (typical conventional heating procedure: see Table 39)

To a stirred solution of 2-(cyanomethylamino)benzonitrile **221a** (50.0 mg, 0.32 mmol) in EtOH (1 mL) was added K_2CO_3 (22 mg, 0.16 mmol) and the mixture was sealed in a thick glass walled tube and heated at ca. 140 ^{o}C in a preheated Wood's metal bath, for 90 min until no starting material remained (TLC). The reaction mixture was then allowed to cool to ca. 20 ^{o}C, added to water (50 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried (Na_2CO_3) and the volatiles removed under reduced pressure to give the title compound **222a** (28.6 mg, 57%) as light yellow cotton fibers, mp 172-173 ^{o}C (lit.,[306] 172-173 ^{o}C) (from cyclohexane/EtOH) identical to that described above.

3-Amino-5,6-dimethoxyindole-2-carbonitrile 222h

Similar treatment of 2-(cyanomethylamino)-4,5-dimethoxybenzonitrile **221h** (69.4 mg, 0.32 mmol) and K_2CO_3 (22 mg, 0.16 mmol) in EtOH (1 mL) gave the title compound (61 mg, 88%) as yellow needles, mp 194-195 ^{o}C (from cyclohexane/EtOH), identical to that described above.

3-Amino-5-nitroindole-2-carbonitrile 222b

Similar treatment of 2-(cyanomethylamino)-5-nitrobenzonitrile **221b** (64.6 mg, 0.32 mmol) and K_2CO_3 (22 mg, 0.16 mmol) in EtOH (1 mL) gave the title compound **222b** (23.9 mg, 37%) as red cotton fibers, mp 310-311 ^{o}C (lit.,[306] 310-311 ^{o}C) (from PhH); identical to identical to that described above.

Synthesis of 2,2'-(2-cyano-4,5-dimethoxyphenylazanediyl)diacetonitrile 264 from 4,5-dimethoxy-2-aminobenzonitrile 219h

To a stirred solution of 4,5-dimethoxy-2-aminobenzonitrile **219h** (200 mg, 1.12 mmol) in AcOH (5 mL), at *ca*. 20 °C, were added paraformaldehyde (141.6 mg, 3.37 mmol), KCN (215.7 mg, 3.37 mmol), zinc chloride (1.20 g, 8.96 mmol) and H_2SO_4 (1 drop, *ca* 16 mg). The mixture was then warmed to *ca.* 55 °C for 1 h until no starting material remained (TLC). The reaction mixture was allowed to cool to ca. 20 °C, poured onto ice and made pH neutral (Na_2CO_3). Filtration of the precipitate gave the *title compound* **264** (195.0 mg, 68%) as colourless needles, mp 158-159 °C (from cyclohexane/EtOH); (found: C, 61.0; H, 4.7; N, 21.8. $C_{13}H_{12}N_4O_2$ requires C, 60.9; H, 4.7; N, 21.9%); λ_{max}(DCM)/nm 232 (log ε 4.29), 264 (4.02), 298 (3.63); ν_{max}/cm^{-1} 2990w, 2961w, 2226m (C≡N), 1715w, 1601m, 1578w, 1518s, 1464m, 1449m, 1439m, 1402m, 1377m, 1354m, 1329w, 1302w, 1275s, 1260m, 1223s, 1200s, 1130m, 1111s, 1045m, 1018w, 978s, 953w, 912m, 878m, 866s, 851w, 820m, 741w, 718w; δ_H(300 MHz; DMSO-d_6) 7.40 (1H, s, Ph *H*), 7.20 (1H, s, Ph *H*), 4.56 (4H, s, C*H*$_2$), 3.89 (3H, s, C*H*$_3$O), 3.81 (3H, s, C*H*$_3$O); δ_C(75 MHz; DMSO-d_6) 154.0, 147.8, 145.2, 118.0 (*C*≡N), 117.0 (*C*≡N), 116.1 (Ph *C*H), 107.8 (Ph *C*H), 100.9, 57.15 (*C*H$_2$), 57.0 (*C*H$_2$), 43.4 (*C*H$_3$); *m/z* (EI) 256 (M$^+$, 53%), 241 (16), 216 (100), 189 (53), 173 (5), 145 (7), 76 (9).

Synthesis of 3-amino-1-(cyanomethyl)-5,6-dimethoxy-1*H*-indole-2-carbonitrile 265 from 2,2'-(2-cyano-4,5-dimethoxyphenylazanediyl)diacetonitrile 264

To a stirred solution of 2,2'-(2-cyano-4,5-dimethoxyphenylazanediyl)diacetonitrile **264** (50.0 mg, 0.20 mmol) in EtOH (1 mL) was added K_2CO_3 (13.5 mg, 0.10 mmol) and the mixture was sealed and heated to ca. 120 °C in a microwave reactor (250W, 180–160 PSI), for 5 min until no starting material remained (TLC). The reaction mixture was then allowed to cool to rt, added to water (50 mL) and extracted with DCM (3 × 10 mL). The combined organic extracts were dried (Na_2CO_3) and the volatiles removed under reduced pressure to give the *title compound* **265** (36.4 mg, 71%) as light yellow needles, mp 226-227 °C (from cyclohexane/EtOH); (found: C, 61.0; H, 4.6; N, 21.9. $C_{13}H_{12}N_4O_2$ requires C, 60.9; H, 4.7; N, 21.9%); λ_{max}(DCM)/nm 231 (log ε 4.33), 252 (4.35), 301 (4.38), 313 (4.47); ν_{max}/cm^{-1} 3458w, 3372m (NH), 2970w, 2940w, 2837w, 2189s (C≡N), 1638m, 1585w, 1560m, 1491s, 1466m, 1454w, 1431m, 1391m, 1348m, 1314m, 1275s, 1221w, 1211s, 1196s, 1179s, 1125w, 1049s, 1013w, 972w, 889m, 831s, 775m, 760m, 733m; δ_H(300 MHz; DMSO-d_6) 7.37 (1H, s, Ph *H*),

7.215 (1H, s, Ph *H*), 6.08 (2H, s, NH_2), 5.27 (2H, s, CH_2), 3.835 (3H, s, CH_3), 3.76 (3H, s, CH_3); δ_C(75 MHz; DMSO-d_6) 151.3, 145.0, 141.9, 134.05, 116.1 (*C*≡N), 115.0 (*C*≡N), 101.9 (Ph *C*H), 93.9 (Ph *C*H), 87.9, 55.8 (*C*H_2), 55.7 (*C*H_3), 55.7 (*C*H_3), 33.2 (*C*H_2); *m/z* (EI) 256 (M^+, 52%), 216 (100), 201 (6), 173 (16), 158 (11), 121 (7), 78 (5), 51 (7).

9.8 Compounds Related to Chapter 8

_N_-(4-Chloro-5_H_-1,2,3-dithiazol-5-ylidene)-4-methoxyaniline 266af (typical procedure)

To a stirred solution of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) in DCM (10 mL) at *ca*. 20 °C and protected with $CaCl_2$ drying tube, was added 4-methoxyaniline (500 mg, 4.07 mmol). After 1 h, to the reaction mixture was added, dropwise, pyridine (658 μL, 8.14 mmol, 2 equiv.) and left to stir at *ca*. 20 °C for additional 2 h. The reaction mixture was adsorbed onto silica and chromatography (hexane) gave S_8 (traces). Further elution (hexane/DCM, 4:1) gave 4-chloro-5*H*-1,2,3-dithiazole-5-thione **55** (10 mg, 6%) and further elution (hexane/DCM, 4:1) gave the *title compound* **266af** (840 mg, 80%) as yellow fibers, mp 83-84 °C (lit.,[42] 89 °C) (from cyclohexane); λ_{max}(DCM)/nm 231 inf (log ε 3.04), 250 (3.09), 307 inf (2.61), 343 inf (2.66), 382 (2.90), 400 (2.92), 424 inf (2.81); ν_{max}/cm^{-1} 3044w, 2968w, 2936w, 2899w, 2837w, 2558w, 1906w, 1605s, 1576w, 1558m, 1541w, 1504s, 1491m, 1454w, 1435m, 1306s, 1296m, 1252s, 1229m, 1182m, 1128s, 1113s, 1020s, 1001w, 957w, 912w, 856s, 837m, 827s, 791s, 758m; δ_H(300 MHz; $CDCl_3$) 7.29 (1H, dd, *J* 2.7, Ph *H*), 7.26 (1h, dd, *J* 2.85, Ph *H*), 7.00 (1H, dd, *J* 2.7, Ph *H*), 6.97 (1H, dd, *J* 2.7, Ph *H*), 3.84 (3H, s, CH_3O); δ_C(75 MHz; $CDCl_3$) 158.2, 155.6, 148.4, 143.0, 121.7 (Ph *C*H), 114.7 (Ph *C*H), 55.5 (*C*H_3O); δ_C(75 MHz; DEPT-135, $CDCl_3$) 121.7 (Ph *C*H), 114.7 (Ph *C*H), 55.5 (*C*H_3O); *m/z* (EI) 260 (M^++2, 27%), 258 (M^+, 63), 243 (5), 223 (5), 194 (5), 165 (16), 159 (29), 150 (23), 133 (100), 122 (26), 107 (14), 103 (27), 95 (6), 92 (14), 90 (31), 78 (12), 77 (23), 64 (65), 51 (13) identical to an authentic sample.

2-(4-Chloro-5_H_-1,2,3-dithiazol-5-ylideneamino)-4,5-diphenylfuran-3-carbonitrile 266ax

Similar treatment of of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 2-amino-4,5-diphenylfuran-3-carbonitrile (1.06 g, 4.07 mmol) in DCM (10 mL) gave the *title compound* **266ax** (1.01 g, 63%) as red prisms, mp 234-235 °C (from cyclohexane/EtOH); (found: C, 57.6; H, 2.6; N, 10.7. $C_{19}H_{10}ClN_3OS_2$ requires C, 57.6; H, 2.6; N, 10.6%);

λ_{max}(DCM)/nm 459 (log ε 2.97), 488 (2.99), 526 (2.74); ν_{max}/cm^{-1} 2220s (C≡N), 1610w, 1597w, 1587m, 1571m, 1554m, 1528m, 1503w, 1477s, 1445m, 1324m, 1259w, 1208w, 1181s, 1160m, 1118m, 1100w, 1073w, 1063w, 1029w, 1001w, 958m, 919w, 881s, 846w, 797s, 769s, 764s, 719s, 704s; δ_H(300 MHz; DMSO-d$_6$) 7.52 (3H, m, Ph *H*), 7.49-7.45 (4H, m, Ph *H*), 7.38-7.37 (3H, m, Ph *H*); δ_C(75 MHz; DMSO-d$_6$) 176.1, 158.9, 155.6, 148.2, 143.8, 130.0, 129.7 (Ph *C*H), 129.3 (Ph *C*H), 129.2 (Ph *C*H), 129.1 (Ph *C*H), 129.0 (Ph *C*H), 128.1, 127.0, 125.0 (Ph *C*H), 124.8, 113.4 (*C*≡N), 92.3 (*C*C≡N); δ_C(75 MHz; DEPT-135, DMSO-d$_6$) 129.7 (Ph *C*H), 129.3 (Ph *C*H), 129.2 (Ph *C*H), 129.1 (Ph *C*H), 129.0 (Ph *C*H), 125.0 (Ph *C*H), *m/z* (EI) 397 (M$^+$+2, 44%), 395 (M$^+$, 100), 302 (18), 296 (13), 268 (14), 216 (44), 214 (27), 189 (18), 139 (11), 137 (25), 105 (11), 102 924), 77 (40), 70 (15), 64 (18), 51 (20).

_N_-(4-Chloro-5_H_-1,2,3-dithiazol-5-ylidene)-3,4-dimethoxyaniline 266ay

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 3,4-dimethoxyaniline (622.7 mg, 4.07 mmol) gave the *title compound* **266ay** (750 mg, 64%) as yellow cotton, mp 110-111 ^{o}C (lit.,[84] 112 ^{o}C) (from cyclohexane); λ_{max}(DCM)/nm 230 (log ε 3.17), 248 inf (3.13), 348 (2.87), 383 inf (2.83), 407 (2.87); ν_{max}/cm^{-1} 1605w, 1572m, 1558m, 1535w, 1512s, 1464m, 1441m, 1416m, 1333s, 1271s, 1238s, 1196s, 1186m, 1165m, 1153m, 1123s, 1020s, 957w, 901w, 860s, 849s, 835m, 816m, 797s, 743s; δ_H(300 MHz; $CDCl_3$) 6.92 (2H, m, Ph *H*), 6.86 (1h, s, Ph *H*), 3.91 (3H, s, C*H*$_3$O), 3.89 (3H, s, C*H*$_3$O); δ_C(75 MHz; $CDCl_3$) 126.0, 149.7, 148.2, 147.8, 143.6, 111.1 (Ph *C*H), 110.7 (Ph *C*H), 105.7 (Ph *C*H), 56.0 (*C*H$_3$O), 55.9 (*C*H$_3$O); δ_C(75 MHz; DEPT-135, $CDCl_3$) 111.1 (Ph *C*H), 110.7 (Ph *C*H), 105.7 (Ph *C*H), 56.0 (*C*H$_3$O), 55.9 (*C*H$_3$O); *m/z* (EI) 290 (M$^+$+2, 53%), 288 (M$^+$, 100), 275 (23), 273 (56), 257 (77), 220 (19), 195 (26), 189 (14), 180 (26), 163 (74), 152 (22), 148 (50), 137 (29), 122 (19), 109 (20), 102 (22), 92 (60), 79 (41), 77 (55), 70 (19), 64 (60), 51 (39) identical to an authentic sample.

_N_-(4-Chloro-5_H_-1,2,3-dithiazol-5-ylidene)-2,4-dimethoxyaniline 266az

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 2,4-dimethoxyaniline (622.7 mg, 4.07 mmol) gave the *title compound* **266az** (1.01 g, 86%) as orange cotton, mp 70-71 ^{o}C (lit.,[92]) (from cyclohexane in the fridge); λ_{max}(DCM)/nm 232 (log ε 2.96), 258 inf (2.91), 346 inf (2.60), 381 inf (2.67), 412 (2.72), 442 inf (2.59); ν_{max}/cm^{-1} 1599s, 1580s, 1558w, 1499s, 1468w, 1452m, 1431w, 1414w, 1306s, 1263s, 1211s, 1155s,

1117s, 1038s, 1026s, 984w, 959w, 924m, 856s, 829s, 800w, 789w, 770s, 752m, 733m; δ_H(300 MHz; $CDCl_3$) 7.13 (1H, d, *J* 8.4, Ph *H*-6), 6.55 (1H, dd, *J* 3.3, Ph *H*-5), 6.52 (1H, d, *J* 2.7, Ph *H*-5), 3.85 (3H, s, CH_3O), 3.83 (3H, s, CH_3O); δ_C(75 MHz; $CDCl_3$) 159.4, 157.4, 151.9, 148.0, 133.2, 119.35 (Ph *C*H), 104.2 (Ph *C*H), 99.8 (Ph *C*H), 55.8 (*C*H_3O), 55.5 (*C*H_3O); δ_C(75 MHz; DEPT-135, $CDCl_3$) 119.35 (Ph *C*H), 104.2 (Ph *C*H), 99.8 (Ph *C*H), 55.8 (*C*H_3O), 55.5 (*C*H_3O); *m/z* (EI) 290 (M^++2, 39%), 288 (M^+, 100), 195 (33), 189 (71), 188 (87), 180 (14), 174 (14), 163 (67), 162 (30), 152 (24), 151 (14), 137 (11), 134 (38), 133 (15), 122 (10), 120 (19), 109 (11), 107 (14), 93 (11), 79 (20), 77 (19), 64 (30), 51 (17) identical to an authentic sample.

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,4,5-trimethoxyaniline 266aaa**

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 2,4-dimethoxyaniline (744.8 mg, 4.07 mmol) gave the *title compound* **266aaa** (1.13 g, 87%) as orange cotton, mp 109-110 °C (lit.,[481] 111-112 °C) (from cyclohexane in the fridge); λ_{max}(DCM)/nm 229 (log ε 3.09), 246 inf (3.01), 342 inf (2.61), 382 inf (2.72), 403 (2.74); ν_{max}/cm^{-1} 3015w, 2995w, 2949w, 2835w, 1576m, 1562w, 1503s, 1472w, 1449w, 1437w, 1411m, 1329m, 1248m, 1233m, 1184w, 1165w, 1125s, 1045w, 1001m, 926w, 854m, 833w, 804w, 789w, 773w, 762w, 737w; δ_H(300 MHz; $CDCl_3$) 6.51 (1H, s, Ph *H*-2/6), 6.50 (1H, s, Ph *H*-6/2), 3.86 (3H, s, CH_3O), 3.85 (3H, s, CH_3O), 3.84 (3H, s, CH_3O); δ_C(75 MHz; $CDCl_3$) 157.8, 154.0, 147.9, 146.7, 136.25, 97.0 (Ph *C*H), 60.95 (*C*H_3O), 56.15 (*C*H_3O); δ_C(75 MHz; DEPT-135, $CDCl_3$) 97.0 (Ph *C*H), 60.95 (*C*H_3O), 56.15 (*C*H_3O); *m/z* (EI) 320 (M^++2, 33%), 318 (M^+, 88), 305 (39), 303 (100), 287 (23), 210 (36), 182 (23), 178 (18), 167 (13), 150 (21), 135 (16), 120 (15), 81 (11), 64 (42), 53 (16) identical to an authentic sample.

