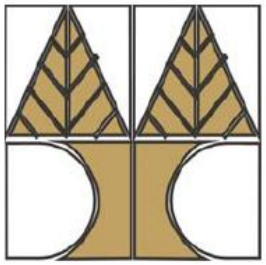


UNIVERSITY OF CYPRUS

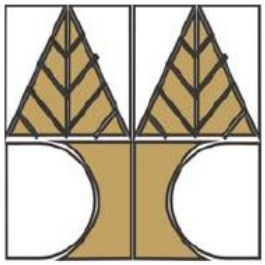
DEPARTMENT OF CHEMISTRY

DOCTORATE THESIS

New Chemistry of Isothiazoles and 1,2,6-Thiadiazines

Heraklidia Achillea Ioannidou

October 2011



UNIVERSITY OF CYPRUS

DEPARTMENT OF CHEMISTRY

DOCTORATE THESIS

Heraklidia Achillea Ioannidou

Examination Committee:

1. Prof. John A. Joule, University of Manchester (External Examiner)
2. Prof. Pierre Audebert, École Normale Supérieure de Cachan (External Examiner)
3. Dr. Savvas Georgiades, University of Cyprus (Committee Chairman)
4. Dr. Athanassios Nicolaides, University of Cyprus (Internal Examiner)
5. Dr. Panayiotis A. Koutentis, University of Cyprus (Project Supervisor)

EXPERIMENTAL PROCESSES ACCOMPLISHMENT STATEMENT

Except where noted below, the work described within this thesis has been carried out exclusively by Heraklidia A. Ioannidou at the Organic Chemistry Research Laboratory, Department of Chemistry, University of Cyprus under the supervision of Dr. Panayiotis A. Koutentis (September 2007-September 2011).

The exceptions include: the synthesis of the 3,5-dichloro-1,2,6-thiadiazin-4-one **24** and preliminary work on the thiadiazines was performed by previous member of the team Mr. Christos Kizas; the polymerization of the thiadiazinone was performed by Dr. Christos Chochos at the Cyprus University of Technology; preliminary work on the canthinones was carried out by Dr. Andreas Gollner and Dr. Aaron Martin; the elemental analysis of all compounds performed by Stephen Boyer at London Metropolitan University.

Date

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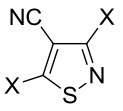
Signature

……..

To my mom and dad



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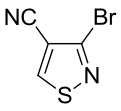
12, X = Br



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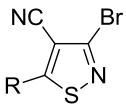
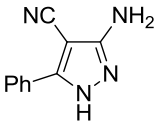


62, 64-86, R = Ar, HAr



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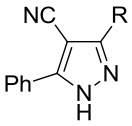
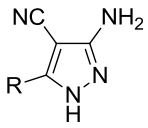
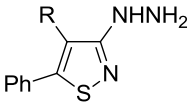


96-100, R = OMe, OH, NHBn, Morpholino, Ph



120-129 and **131-136**
R = Ar, Har



143, R = Br
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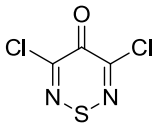

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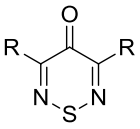

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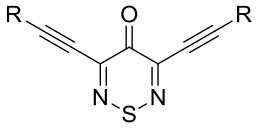
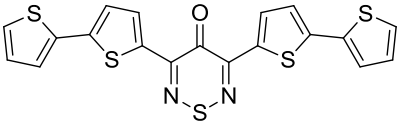


193-197, R = Ph, thien-3-yl, pyrid-3-yl, Fc



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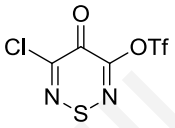

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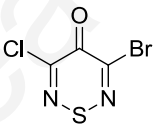

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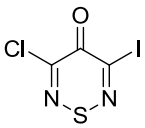

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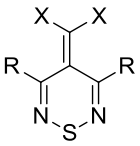
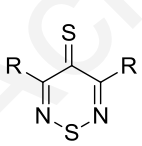
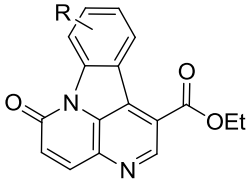


218, X = H, R = Ph
219, X = H, R = Thien-2-yl
221, X = Cl, R = Ph
222, X = Br, R = Ph
225, X = CN, R = Ph
227, X = CN, R = Thien-2-yl



223, R = Ph
224, R = Thien-2-yl



261-270, R = H, Cl, Me, OMe, F, CF_3

ABSTRACT

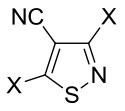
A brief introduction on heterocyclic chemistry and the chemistry of 3,5-dihaloisothiazole-4-carbonitriles **11** and **12** and 3,5-dichloro-1,2,6-thiadiazin-4-one **24** is described in Chapter 1. The results and discussion section of the thesis is then divided into 3 parts.

In the first part, Chapters 2, 3 and 4 describe the chemistry of the useful isothiazole scaffolds **11** and **12**. In Chapter 2, the selective dehalogenation of 3,5-dihaloisothiazole-4-carbonitriles **11** and **12** is described. The full optimization of the reaction conditions is discussed and some reactions of the potential scaffold 3-bromoisothiazole-4-carbonitrile **48** are given. In Chapter 3 the isothiazole **48** undergoes palladium-catalyzed direct C-H arylation reaction to give 5-aryl and heteroaryl-3-bromoisothiazole-4-carbonitriles **62**, **64-86**. The reaction is optimized and full discussion is given. Finally, Chapter 4 describes the transformation of isothiazoles into pyrazoles **89**, **96-102**, **120-129**, **131-136**, **141** and **147**. The scope and limitations of the reaction are described. The first synthesis of the 3-hydrazinylisothiazoles **143** and **146** is reported.

In the second part, new chemistry of 3,5-dichloro-1,2,6-thiadiazin-4-one **24** is described. In Chapter 5 the C-C coupling reactions (Suzuki, Stille, Sonogashira) are applied onto the scaffold **24** to afford bis-aryl and heteroaryl thiadiazines **172-186** and bis-alkynylated thiadiazines **193-197**, in high yields. The synthesis of the potentially useful 3,5-bis[(2,2'-bithien)-5-yl]-4*H*-1,2,6-thiadiazin-4-one **188** is described. In Chapter 6 the synthesis of non symmetrical di-heteroaryl thiadiazinones is described *via* the synthesis of non symmetrical di-halo thiadiazinones **200** and **201** as well as the chloro-triflate thiadiazinone **199**, while Chapter 7 describes the modification of the 3,5-dichloro-1,2,6-thiadiazin-4-one's **24** C-4 position. The methanes **218** and **219**, dihalomethanes **221** and **222**, dicyanoylidenes **225** and **227** and the thiones **223** and **224** of the analogous 3,5-diphenyl and 3,5-di(thien-2-yl)thiadiazin-4-ones **172** and **184** were synthesized.

In the third and final part, the three-step synthesis of canthinone-1-esters **261-270** is described (chapter 8).

Experimental procedures for the preparation of all new compounds together with their full characterization are described in Chapter 9.



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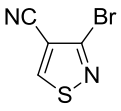
12, X = Br



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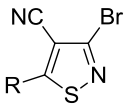
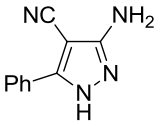


62, 64-86, R = Ar, HAr



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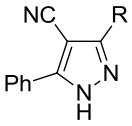
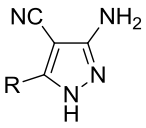
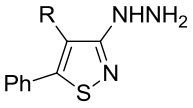


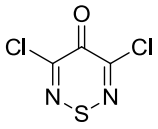
96-100, R = OMe, OH, NHBn, Morpholino, Ph



120-129 and **131-136**
R = Ar, Har



143, R = Br
146, R = Ph



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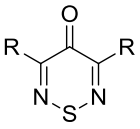

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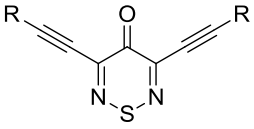
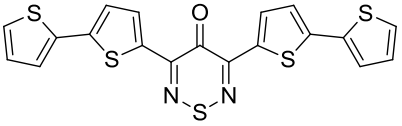


193-197, R = Ph, thien-3-yl, pyrid-3-yl, Fc



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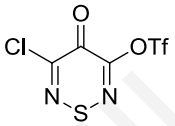

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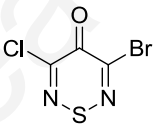

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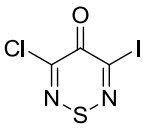

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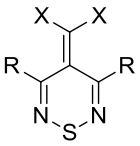
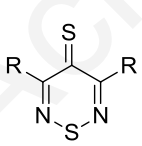
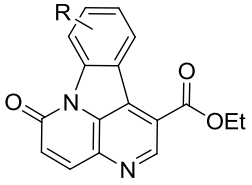


218, X = H, R = Ph
219, X = H, R = Thien-2-yl
221, X = Cl, R = Ph
222, X = Br, R = Ph
225, X = CN, R = Ph
227, X = CN, R = Thien-2-yl



223, R = Ph
224, R = Thien-2-yl



261-270, R = H, Cl, Me, OMe, F, CF_3

ΠΕΡΙΛΗΨΗ

Στο Κεφάλαιο 1 παρατίθεται μια σύντομη εισαγωγή για την ετεροκυκλική χημεία καθώς και τη χημεία των 3,5-διαλογονοϊσοθειαζολών-4-καρβονιτρίλια **11** και **12** και της 3,5-διχλωρο-1,2,6-θειαδιαζιν-4-όνης **24**. Τα αποτελέσματα και η συζήτηση της διατριβής χωρίζονται σε 3 μέρη.