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-methoxy-2-methylaniline 266aab**

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 2,4-dimethoxyaniline (557.6 mg, 4.07 mmol) gave the *title compound* **266aab** (786 mg, 71%) as orange needles, mp 86-87 °C (from cyclohexane); (found: C, 43.9; H, 3.4; N, 10.2. $C_{10}H_9ClN_2OS_2$ requires C, 44.0; H, 3.3; N, 10.3%); λ_{max}(DCM)/nm 233 (log ε 3.06), 254 (3.03), 309 inf (2.54), 349 inf (2.67), 382 inf (2.81), 405 (2.84), 431 inf (2.73); ν_{max}/cm^{-1} 3013w, 2965w, 2941w, 2924w, 2839w, 1607m, 1591w, 1578w, 1489m, 1450w, 1431w, 1373w, 1306s, 1281m, 1250s, 1221s, 1165m, 1146m, 1109s, 1049m, 991w, 928w, 922w,

854s, 820m, 802m, 775m, 762s, 723m; δ_H(300 MHz; $CDCl_3$) 7.15 (1h, d, *J* 8.7, Ph *H*-6), 6.86 (1H, d, *J* 2.7, Ph *H*-3), 6.80 (1H, dd, *J* 2.85, 8.55, Ph *H*-5), 3.82 (3H, s, CH_3O), 2.31 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 158.1, 155.4, 148.4, 142.3, 133.9, 116.8 (Ph *C*H), 116.6 (Ph *C*H), 111.45 (Ph *C*H), 55.4 (*C*H_3O), 18.1 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$) 116.8 (Ph *C*H), 116.6 (Ph *C*H), 111.45 (Ph *C*H), 55.4 (*C*H_3O), 18.1 (*C*H_3); *m/z* (EI) 274 (M^++2, 30%), 272 (M^+, 64), 257 (10), 237 (9), 181 (10), 179 (20), 173 (36), 147 (100), 136 (13), 132 (17), 117 (18), 104 (19), 91 (21), 77 (63), 64 (46), 51 (32).

5-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-2-methoxyphenol 266aac

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 2-methoxyphenol (565.7 mg, 4.07 mmol) gave the *title compound* **266aac** (513 mg, 46%) as orange prisms, mp 121-122 ^oC (from cyclohexane); (found: C, 39.3; H, 2.5; N, 10.2. $C_9H_7ClN_2O_2S_2$ requires C, 39.3; H, 2.6; N, 10.2%); λ_{max}(DCM)/nm 230 (log ε 2.96), 250 (2.99), 307 inf (2.49), 345 inf (2.60), 383 inf (2.75), 404 (2.78); ν_{max}/cm^{-1} 3466w, 3423w, 3402w, 2972w, 2947w, 2841w, 1620w, 1572m, 1547w, 1503s, 1468w, 1458w, 1443m, 1337w, 1331w, 1298m, 1275s, 1234m, 1211m, 1163s, 1117m, 1024m, 972m, 908w, 860s, 851m, 799m, 760m, 750m, 714w; δ_H(300 MHz; $CDCl_3$) 6.92 (1h, d, *J* 2.7, Ph *H*-5), 6.90 (1H, s, Ph *H*-2), 6.82 (1H, dd, *J* 2.4, 8.4, Ph *H*-6), 5.78 (1H, br s, O*H*), 3.92 (3H, s, CH_3O); δ_C(75 MHz; $CDCl_3$) 156.4, 148.25, 146.35, 145.2, 144.2, 111.9 (Ph *C*H), 111.0 (Ph *C*H), 106.95 (Ph *C*H), 56.1 (*C*H_3O); δ_C(75 MHz; DEPT-135, $CDCl_3$) 111.9 (Ph *C*H), 111.0 (Ph *C*H), 106.95 (Ph *C*H), 56.1 (*C*H_3O); *m/z* (EI) 276 (M^++2, 41%), 274 (M^+, 100), 261 (23), 259 (56), 245 (16), 243 (34), 239 (13), 181 (15), 175 (18), 166 (32), 149 (80), 138 (39), 134 (85), 123 (19), 106 (48), 64 (41), 51 (47).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-fluoro-3-methoxyaniline 266aad**

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 4-fluoro-3-methoxyaniline (573.9 mg, 4.07 mmol) gave the *title compound* **266aad** (730.2 mg, 65%) as yellow prisms, mp 87-88 ^oC (from cyclohexane); (found: C, 39.0; H, 2.1; N, 10.1. $C_9H_6ClFN_2OS_2$ requires C, 39.1; H, 2.2; N, 10.1%); λ_{max}(DCM)/nm 231 inf (log ε 3.13), 248 (3.17), 306 inf (2.63), 340 inf (2.73), 382 (2.97), 399 (2.98), 424 inf (2.84); ν_{max}/cm^{-1} 2970w, 2938w, 2907w, 2843w, 1616m, 1572m, 1564m, 1541w, 1514s, 1468w, 1454m, 1447m, 1429w, 1315s, 1279s, 1227s, 1188m, 1161s, 1109s, 1022s, 964m, 905w, 866s, 856s, 799s,

781m, 766w, 748s; δ_H(300 MHz; $CDCl_3$) 7.11(1h, dd, *J* 1.35, Ph *H*), 7.08-7.00 (2H, m, Ph *H*), 3.92 (3H, s, CH_3O); δ_C(75 MHz; $CDCl_3$) 157.0, 154.1, 150.8, 148.2, 146.2 (d, J_{FC} 11.25, F C-3), 143.3 (d, J_{FC} 8.25, F *C*-4), 115.9 (d, J_{FC} 3.75, F *C*H-5), 113.7 (d, J_{FC} 2.25, F *C*H-6), 109.1 (d, J_{FC} 20.25, F *C*H-2), 56.4 (*C*H_3O); δ_C(75 MHz; DEPT-135, $CDCl_3$) 115.9 (d, J_{FC} 3.75, F *C*H-5), 113.7 (d, J_{FC} 2.25, F *C*H-6), 109.1 (d, J_{FC} 20.25, F *C*H-2), 56.4 (*C*H_3O); *m/z* (EI) 278 (M^++2, 43%), 276 (M^+, 45), 263 (12), 245 (12), 183 (14), 168 (23), 151 (100), 140 (13), 136 (23), 125 (19), 108 (22), 96 (11), 85 (29), 71 (42), 64 (21), 57 (56), 44 (55).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-methyl-4-(trifluoromethoxy)aniline 266aae**

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 2-methyl-4-(trifluoromethoxy)aniline (777.4 mg, 4.07 mmol) gave the *title compound* **266aae** (345 mg, 26%) as yellow prisms, mp 49-50 °C (from cyclohexane); (found: C, 36.7; H, 1.9; N, 8.7. $C_{10}H_6ClF_3N_2OS_2$ requires C, 36.8; H, 1.9; N, 8.6%); λ_{max}(DCM)/nm 226 (log ε 3.29), 274 (3.54), 372 (2.93); ν_{max}/cm^{-1} 2955w, 2924w, 2853w, 1607w, 1591w, 1570w, 1485m, 1381w, 1250s, 1200s, 1157s, 1138w, 1107m, 1040w, 1009w, 976w, 891w, 878m, 847m, 822m, 793m, 773s, 723m; δ_H(300 MHz; $CDCl_3$) 7.16 (1H, s, Ph *H*-3), 7.12-7.10 (2H, m, Ph *H*-5 & 6), 2.28 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 159.0 (O*C*F_3), 148.5, 147.3 (d, J_{FC} 62.25, F *C*), 132.5, 123.7 (Ph *C*H), 122.2, 119.6 (Ph *C*H), 118.75, 117.1 (Ph *C*H), 17.7 (*C*H_3); δ_C(75 MHz; DEPT-135, $CDCl_3$) 123.7 (Ph *C*H), 122.2, 119.6 (Ph *C*H), 117.1 (Ph *C*H), 17.7 (*C*H_3); *m/z* (EI) 328 (M^++2, 25%), 326 (M^+, 50), 291 (5), 265 (6), 241 (10), 227 (37), 201 (100), 169 (13), 147 (12), 136 (10), 132 (15), 125 (17), 116 (12), 109 (22), 104 (12), 83 (19), 77 (33), 69 (64), 64 (62), 51 (21).

3-Chloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-(trifluoromethoxy)aniline 266aaf

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 3-chloro-4-(trifluoromethoxy)aniline (858.8 mg, 4.07 mmol) gave the *title compound* **266aaf** (521 mg, 37%) as yellow needles, mp 52-53 °C (from cyclohexane); (found: C, 31.2; H, 0.9; N, 8.0. $C_9H_3Cl_2F_3N_2OS_2$ requires C, 31.1; H, 0.9; N, 8.1%); λ_{max}(DCM)/nm 230 (log ε 3.20), 246 inf (3.11), 374 (2.91), 389 inf (2.86); ν_{max}/cm^{-1} 1628w, 1601m, 1564w, 1522w, 1487m, 1393w, 1277s, 1260w, 1177s, 1148w, 1134w, 1053m, 934w, 897w, 870s, 853m, 802w, 781m, 731w; δ_H(300 MHz; $CDCl_3$) 7.41 (1H, dd, *J* 1.05, 8.4, Ph *H*-5), 7.34 (1H, d, *J* 2.4, Ph *H*-2), 7.14 (1H, dd, *J* 2.4, 8.7, Ph *H*-6); δ_C(75 MHz; $CDCl_3$) 160.5 (O*C*F_3), 149.0 (d, J_{FC} 173.25, F

C), 142.8, 128.8, 123.9 (Ph *C*H), 122.2, 122.05 (Ph *C*H), 118.9 (Ph *C*H), 118.7; δ_C(75 MHz; DEPT-135, $CDCl_3$) 123.9 (Ph *C*H), 122.05 (Ph *C*H), 118.9 (Ph *C*H); *m/z* (EI) 348 (M^++2, 31%), 346 (M^+, 40), 285 (19), 247 (17), 223 (11), 221 (35), 184 (16), 156 (16), 129 (21), 125 (25), 93 (15), 69 (89), 64 (100).

3-Bromo-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-(trifluoromethoxy)aniline 266aag

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 3-bromo-4-(trifluoromethoxy)aniline (1.04 g, 4.07 mmol) gave the *title compound* **266aag** (1.12 g, 70%) as orange cotton, mp 43-44 °C (from pentane in the fridge); (found: C, 27.7; H, 0.8; N, 7.1. $C_9H_3BrClF_3N_2OS_2$ requires C, 27.6; H, 0.8; N, 7.2%); λ_{max}(DCM)/nm 231 (log ε 3.27), 251 inf (3.07), 375 (2.91), 395 inf (2.68); ν_{max}/cm^{-1} 2924w, 2851w, 1597m, 1555w, 1518w, 1481m, 1385w, 1285s, 1273s, 1248w, 1202s, 1179s, 1171s, 1153w, 1134w, 1042m, 928w, 870s, 853m, 837w, 804w, 777m, 729m; δ_H(300 MHz; $CDCl_3$) 7.51 (1H, d, *J* 2.7, Ph *H*-2), 7.40 (1H, dd, *J* 0.9, 9.15, Ph *H*-5), 7.18 (1h, dd, *J* 2.4, 8.7, Ph *H*-6); δ_C(75 MHz; $CDCl_3$) 160.4 (O*C*F_3), 149.1 (d, J_{FC} 179, F *C*), 144.1, 125.0 (Ph *C*H), 123.4 (Ph *C*H), 122.2, 119.65 (Ph *C*H), 118.7, 117.4; δ_C(75 MHz; DEPT-135, $CDCl_3$) 125.0 (Ph *C*H), 123.4 (Ph *C*H), 119.65 (Ph *C*H); *m/z* (EI) 394 (M^++2, 12%), 392 (M^+, 45), 390 (24), 331 (11), 267 (25), 265 (26), 250 (9), 230 (9), 175 (8), 125 (19), 94 (17), 69 (72), 64 (100).

2,6-Dichloro-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-(trifluoromethoxy)aniline 266aah

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 2,6-dchloro-4-(trifluoromethoxy)aniline (1.00 g, 4.07 mmol) gave the *title compound* **266aah** (386.7 mg, 25%) as yellow prisms, mp 83-84 °C (from cyclohexane); (found: C, 28.4; H, 0.5; N, 7.3. $C_9H_2Cl_3F_3N_2OS_2$ requires C, 28.3; H, 0.5; N, 7.3%); λ_{max}(DCM)/nm 230 (log ε 3.07), 240 inf (2.98), 286 inf (2.28), 350 (2.81), 374 inf (2.69); ν_{max}/cm^{-1} 3086w, 2961w, 2949w, 2924w, 2851w, 1587s, 1560m, 1443m, 12378s, 1213w, 1196s, 1169s, 984w, 872s, 824m, 812m, 775m, 735w; δ_H(300 MHz; $CDCl_3$) 7.31 (2H, d, *J* 0.9, Ph *H*); δ_C(75 MHz; $CDCl_3$) 164.45 (O*C*F_3), 146.7, 145.4 (d, J_{FC} 21.75, F *C*), 125.5, 121.9 (Ph *C*H), 118.5; δ_C(75 MHz; DEPT-135, $CDCl_3$) 121.9 (Ph *C*H); *m/z* (EI) 382 (M^++2, 18%), 380 (M^+, 16), 321 (12), 319 (16), 255 (9), 218 (6), 190 (6), 125 (70, 97 (9), 69 (53), 64 (78), 44 (100).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-propoxyaniline 266aai**

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847,6 mg, 4.07 mmol) and 4-propoxyaniline (614.6 mg, 4.07 mmol) gave the *title compound* **266aai** (1.06 g, 91%) as yellow needles, mp 71-72 ^{o}C (from cyclohexane); (found: C, 46.1; H, 4.0; N, 7.8. $C_{11}H_{11}ClN_2OS_2$ requires C, 46.1; H, 3.9; N, 9.8%); λ_{max}(DCM)/nm 230 inf (log ε 3.11), 251 (3.14), 309 (2.66), 343 inf (2.71), 382 inf (2.96), 402 (2.99). 424 inf (2.89); ν_{max}/cm^{-1} 2972w, 2943w, 2913w, 2878w, 1605m, 1574m, 1562m, 1531w, 1499m, 1472m, 1391w, 1288w, 1250s, 1219m, 1171w, 1136s, 1115m, 1047m, 1013s, 970w, 953w, 941w, 912w, 899w, 860s, 831s, 802m, 766s; δ_H(300 MHz; $CDCl_3$) 7.28 (1h, dd, *J* 2.7, 2.85, Ph *H*), 7.25 (1H, dd, *J* 2.7, Ph *H*), 6.99 (1H, dd, *J* 2.85, Ph *H*), 6.96 (1H, dd, *J* 2.85, Ph *H*), 3.95 (2h, t, *J* 6.45, -C*H*$_2$O), 1.88-1.77 (2H, m, $CH_3CH_2CH_2O$), 1.05 (3H, t, *J* 7.5, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 157.9, 155.25, 148.5, 142.7, 121.8 (Ph *C*H), 115.2 (Ph *C*H), 69.8 (*C*H$_2$), 22.55 (*C*H$_2$), 10.5 (*C*H$_3$); δ_C(75 MHz; DEPT-135, $CDCl_3$) 121.8 (Ph *C*H), 115.2 (Ph *C*H), 69.8 (*C*H$_2$), 22.55 (*C*H$_2$), 10.5 (*C*H$_3$); *m/z* (EI) 288 (M^++2, 23%), 286 (M^+, 56), 244 (37), 183 (12), 151 (27), 145 (19), 119 (100), 93 (13), 64 (30), 41 (35).