Στο πρώτο μέρος, Κεφάλαια 1, 2 και 3, περιγράφεται χημεία των χρήσιμων ισοθειαζολών **11** και **12**. Στο Κεφάλαιο 2, περιγράφεται η εκλεκτική αφαλογόνωση των 3,5-διαλογονοϊσοθειαζολών-4-καρβονιτρίλια **11** και **12**. Γίνεται συζήτηση για τις συνθήκες βελτιστοποίησης της αντίδρασης και παρατίθενται μερικές αντιδράσεις της 3-βρωμοϊσοθειαζόλης-4-καρβονιτρίλιο **48**. Στο Κεφάλαιο 3, η ισοθειαζόλη **48** υπόκειται σε απευθείας αρυλίωση καταλυμένη από παλλάδιο για να δώσει 5-αρυλο και ετεροάρυλο-3-βρωμοϊσοθειαζόλες-4-καρβονιτρίλια **62**, **64-86**. Η αντίδραση βελτιστοποιήθηκε και δίνεται πλήρης συζήτηση. Τέλος, στο Κεφάλαιο 4, περιγράφεται η μετατροπή ισοθειαζολών σε πυραζόλες **89**, **96-102**, **120-129**, **131-136**, **141** και **147** και παρουσιάζονται τα όρια και οι περιορισμοί της αντίδρασης. Επίσης, αναφέρεται η πρώτη σύνθεση των 3-υδραζινοϊσοθειαζολών **143** και **146**.

Στο δεύτερο μέρος, περιγράφεται καινούρια χημεία της 3,5-διχλωρο-1,2,6-θειαδιαζιν-4-όνης **24**. Στο Κεφάλαιο 5, αντιδράσεις σύζευξης C-C (Suzuki, Stille, Sonogashira) εφαρμόζονται στη θειαδιαζινόνη **24** για να δώσουν δι-αρυλο και ετεροάρυλο θειαδιαζινόνες **172-186** καθώς και δι-αλκινικές θειαδιαζινόνες **193-197**, σε ψηλές αποδόσεις. Περιγράφεται επίσης η χημεία της δυνητικά χρήσιμης 3,5-δις[(2,2'-διθειεν)-5-υλ]-4*H*-1,2,6-θειαδιαζιν-4-όνης **188**. Στο Κεφάλαιο 6, περιγράφεται η σύνθεση μη συμμετρικών δι-ετεροάρυλο θειαδιαζινονών μέσω της σύνθεσης των μη συμμετρικών δι-αλογονο θειαδιαζινονών **200** και **201**, καθώς και της τριφλικής-χλωρο θειαδιαζινόνης **199** ενώ το Κεφάλαιο 7 περιγράφει τροποποίηση της 4 θέσης της 3,5-διχλωρο-1,2,6-θειαδιαζιν-4-όνης **24**. Επιτεύχθηκε η σύνθεση των μεθυλενίων **218** και **219**, διαλογονομεθυλενίων **221** και **222**, δικυανοϋλιδενίων **225** και **227** καθώς και των θειόνων **223** και **224** των αντίστοιχων 3,5-διφαινυλο και 3,5-δι(θειεν-2-υλ)θειαδιαζινον-4-ονών **172** και **184**.

Στο τρίτο και τελευταίο μέρος, περιγράφεται η σύνθεση τριών σταδίων των 1-εστέρων κανθινονών **261-270** (Κεφάλαιο 8).

Στο Κεφάλαιο 9 περιγράφονται οι πειραματικές διαδικασίες όλων των νέων ενώσεων μαζί με τον πλήρη χαρακτηρισμό τους.

ACKNOWLEDGEMENTS

Coming to the end of this unforgettable period of my life, I would like to thank my supervisor Dr. P. A. Koutentis for providing the opportunity to work on the projects described herein. I thank him for being helpful and for the valuable discussions.

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I would like to deeply thank my parents for their love, support and endless encouragement to keep following my dreams. I am really grateful because, apart from everything else, they taught me how to work hard, as they always have been doing. I also thank my brother Arsenios and sisters Maria-Malevi, Efremia and Porfiria as well as father John, his wife Elena and family. Special thanks go to my godson Achilleas and little nephew Tilemachos who made me smile every time with their innocent comments and always were wondering why they never see me!

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ABBREVIATIONS

Å	Ångström unit
Acac	acetylacetonate
AcOH	acetic acid
Adogen 464®	methyltrialkyl(C_8-C_{10})ammonium chloride
Aliquat 336®	*N*-methyl-*N*,*N*-dioctyloctan-1-ammonium chloride
Alk	alkyl
amyl	pentyl
APT	Attached Proton Test NMR
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
ca.	approximately (latin: *circa*)
CD_2Cl_2	deuterated dichloromethane
$CDCl_3$	deuterated chloroform
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)
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	double doublet
ddd	doublet of double doublets
decomp.	decomposition
DEPT	distortionless enhancement by polarization transfer

DMA	1,2-dimethylacetamide
DMCDA	*trans*-*N*,*N'*-dimethyl-1,2-cyclohexanediamine
DME	dimethoxyethane
DMEDA	*N*,*N'*-dimethylethyldiamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
e.g.	for example, (Latin: *exempli gratia*)
EI	electron ionization
equiv.	equivalent
Et	ethyl
Et_2O	diethylether
EtOH	ethanol
FTIR	Fourier transform infrared
g	gas
GCMS	gas chromatography mass spectrometry
h	hour
Hal	halogen
Hünig's base	diisopropylethylamine
Hz	Hertz unit
inf	Inflection
in vacuo	under reduced pressure
IR	infrared
J	coupling constant
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
l	liquid
LG	leaving group
lit.	literature
LRMS	low resolution mass spectrometry
m	multiplet (NMR) or medium (IR)
m/z	mass to charge ratio
M^+	molecular ion

m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeOH	methanol
MHz	megahertz unit
min	minutes
mmHg	millimeters of mercury (760 mmHg equals to 101325 Pa)
mp	melting point
MW	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
nm	nanometer unit
NMR	nuclear magnetic resonance
nr	no reaction
Nuc	nucleophile
^{o}C	celsius degrees
ox	oxidation
Ph	phenyl
PhCl	chlorobenzene
PhH	benzene
PhMe	toluene
PMHS	polymethylhydrosiloxane
ppm	parts per million
psi	pounds per square inch (1 psi equals to 6894.76 Pa)
p-TSA	4-toluenesulfonic acid
Py	pyridine
q	quartet
rt	room temperature (*ca.* 20 ^{o}C)
s	singlet (NMR) or strong (IR)
sat.	saturated
t	triplet
TCNE	tetracyanoethylene
TCNEO	tetracyanoethyleneoxide

Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
UV	ultra-violet
Vis	visible
w	weak (IR)
δ	chemical shift relative to a standard
λ_{max}	maximum wavelength
μl	microliter unit

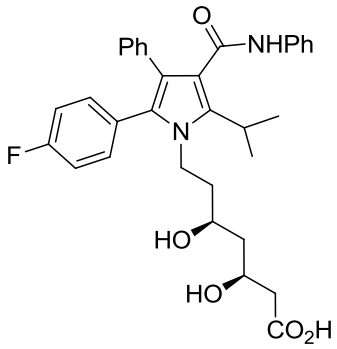
CHAPTER 1

Introduction

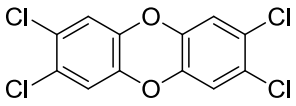
Contents

1.1. Heterocyclic Chemistry

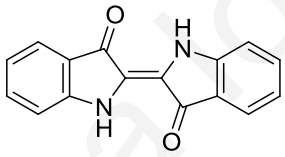
Heterocyclic compounds are beyond any doubt very important. About 50% of known organic compounds are heterocyclic and many find applications in everyday life, as drugs [*e.g.*, atorvastatin (trade name Lipitor®) which is a substituted pyrrole that lowers blood cholesterol],[1] agrochemicals [2,3,7,8-tetrachlorodibenzodioxin (TCDD) which was a component of Agent Orange used during the Vietnam War],[2] dyes (*e.g.*, indigo blue that is used to dye jeans),[3] and as components in organic electronics [*e.g.*, a polythiophene in organic solar cells].[4] Many common foods and beverages also contain heterocycles such as coffee (*e.g.*, caffeine[5]), fruit (*e.g.*, fructose[6]), meat (*e.g.*, the essential amino acid histidine[7]) etc.



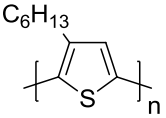
Atorvastatin



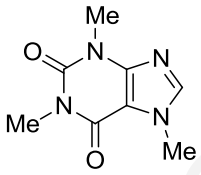
2,3,7,8-Tetrachlorodibenzodioxin



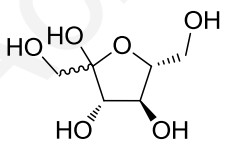
Indigo blue



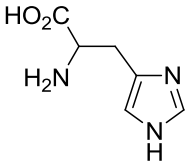
Polythiophene



Caffeine

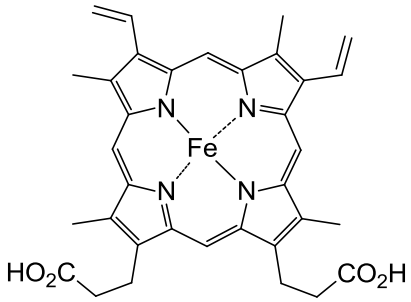


Fructose

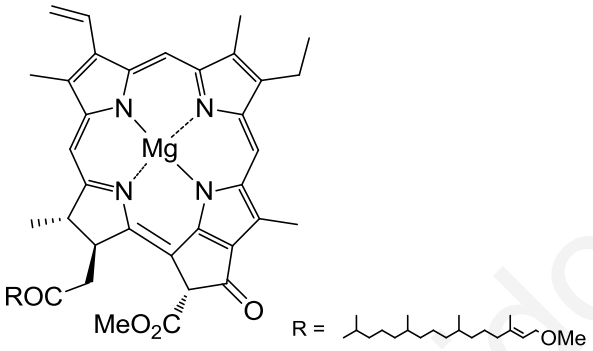


Histidine

Some heterocycles are biosynthesized by animals such as haem B, which is found in blood and is responsible for oxygen transport in the red blood cells[8] or by plants such as chlorophyll, which is essential for photosynthesis.[9]

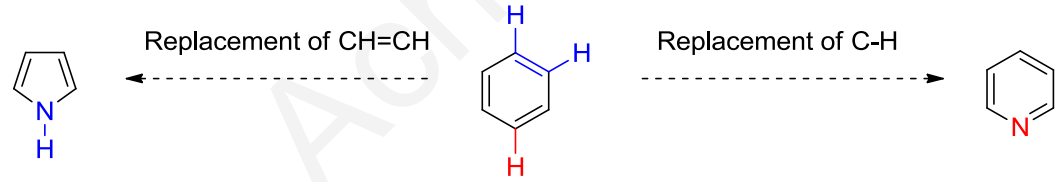


Haem B



Chlorophyll a

Fully unsaturated heterocyclic compounds that are planar and obey Hückel's aromaticity rule (4n + 2) are described as **aromatic** or **heteroaromatic** and some of them have similarities to benzene. Pyridine (azabenzene), for example, is formally derived from benzene on replacing one CH unit by N. Analogously, the formal replacement of a CH=CH unit in benzene by NH gives the 5-membered pyrrole (Scheme 1). The introduction of heteroatoms into the aromatic ring and the change of the ring size, can greatly affect the chemistry and physical properties of the ring systems.



Scheme 1

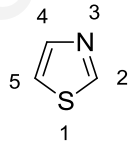
While there is a lot of literature investigating the chemistry and applications of compounds containing one heteroatom there are less reports on systems with more than one heteroatom (2 > 3 > 4 etc.). Interestingly, systems with two identical heteroatoms (*e.g.*, N such as pyrimidine, pyridazine, pyrazine, imidazole and pyrazole) have been better explored than those with mixed heteroatoms in the ring, such as O and N (*e.g.*, oxazole and isoxazole) or S and N (*e.g.*, thiazole and isothiazole) (Table 1).

Table 1. Number of publications that have appeared in the literature for selected heterocycles according to the Web of Science website based on the name of the heterocycle as keyword.

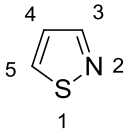
No. of heteroatoms	Heterocycle (Keyword)[a]	Year of appearance	No. of references
1	Pyridine	1900	67,389
2	Pyrimidine	1900	33,455
2	Pyridazine	1901	2,565
1	Pyrrole	1900	19,201
2	Pyrazole	1902	9,022
2	Imidazole	1901	24,731
1	Furan	1900	15,637
2	Oxazole	1906	1,865
2	Isoxazole	1909	3,152
1	Thiophene	1903	19,994
2	Thiazole	1910	**7,011**
2	Isothiazole	**1956**	**360**

[a] Keyword used in the search contains no additional filters.

The amount of work reported, in part is related to the relative abundance of the ring system in nature: thiazoles, which occur in many natural products, have received considerably more attention than the isomeric isothiazoles, natural products of which are rare. As such, there is considerable room for development of both the chemistry and applications of isothiazoles.



1,3-Thiazole



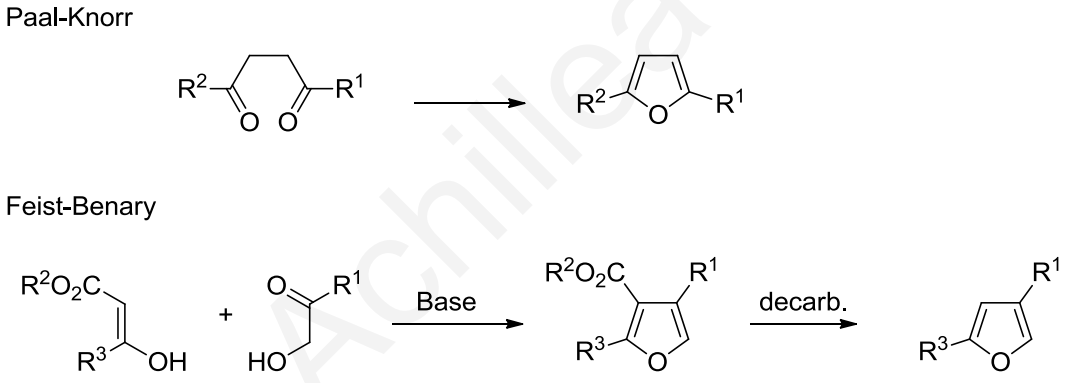
Isothiazole (1,2-Thiazole)

1.1.1 Synthesis of Heterocycles

The synthesis of a substituted compound with a heterocyclic core can follow two pathways: a) product specific, which includes cyclization of acyclic precursors to give directly the heterocycle with the desired substituents and b) non-product specific, which for example can be based on a readily available heterocyclic scaffold that can be further functionalized to afford the desired target compound.

1.1.1.1 Product Specific Synthesis

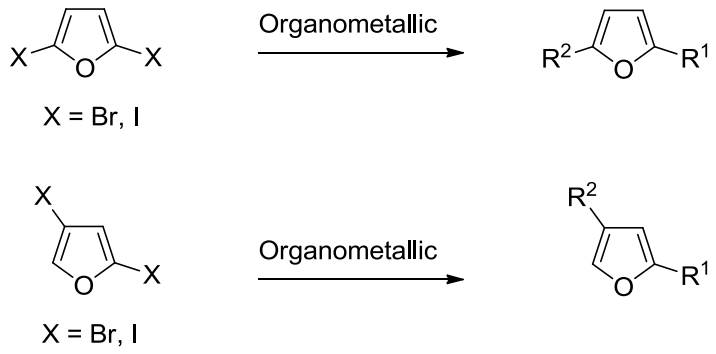
Representative examples of product specific syntheses, are the Paal-Knorr[10,11] cyclization of 1,4-diketones that gives 2,5-disubstituted furans and the Feist-Benary[12,13] synthesis which affords 2,4-disubstituted furans (Scheme 2). In these syntheses the desired substituents (R^1 and R^2) are present in the starting acyclic precursors.



Scheme 2

1.1.1.2 Non-Product Specific Synthesis

Alternatively, the use of 2,4- and 2,5-dihalofurans, which are readily available,[14,15] combined with modern methods in organometallic chemistry can offer fast non-product specific routes to 2,4- and 2,5-disubstituted furans, respectively (Scheme 3).



Scheme 3

When large libraries of heterocycles need to be prepared that vary in substituents R^1 and R^2 then the latter non-product specific route offers many advantages over the former, particularly with respect to cost and speed of library construction.