4-Butoxy-*N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)aniline 266aaj

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 4-butoxyaniline (671.6 mg, 4.07 mmol) gave the *title compound* **266aaj** (1.05 g, 86%) as yellow cotton, mp 61-62 ^{o}C (from cyclohexane); (found: C, 48.0; H, 4.3; N, 9.3. $C_{12}H_{13}ClN_2OS_2$requires C, 47.9; H, 4.4; N, 9.3%); λ_{max}(DCM)/nm 231 inf (log ε 3.11), 252 (3.16), 309 (2.68), 343 inf (2.72), 382 inf (2.98), 402 (3.01), 425 inf (2.91); ν_{max}/cm^{-1} 2963w, 2940w, 2872w, 1607m, 1570w, 1562w, 1501m, 1470w, 1395w, 1296w, 1252s, 1175w, 1121s, 1096s, 1036m, 1007m, 930m, 903s, 856m, 829m, 800w, 762m; δ_H(300 MHz; $CDCl_3$) 7.28 (1h, dd, *J* 2.55, 2.7, Ph *H*), 7.25 (1H, dd, *J* 2.7, Ph *H*), 6.99 (1H, dd, *J* 2.7, Ph *H*), 6.96 (1H, dd, *J* 2.7, Ph *H*), 3.99 (2H, t, *J* 6.45, C*H*$_2$O), 1.83-1.74 (2H, m, -$CH_2CH_2CH_2O$), 1.57-1.45 (2H, m, $CH_3CH_2CH_2$-), 0.99 (3H, t, *J* 7.35, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 157.9, 155.2, 148.5, 142.7, 121.8 (Ph *C*H), 115.2 (Ph *C*H), 67.9 (*C*H$_2$), 31.3 (*C*H$_2$), 19.2 (*C*H$_2$), 13.8 (*C*H$_3$); δ_C(75 MHz; DEPT-135, $CDCl_3$) 121.8 (Ph *C*H), 115.2 (Ph *C*H), 67.9 (*C*H$_2$), 31.3 (*C*H$_2$), 19.2 (*C*H$_2$), 13.8 (*C*H$_3$); *m/z* (EI) 302 (M^++2, 26%), 300 (M^+, 51), 244 (59), 227 (11), 183 (18), 151 (28), 145 (23), 119 (100), 93 (16), 64 (35), 57 (20), 41 (50).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-phenoxyaniline 266aak**

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 4-phenoxyaniline (753.0 mg, 4.07 mmol) gave the *title compound* **266aak** (1.25 g, 96%) as yellow needles, mp 45-46 ^{o}C (from pentane in the fridge); (found: C, 52.5; H, 2.8; N, 8.8. $C_{14}H_9ClN_2OS_2$ requires C, 52.4; H, 2.8; N, 8.7%); λ_{max}(DCM)/nm 231 (log ε 3.18), 246 (3.17), 304 (2.55), 340 inf (2.64), 383 (2.88), 396 (2.88), 425 inf (2.71); ν_{max}/cm^{-1} 1585m, 1568m, 1485s, 1454w, 1236s, 1213s, 1190m, 1161m, 1140m, 1105m, 1070w, 1022w, 1005w, 959w, 901w, 876m, 864s, 853m, 841m, 785m, 772m, 752m, 742m; δ_H(300 MHz; $CDCl_3$) 7.39-7.34 (2H, m, Ph *H*), 7.28-7.24 (2H, m, Ph *H*), 7.16-7.03 (5H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) 156.8, 156.7, 155.85, 148.3, 145.35, 129.85 (Ph *C*H), 123.7 (Ph *C*H), 121.6 (Ph *C*H), 119.5 (Ph *C*H), 119.2 (Ph *C*H); δ_C(75 MHz; DEPT-135, $CDCl_3$) 129.85 (Ph *C*H), 123.7 (Ph *C*H), 121.6 (Ph *C*H), 119.5 (Ph *C*H), 119.2 (Ph *C*H); *m/z* (EI) 322 (M^++2, 49%), 320 (M^+, 100), 227 (42), 221 (31), 195 (90), 167 (34), 141 (22), 122 (12), 115 (21), 77 (94), 64 (37), 51 (49).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine 266aal**

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 2,3-dihydrobenzo[*b*][1,4]dioxin-6-amine (614.6 mg, 4.07 mmol) gave the *title compound* **266aal** (1.04 g, 89%) as orange cotton, mp 128-129 ^{o}C (lit.,[108] 134 ^{o}C) (from cyclohexane/EtOH); λ_{max}(DCM)/nm 231 inf (log ε 3.13), 248 (3.17), 306 inf (2.63), 340 inf (2.73), 382 (2.97), 399 (2.98), 424 inf (2.84); ν_{max}/cm^{-1} 1607m, 1584m, 1566m, 1499s, 1449m, 1420w, 1391w, 1364w, 1312s, 1287s, 1265m, 1244m, 1211m, 1165s, 1136s, 1107m, 1063s, 1040m, 959m, 914m, 885m, 853s, 826s, 800m, 762m, 748m; δ_H(300 MHz; $CDCl_3$) 6.94 (1H, d, *J* 8.4, Ph *H*-7), 6.86 (1H, d, *J* 2.4, Ph *H*-2), 6.82 (1H, dd, *J* 2.4, 8.4, Ph *H*-8), 4.29 (4H, s, -CH_2CH_2-); δ_C(75 MHz; $CDCl_3$) 156.25, 148.3, 144.0, 143.95, 142.3, 118.0 (Ph *C*H), 113.8 (Ph *C*H), 109.1 (Ph *C*H), 64.35 (-*C*H_2*C*H_2-); δ_C(75 MHz; DEPT-135, $CDCl_3$) 118.0 (Ph *C*H), 113.8 (Ph *C*H), 109.1 (Ph *C*H), 64.35 (-*C*H_2*C*H_2-); *m/z* (EI) 288 (M^++2, 42%), 286 (M^+, 94), 255 (20), 251 (27), 222 (8), 193 (27), 187 (28), 161 (100), 146 (31), 137 (28), 135 (27), 109 (24), 107 (20), 105 (63), 83 (15), 79 (25), 77 (65), 64 (37), 51 (53).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)benzo[*d*][1,3]dioxol-5-amine 266aam**

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and benzo[*d*][1,3]dioxol-5-amine (557.6 mg, 4.07 mmol) gave the *title compound* **266aam** (741.7 mg, 67%) as yellow cotton, mp 100-101 ^{o}C (from cyclohexane / EtOH); (found: C, 39.7; H, 1.9; N, 10.3 $C_9H_5ClN_2O_2S_2$ requires C, 39.6; H, 1.9; N, 10.3%); λ_{max}(DCM)/nm 230 inf (log ε 3.08), 253 (3.09), 312 (2.70), 345 inf (2.75), 383 inf (2.86), 407 (2.90); ν_{max}/cm^{-1} 2911w, 1618w, 1566w, 1555m, 1495m, 1483m, 1439m, 1344s, 1252s, 1188s, 1152s, 1123w, 1088m, 1030s, 932s, 860s, 818m, 800m, 768s, 718w; δ_H(300 MHz; $CDCl_3$) 6.88 (1H, d, *J* 8.1, Ph *H*-6), 6.87 (1H, d, *J* 2.1, Ph *H*-2), 6.79 (1H, dd, *J* 1.95, 8.25, Ph *H*-7), 6.02 (2H, s, -CH_2-); δ_C(75 MHz; $CDCl_3$) 156.5, 148.6, 148.2, 146.2, 144.85, 113.0 (Ph *C*H), 108.6 (Ph *C*H), 102.0 (Ph *C*H), 101.7 (-*C*H_2-); δ_C(75 MHz; DEPT-135, $CDCl_3$) 113.0 (Ph *C*H), 108.6 (Ph *C*H), 102.0 (Ph *C*H), 101.7 (-*C*H_2-); *m/z* (EI) 274 (M^++2, 26%), 272 (M^+, 71), 242 (13), 237 (16), 207 (12), 179 (29), 173 (22), 146 (100), 121 (33), 89 (10), 70 (20), 63 (53), 44 (39).

2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)pyridin-3-yl acetate 70o

Similar treatment of 4,5-dichloro-1,2,3-dithiazolium chloride **42** (847.6 mg, 4.07 mmol) and 2-aminophenyl acetate (614.6 mg, 4.07 mmol) gave the *title compound* **70o** (420.5 mg, 36%) as yellow-green needles, mp 97-98 ^{o}C (from cyclohexane / EtOH); (found: C, 37.6; H, 2.2; N, 14.5 $C_9H_6ClN_3O_2S_2$ requires C, 37.6; H, 2.1; N, 14.6%); λ_{max}(DCM)/nm 247 (log ε 2.76), 253 inf (2.71), 296 (2.47), 372 inf (2.56), 391 (2.84), 410 (2.94), 424 (2.74); ν_{max}/cm^{-1} 1757s, 1568m, 1533s, 1489m, 1454m, 1428s, 1367m, 1280w, 1259m, 1199s, 1177s, 1171s, 1112s, 1043w, 1012w, 918w, 890s, 873s, 865w, 828m, 798m, 786m, 764m; δ_H(300 MHz; DMSO-d_6) 8.57 (1H, d, *J* 4.9, Ph *H*-4), 8.36 (1H, d, *J* 7.8, Ph *H*-6), 7.52-7.48 (1H, m Ph *H*-5), 2.38 (3H, s, CH_3); δ_C(75 MHz; DMSO-d_6) 168.9, 158.6, 148.5, 147.8, 142.4, 142.1 (Ph *C*H), 131.7 (Ph *C*H), 123.0 (Ph *C*H), 20.6 (*C*H_3); δ_C(75 MHz; DEPT-135, DMSO-d_6) 142.1 (Ph *C*H), 131.7 (Ph *C*H), 123.0 (Ph *C*H), 20.6 (*C*H_3); *m/z* (EI) 289 (M^++2, 9%), 287 (M^+, 14), 247 (22), 245 (50), 210 (9), 181 (5), 146 (100), 123 (8), 94 (13), 64 (17), 43 (50).

9.9 Experimental Procedures for Chapter 8

9.9.1 Cytotoxicity against Cancer Cells

Cytotoxicity studies were performed using the sulforhodamine B assay. Cytotoxicity of each drug was evaluated by the GI_{50} value, representing the 50% growth inhibition compared to non-treated control and a control at the time of drug addition (T_0). In brief, cells were seeded on 96-well plates (Nunc, Denmark) in 100 µL of culture medium (10.000, 10.000 and 5000 cells/well for MCF-7, SF268 and NCI-H460 respectively). Twenty-four hours later, 100 µL of medium containing 10 µM of desired compounds was added duplicate to the respective well. The plates were incubated for 48 h at 37 ^{o}C before fixing with 50% cold trichloroacetic acid for one hour after which the plates were washed five times with distilled water. The plates were then air-dried at room temperature. The fixed cells were stained with 100 µL of 0.4% (w/v) SRB in 1% acetic acid for 10 min. Excess SRB was removed by washing the plates four times with 1% acetic acid. After drying, 100 µL of 10 mM Tris base (pH 10.5) were added to solubilize the protein bound SRB and mixed. The absorbance was measured at 515 nm using a Versamax microtitre plate reader (Molecular Devices) and GI_{50} was calculated from 5 dosage responses using Softmax®Pro 3.0 software based on point to point plot (Table 50).

Percentage of net growth was calculated as below:

If $T_0 \geq T$, % of net growth = $[(T-T_0)/(C-T_0)]x100$

If $T_0 < T$, % of net growth = $[(T-T_0)/(T_0)]x100$

T is the optical density of the test well after 48 h drug exposure. T_0 is the optical density at time zero and C is the control optical density after 48 h.

Positive control: Paclitaxel (sigma Aldrich)

Negative control: Cells without drug addition

9.9.2 Fetax Toxicity Screen

Initially the FETAX solution was prepared which consists of 625 mg NaCl, 96 mg $NaHCO_3$, 30 mg KCl, 15 $CaCl_2$, 60 mg $CaSO_4.2H_2O$ and 75 mg $MgSO_4$ in distilled water with a pH of 7.5. Previously characterized compounds like $ZnSO_4$, Bio, ethanol and HDC inhibitors were diluted at several concentrations above and below the threshold of toxicity for each one. Before the experiment the jelly covering the embryos was removed, using 2% cysteine pH=8

diluted in FETAX solution. Embryos were then placed in 24 well plates and each well contained 10 embryos. During the procedure temperature and pH were maintained at 24 ± 2 ^{o}C and 6.5 – 9.0 respectively. Embryos were allowed to develop for 96 hours. During the protocol dead embryos were removed and registered and the solution was replaced. Moprhological abnormalities were identified and documented. The same was done for control embryos followed by the phenotypic documentation of abnormalities and quantification of toxicity using the teratogenic index (TI). This was the ratio of LC50 (concentration which produces lethality) and the EC50 (concentration which causes malformations). The embryos belonged to the same batch both control and test therefore the tail length measurement indicated growth delay if any. At the end of the experiment the TI and the resulting phenotypic abnormalities were registered. By the end of this WP we had establlished the FETAX assay and verified that the NR can implement it reproducibly and reliably to obtain data comparable to the existing ones for the control compounds.

Several concentrations in FETAX solution of the compounds were prepared. All compounds were diluted at the most active concentration based on prior biological activity testing and scored for solubility under the microscope. Compounds showing limited solubility were re-evaluated with the addition of DMSO in the FETAX solution at increasing concentrations and the solubility and DMSO concentration data was tabulated. DMSO safe concentration was set as used in cell cultures (0.5%). This DMSO concentration was tested and does not affect any of the three FETAX end points. Ethanol toxicity in FETAX solution was evaluated independently and results indicated that it should not be used as a dilution agent. After solubility conditions were established for all compounds the next step was the initial testing of all the compounds to determine their active concentration range using the existing biological activity concentration as a starting point. The preparation of 10 (ten) dilutions with a factor of 2.5 μM difference was done for each compound to ensure that the experimental error is minimal. Embryos were dejellied using 2% cysteine. 24 Well plates were used for each substance and each concentration was tested in duplicate. Controls were also done for each batch of embryos and these included FETAX solution and FETAX + DMSO since the entire compound library was diluted in DMSO. In addition at least one compound, for example $ZnSO_4$, with a previously characterized phenotype was used as a positive control in each experiment. Embryos were monitored and documented every 6 hours after the addition of each

compound and allowed to develop for 96 hours under constant temperature conditions. During this time dead embryos were removed, remaining embryos were washed with clean FETAX solution and the substance was replaced. At the end of this period embryos were scored using the three accepted endpoints lethality, malformation and growth rate. The Teratogenic index of each compound was also calculated using the ratio of LC50 (concentration which produces lethality) and the EC50 (concentration which induces malformations). A ratio between 1,5 and 2,0 qualifies a teratogenic substance. Finally all three end points (mortality, growth rate, malformations) were documented and used to determine overall toxicity for each compound. Compounds which did not affect any of the three end points at their respective active concentration (based on existing data from the activity evaluation for each compound) were considered non toxic.

APPENDIX

Crystallographic data

Introduction

This appendix records relevant data for all the new compounds in this thesis studies by single crystal X-ray diffraction.

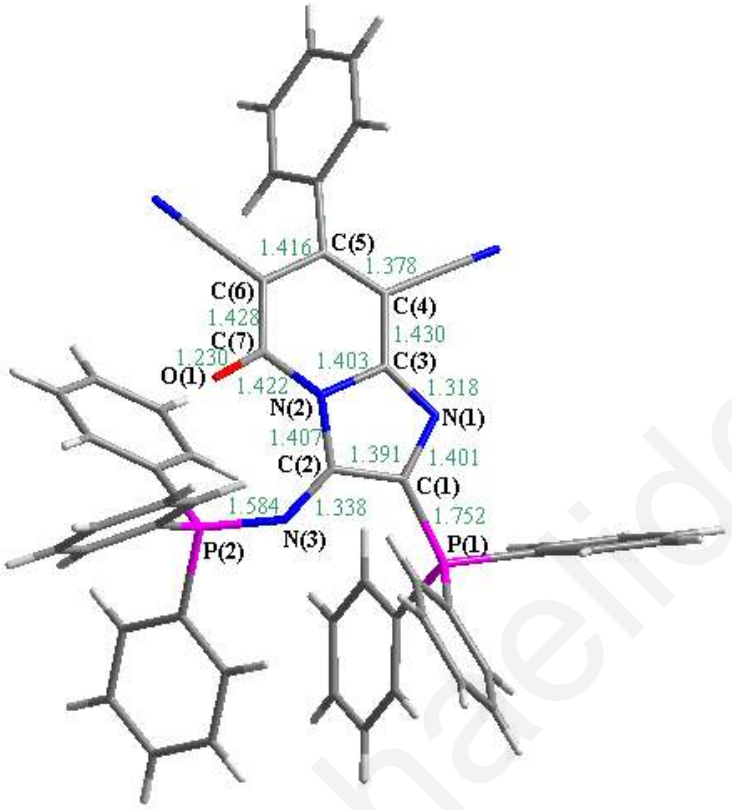


Figure 9 X-ray structure of 6-cyano-5-oxo-7-phenyl-2,5-bis(triphenylphosphino)imidazo [1,2-*a*]pyridin-4-ium-1-ide **214**.

Space Group: P 2_1/c

Cell Lengths (Å): a 11.7336(8), b 11.9335(9), c 16.2286(9)

Cell Angles(^{o}): a 88.155(5), b 70.552(6), c 75.258(6)

Cell Volume: 2068.7(2)

Cell Formula Units: Z 3, Z' 0

R factor (%): 8.63

Table 56. Bond lenghts of 6-cyano-5-oxo-7-phenyl-2,5-bis(triphenylphosphino)imidazo [1,2-**a**]pyridin-4-ium-1-ide **214** received from x-ray chrystallography.

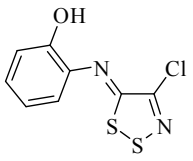
Atom 1	Atom 2	Length (Å)
P1	C1	1.752(2)
P1	N3	1.584(2)
O1	C7	1.231(3)
N1	C3	1.318(3)
N1	C1	1.401(3)
N2	C3	1.403(3)
N2	C2	1.407(3)
N2	C7	1.421(3)
N3	C2	1.338(3)
C1	C2	1.391(3)
C3	C4	1.430(3)
C4	C5	1.378(3)
C5	C6	1.416(3)
C6	C7	1.428(3)

Table 57. Bond angles of 6-cyano-5-oxo-7-phenyl-2,5-bis(triphenylphosphino)imidazo [1,2-*a*]pyridin-4-ium-1-ide **214** received from x-ray chrystallography.

Atom 1	Atom 2	Atom 3	Angle (°)
C3	N1	C1	104.5(2)
C3	N2	C2	106.9(2)
C3	N2	C7	123.5(2)
C2	N2	C7	129.3(2)
C2	N3	P2	133.2(2)
C2	C1	N1	112.3(2)
C2	C1	P1	123.8(2)
N1	C1	P1	123.3(2)
N3	C2	C1	126.9(2)
N3	C2	N2	129.2(2)
C1	C2	N2	103.8(2)
N1	C3	N2	112.4(2)
N1	C3	C4	129.4(2)
N2	C3	C4	117.9(2)
C5	C4	C3	119.8(2)
C4	C5	C6	119.8(2)
C5	C6	C7	123.0(2)
O1	C7	N2	119.6(2) .
O1	C7	C6	127.0(2)
N2	C7	C6	113.4(2)

LIST OF COMPOUNDS PREPARED

Compound number in bold followed by page number where compound appears in Chapter 9 (Experimental).