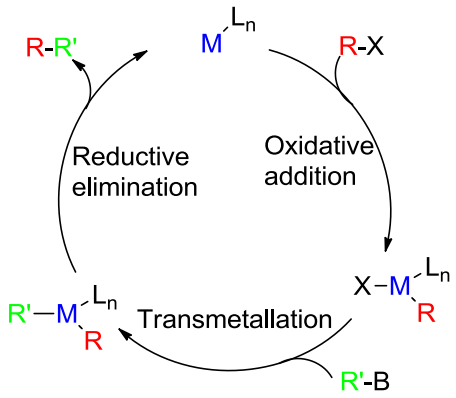
1.2 Organometallic Chemistry

In the second half of the 20th century the use of organometallic chemistry in synthesis has surged: novel synthetic methods, chemical compounds and catalysts have led to a chemical renaissance.[16] Several Nobel prizes have been awarded for the work on organometallics, and notably the 2010 Nobel Prize was awarded to Heck, Suzuki and Negishi for their work on C-C coupling reactions.

Inter- or intramolecular C-C and C-N coupling reactions can be performed, using a wide range of transition metal catalysts (*e.g.*, palladium, platinum, copper, silver, rhodium, ruthenium etc) allowing for the fast and efficient synthesis of aryl, heteroaryl, alkynylated, alkenylated and alkyl substituted systems. Many readily available halo-substituted compounds especially halo-heterocyclic scaffolds exist in the literature that can be easily derivatized by organometallic chemistry.

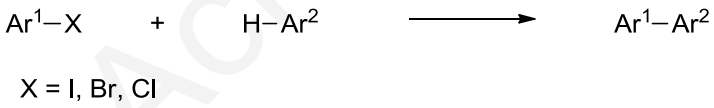
1.2.1 Mechanism of C-C and C-N Coupling Reactions

The mechanism for this type of reactions usually begins with an oxidative addition of one organic halide to the catalyst. The organometallic reagent undergoes transmetallation, a step that places both reagents on the same metal catalyst. Reductive elimination, the last step, affords the product, together with regeneration of the catalyst to continue the catalytic cycle (Scheme 4).[17]



Scheme 4

Despite the importance of C-C coupling reactions, they require access to expensive or sometimes difficult to make organometallics, such as boronic acids or esters (Suzuki-Miyaura coupling) or toxic stannyl reagents (Stille reaction) etc. The area of transition metal catalyzed **direct arylation**[18] which has developed rapidly over the last few years, overcomes this problem and offers an efficient route to useful compounds, by simply combining an organic halide with an active arene (Scheme 5).

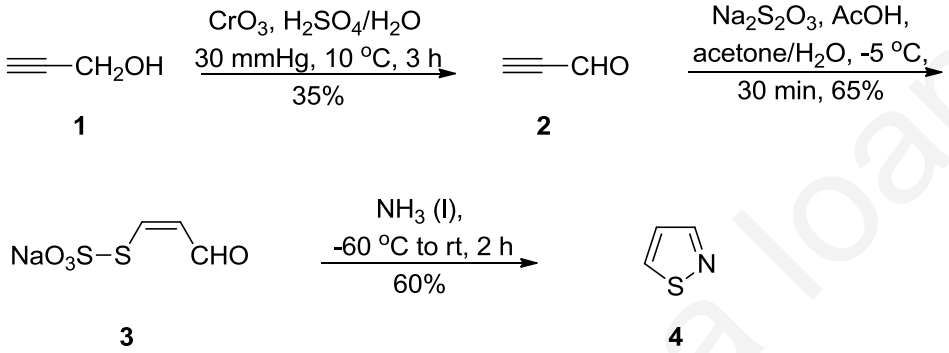


Scheme 5

There are a number of potentially useful and readily available isothiazole scaffolds. By applying the powerful C-C and/or C-N coupling techniques to these scaffolds it should be possible to both dramatically extend the known chemistry of isothiazoles and provide more facile routes to isothiazole derivatives.

1.3 Isothiazole Scaffolds

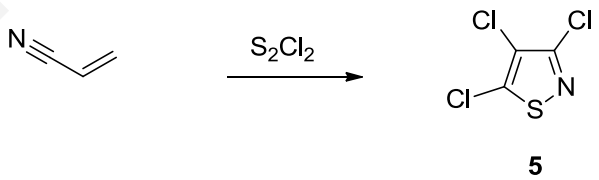
The most common routes to isothiazoles are *via* the formation of the N-S bond.[19] The parent isothiazole can be prepared in three steps starting from prop-2-yn-1-ol (propargyl alcohol) **1**. Oxidation of the latter with CrO_3 under reduced pressure gives propiolaldehyde **2**, which on treatment with sodium thiosulfate affords aldehyde dithionite **3**. Cyclization of **3** in NH_3 (l) gives isothiazole **4** in an overall yield of 14% (Scheme 6).[20]



Scheme 6

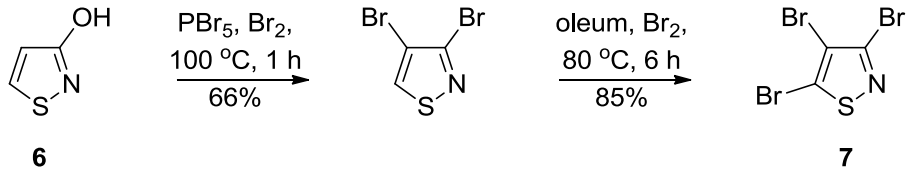
The parent isothiazole **4**, however, is a rather limited scaffold for further functionalisation. Its chemistry includes mainly base activation of the C-5 position and subsequent reaction with electrophiles.[21-23] There are also a few examples of substitution on the N-2 position.[24,25]

The potentially more useful 3,4,5-trichloroisothiazole **5** was synthesized by treatment of acrylonitrile with disulfur dichloride in 31% yield (Scheme 7),[26] however, only the *N*-methylation has been reported.[27]



Scheme 7

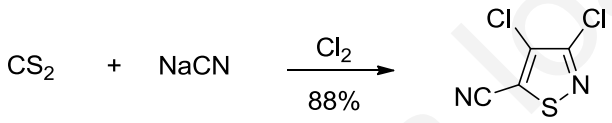
The analogous 3,4,5-tribromoisothiazole **7** was synthesized in two steps starting with 3-hydroxyisothiazole **6** (Scheme 8).[28] This isothiazole has been further derivatized using transition metal catalyzed C-C coupling chemistry (see Section 1.3.1).



6 **7**

Scheme 8

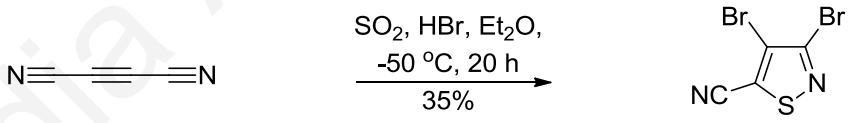
Another useful halo-substituted isothiazole is the 3,4-dichloroisothiazole-5-carbonitrile **8** which is readily available in good yield by reaction of carbon disulfide, sodium cyanide and chlorine gas (Scheme 9).[29] An alternative synthesis involves heating a mixture of trichloroacetonitrile and elemental sulfur at 300 °C.[30]



8

Scheme 9

The analogous 3,4-dibromoisothiazole-5-carbonitrile **9** was synthesized by treatment of dicyanoacetylene with sulfur dioxide and hydrogen bromide (Scheme 10).[31] This route is limiting because of the low yielding synthesis and the need to prepare dicyanoacetylene.

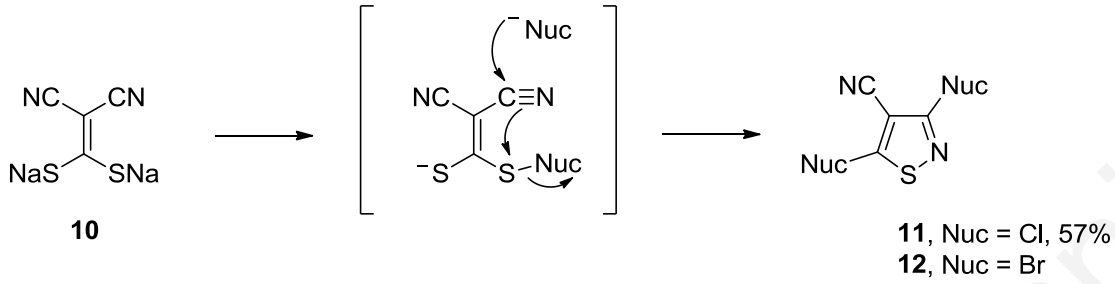


9

Scheme 10

In 1964 Hatchard reported a two step synthesis of another useful scaffold 3,5-dichloro-isothiazole-4-carbonitrile **11**. Treating a mixture of malononitrile and carbon disulfide in EtOH with sodium hydroxide gave sodium 2,2-dicyanoethene-1,1-bis(thiolate) **10** in high yield. This salt cyclized on treatment with chlorine gas to afford 3,5-dichloroisothiazole-4-carbonitrile **11** in 57% yield. The analogous 3,5-dibromoisothiazole-4-carbonitrile **12** was also

prepared on treatment of **10** with excess bromine, but the yield was not reported (Scheme 11).[32]

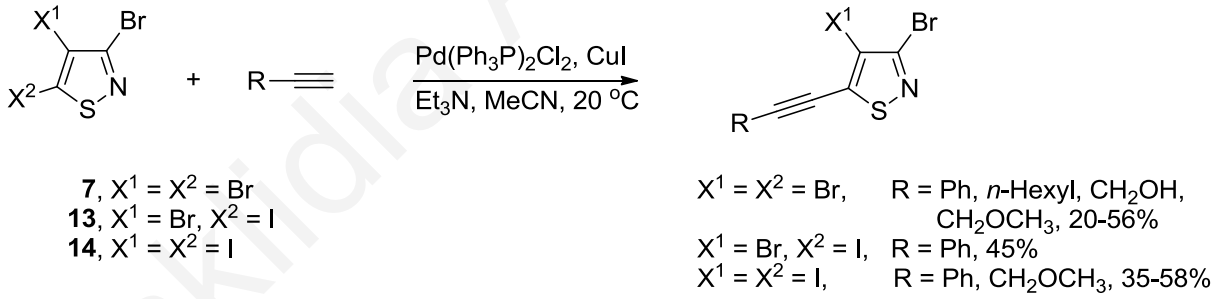


Scheme 11

Several of these scaffolds have already been exploited as for the development of organometallic mediated protocols for the non-product specific synthesis of isothiazoles.

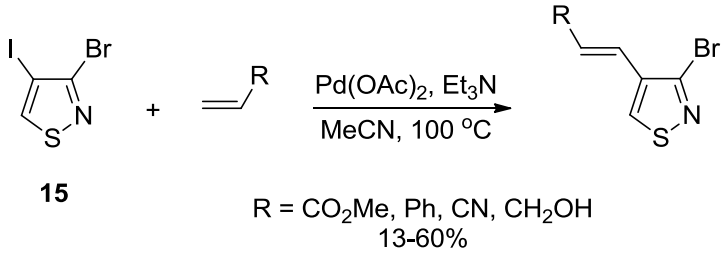
1.3.1 Transition Metal Mediated Modification of Isothiazole Scaffolds

Recently, C-C coupling reactions were applied on some halogenated isothiazoles. More specifically, 3,4,5-tribromoisothiazole **7**, 3,4-dibromo-5-iodoisothiazole **13** and 3-bromo-4,5-diiodoisothiazole **14** underwent Sonogashira C-C coupling reaction to afford the 5-alkynylated products in low to moderate yields (Scheme 12).[33]



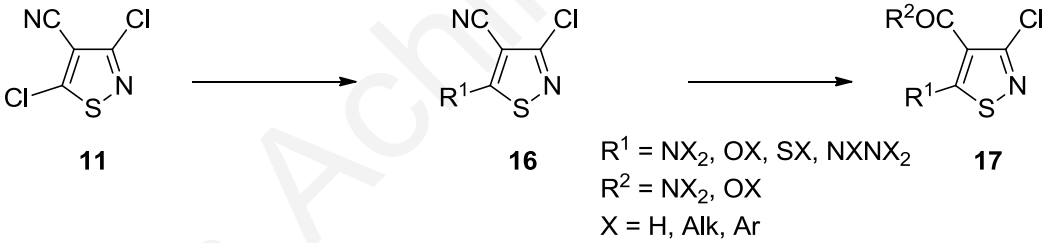
Scheme 12

The tribromoisothiazole **7** failed to give a regioselective Heck coupling reaction at C-5 due to protodebromination of the starting isothiazole to 3,4-dibromoisothiazole. A successful Heck reaction was eventually achieved at the C-4 position of 3-bromo-4-iodoisothiazole **15** in low to moderate yields using $Pd(OAc)_2/Et_3N$ in refluxing MeCN (Scheme 13).[34]



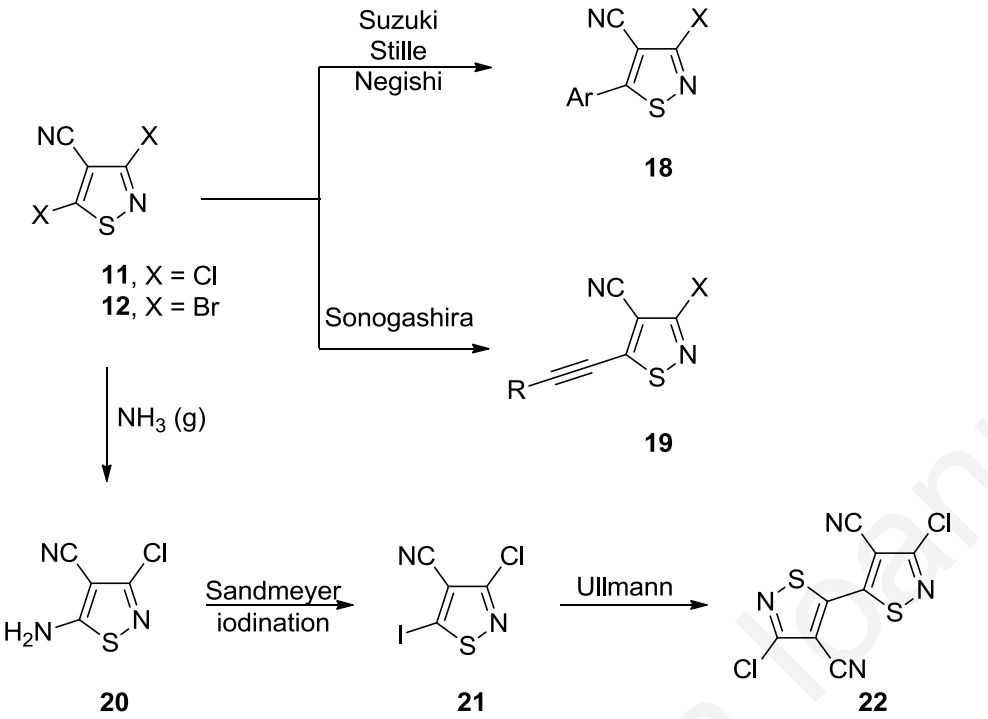
Scheme 13

The 3,5-dihaloisothiazole-4-carbonitriles **11** (Hal = Cl) and **12** (Hal = Br) mentioned above (Scheme 11), appeared to be superior building blocks, owing to their facile synthesis, the presence of a stable nitrile substituent at C-4 that could be modified readily at later stages and the presence of two non-chemically equivalent halogen substituents at C-3 and C-5 that promised potential chemoselectivity. The chemistry of 3,5-dihaloisothiazole-4-carbonitriles **11** (Hal = Cl), however, until recently, was limited to mostly nucleophilic displacement of the C-5 halogen forming 5-amino, alkoxy and thio-substituted isothiazoles **16** and further modification of the C-4 nitrile to give amides, esters and acids **17** (Scheme 14).[32]



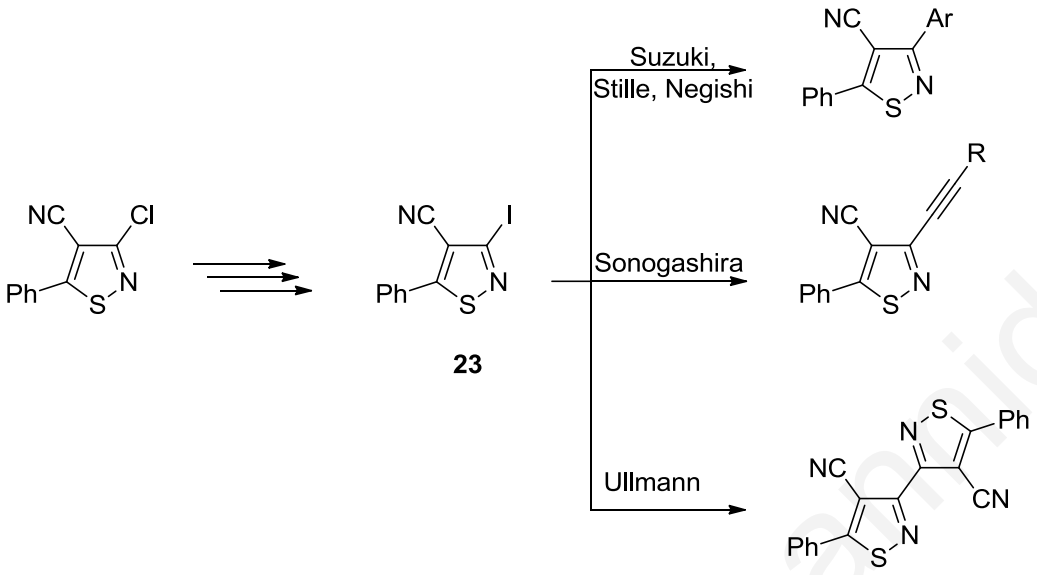
Scheme 14

Suzuki, Stille, Sonogashira and Negishi coupling reactions on isothiazoles **11** and **12**, were recently demonstrated by Christoforou *et al.*,[35,36] affording 3-chloro and 3-bromo-5-aryl and 5-alkynylated isothiazole-4-carbonitriles **18** and **19** in very high yields (Scheme 15). Furthermore, a successful Ullmann type reaction of 3-chloro-5-iodoisothiazole-4-carbonitrile **21** (which was prepared from readily available 5-amino-3-chloroisothiazole-4-carbonitrile **20**[32] using either catalytic or stoichiometric $Pd(OAc)_2$ in refluxing DMF gave the 5,5'-bisisothiazole **22** in high yield (Scheme 15).[36]