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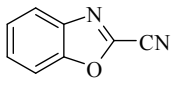

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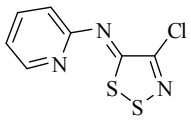

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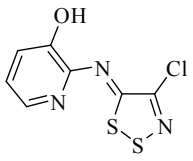

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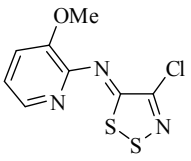

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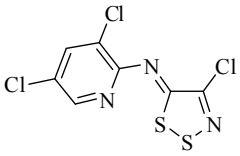

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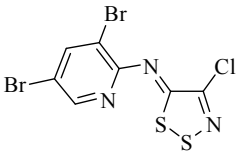

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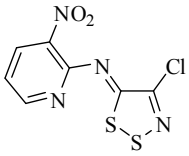

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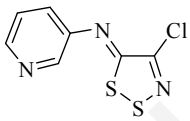

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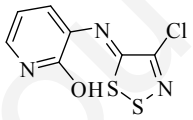

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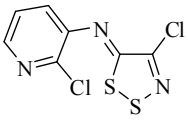

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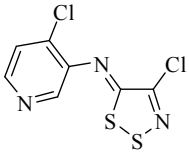

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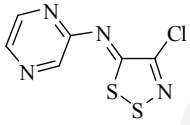

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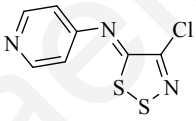

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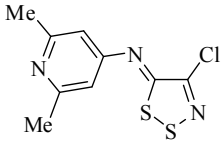

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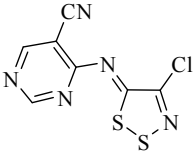

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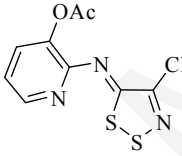

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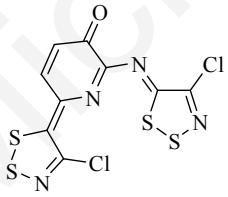

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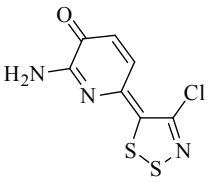

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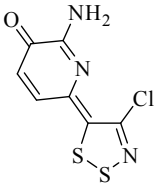

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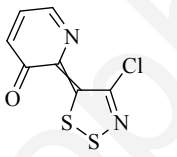

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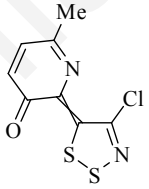

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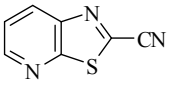

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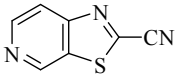

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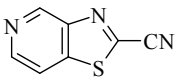

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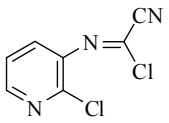

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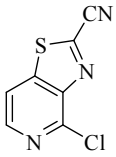

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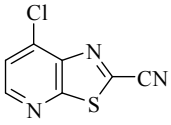

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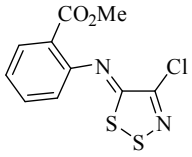

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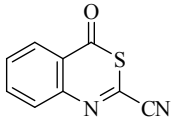

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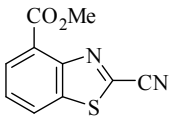

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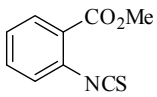

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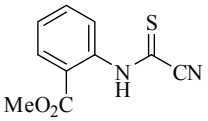

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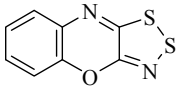

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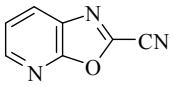

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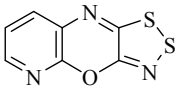

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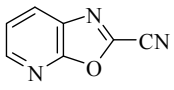

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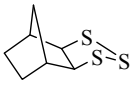

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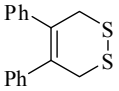

129
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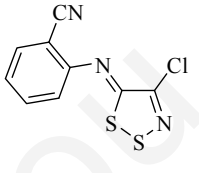

142a
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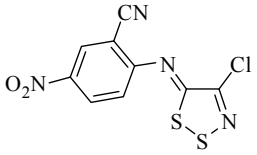

142b
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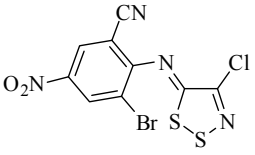

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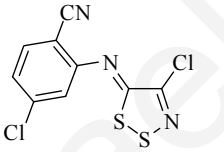

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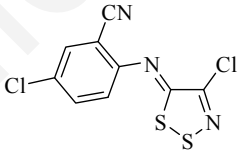

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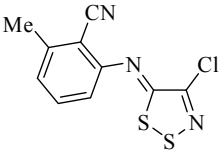

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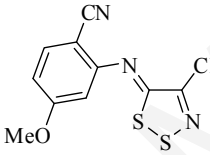

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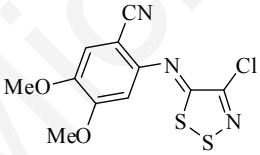

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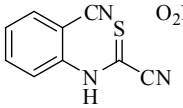

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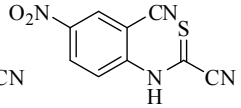

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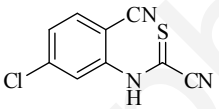

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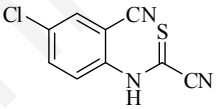

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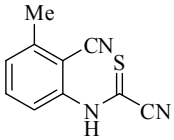

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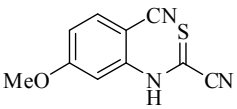

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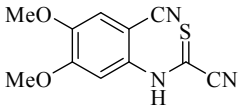

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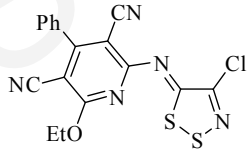

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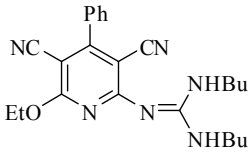

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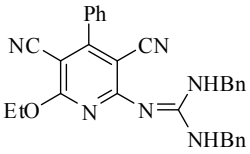

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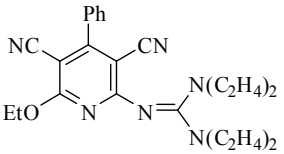

161f
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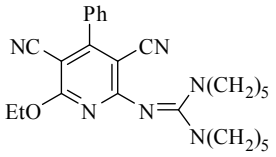

161g
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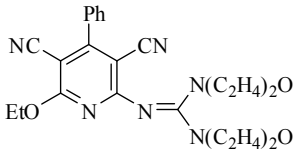

161h
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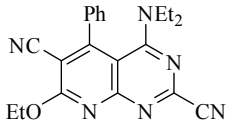

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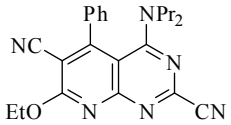

167d
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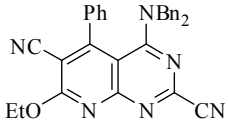

167e
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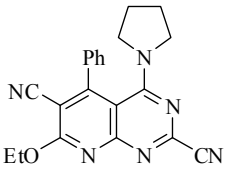

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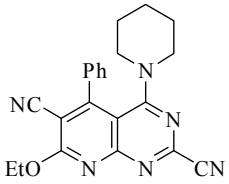

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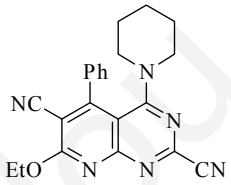

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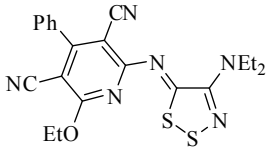

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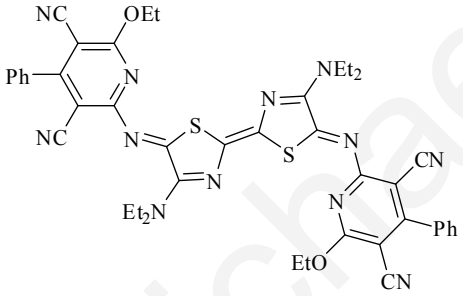

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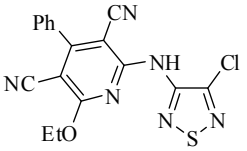

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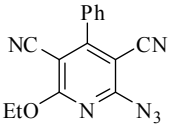

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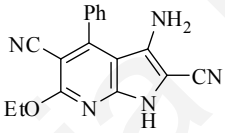

212
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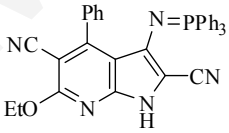

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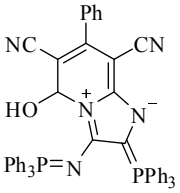

214
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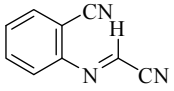

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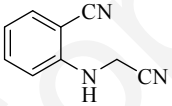

221a
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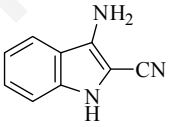

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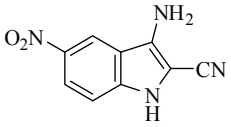

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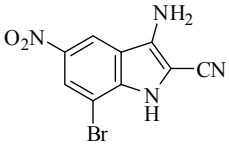

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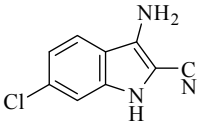

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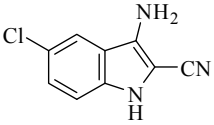

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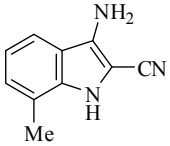

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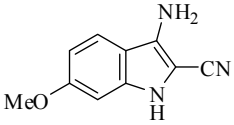

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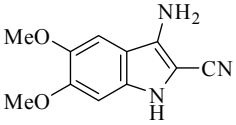

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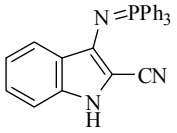

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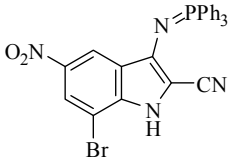

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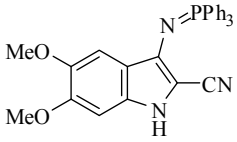

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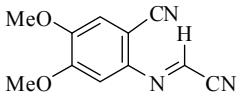

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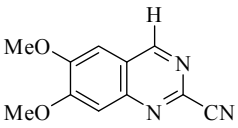

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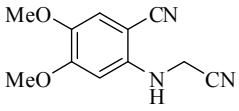

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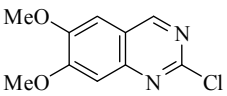

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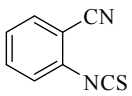

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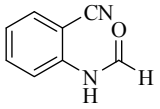

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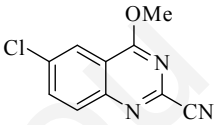

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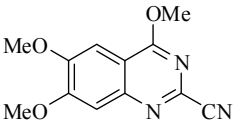

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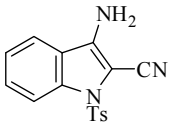

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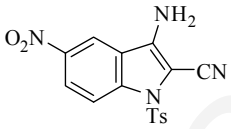

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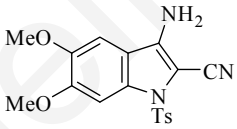

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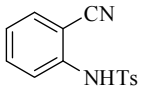

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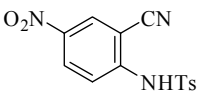

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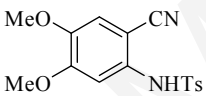

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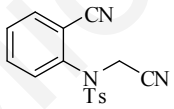

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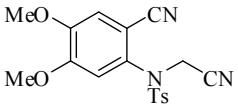

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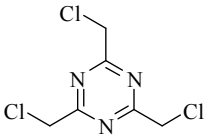

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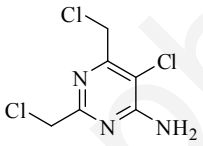

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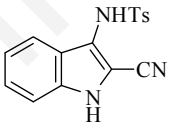

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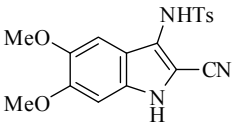

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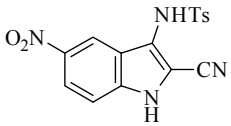

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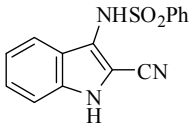

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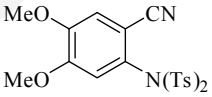

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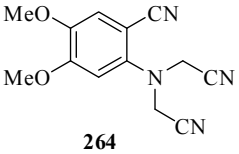

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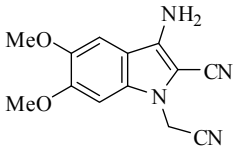

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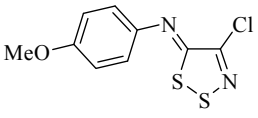

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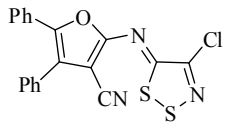

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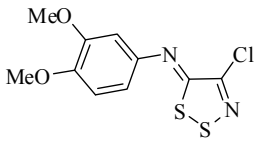

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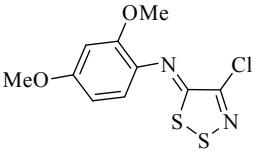

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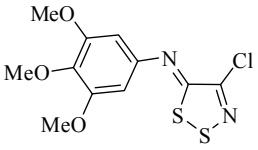

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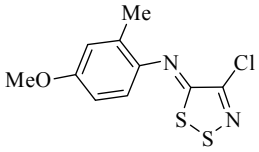

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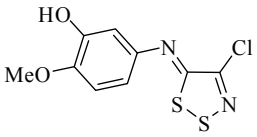

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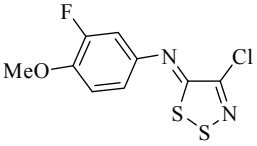

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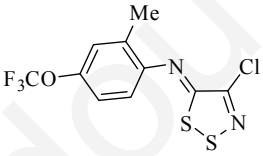

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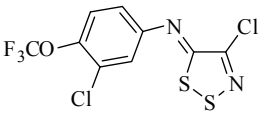

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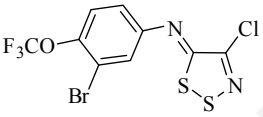

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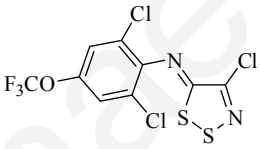

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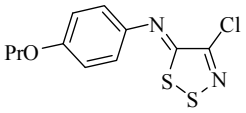

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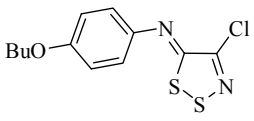

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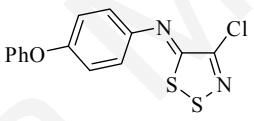

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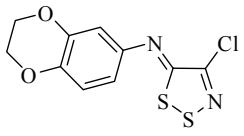

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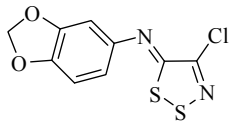

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REFERENCES

1. Sequin-Frey, M. *J. Chem. Ed.* **1960**, *58*, 301.
2. Nelson, J. M.; Chiller, T. M.; Powers, J. H.; Angulo, F. J. *Clin. Infect. Dis.* **2007**, *44*, 977.
3. Kawahara, S. *Nippon Rinsho* **1998**, *56*, 3096.
4. Dalal, N. B.; Shah, R. C. *Current Sci.* **1949**, *18*, 440.
5. Scheehan, J. C.; Kenneth, R. H.-L. *J. Am. Chem. Soc.* **1959**, *81*, 3089.
6. Worlock, A. *British Med. J.* **1956**, *5001*, 1099.
7. Dotevall, G.; Herner, B. *British Med. J.* **1957**, *5073*, 757.
8. Wudl, F.; Smith, G. M.; Hufnagel, E. J. *Chem. Commun.* **1970**, 1453.
9. Street, G. B.; Clarke, T. C. *IBM J. Res. Dev.* **1981**, *25*, 51.
10. Baysinger, G.; Berger, L. I.; Goldberg, R. N.; Kehiaian, H. V.; Kuchitsu, K.; Rosenblatt, G.; Roth, D. L.; Zwillinger, D. (eds. Lide, D. R.) CRC Handbook of Chemistry and Physics CRC Press, Boca Raton, FL, **2005**, 56.
11. Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104*, 2777.
12. Hegedus, L. S.; Perry, R. J. *J. Org. Chem.* **1985**, *50*, 4955.
13. Mackay, D.; Neeland, E. G.; Taylor, N. J. *J. Org. Chem.* **1986**, *51*, 2351.
14. Joule, J. A.; Mills, K. (Eds); Blackwell Publishing, Fourth Edition, *Heterocyclic Chemistry*, **1972**, 251.
15. Venkataraman, A.; Kalyani, A. *J. Org. Chem.* **1995**, *60*, 301.
16. Bagley, M. C. *Synthesis* **2007**, 2459.
17. Bagley, M. C.; Dale, J. W.; Bower, J. *Synlett* **2001**, 1149.
18. Bakulev, V. A.; Mokrushin, V. S.; Pushkareva, Z. V. *Chem. Heterocycl. Comp.* **1982**, *18*, 539.
19. Corriu, R. J. P.; Huynh, V.; Moreau, J. J. E.; Pataud-Sat, M. *Tetrahedron Lett.* **1982**, *23*, 3257.
20. Bambury, R. E.; Miller, L. F. *J. Heterocycl. Chem.* **1970**, *7*, 269.
21. Kharchenko, V. G.; Markova, L. I.; Fedotova, O. V.; Pchelintseva, N. V. *Chem. Heterocycl. Comp.* **2003**, *39*, 1121.
22. Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* **1986**, *108*, 6402.
23. Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* **1986**, *51*, 4085.