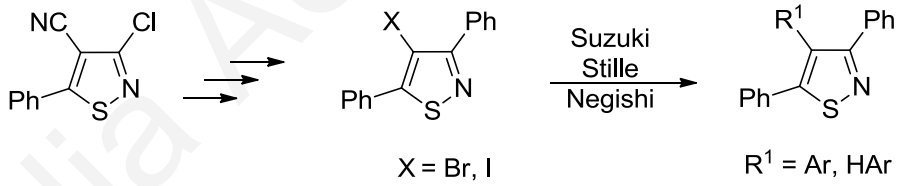
Scheme 15

The 5-aryl-3-chloroisothiazole-4-carbonitriles were also useful scaffolds as further chemistry could be achieved at both C-3 and C-4. Coupling at C-3, however, required activation since the chlorine atom at this site was not sufficiently reactive. This was overcome by converting the chlorine atom at C-3 into the more reactive iodine using a 3-step protocol which included nucleophilic displacement of chlorine by benzylamine, deprotection to afford the 3-amino-isothiazole, which on Sandmeyer iodination gave the desired 3-iodoisothiazole **23**. The latter was shown to undergo successfully Suzuki, Stille, Negishi, Sonogashira and Ullmann type reactions (Scheme 16).[36]

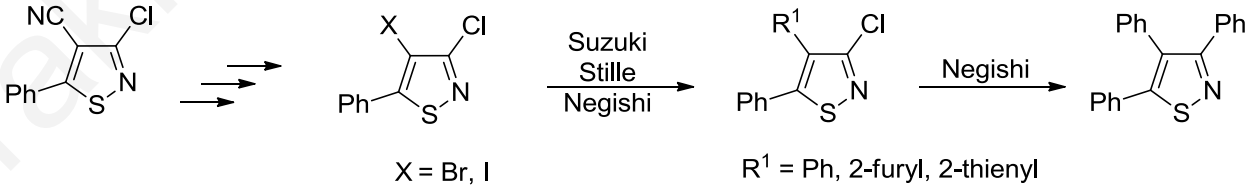


Scheme 16

Later, Christoforou *et al.*,[37] also demonstrated that the isothiazole could be modified in all positions synthesizing 3,4,5-triarylisothiazole *via* two different sequences *i.e.* C-5:C-3:C-4 and C-5:C-4:C-3. While the first sequence worked well for all three Suzuki, Stille and Negishi reactions, the second sequence which involved arylation of the C-3 position at the last step, worked only under Negishi conditions (Scheme 17 and 18).



Scheme 17



Scheme 18

The availability of useful sulfur-nitrogen heterocyclic scaffolds that can be exploited is not limited to 5-membered heterocycles such as isothiazole. Useful 6-membered scaffolds exist

and somewhat similar to 3,5-dichloroisothiazole-4-carbonitrile **11** is 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (Scheme 19). Both isothiazole **11** and thiadiazinone **24** contain a three carbon unit in the ring skeleton, adjacent mixed N and S heteroatoms, a Cl-N=S unit, and two active chlorines at the extremities of the three carbon skeleton separated by a central electron deficient carbon substituted by an electron withdrawing group (C-C≡N *vs* C=O). Furthermore, both have existed for some time in the literature but have had comparatively little chemistry reported.

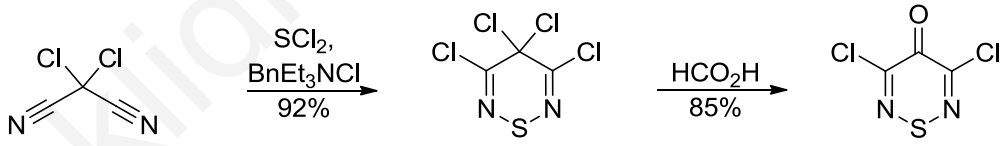
11 **24**

Scheme 19

1.4 3,5-Dichloro-4*H*-1,2,6-thiadiazin-4-one

*1.4.1 Synthesis of 3,5-Dichloro-4*H*-1,2,6-thiadiazin-4-one 24 and Related Thiadiazines*

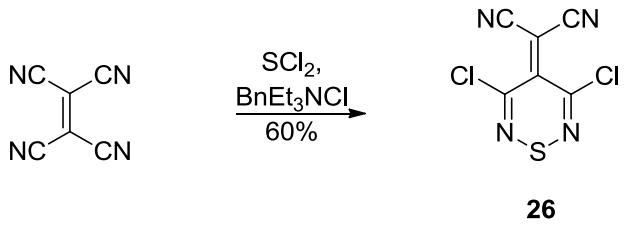
3,5-Dichloro-4*H*-1,2,6-thiadiazin-4-one **24** is readily available and can be made in two steps starting from dichloromalononitrile. This reacts with sulfur dichloride to afford the tetrachloro-1,2,6-thiadiazine **25**, which after treatment with formic acid can give the thiadiazinone **24** in good overall yield (78%) (Scheme 20).[38]



25 **24**

Scheme 20

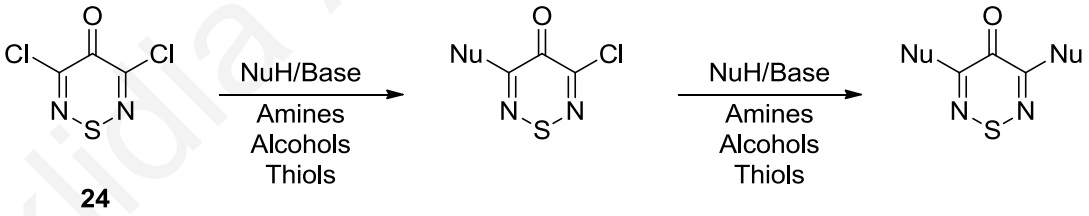
Interestingly, the condensation reaction of thiadiazinone **24** with malononitrile was unsuccessful, but the analogous 4-dicyanomethylene, 2-(3,5-dichloro-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile **26** was synthesized from tetracyanoethylene (TCNE) on treatment with sulfur dichloride in moderate yield (Scheme 21).[39,40]



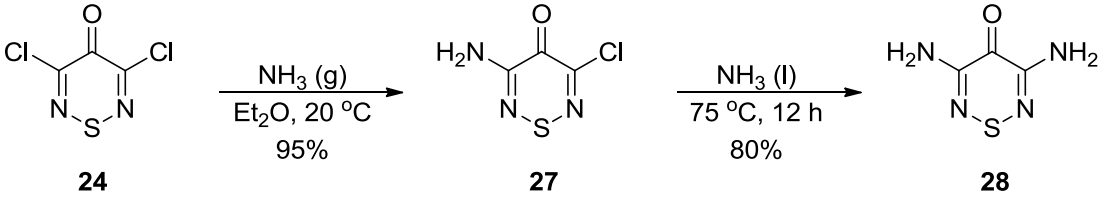
Scheme 21

*1.4.2 Chemistry of 3,5-Dichloro-4*H*-1,2,6-thiadiazin-4-one 24 and Related Thiadiazines*

While the chemistry of the thiadiazine-oxides and dioxides has been well explored,[41,42] that of the non-oxidized 4*H*-1,2,6-thiadiazines has not. The majority of work on 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** and its 4-dicyanomethylene analogue **26** revolves around the nucleophilic substitution of the C-3 and/or C-5 chlorine atoms by nitrogen, oxygen and sulfur nucleophiles (Scheme 22).[43-45] Interestingly, while the initial nucleophilic displacement of the one chlorine atom occurred rapidly and under mild conditions, the second required harsher conditions. For example, while the mono-amino substitution reaction of dichlorothiadiazinone **24** with NH_3 (g) occurs at rt affording the 3-amino-5-chloro-4*H*-1,2,6-thiadiazin-4-one **27** in quantitative yield, the formation of the bis-amino compound **28** required prolonged heating of the mono-amino compound **27** in liquid ammonia in a sealed tube (Scheme 23).