24. Huisgen, R.; Langhals, E.; Noth, H. *Tetrahedron Lett.* **1986**, *27*, 5475.
25. Lukyanenko, N. G.; Kirichenko, T. I.; Limich, V. V. *Synthesis* **1986**, 928.
26. Van der Plas, H. C. *Heterocycles* **1978**, *9*, 33.
27. Eicher, T.; Hauptmann, S.; Speicher, A. (Eds); Wiley-VCH GmbH & Co. KGaA. Second Edition, *The Chemistry of Heterocycles*, *Structure*, *Reactions*, *Synthesis and Applications*, **2003**, 1.
28. Van der Plas, H. C.; Jongejan, H. *Tetrahedron Lett.* **1967**, *8*, 4385.
29. Sharp, J. T.; Katritzky, A. R.; Rees, C. W. Lwowski, W. (Eds); Pergamon Press: New York, Oxford, *Comprehensive Heterocyclic Chemistry*, **1984**, *7*, 617.
30. Ciamician, G. L.; Dennstedt, M. *Chem. Ber.* **1881**, *14*, 1153.
31. Skell, P. S.; Sandler, R. S. *J. Am. Chem. Soc.* **1958**, *80*, 2024.
32. Padwa, A.; Ku, H.; Mazzu, A. *J. Org. Chem.* **1978**, *43*, 381.
33. Isomura, K.; Okada, M.; Taniguchi, H. *Chem. Lett.* **1972**, 629.
34. Padwa, A.; Smolanoff, J.; Tremper, A. *J. Am. Chem. Soc.* **1975**, 4682.
35. Van der Plas, H. C. *Tetrahedron* **1985**, *41*, 237.
36. Van der Plas, H. C. *Acc. Chem. Res.* **1978**, 462.
37. Van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, *74*, 9.
38. Van der Plas, H. C. *J. Heterocycl. Chem.* **2000**, *37*, 427.
39. Li, J. J. Chemistry and Material Sciences, *Name Reactions: A Collection of Detailed Mechanisms and Synthetic Applications*, Springer, **2009**, 73.
40. Boulton, A. J.; Katritzky, A. R.; Hamid, A. M. *J. Chem. Soc.* **1967**, 2005.
41. Rusinov, V. L.; Chupakhin, O. N.; Van der Plas, H. C. *Heterocycles* **1995**, *40*, 442.
42. Appel, R.; Janssen, H.; Siray, M.; Knoch, F. *Chem. Ber.* **1985**, *118*, 1632.
43. Corsaro, A.; Compagnihi, A.; Chiacchio, U.; Purrello, G. *Synthesis* **1984**, 515.
44. Gray, M. A.; Rees, C. W. *J. Chem. Soc.*, *Perkin Trans. 1* **1993**, 3077.
45. Wai, K. F.; Sammes, M. P. *J. Chem. Soc.*, *Perkin Trans. 1* **1992**, 2065.
46. Moore, J. E. U.S. Patent 4,059,590, 1977.
47. Appel, R.; Heinz, J.; Ingo, H.; Manfred, P. D.E. Patent 2,848,221, 1980.
48. Besson, T.; Rees, C. W.; Cottenceau, G.; Pons, A.-M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2343.
49. Cottenceau, G.; Besson, T.; Gautier, V.; Rees, C. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 529.

50. Thiéry, V.; Rees, C. W.; Besson, T.; Cottenceau, G.; Pons, A.-M. *Eur. J. Med. Chem.* **1998**, *33*, 149.
51. Mayer, R.; Eckhart, F.; Brigitte, M. DD 212387, 1984.
52. Beer, L.; Britten, J. F.; Clements, O. P.; Haddon, R. C.; Itkis, M. E.; Matkovich, K. M.; Oakley, R. T.; Reed, R. W. *Chem. Mater.* **2004**, *16*, 1564.
53. Beer, L.; Brusso, J. L.; Cordes, A. W.; Godde, E.; Haddon, R. C.; Itkis, M. E.; Oakley, R. T.; Reed, R. W. *Chem. Commun.* **2002**, 2562.
54. Beer, L.; Britten, J. F.; Brusso, J. L.; Cordes, A. W.; Haddon, R. C.; Itkis, M. E.; MacGregor, D. S.; Oakley, R. T.; Reed, R. W.; Robertson, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 14394.
55. Beer, L.; Cordes, A. W.; Haddon, R. C.; Itkis, M. E.; Oakley, R. T.; Reed, R. W.; Robertson, C. M. *Chem. Commun.* **2002**, 1872.
56. Barclay, T. M.; Cordes, A. W.; Burgess, I. J.; Oakley, R. T.; Reed, R. W. *Chem. Commun.* **1998**, 1939.
57. Barclay, T. M.; Beer, L.; Cordes, A. W.; Oakley, R. T.; Preuss, K. E.; Taylor, N. J.; Reed, R. W. *Chem. Commun.* **1999**, 531.
58. Barclay, T. M.; Cordes, A. W.; Oakley, R. T.; Preuss, K. E.; Reed, R. W. *Chem. Commun.* **1998**, 1039.
59. Barclay, T. M.; Cordes, A. W.; Oakley, R. T.; Preuss, K. E.; Reed, R. W. *Chem. Mater.* **1999**, *11*, 164.
60. Barclay, T. M.; Cordes, A. W.; Haddon, R. C.; Itkis, M. E.; Oakley, R. T.; Reed, R. W.; Zhang, H. *J. Am. Chem. Soc.* **1999**, *121*, 969.
61. Warburton, W. K. *Chem. Rev.* **1957**, *57*, 1011.
62. Mayer, R. *Phosphorus*, *Sulfur*, *Silicon Relat. Elem.* **1985**, *23*, 277.
63. Koutentis, P. A. *Molecules* **2005**, *10*, 346.
64. Gray, M. A.; Rees, C. W.; Williams, D. J. *Heterocycles* **1994**, *37*, 1827.
65. Kim, K. *J. Sulfur Chem. (Sulfur Rep.)* **1998**, *21*, 147.
66. Emayan, K.; Rees, C. W. *Bull. Soc. Chim. Belg.* **1997**, *106*, 605.
67. Konstandinova, L. S.; Bol'shakov, O. A.; Obruchnikova, N. V.; Laborie, H.; Tanga, A.; Sopéna, V.; Lanneluc, I.; Picot, L.; Sablé, S.; Thiery, V.; Rakitin, O. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 136.

68. Popov, V. V.; Bol'shakov, O. A.; Konstandinova, L. S.; Rakitin, O. A. *Russ. Chem. Bull.* **2009**, *58*, 437.
69. Markovskii, L. N.; Dubinina, T. N.; Barashenkov, G. C.; Romanenko, E. A.; Shermolovich, Y. G. *Zh. Org. Khim.* **1993**, *29*, 491.
70. Rees, C. W. *J. Heterocycl. Chem.* **1992**, *29*, 639.
71. Emayan, K.; English, R. F.; Koutentis, P. A.; Rees, C. W. *J. Chem. Soc.*, *Perkin Trans. 1* **1997**, 3345.
72. Barclay, T. M.; Beer, L.; Cordes, A. W.; Haddon, R. C.; Itkis, M. E.; Oakley, R. T.; Preuss, K. E.; Reed, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6657.
73. Yarovenko, V. N.; Es'kov, A. A.; Zatonsky, G. V.; Zavarzin, I. V.; Krayushkin, M. M.; Averkiev, B. B.; Antipin, M. Y. *J. Heterocycl. Chem.* **2004**, *41*, 37.
74. Barclay, T. M.; Beer, L.; Cordes, A. W.; Oakley, R. T.; Preuss, K. E.; Reed, R. W.; Taylor, N. J. *Inorg. Chem.* **2001**, *40*, 2709.
75. English, R. F.; Rakitin, O. A.; Rees, C. W.; Vlasova, O. G. *J. Chem. Soc.*, *Perkin Trans. 1* **1997**, 201.
76. Thiéry, V.; Bénéteau, V.; Guillard, J.; Lamazzi, C.; Besson, T.; Cottenceau, G.; Pons, A.-M. *Pharm*. *Pharmacol. Commun.* **1998**, *4*, 39.
77. Yarovenko, V. N.; Es'kov, A. A.; Kondrashev, P. A.; Ignatenko, A. V.; Zavarzin, I. V.; Vorontsova, L. G.; Sedishev, I. P.; Krayushkin, M. M.; Starikova, Z. A. *Heterocycles* **2005**, *65*, 1601.
78. Appel, R., Janssen, H., Haller, I., Plempel, M. DE 2,848,221, 1978.
79. Kalogirou, A. S.; Koutentis, P. A. *Tetrahedron* **2009**, *65*, 6855.
80. Kalogirou, A. S.; Koutentis, P. A. *Tetrahedron* **2009**, *65*, 6859.
81. Folmer, J. J.; Weinreb, S. M. *Tetrahedron Lett.* **1993**, *34*, 2737.
82. Huber, K. P.; Herzberg, G. (Eds); Van Nostrand, New York. *Molecular Spectra and Molecular Structure Constants of Diatomic Molecules*, **1979**.
83. Kondratiev, V. N. (Eds); Mauka Publishing House; Moscow *Bond Dissociation Energies*, *Ionization Potentials and Electron Affinities*, **1974**.
84. Besson, T.; Emayan, K.; Rees, C. W. *J. Chem. Soc.*, *Perkin Trans. 1* **1995**, 2097.
85. Christoforou, I. C.; Koutentis, P. A.; Michaelidou, S. S. *Arkivoc* **2006**, *7*, 207.
86. Rakitin, O. A.; Rees, C. W.; Vlasova, O. G. *Chem. Commun.* **1996**, 1273.
87. Clarke, D.; Emayan, K.; Rees, C. W. *J. Chem. Soc.*, *Perkin Trans. 1* **1998**, 77.

88. Christoforou, I. C.; Koutentis, P. A. *J. Chem. Soc.*, *Perkin Trans. 1* **2002**, 1236.
89. Besson, T.; Dozias, M.-J.; Guillard, J.; Jacquault, P.; Legoy, M.-D.; Rees, C. W. *Tetrahedron* **1998**, *54*, 6475.
90. Christoforou, I. C.; Kalogirou, A. S.; Koutentis, P. A. *Tetrahedron* **2009**, *65*, 9967.
91. Lee, H.; Kim, K.; Whang, D.; Kim, K. *J. Org. Chem.* **1994**, *59*, 6179.
92. Jeon, M.–K.; Kim, K.; Park, Y. J. *J. Chem. Soc.*, *Chem. Commun*. **2001**, 1412.
93. Baraldi, P. G.; Pavani, M. G.; Nuñez, M del C.; Brigidi, P.; Vitali, B.; Gambari, R.; Romagnoli, R. *Bioorg. Med. Chem*. **2002**, *10*, 449.
94. Besson, T.; Dozias, M. J.; Guillard, J.; Rees, C. W. *J. Chem. Soc.*, *Perkin Trans. 1* **1998**, 3925.
95. Rakitin, O. A.; Rees, C. W.; Vlasova, O. G. *Tetrahedron Lett*. **1996**, *37*, 4589.
96. Besson, T.; Guillaumet, G.; Lamazzi, C.; Rees, C. W. *Synlett* **1997**, 704.
97. Besson, T.; Gerald, G.; Lamazzi, C.; Rees, C. W.; Thiéry, V. *J. Chem. Soc*., *Perkin Trans. 1* **1998**, 4057.
98. Besson, T.; Rees, C. W. *J. Chem. Soc*., *Perkin Trans. 1* **1996**, 2857.
99. Yamazaki, D.; Ito, M.; Gomibuchi, T.; Shibuya, K.; Shimojo, E.; Emoto, A.; Yamazaki, D.; Ito, M.; Gomibuchi, T.; Shibuya, K.; Shimojo, E.; Emoto, A. WO 131680 A1, **2007**.
100. Besson, T.; Guillard, J.; Rees, C. W. *J. Chem. Soc.*, *Perkin Trans. 1* **2000**, 563.
101. Alexandre, F. R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron Lett*. **2003**, *44*, 4455.
102. Lee, H.; Kim, K. *J. Org. Chem*. **1993**, *58*, 7001.
103. Frere, S.; Thiery, V.; Besson, T. *Synth. Commun*. **2003**, *33*, 3795.
104. Frère, S.; Thiéry, V.; Bailly, C.; Besson, T. *Tetrahedron* **2003**, *59*, 773.
105. Besson, T.; Rees, C. W. *J. Chem. Soc.*, *Perkin Trans. 1* **1995**, 1659.
106. Chang, Y.-G.; Kim, K. *Heterocycles* **1999**, *51*, 2653.
107. Lee, H. S.; Chang, Y. G.; Kim, K. *J. Heterocycl. Chem*. **1998**, *35*, 659.
108. Besson, T.; Guillard, J.; Rees, C. W.; Thiéry, V. *J. Chem. Soc.*, *Perkin Trans. 1* **1998**, 889.
109. Besson, T.; Guillard, J.; Rees, C. W.; Therisod, M. *J. Chem. Soc.*, *Chem. Commun*. **1997**, 881.
110. Lee, H.; Kim, K. *Bull. Korean Chem. Soc*. **1992**, *13*, 107.

111. Mohanta, P. K.; Kim, K. *Tetrahedron Lett*. **2002**, *43*, 3993.
112. Pereira, M.-F.; Thiery, V.; Besson, T. *Tetrahedron* **2007**, *63*, 847.
113. Lee, H.-S.; Kim, K. *Tetrahedron Lett*. **1996**, *37*, 869.
114. Besson, T.; Emayan, K.; Rees, C. W. *J. Chem. Soc.*, *Chem. Commun*. **1995**, 1419.
115. Le, V.-D.; Rees, C. W.; Sivadasan, S. *Tetrahedron Lett*. **2000**, *41*, 9407.
116. Le, V.-D.; Rees, C. W.; Sivadasan, S. *J. Chem. Soc.*, *Perkin Trans. 1* **2002**, 1543.
117. Konstandinova, L. S.; Rakitin, O. A.; Rees, C. W.; Sivadasan, S.; Torrobas, T. *Tetrahedron* **1998**, *54*, 9639.
118. Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591.
119. Hermann, K.; Simchen, G. *Liebigs Ann. Chem*. **1981**, *1981*, 333.
120. Fujii, M.; Ozaki, K.; Sekine, M.; Hata, T. *Tetrahedron* **1987**, *43*, 3395.
121. Reed, R.; Reau, R.; Dahan, F.; Bertrand, G. *Angew. Chem. Int. Ed*. **1993**, *32*, 399.
122. Lesnikowski, Z. J.; Zabawska, D.; Jaworska-Maslanka, M. M.; Schinazi, R. F.; Stec, W. J. *New J. Chem*. **1994**, *18*, 1197.
123. Dyer, P.; Guerret, O.; Dahan, F.; Baceiredo, A.; Bertrand, G. *J. Chem. Soc.*, *Chem. Commun*. **1995**, 2339.
124. Bouhadir, G.; Reed, R. W.; Reau, R.; Bertrand, G. *Heteroat. Chem*. **1995**, *6*, 371.
125. Karsch, H. H.; Rupprich, T.; Heckle, M. *Chem. Ber*. **1995**, *128*, 959.
126. Merckling, F. A.; Rüedi, P. *Tetrahedron Lett*. **1996**, *37*, 2217.
127. Kers, A.; Stawiński, J.; Dembkowski, L.; Kraszewski, A. *Tetrahedron* **1997**, *53*, 12691.
128. Kers, A.; Kers, I.; Bollmark, M.; Stawinski, J. *Acta Chem. Scand*. **1998**, *52*, 1405.
129. Kers, A.; Kers, I.; Stawinski, J. *J. Chem. Soc.*, *Perkin Trans. 2* **1999**, 2071.
130. Blättner, M.; Nieger, M.; Ruban, A.; Schoeller, W. W.; Niecke, E. *Angew. Chem. Int. Ed*. **2000**, *39*, 2768.
131. Ionkin, A. S.; Marshall, W. J. *Heteroat. Chem*. **2003**, *14*, 197.
132. Dąbkowski, W.; Tworowska, I.; Kazimierczak, Ł.; Michalski, J. *Pol. J. Chem*. **2005**, *79*, 467.
133. Richter, R. *Chem. Ber*. **1968**, *101*, 3002.
134. House, H. O.; DeTar, M. B.; VanDerveer, D. *J. Org. Chem*. **1979**, *44*, 3793.
135. McCoy, L. L.; Mal, D. *J. Org. Chem*. **1981**, *46*, 1016.
136. Alder, R. W.; Sessions, R. B. *Tetrahedron Lett*. **1982**, *23*, 1121.

137. Juneja, T. R.; Garg, D. K.; Schäfer, W. *Tetrahedron* **1982**, *38*, 551.
138. Forlani, L.; Sintoni, M.; Todesco, P. E. *J. Chem. Res. (S)* **1986**, 344.
139. Collina, G.; Forlani, L. *J. Phys. Org. Chem*. **1988**, *1*, 351.
140. Forlani, L.; Cimarelli, C. *J. Phys. Org. Chem*. **1989**, *2*, 653.
141. Reid, J. G.; Runge, J. M. R. *Tetrahedron Lett*. **1990**, *31*, 1093.
142. Reisch, J.; Iding, M.; von Bassewitz, I. *Monatsh. Chem*. **1993**, *124*, 1225.
143. Schenk, W. A.; Urban, P.; Dombrowski, E. *Chem. Ber*. **1993**, *126*, 679.
144. Chambers, R. D.; Roche, A. J.; Batsanov, A. S.; Howard, J. A. K. *J. Chem. Soc.*, *Chem. Commun*. **1994**, 2055.
145. Lammers, H.; Cohen-Fernandes, P.; Habraken, C. L. *Tetrahedron* **1994**, *50*, 865.
146. Ma, L.; Dolphin, D. *Tetrahedron* **1996**, *52*, 849.
147. Johnson, M. G.; Foglesong, R. J. *Tetrahedron Lett*. **1997**, *38*, 7003.
148. Lönnqvist, J.-E. S.; Jalander, L. F. *J. Chem. Res. (M)* **1999**, 0430.
149. Stewart, R.; Harris, M. G. *J. Org. Chem*. **1978**, *43*, 3123.
150. L'abbe, G.; D'hooge, B.; Dehaen, W. *J. Chem. Soc.*, *Perkin Trans. 1* **1995**, 2379.
151. L'abbe, G.; Bastin, L.; Dehaen, W.; Toppet, S.; Delbeke, P.; Vlieghe, D.; Van Meerveek, L. *J. Chem. Soc.*, *Perkin Trans. 1* **1994**, 2545.
152. Konstandinova, L. S.; Rakitin, O. A. *Russ. Chem. Rev*. **2008**, *77*, 521.
153. Cuadro, A. M.; Alvarez-Builla, J. *Tetrahedron* **1994**, *50*, 10037.
154. Pretsch E., Clerc J. T.; Seibl J.; Simon W.; Biemann K. "*Tables of Spectral Data for Structure Determination of Organic Compounds*" 2nd ed., Springer Verlag **1998**.
155. Jeon, M.-K.; Kim, K. *Tetrahedron* **1999**, *55*, 9651.
156. Bayer, C. A. WO 131680 A1, 2007.
157. Beneteau, V.; Besson, T.; Rees, C. W. *Synth. Commun*. **1997**, *27*, 2275.
158. Beneteau, V.; Besson, T.; Guillard, J.; Leonce, S.; Pfeiffer, B. *Eur. J. Med. Chem*. **1999**, *34*, 1053.
159. Akihama S., Okhude M., Mizno A. *Meiji Yakka Diagakn Kenkyu Kiyo* **1966**, 1; Chem. Abstr., **1968**, *68*, 10369v.
160. Russo, F.; Santagati, M. *Farm. Ed. Science* **1976**, *31*, 41.
161. Ghoneim, K. M.; Basil, S. E.; Osman, A. N.; Said, M. M.; Megahed, S. A. *Rev. Roum. Chim*. **1991**, *36*, 1355.
162. Singh, S. P.; Seghal, S. *Indian J. Chem*. **1988**, *27*, 941.

163. Musser, J. H.; Brown, R. E.; Love, B.; Baily, K.; Jones, H.; Kahen, R.; Huang, F.; Khandwala, A.; Leibowitz, M. *J. Med. Chem*. **1984**, *27*, 121.

164. Pattan, S. R.; Suresh, C.; Pujar, V. D.; Reddy, V. V. K.; Rasal, V. P.; Kotti, B. C. *Indian J. Chem*. **2005**, *4B*, 2404.

165. Yoshida, M.; Hayakawa, I.; Hyashi, N.; Agatsuma, T.; Oda, Y.; Tanzawa, F.; Iwasaki, S.; Koyama, K.; Furukawa, H.; Kurakata, S.; Sugano, Y. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 3328.

166. Sawhney, S. N.; Bansal, O. P. *Indian J. Chem*. **1977**, *15B*, 121.

167. Brown, H. D. U.S. Patent 3,262,872, 1966.

168. Chaudhary, P.; Sharma, P. K.; Sharma, A.; Varshney, J. *Int. J. Current Pharm. Res*. **2010**, *2*, 5.

169. Heal, C. W.; Chen, B., Heal, C. W.; Chen, B. (eds. in Chief: Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K.). In Comprehensive Heterocyclic Chemistry III; Heal, C. W.; Chen, B., Eds.; Elsevier: Oxford, 2008, Vol. 3, (Chapter 4.06), p 635.

170. White, E. H.; McCapra, F.; Field, G. F. *J. Am. Chem. Soc*. **1963**, *85*, 337.

171. Baudet, P.; Otten, C. *Helv. Chim. Acta*. **1970**, *53*, 1683.

172. Kristinsson, H. *Synthesis* **1979**, 102.

173. White, E. H.; Woerther, H. *J. Org. Chem*. **1966**, *31*, 1484.

174. Koutentis, P. A.; Rees, C. W. *J. Chem. Soc*., *Perkin Trans. 1* **2002**, *3*, 315.

175. Ohmoto, K.; Hisaichi, K.; Okuma, M.; Tanaka, M.; Kawada, N. EP 1,724,264 A1, 2006.

176. Chi, B. V.; Milne, J. C.; Carney, D. P.; Song, J.; Choy, W.; Lambert, P. D.; Gagne, D. J.; Hirsch, M.; Cote, A.; Davis, M.; Lainez, E.; Meade, N.; Normington, K.; Jirousek, M. R.; Perni, R. B. *Bioorg. Med. Chem*. *Lett*. **2009**, *19*, 1416.

177. Vu, C. B. WO 14674, 2009.

178. Vu, C. B. WO 100423 A1, 2008.

179. Guillard, J.; Besson, T. *Tetrahedron* **1999**, *55*, 5139.

180. Logé, C.; Testard, A.; Thiéry, V.; Lozach, O.; Blairvacq, M.; Robert, J.–M.; Meijer, L.; Besson, T. *Eur. J. Med. Chem*. **2008**, *43*, 1469.

181. Testard, A.; Logé, C.; Léger, B.; Robert, J.–M.; Lozach, O.; Blairvacq, M.; Meijer, L.; Thiéry, V.; Besson, T. *Bioorg. Med. Chem*. **2006**, *16*, 3419.

182. Beauchard, A.; Chabane, H.; Sinbandhit, S.; Gulnot, P.; Thiery, V.; Besson, T. *Tetrahedron* **2006**, *62*, 1895.

183. Komoriya, S.; Kobayashi, S.; Osanai, K.; Yoshino, T.; Nagata, T.; Haginoya, N.; Nakamoto, Y.; Mochizuki, A.; Nagahara, T.; Suzuki, M.; Shimada, T.; Watanabe, K.; Isobe, Y.; Furugoori, T. *Bioorg. Med. Chem*. **2006**, *14*, 1309.

184. Pitts, W. J.; Belema, M.; Gill, P.; Kempson, J.; Qiu, Y.; Quesnelle, C.; Spergel, S. H. U.S. Patent 106293 A2, 2004.

185. Tagat, J. R.; Guzi, T. J.; Labroli, M.; Poker, C.; Xiao, Y.; Kerekes, A. D.; Yu, T.; Paliwal, S.; Tsui, H.-C.; Shih, N.-Y.; McCombie, S. W.; Madison, V. S.; Lesburg, C. A.; Duca, J. S. U.S. Patent 98961 A2, 2006.

186. Altland, H. W.; Molander, G. A. *J. Heterocycl. Chem*. **1977**, *14*, 129.

187. Gauyral, P.; Bourdais, J.; Lorre, A.; Abenhaim, D. *Eur. J. Med. Chem*. **1978**, *13*, 171.

188. Bourdais, J.; Abenhaim, D.; Sabourault, B.; Lorre, A. *J. Heterocycl. Chem*. **1975**, *13*, 491.

189. Dunbrook, R. F.; Zimmermann, M. H. *J. Am. Chem. Soc*. **1934**, *56*, 2734.

190. Haginoya, N.; Komoriya, S.; Osanai, K.; Yoshino, T.; Nagata, T.; Nagamochi, M.; Muto, R.; Yamaguchi, M.; Nagahara, T.; Kanno, H. *Heterocycles* **2004**, *63*, 1555.

191. Chankeshwava, S. V.; Chakraborti, A. K. *Tetrahedron Lett*. **2006**, *46*, 1087.

192. Kempson, J.; Spergel, S. H.; Guo, J.; Quesnelle, C.; Gill, P.; Belanger, D.; Dyckman, A. J.; Li, T.; Watterson, S. H.; Langevine, C. M.; Das, J.; Moquin, R. V.; Furch, J. A.; Marinier, A.; Dodier, M.; Martel, A.; Nirschl, D.; Kirk, K. V.; Burke, J. R.; Pattoli, M. A.; Gillooly, K.; Mclntyre, K. W.; Chen, L.; Yang, Z.; Marathe, P. H.; Wang-Iverson, D.; Dodd, J. H.; McKinnon, M.; Barrish, J. C.; Pitts, W. J. *J. Med. Chem*. **2009**, *52*, 1994.

193. Kempson, J.; Guo, J.; Das, J.; Moquin, R. V.; Spergel, S. H.; Watterson, S. H.; Langevine, C. M.; Dyckman, A. J.; Pattoli, M.; Burke, J. R.; Yang, X. X.; Gillooly, K. M.; McIntyre, K. W.; Chen, L.; Dodd, J. H.; McKinnon, M.; Barrish, J. C.; Pitts, W. J. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 2646.

194. Parlati, F.; Ramesh, U. V.; Singh, R.; Payan, D. G.; Lowe, R.; Look, G. C. WO 37845 A1, 2005.

195. Loza-Mejía, M. A.; Olvera-Vázquez, S.; Maldonado-Hernández, K.; Guadarrama-Salgado, T.; González-Sánchez, I.; Rodríguez-Hernández, F.; Solano, J. D.; Rodríguez-Sotres, R.; Lira-Rocha, A. *Bioorg. Med. Chem*. **2009**, *17*, 3266.

196. Mylari, B. L.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Singleton, D. H. *J. Med. Chem*. **1991**, *34*, 108.

197. Uchikawa, O.; Fukatsu, K.; Suno, M.; Aono, T.; Doi, T. *Chem. Pharm. Bull*. **1996**, *44*, 2070.

198. Das, J.; Chen, P.; Norris, D.; Padmanabha, R.; Lin, J.; Moquin, R. V.; Shen, Z.; Cook, L. S.; Doweyko, A. M.; Pitt, S.; Pang, S.; Shen, D. R.; Fang, Q.; de Fex, H. F.; McIntyre, K. W.; Shuster, D. J.; Gillooly, K. M.; Behnia, K.; Schieven, G. L.; Wityak, J.; Barrish, J. C. *J. Med. Chem*. **2006**, *49*, 6819.

199. Das, J.; Lin, J.; Moquin, R. V.; Shen, Z.; Spergel, S. H.; Wityak, J.; Doweyko, A. M.; DeFex, H. F.; Fang, Q.; Pang, S.; Pitt, S.; Shen, D. R.; Schieven, G. L.; Barrish, J. C. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 2145.

200. Bacani, G. M.; Broggini, D.; Cheung, E. Y.; chrovian, C. C.; Deng, X.; Gomez, L.; Grice, C. A.; Kearney, A. M.; Landry-Bayle, A. M.; Lee-Dutra, A.; Liang, J. T.; Lochner, S.; Mani, N. S.; Santillán, A. Jr.; Sappey, K.; Sepassi, K.; Tanis, V. M.; Wickboldt, A. T.; wiener, J. J. M.; Zinser, H. U.S. Patent 7,939,527 A1, 2009.

201. Wang, T.; Aronov, A.; Cornebise, M.; Maltais, F.; Ledoboer, M.; Le, T. A.; Marone, V.; Messersmith, D.; Cottrell, K. WO 129211 A1, 2009.

202. Kanda, Y.; Sato, H.; Yamada, T.; Kato, A.; Satoh, M. WO 18847 A2, 2010.

203. Pappne, B. A.; Batori, S.; Bartane, B. V.; Szlavik, Z.; Bata, I.; U. S. K.; Kapui, Z.; Mikus, E. WO 13078 A2, 2010.

204. Swinnen, D.; Jorand-Lebrun, C.; Grippi-Vallotton, T.; Gerber, P.; Gonzalez, J.; Shaw, J.; Jeyaprakashnarayanan, S. WO 100144 A1, 2010.

205. Borthwick, A. D.; Davies, D. E.; Ertl, P. F.; Exall, A. M.; Haley, T. M.; Hart, G. J.; Jackson, D. L.; Parry, N. R.; Patikis, A.; Trivedi, N.; Weingarten, G. G.; Woolven, J. M. *J. Med. Chem*. **2003**, *46*, 4428.

206. Barlin, G. B.; Ireland, S. J.; Rowland, B. J. *Aust. J. Chem*. **1984**, *37*, 1729.

207. Koehler, M. F. T.; Gazzard, L. J.; Tsui, V. H.–W. WO 106192 A2, 2007.

208. Tanaka, Y.; Takeda, S.; Higashi, H.; Matsuura, M.; Kobayashi, F.; Hamada, M.; Tanaka, M. E.P. Patent 1,801,108 A1, 2007.

209. Haydon, D. J.; Bennett, J. M.; Brown, D.; Collins, I.; Galbraith, G.; Lancett, P.; MacDonald, R.; Stokes, N. R.; Chauhan, P. K.; Sutariya, J. K.; Nayal, N.; Srivastava, A.; Beanland, J.; Hall, R.; Henstock, V.; Noula, C.; Rockley, C.; Czaplewski, L. *J. Med. Chem*. **2010**, *53*, 3927.

210. Aicher, T. D.; Boyd, S. A.; Chicarelli, M. J.; Condroski, K. R.; Hinklin, R. J.; Singh, A.; Turner, T. M.; Rustam, F. G. WO 89512 A1, 2007.

211. Duncton, M.; O'Mahony, D. J. R.; Cox, M.; Estiarte-Martinez, M de Los A. WO 89057 A1, 2009.

212. Ternansky, R. J.; Draheim, S. E.; Pike, A. J.; Bell, W. F.; West, S. J.; Jordan, C. L.; Wu, C. Y. E.; Preston, D. A.; Alborn, W. Jr. *J. Med. Chem*. **1993**, *36*, 1971.

213. Walczynski, K.; Zuiderreld, O. P.; Timmerman, H. *Eur. J. Med. Chem*. **2005**, *40*, 15.

214. Rodriguez, -L. P.; Quintero, A.; Rodriguez, -S. R.; Solano, J. D.; Lira, -R. A. *J. Med. Chem*. **2004**, *39*, 5.

215. Loza-Mejía, M. A.; Maldonado-Hernández, K.; Rodríguez-Hernández, F.; Rodríguez-Sotres, R.; González-Sánchez, I.; Quintero, A.; Solano, J. D.; Lira-Rocha, A. *Bioorg. Med. Chem*. **2008**, *16*, 1142.

216. Alvarez, -I., C.; Fernandez, -G. R.; Quiroga, M. L.; Carbonell, A.; Cardenas, F.; Giralt, E. *J. Med. Chem*. **1997**, *40*, 668.

217. Bebernitz, G. R.; Beaulieu, V.; Dale, B. A.; Deacon, R.; Duttaroy, A.; Gao, J.; Grondine, M. S.; Gupta, R. C.; Kakmak, M.; Kavana, M.; Kirman, L. C.; Liang, J.; Maniara, W. M.; Munshi, S.; Nadkarni, S. S.; Schuster, H. F.; Stams, T.; Denny, I. St.; Taslimi, P. M.; Vash, B.; Caplan, S. L. *J. Med. Chem*. **2009**, *52*, 6142.

218. Bernstein, J.; Stearns, B.; Dexter, M.; Lott, W. A. *J. Am. Chem. Soc*. **1947**, *69*, 1147.

219. Okafor, C. O. *J. Med. Chem*. **1967**, *10*, 126.

220. Tanaka, J.; Iida, H.; Abe, M.; Yuda, Y.; Inoue, S.; Okabe, S. *Arzneim. Forsch*. **2004**, *54*, 221.

221. Haydon, D. J.; Czaplewski, L. G. WO 74812 A1, 2009.

222. Tsushima, M.; Iwamatsu, K.; Tamura, A.; Shibahara, S. *Bioorg. Med. Chem*. **1998**, *6*, 1009.

223. Choi, S.; Branstrom, A.; Gothe, S. A.; Lipman, R.; Tamilarasu, N.; Wilde, R. G. WO 127275 A2, 2008.

224. Ghorpade, S. R.; Kale, M. G.; McKinney, D. C.; Peer, M. S. H.; Raichurkar, A. K. V. WO 147431 A1, 2009.
225. Brown, D. R.; Collins, I.; Czaplewski, L. G.; Hayden, D. J. WO 107758 A1. 2007.
226. Tsuruoka, A.; Kaku, Y.; Kakinuma, H.; Tsukada, I.; Yanagisawa, M.; Nara, K.; Naito, T. *Chem. Pharm. Bull*. **1998**, *46*, 623.
227. Lee, S.; Hokama, T.; Anderson, R. U.S. Patent 277663, A1. 2005.
228. Pardasani, R. T.; Pardasani, P.; Muktawat, S.; Chaturredi, V.; Mukherjee, T. *Phosphorus*, *Sulfur*, *Silicon Relat. Elem*. **1998**, *142*, 221.
229. Van der Plas, H. C. *Adv. Heterocycl. Chem*. **1999**, *74*, 87.
230. Besson, T.; Guillard, J.; Rees, C. W. *Tetrahedron Lett*. **2000**, *41*, 1027.
231. Pereira, M.-F.; Alexandre, F. R.; Thiéry, V.; Besson, T. *Tetrahedron Lett*. **2004**, *45*, 3097.
232. Deck, L.M.: Papadopoulos, P. E.; Smith, K. A. *J. Heterocycl. Chem*. **2003**, *40*, 885.
233. Besson, T.; Rees, C. W.; Roe, D. G.; Thiery, V. *J. Chem. Soc*., *Perkin Trans. 1* **2000**, 555.
234. Rees, C. W.; Roe, D. G.; Thiéry, V. *Chem. Commun*. **1996**, 2775.
235. Koutentis, P. A.; Rees, C. W. *J. Chem. Soc*., *Perkin Trans. 1* **1998**, 2505.
236. Boberg, F. *Liebigs Ann. Chem*. **1964**, *679*, 109.
237. Ogurtsov, V. A.; Rakitin, O. A.; Rees, C. W.; Smolentsev, A. A.; Lyssenko, K. A. *Mendeleev Commun*. **2005**, *15*, 20.
238. Jeon, M.-K.; Kim, K. *J. Chem. Soc*., *Perkin Trans. 1* **2000**, 3107.
239. pKa Data Compiled by R. Williams. Available online: http://research.chem.psu.edu/ brpgroup/pKa_compilation.pdf
240. Nonell, S.; Ferreras, L. R.; Cañete, A.; Lemp, E.; Günther, G.; Pizarro, N.; Zanocco, A. L. *J. Org. Chem*. **2008**, *73*, 5371.
241. Sobarzo-Sánchez, E.; Jullian, C.; Cassels, B. K.; Saitz, C. *Synth. Commun*. **2002**, *32*, 3687.
242. Saitz, C.; Rodriguez, H.; Márquez, A.; Cañete, A.; Jullian, C.; Zanocco, A. *Synth. Commun*. **2001**, *31*, 135.
243. Sobarzo-Sánchez, E.; Cassels, B. K.; Saitz-Barria, C.; Jullian, C. *Magn. Reson. Chem*. **2001**, *39*, 361.
244. Medaer, B. P.; Hoornaert, G. J. *Tetrahedron* **1999**, *55*, 3987.