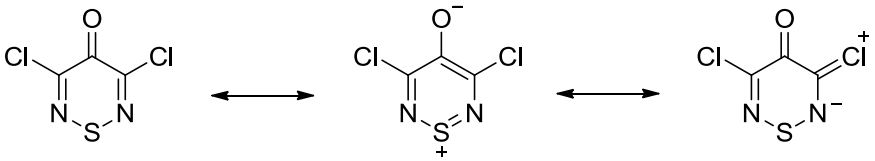


Scheme 22



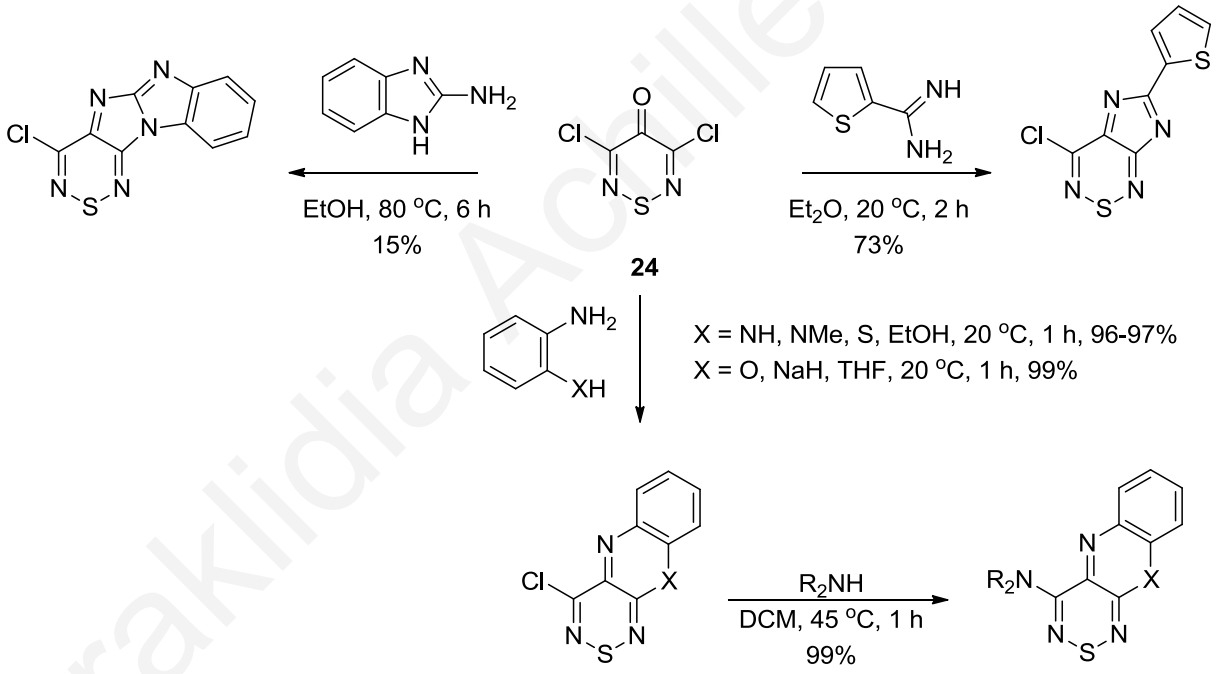
Scheme 23

Furthermore, while the C-4 position bears a carbonyl group, its selective modification in the presence of the highly reactive chlorines at C-3 and C-5, was difficult. Resonance structures indicate considerable electron density on the carbonyl oxygen and this may partially explain the carbonyl's poor reactivity (Scheme 24).



Scheme 24

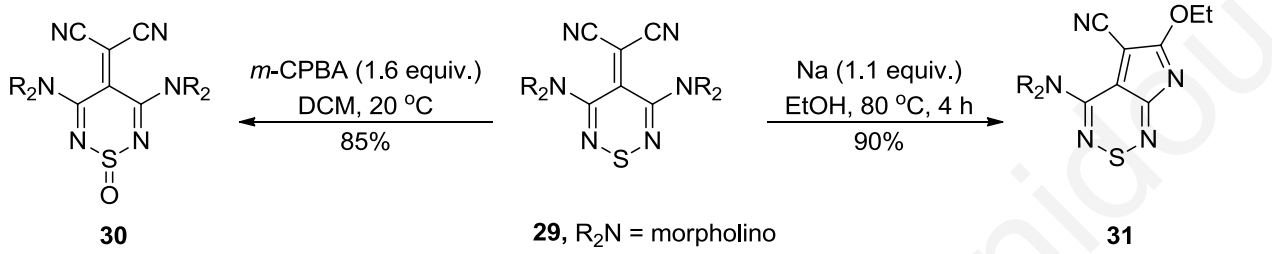
Nevertheless, an intramolecular cyclization onto the carbonyl group was achieved using bis-nucleophiles (*e.g.*, 1,2-diaminobenzene, 2-aminophenoxide, *N*-methyl-1,2,-diaminobenzene etc). Initial displacement of C-3 chlorine by the bisnucleophile was followed by an intramolecular cyclocondensation onto the carbonyl to give fused thiadiazines (Scheme 25).[43]



Scheme 25

In a similar manner the ylidenemalononitrile **26** can react with nucleophiles to afford mono- and eventually bis-substituted systems. Bis-amino substituted ylidenemalononitriles **29** can react further: in the presence of *m*-CPBA the sulfoxide **30** can be formed while with sodium

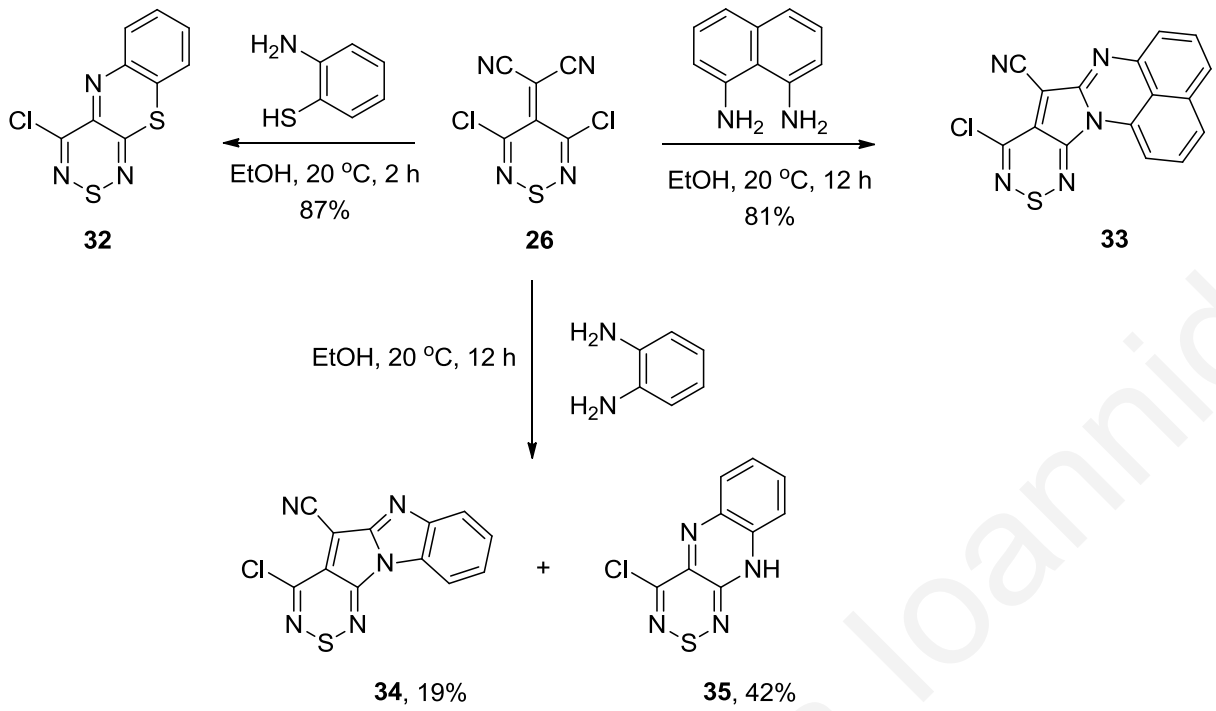
ethoxide the cyclized 6-ethoxy-4-morpholinopyrrolo[2,3-c][1,2,6]thiadiazine-5-carbonitrile **31** was obtained (Scheme 26).[44-46]