245. St. Georgiev, V.; Kropp, P. L.; Carlson, R. R.; Van Inwegen, R. G.; Mack, R. A. *Eur. J. Med. Chem*. **1989**, *24*, 639.
246. Tauer, E.; Grellmann, K.-H. *Chem. Ber*. **1986**, *119*, 215.
247. Reichen, W. *Helv. Chim. Acta* **1977**, *60*, 186.
248. Rabilloud, G. *Comptes Rendus des Seances de l'Academie des Sciences, Serie C: Sciences Chimique*s **1970**, *270*, 2019.
249. Dickoré, K.; Sasse, K.; Bode, K.-D. *Liebigs Ann. Chem*. **1970**, *733*, 70.
250. Weidinger, H.; Kranz, J. *Chem. Ber*. **1964**, *97*, 1599.
251. Tardif, S. L.; Rys, A. Z.; Abrams, C. B.; Abu-Yousef, I. A.; Lesté-Lasserre, P. B. F.; Schultz, K. V.; Harpp, D. N. *Tetrahedron* **1997**, *53*, 12225.
252. Simmons, H. E.; Vest, R. D.; Blomstrom, D. C.; Roland, J. R.; Cairns, T. L. *J. Am. Chem. Soc*. **1962**, *84*, 4746.
253. Thompson, Q. E.; Crutchfield, M. M.; Dietrich, M. W.; Pierron, E. *J. Org. Chem*. **1965**, *30*, 2692.
254. Tardif, S. L.; Williams, C. R.; Harpp, D. N. *J. Am. Chem. Soc*. **1995**, *117*, 9067.
255. Zysman-Colman, E.; Harpp, D. N. *J. Org. Chem*. **2005**, *70*, 5964.
256. Micallef, A. S.; Bottle, S. E. *Tetrahedron Lett*. **1997**, *38*, 2303.
257. Rudzinski, D. M.; Priefer, R. *Tetrahedron Lett*. **2009**, *50*, 1629.
258. Rudzinski, D. M.; McCourt, M. P.; Priefer, R. *Tetrahedron Lett*. **2009**, *50*, 5520.
259. Henkelu, C. D.E. Patent 2,021,679. 1970.
260. Gilchrist, T. L.; Wood, J. E. *J. Chem. Soc.*, *Chem. Commun*. **1992**, 1460.
261. Oh, K. C.; Lee, H.; Kim, K. *Tetrahedron Lett*. **1992**, *33*, 4963.
262. Yasuhiro, M.; Koichi, K.; Kazuyuki, T.; Shigeo, Y. E.P. Patent 1,911,350 A1. 2008.
263. Chang, Y. G.; Kim, K. *Synlett* **2002**, 1423.
264. Mohanta, P. K.; Kim, K. *Heterocycles* **2002**, *57*, 1471.
265. Pereira, M.-F.; Thiery, V.; Besson, T. *Tetrahedron Lett*. **2007**, *48*, 7657.
266. Pereira, M.-F.; Picot, L.; Guillot, J.; Leger, J. M.; Jarry, C.; Thiery, V.; Besson, T. *Tetrahedron Lett*. **2005**, *46*, 3445.
267. Girardet, J. L.; Gunic, E.; Ester, C.; Cieslak, D.; Pietrzowski, Z.; Wang, G. *J. Med. Chem*. **2000**, *43*, 3704.
268. Bagley, M. C.; Hughes, D. D.; Lioyd, R.; Powers, R. E. C. *Tetrahedron Lett*. **2001**, *42*, 6585.

269. Nam, G.; Yoom, C. M.; Kim, E.; Rhee, C. K.; Kim, J. H.; Shim, J. H.; Kim, S. H. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 611.

270. Matsumoto, J. I.; Minami, S. *J. Med. Chem*. **1975**, *18*, 74.

271. Quintela, J. M.; Peinadov, C.; Veiga, M. C.; Botana, L. M.; Alfonso, A.; Riquera, R. *J. Med. Chem*. **1998**, *33*, 887.

272. Zheng, G. Z.; Mao, Y.; Lee, C. H.; Pratt, J. K.; Koenig, J. R.; Perner, R. J.; Cowart, M. D.; Gfesser, G. A.; McGaraughty, S.; Chu, K. L.; Zhu, C.; Yu, H.; Kohlhass, K.; Alexander, K. M.; Wismer, C. T.; Mikusa, J.; Jarvis, M. F.; Kowaluk, E. A.; Stewart, A. O. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 3041.

273. Grivsky, E. M.; Lee, S.; Sigel, C. W.; Duch, D. S.; Nichol, C. A. *J. Med. Chem*. **1980**, *23*, 327.

274. Bilodeau, M. T.; Chen, C.; Cosford, N. D. P.; Eastman, B. W.; Hartnett, J. C.; Hu, E. H.; manley, P. J.; Neilson, L. A.; Tehrani, L. R.; Wu, Z. WO 100356 A1, 2005.

275. Bilodeau, M. T.; Cosford, N. D. P.; Hartnett, J. C.; Liang, J.; Manley, P. J.; Neilson, L. A.; Siu, T.; Wu, Z.; Li, Yiwei. WO 36395 A2, 2006.

276. Taylor, E. C. J.; Crovetti, A. J. *J. Org. Chem*. **1954**, *19*, 1633.

277. Cailly, T.; Fabis, F.; Lemaître, S.; Bouillon, A.; Rault, S. *Tetrahedron Lett*. **2005**, *46*, 135.

278. Alvarez-Insua, S.; Tamayo, M. L.; Soto, J. L. *J. Heterocycl. Chem*. **1970**, *7*, 1305.

279. Quintela, J. M.; Peinador, C.; Botana, L.; Estévez, M.; Riguera, R. *Bioorg. Med. Chem*. **1997**, *5*, 1543.

280. Yamanouchi, P. C. L. E.P. Patent 1,302,463 A1, 2001.

281. Harada, H.; Watanuki, S.; Takuwa, T.; Kawaguchi, K.; Okazaki, T.; Hirano, Y.; Saitoh, C. E.P. Patent 1,302,463 A1, 2003.

282. Barber, C. G.; Dickinson, R. P.; Horne, V. A. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 181.

283. Molina, P.; Aller, E.; Lorenz, A. *Synlett* **2003**, 714.

284. Taniyama, T. *Yakagaku Zasshi* **1957**, *77*, 1248.

285. Takahashi, T. *Yakagaku Zasshi* **1946**, *66*, 38.

286. Foroughifar, N.; Leffek, K. T.; Lee, Y. G. *Can. J. Chem*. **1992**, *70*, 2856.

287. Liu, C.; Zhou, S.; Wang, S.; Zhang, L.; Yang, G. *J. Chem. Soc*., *Dalton Trans*. **2010**, *39*, 8994.

288. Kopp, M.; Lancelot, J.-C.; Dagdag, S.; Miel, H.; Rault, S. *J. Heterocycl. Chem*. **2002**, *39*, 1061.
289. Yamamoto, Y.; Mizuno, H.; Tsuritani, T.; Mase, T. *Tetrahedron Lett*. **2009**, *50*, 5813.
290. Suzuki, K.; Tomura, M.; Tanaka, S.; Yamashita, Y. *Tetrahedron Lett*. **2000**, *41*, 8359.
291. Choi, S. H.; Kim, K. *Tetrahedron* **1996**, *52*, 8413.
292. Konstantinova, L. S.; Bol'shakov, O. A.; Obruchnikova, N. V.; Golova, S. P.; Nelyubina, Y. V.; Lyssenko, K. A.; Rakitin, O. A. *Mendeleev Commun*. **2009**, *19*, 84.
293. Konstandinova, L. S.; Bol'shakov, O. A.; Obruchnikova, N. V.; Golova, S. P.; Nelyubina, Y. V.; Lyssenko, K. A.; Rakitin, O. A. *Tetrahedron* **2010**, *66*, 4330.
294. Geevers, J.; Trompen, W. P. *Tetrahedron Lett.* **1974**, *15*, 1687.
295. Besson, T.; Guillaumet, G.; Lamazzi, C.; Rees, C. W.; Thiéry, V. *J. Chem. Soc*., *Perkin Trans. 1* **1998**, 4054.
296. Koutentis, P. A.; Rees, C. W.; White, A. J. P.; Williams, D. J. *J. Chem. Soc.*, *Perkin Trans. 1* **1998**, 2765.
297. Denney, D. B.; Ross, S. T. *J. Org. Chem.* **1962**, *27*, 998.
298. Ramirez, F.; Dershowitz, *S. J. Org. Chem.* **1957**, *22*, 41.
299. Ammon, H. L.; Wheeler, G. L.; Watts, P. H. *J. Am. Chem. Soc.* **1973**, *95*, 6158.
300. Bolboaca, M.; Stey, T.; Murso, A.; Stalke, D.; Kiefer, W. *Applied Spectroscopy* **2003**, *57*, 970.
301. Huheey, pps. A-21 to A-34; Cottrell, T. L. "The Strengths of Chemical Bonds," 2nd ed., Butterworths, London, **1958**; Darwent, B. de B. "National Standard Reference Data Series," National Bureau of Standards, No. 31, Washington, DC, 1970; Benson, S. W. *J. Chem. Educ*. **1965**, *42*, 502
302. MacKnight, W. *Annals of the New York Academy of Sciences* **2006**, *159*, 267.
303. Okawa, T.; Toda, M.; Eguchi, S.; Kakehi, A. *Synthesis* **1998**, 1467.
304. Clarke, K.; Fox, W. R.; Scrowston, R. M. *J. Chem. Res. (M)* **1980**, 0833.
305. Ryabova, S. Y.; Alekseeva, L. M.; Lisitsa, E. A.; Granik, V. G. *Russ. Chem. Bull.* **2006**, *55*, 1248.
306. d'Ischia, M.; Napolitano, A.; Pezzella, A. (eds. in Chief: Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K.). *In Comprehensive Heterocyclic Chemistry III; Jones*, *G*., *Ramsden*, *C. A*. *Eds.; Elsevier: Oxford*, **2008**, Vol. *3*, (Chapter 3.04), p 353.
307. Eger, K.; Lanzner, W.; Rothenhäusler, K. *Liebigs Ann.* **1993**, *1993*, 465.

308. Fuchter, M. J.; Beall, L. S.; Baum, S. M.; Montalban, A. G.; Sakellariou, E. G.; Mani, N. S.; Miller, T.; Vesper, B. J.; White, A. J. P.; Williams, D. J.; Barett, A. G. M.; Hoffman, B. M. *Tetrahedron* **2005**, *61*, 6115.
309. Kung, P.-P.; Cook, P. D.; Guinosso, C. J. U.S. Patent 6,156,758, 2000.
310. Jennings, M.; Preuss, K. E.; Wu, J. *Chem. Commun.* **2006**, 341.
311. El-Gaby, M. S. A.; El-Sharief, A. M. S.; Atalla, A. A.; El-Adasy, A. A. A. M. *J. Chin. Chem.* **2004**, *51*, 327.
312. El-Sharief, A. M. S.; Ammar, Y. A.; Zahran, M. A.; Sabet, H. K. *J. Chem. Res. (S)* **2003**, 162.
313. El-Sharief, A. M. S.; El-Gaby, M. S. A.; Atalla, A. A.; El-Adasy, A.-B. A. A. M. *Heteroatom Chem.* **2005**, *16*, 218.
314. El-Sharief, A. M. S.; Al-Amri, A. M.; Al-Raqa, S. Y. *J. Sulfur Chem.* **2006**, *27*, 245.
315. Friedrich, J. D. *J. Org. Chem.* **1987**, *52*, 2442.
316. Gonda, J.; Kristian, P. *Coll. Czech. Chem. Commun.* **1988**, *53*, 1761.
317. Walter, W.; Hell, P.-M. *Liebigs Ann. Chem.* **1969**, *727*, 22.
318. Walter, W.; Bode, K.-D. *Liebigs Ann. Chem.* **1966**, *698*, 131.
319. Reissert, A.; Bruggemann, K. *Chem. Ber.* **1924**, *57*, 981.
320. Sekine, M.; Kume, A.; Hata, T. *Tetrahedron Lett.* **1981**, *22*, 3617.
321. Bard, R. R.; Strauss, M. J. *J. Am. Chem. Soc.* **1975**, *97*, 3789.
322. Miller, J.; Miyata, Y.; Sakazaki, E.; de Santos, T. W. *J. Chem. Res. (S)* **1986**, 396.
323. Hosseini-Sarvari, M.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652.
324. Kawashima, T. *Chin. J. Chem.* **2005**, *23*, 1267.
325. Abdou, W. A. *Phosphorus*, *Sulfur*, *Silicon Relat. Elem.* **1999**, *144-146*, 393.
326. Abdou, W. A.; Yakout, E.-S. M. A. *Tetrahedron* **1993**, *49*, 6411.
327. Wallenfels, K.; Friedrich, K.; Rieser, J. *Liebigs Ann.* **1976**, *1976*, 656.
328. Sase, S.; Kano, N.; Kawashima, T. *Chem. Lett.* **2004**, *33*, 1434.
329. Harwood, L. M. *Aldrichimica Acta* **1985**, *18*, 25.
330. Kasuga, K.; Hirobe, M.; Okamoto, T. *Yakugaku Zasshi* **1974**, *94*, 945; Chem. Abstr. **1974**, *81*, 136093.
331. Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608.
332. Gribble, G. W., Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. (Eds); Pergamon Press: New York, Oxford, *In Comprehensive Heterocyclic Chemistry II* **1996**, *2*, 207.

333. Von Angerer, E.; Knebel, N.; Kager, M.; Ganss, B. *J. Med. Chem.* **1990**, *33*, 2635.

334. Ismail, M. F.; Shmeiss, N. A. M. M.; El-Diwani, H. I.; Arbid, M. S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1997**, *36B*, 288.

335. Biberger, C.; Von Angerer, E. *J. Steroid Biochem. Mol. Biol.* **1998**, *64*, 277.

336. Medarde, M.; Ramos, A. C.; Caballero, E.; De Clairac, R. P. L.; Lopez, J. L.; Gravalos, D. G.; Feliciano, A. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2303.

337. Stevenson, G. I.; Smith, A. L.; Lewis, S.; Michie, S. G.; Neduvelil, J. G.; Patel, S.; Marwood, R.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2697.

338. Colletti, S. L.; Li, C.; Fisher, M. H.; Wyvratt, M. J.; Meinke, P. T. *Tetrahedron Lett.* **2000**, *41*, 7825.

339. Saint-Gratien, G. L.; Claye-Souilly, S. F.; Livry-Gargan, A. J.; Paris, H. R.; Aulnay-sous-Bois, J. J. V. U.S. Patent 5,354,870, 1992.

340. Sarac, A. S.; Serantoni, M.; Tofail, S. A.; Cunnane, V. J. *J. Nanosci. Nanotechnol.* **2005**, *5*, 1677.

341. Makriyannis, A.; Hongfeng, D. U.S. Patent 1,098,260, 2004.

342. Gul, W.; Hamann, M. T. *Life Sciences* **2005**, *78*, 442.

343. Gribble, G. W.; Joule, J. A. *Prog. Heterocycl. Chem. 19*, 160.

344. Radwanski, E. R.; Last, R. L. *Plant Cell* **1995**, *7*, 921.

345. Kohmoto, S.; Kashman, Y.; McConnell, O. J.; Rinehart, K. L.; Wright, A.; Koehn, F. *J. Org. Chem*. **1988**, *53*, 3116.

346. Bobzin, S. C.; Faulkner, D. J. *J. Org. Chem.* **1991**, *56*, 4403.

347. Shimizu, K.; Geng, X.; Hashiguchi, M.; Suhara, H.; Fukunaga, S.; Yasutake, S.; Kondo, R.; Tsutsui, M.; Sato, I. *J. Wood. Sci.* **2003**, *49*, 349.

348. Aroca, P.; Solano, F.; Garcia-Borron, J. C.; Lozano, J. A. *Biochem.* **1991**, *277*, 393.

349. Bernardi, L.; Bosisio, G.; Mantegani, S.; Sapini, O.; Temperilli, A.; Salvati, P.; di Salle, E.; Arcari, G.; Bianchi, G. *Arzneim.-Forsch.* **1983**, *33*, 1094.

350. Fukami, T.; Yamakawa, T.; Niiyama, K.; Kojima, H.; Amano, Y.; Kanda, F.; Ozaki, S.; Fukuroda, T.; Ihara, M.; Yano, M.; Ishikawa, K. *J. Med. Chem.* **1996**, *39*, 2313.

351. Rowe, D. J. *Chemistry and Technology* of *Flavors and Fragrances*, Blackwell, Oxford, **2005**.

352. Golantsov, N. E.; Karchava, A. V.; Nosova, V. M.; Yurovskaya, M. A. *Russ. Chem. Bull. In. Ed.* **2005**, *54*, 226.

353. Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276.

354. Cheng, K. F.; Chan, T. T.; Lai, T. F.; Kong, Y. C. *J. Chem. Soc.*, *Perkin Trans. 1* **1988**, 3317.

355. Rahtz, D.; Huth, A.; Schmiechen, R.; Kehr, W.; Schneider, H. H.; Braestrup, C. T. U.S. Patent 4,564,610, 1986.

356. Rastorgueva, N. A.; Ryabova, S. Y.; Lisitsa, E. A.; Alekseeva, L. M.; Granik, V. G. *Pharm. Chem. J.* **2004**, *38*, 109.

357. Eakin, M. A.; Hayter, A. J.; Furr, B. J. A. U.S. Patent 4,533,672, 1985.

358. Portonov, Y. N.; Bulaga, S. N.; Zabrodnyaya, V. G.; Smirnov, L. D. *Heterocycl. Compd.* **1991**, *27*, 325.

359. Landwehr, J.; Troschü tz, R. *Synthesis* **2005**, 2414.

360. Volovenko, Y. M.; Volovnenko, T. A. *Chem. Heterocycl. Comp.* **2001**, *37*, 1092.

361. Dave, C. G.; Shah, P. R.; Upadhyaya, S. P.; Gandhi, T. P.; Patel, R. B. *Indian J. Chem.*, *Sect. B* **1988**, *27*, 778.

362. Hess, S.; Müller, C. E.; Frobenius, W.; Reith, U.; Klotz, K.-N.; Eger, K. *J. Med. Chem.* **2000**, *43*, 4636.

363. Dotzauer, B.; Grünert, R.; Bednarski, P. J.; Lanig, H.; Landwehr, J.; Troschütz, R. *Bioorg. Med. Chem.* **2006**, *14*, 7282.

364. Rauscher, F. M.; Sanders, R. A.; Watkins, J. B. *J. Biochem. Mol. Toxicol.* **2000**, *14*, 189.

365. Rekosh, D.; Hammarskjold, M.-L. U.S. Patent 318959 A1, 2008.

366. Hall, E. D.; Andrus, P. K.; Smith, S. L.; Fleck, T. J.; Scherch, H. M.; Lutzke, B. S.; Sawada, G. A.; Althaus, J. S.; Vonvoigtlander, P. F.; Padbury, G. E.; Larson, P. G.; Palmer, J. R.; Bundy, G. L. *J. Pharm. Exp. Ther.* **1997**, *281*, 895.

367. Bundy, G. L.; Bayer, D. E.; Banitt, L. S.; Belonga, K. L.; Mizsak, S. A.; Palmer, J. R.; Tustin, J. M.; chin, J. E.; Hall, E. D. *J. Med. Chem.* **1995**, *38*, 4161.

368. Mueller, C. E.; Geis, U.; Grahner, B.; Lanzner, W.; Eger, K. *J. Med. Chem.* **1996**, *39*, 2482.

369. Lim, M.-I.; Klein, R. S.; Fox, J. J. *J. Org. Chem.* **1979**, *44*, 3826.

370. Lim, M.-I.; Klein, R. S.; Fox, J. J. *Tetrahedron Lett.* **1981**, *22*, 25.

371. Kurisaki, T.; Naniwa, T.; Yamamoto, H.; Imagawa, H.; Nishizawa, M. *Tetrahedron Lett.* **2007**, *48*, 1871.

372. Lerch, U.; Moffatt, J. G. *J. Org. Chem.* **1971**, *36*, 3686.
373. Sharma, A. K.; Das, S. K. *Synth. Commun.* **2004**, *34*, 3807.
374. Ming, L.; Le, T. X.; Yu-Guang, W. *Helv. Chim. Acta* **2006**, *89*, 532.
375. Martin, M.; Patrik, P.; Miroslaw, L. *Coll. Czech. Chem. Commun.* **2004**, *69*, 1479.
376. Na, Z.; Yu-Lu, W. *J. Chem. Res. (S)* **2004**, *5*, 366.
377. Koh, P. K.; Joo, L. J.; Jaegyung, R. *Tetrahedron* **2003**, *59*, 7651.
378. Hidetoshi, T.; Masashi, S.; Toshihiro, U.; Tohru, F. *Heterocycles* **2001**, *54*, 105.
379. Kenneth, A.; Sumalee, K. C.; Debra, M. J. *J. Org. Chem.* **1988**, *53*, 4667.
380. Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, 26, 2778.
381. Shastin, A. V.; Godovikova, T. I.; Korsunskii, B. L. *Chem. Heterocycl. Comp.* **1998**, *34*, 1195.
382. Schaefer, F. C.; Peters, G. A.; Peters, D. U.S. Patent 2,953,563, 1960.
383. Johnson, KE, Xiao L, Driver G. **2002**. "*Significance of cations in ionic liquids chemistry*," in Ionic Liquids: Industrial Applications in Green Chemistry, Rogers R. D. and Seddon K. R. (Eds.), ACS Symposium Series 818, American Chemical Society, Washington DC, 230.
384. Berlin, K. D.; Ranganathan, R.; Haberlein, H. *J. Org. Chem.* **1968**, *5*, 813.
385. Dave, K. G.; Shishoo, C. J.; Devani, M. B.; Kalyanaraman, R.; Ananthan, S.; Ullas, G. V.; Bhadti, V. S. *J. Heterocycl. Chem.* **1980**, *17*, 1497.
386. Davis, B. R.; Garratt, P. J. *Compr. Org. Synth.* **1991**, *2*, 848.
387. Baron, H.; Remfry, F. G. P.; Thorpe, Y. F. *J. Chem. Soc.* **1904**, *85*, 1726.
388. Ziegler, K.; Eberie, H.; Ohlinger, H. *Justus Liebigs Ann. Chem.* **1933**, *504*, 94.
389. Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367.
390. Heathcock, C. H.; Smith, K. M.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 5022.
391. Schultz, A. G.; McCloskey, P. J.; Court, J. J. *J. Am. Chem. Soc.* **1987**, *109*, 6493.
392. Yamazaki, N.; Kibayashi, C. *J. Am. Chem. Soc.* **1989**, *111*, 1396.
393. Dalko, P. I.; Burn, V.; Langlois, Y. *Tetrahedron Lett.* **1998**, *39*, 8979.
394. Alonso, D. A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 9455.
395. Sabitha, G.; Abraham, S.; Reddy, B. V. S.; Yadav, J. S. *Synlett* **1999**, 1745.
396. McIntosh, J. M.; Matassa, L. C. *J. Org. Chem.* **1988**, *53*, 4452.
397. Heathcock, C. H.; Blumenkopf, T. A.; Smith, K. M. *J. Org. Chem.* **1989**, *54*, 1548.

398. Bergmeier, S. C.; Seth, P. P. *Tetrahedron Lett.* **1999**, *40*, 6181.
399. Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657.
400. Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D., Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.
401. Katoh, T. E. I.; Yoshino, T.; Terashima, S. *Tetrahedron Lett.* **1996**, *37*, 3471.
402. Zhou, W.-S.; Xie, W.-G.; Liu, Z.-H.; Pan, X. F. *Tetrahedron Lett.* **1995**, *36*, 1291.
403. Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, *114*, 4403.
404. Alonso, E.; Ramón, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355.
405. Chowdhury, M. A.; Reissig, H.-U. *Synlett* **2006**, 2383.
406. Fleming, I.; Frackenpohl, J.; Ila, H. *J. Chem. Soc.*, *Perkin Trans. 1* **1998**, 1229.
407. Greene, T. W.**;** Wuts, P. G. M. *Protective Groups in Organic Synthesis 3rd ed***.** New York: Wiley **1999**, *115*. (doi:10.1002/0471220574)
408. Gilbert, E. J.; Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **1999**, *64*, 5670.
409. Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 13179.
410. Bajwa, J. S.; Chen, G.–P.; Prasad, K.; Repiĉ, O.; Blacklock, T. *Tetrahedron Lett.* **2006**, *47*, 6425.
411. Witulski, B.; Alayrac, C. *Angew. Chem.*, *Int. Ed.* **2002**, *41*, 3281.
412. Nyasse, B.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc. Chem. Commun.* **1997**, 1017.
413. Muratake, H.; Natsume, M. *Heterocycles* **1989**, *29*, 783.
414. MacCoss, R. N.; Henry, D. J.; Brain, C. T.; Ley, S. V. *Synlett* **2004**, 675.
415. Haskins, M. C.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 599.
416. Jordis, U.; Sauter, F.; Siddiqi, S. M.; Küenburg, B.; Bhattacharya, K. *Synthesis* **1990**, 925.
417. Compagnone, R. S.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1713.
418. Kudav, D. P.; Samant, S. P.; Hosangadi, B. D. *Synth. Commun.* **1987**, *17*, 1185.
419. Portoghese, P. S.; Mikhail, A. A. *J. Org. Chem.* **1966**, *31*, 1059.
420. Birkinshaw, T. N.; Holmes, A. B. *Tetrahedron Lett.* **1987**, *28*, 813.
421. Chavez, F.; Sherry, A. D. *J. Org. Chem.* **1989**, *54*, 2990.
422. Forshee, P. B.; Sibert, J. W. *Synthesis* **2006**, 756.
423. Signa, C. L. U.S. Patent 306391, 2009.

424. Nyasse, B.; Grehn, L.; Maia, H. L. S.; Monteiro, L. S.; Ragnarsson, U. *J. Org. Chem*. **1999**, *64*, 7135.
425. Senboku, H.; Nakahara, K.; Fukuhara, T.; Hara, S. *Tetrahedron Lett*. **2010**, *51*, 435.
426. Xu, H.; Fan, L. L. *Chem*. *Phar. Bull*. **2009**, *57*, 321.
427. Miyagi, T.; Hari, Y.; Aoyama, T. *Tetrahedron Lett.* **2004**, *45*, 6303.
428. Kyzioł, J. B.; Daszkiewicz, Z. *Tetrahedron* **1984**, *40*, 1857.
429. Kasaya, Y.; Hoshi, K.; Terada, Y.; Nishida, A.; Shuto, S.; Arisawa, M. *Eur. J. Org. Chem*. **2009**, 4606.
430. Chakrabarti, A.; Goutam, K. B.; Chakraborty, D. P. *Tetrahedron* **1989**, *45*, 5059.
431. Yarosh, A. V.; Velezheva, V. S.; Kozik, T. A.; Suvorov, N. N. *Khim. Geterotsikl Seodin.* **1977**, *4*, 481.
432. Elliott, D. F.; Robinson, F. A. *J. Chem. Soc.* **1944**, 632.
433. Andersen, K. K.; Gowda, G.; Jewell, L.; McGraw, P.; Phillips, B. T. *J. Org. Chem.* **1982**, *47*, 1884.
434. Hu, Y.; Chen, Z.-C.; Le, Z.-G.; Zheng, Q.-G. *J. Chem. Res. (S)* **2004**, 267.
435. Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Synlett* **2003**, 361.
436. Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608.
437. Cowie, D. W.; Gibson, D. T. *J. Chem. Soc.* **1933**, 308.
438. Cowie, D. W.; Gibson, D. T. *J. Chem. Soc.* **1934**, 46.
439. Semenov, B. B.; Granik, V. G. *Pharm. Chem. J.* **2004**, *38*, 287.
440. Cope, A. C.; Morrison, D. E.; Field, L. *J. Am. Chem. Soc.* **1950**, *72*, 59.
441. Wragg, A. H.; McFadyen, J. S.; Stevens, T. S. *J. Chem. Soc.* **1958**, 3603.
442. Darwish, D.; McLaren, R. *Tetrahedron Lett.* **1962**, *3*, 1231.
443. Darwish, D.; Preston, E. A. *Tetrahedron Lett.* **1964**, *5*, 113.
444. Ciuffarin, E.; Isola, M.; Fava, A. *J. Am. Chem. Soc.* **1968**, *90*, 3594.
445. Baldwin, J. E.; Lever, W., Jr.; Tzodikov, N. R. *J. Org. Chem.* **1976**, *41*, 2312.
446. Hiroi, K.; Kitayama, R.; Sato, S. *J. Chem. Soc.*, *Chem. Commun.* **1983**, 1470.
447. Hiroi, K.; Kitayama, R.; Sato, S. *Chem. Pharm. Bull.* **1984**, *32*, 2628.
448. Knight, D. J.; Whitham, G. H.; Williams, J. G. *J. Chem. Soc.*, *Perkin Trans. 1* **1987**, 2149.
449. Kimura, M.; Horino, Y.; Mori, M.; Tamaru, Y. *Chem. Eur. J.* **2007**, *13*, 9686.

450. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *Tetrahedron Lett.* **2000**, *41*, 7437.

451. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3167.

452. Fischer, E.; Schmitt, T. *Chem. Ber.* **1888**, *21*, 1071.

453. Tidwell, R. R.; Geratz, J. D.; Dann, O.; Volz, G.; Zeh, D.; Loewe, H. *J. Med. Chem.* **1978**, *21*, 613.

454. Buchi, G.; Lee, G. C. M.; Yang, D.; Tannenbaum, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 4115.

455. Huang, -H. M. F. G. *J. Chem. Soc.* **1949**, 2911.

456. Kalb, L.; Bayer, J. *Chem. Ber.* **1912**, *45*, 2150.

457. Angelico, F.; Capuano, S. *Gazz. Chim. Ital.* **1937**, *67*, 633.

458. Lin, C.-D.; Fang, J.-M. *J. Chin. Chem. Soc. (Taipei)* **1993**, *40*, 571.

459. Denison, S.; Hilton, S. T. *Synlett* **2004**, 2806.

460. Hartter, D. R. U.S. Patent 3,714,222, 1973.

461. Hayakawa, I.; Shioya, R.; Agatsuma, T.; Furukawa, H.; Naruto, S.; Sugano, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4383.

462. Nishimura, T.; Yamada, K.; Takebe, T.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 2601.

463. Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.

464. Erian, A. W.; Sherif, S. M.; Mohamed, N. R. *Arkivoc* **2001**, *10*, 85.

465. Erian, A. W.; Sherif, S. M.; Mohamed, N. R. *Synth. Commun.* **2003**, *33*, 1563.

466. Ryndina, S. A.; Kadushkin, A. V.; Solov'eva, N. P.; Granik, V. G. *Chem. Heterocycl. Compd.* **2000**, *36*, 1409.

467. Evans, G. B.; Furneaux, R. H.; Gainsford, G. J.; Schramm, V. L.; Tyler, P. C. *Tetrahedron* **2000**, *56*, 3053.

468. Evans, G. B.; Furneaux, R. H.; Schramm, V. L.; Singh, V.; Tyler, P. C. *J. Med. Chem.* **2004**, *47*, 3275.

469. Kamath, V. P.; Zhang, J.; Morris, P. E., Jr.; Babu, Y. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2662.

470. Kamath, V. P.; Ananth, S.; Bantia, S.; Morris, P. E., Jr. *J. Med. Chem.* **2004**, *47*, 1322.

471. Tuncbilek, M.; Schneller, S. W. *Bioorg. Med. Chem.* **2003**, *11*, 3331.

472. Chun, B. K.; Chu, C. K. *Tetrahedron Lett.* **1999**, *40*, 3309.

473. Liang, C.; Ma, T.; Cooperwood, J. S.; Du, J.; Chu, C. K. *Carbohydr. Res.* **1997**, *303*, 33.

474. Buchanan, J. G.; Craven, D. A.; Wightman, R. H.; Harnden, M. R. *J. Chem. Soc.*, *Perkin Trans. 1* **1991**, 195.

475. McFarlane, M. D.; Moody, D. J.; Smith, D. M. *J. Chem. Soc.*, *Perkin Trans. 1* **1988**, 691.

476. Tabuchi, T.; Yamamoto, T.; Nakayama, M. U.S. Patent 6,586,617, 2003.

477. Taylor, E. C.; Knopf, R. J.; Cogliano, J. A.; Barton, J. W.; Pleiderer, W. *J. Am. Chem. Soc*. **1960**, *82*, 6058.

478. Mayer, R.; Forster, E.; Matauschek, B. D. DD 212387, 1984.

479. Joseph, R. W.; Antes, D. L.; Osei-Gymah, P., U.S. Patent 5,688,744, **1997**.

480. Sahm, D. F.; Wasington, J. A., In *Antibacterial susceptibility tests: Dilution methods*; Balows, A.; Hausler, W. J.; Herrmann, K. L. Jr.; Isenberg, H. D.; Shadomy, H. J (Eds); Manual of clinical microbiology, 5th ed. American Society for Microbiology, Washington, D. C., 1991, p. 1105, **1991**.

481. Besson, T.; Rees, C. W.; Thiery, V. *Synthesis* **1998**, 1345.