30 **29**, R_2N = morpholino **31**

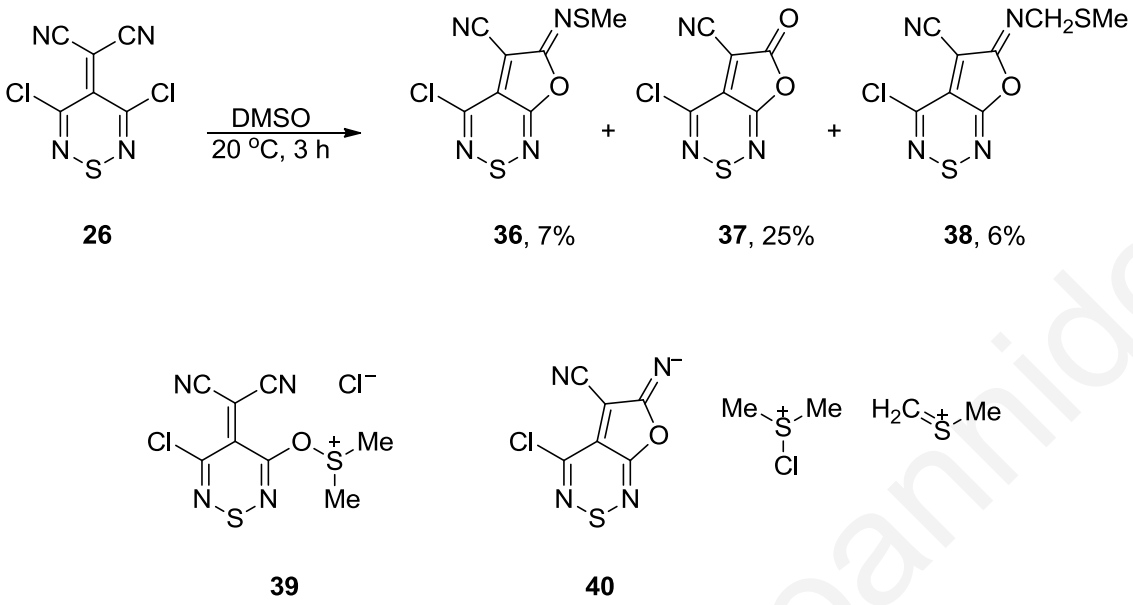
Scheme 26

Cyclization to form fused thiadiazine systems, in a similar way to that of thiadiazinone **24**, can also occur when the ylidenemalononitrile **26** reacts with bis-nucleophiles such as 1,2-diamino-benzene, 2-aminobenzenethiol and 1,8-diaminonaphthalene (Scheme 27). With the ylidene-malononitrile **26** the cyclization can occur either at C-4 to afford 6-membered fused compounds by displacing malononitrile (*e.g.*, with 2-aminobenzenethiol, 4-chlorobenzo [5,6][1,4]thiazino[2,3-c][1,2,6]thiadiazine **32** is formed), or at the nitrile group to afford the 5-membered fused compounds (*e.g.*, with 1,8-diaminonaphthalene, 9-chloro-[1,2,6]thiadiazino[4',3':4,5]pyrrolo[1,2-a]perimidine-8-carbonitrile **33** is formed). When 1,2-diaminobenzene was used, both 5-membered and 6-membered fused systems **34** and **35** were formed with the main product being the latter (Scheme 27).[43]



Scheme 27

Unexpectedly, the ylidenemalononitrile **26** reacts with DMSO to form the unprecedented products **36**-**38**. A possible mechanism was proposed and included initial attack of DMSO (as the nucleophile) and displacement of the chlorine to afford the intermediate salt **39**. This on cleavage could form an anion on the oxygen atom, which on subsequent cyclization onto the nitrile could afford product **36**. The formation of the other products can be explained by further reaction of anion **40** with DMSO species (Scheme 28).[46]



Scheme 28

While the 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** bears two chlorine atoms which can readily be modified using non product specific routes (such as organometallic chemistry shown above for the isothiazoles), the known chemistry for the system is presently restricted to only nucleophilic displacement of the chlorines and some intramolecular cyclocondensation reactions.

In this thesis we will examine (Part 2) the potential organometallic mediated chemistry of this useful thiadiazinone scaffold **24**. Particular emphasis will be placed on synthesizing symmetrical and non symmetrical bis-arylated thiadiazinones using non product specific, divergent routes and investigating the reactivity of the C-4 position.

Furthermore, the related 3,5-dihaloisothiazole-4-carbonitrile **11** and **12** scaffolds will be investigated further (Part 1) for its activity towards different types of reagents/reactions emphasizing the synthesis of new isothiazole analogues.

In the third and last part of the thesis, the three-step synthesis of canthinone-1-carboxylates will be described by applying the C-C and C-N coupling methods on bromonaphthyridines. This work is non-related with the projects described in parts 1 and 2 and is considered as "Extra work".

PART 1

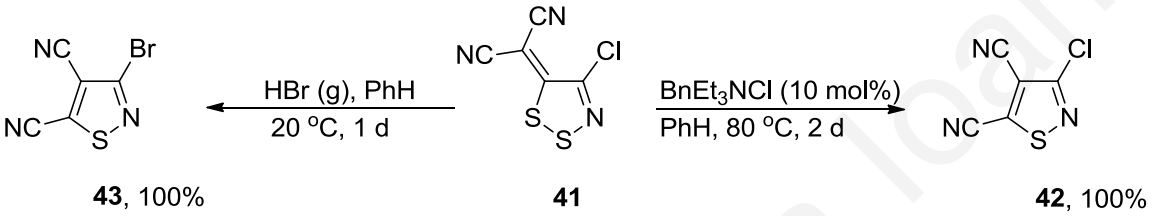
CHAPTER 2

Regioselective Hydrodehalogenation of 3,5-Dihaloisothiazole-4-carbonitriles: Synthesis of 3-Haloisothiazole-4-carbonitriles

Sections

2.1 Introduction

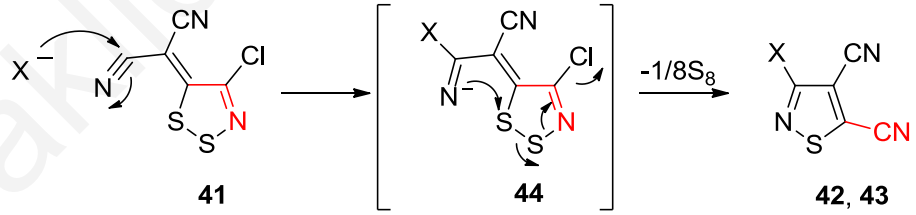
3-Haloisothiazole-4,5-dicarbonitriles **42** (Halo = Cl) and **43** (Halo = Br)[47,48] are important building blocks for the synthesis of new isothiazole biocides.[49] The former can be prepared quantitatively by treating (dithiazolylidene)malononitrile **41** with tetraalkylammonium chloride in refluxing PhH for 2 days while the latter can be prepared in high yield (83%) by treating (dithiazolylidene)malononitrile **41** with hydrogen bromide in toluene for 1 day (Scheme 29).



43, 100% **41** **42**, 100%

Scheme 29

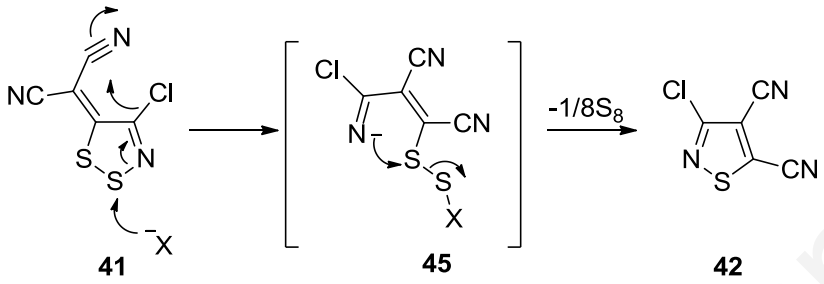
An early proposed mechanism for the formation of isothiazoles **42** and **43** involved nucleophilic attack by either bromide or chloride on the nitrile group leading to the formation of the intermediate **44** which undergoes a variant of the Boulton-Katritzky rearrangement in which a three-atom side chain on a 5-membered heterocycle cyclizes onto that ring forcing the ring to open to afford a new 5-membered heterocycle.[50] Intramolecular cyclization of the proposed imidine intermediate **44** onto the dithiazole ring sulfur atom (S-1) afforded the aromatic isothiazole; concomitant cleavage of the dithiazole released the new nitrile group (Scheme 30).



Scheme 30

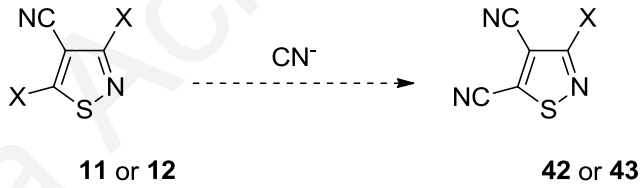
In the case of the chloro analogue, an alternative thiophilic mechanism could also be proposed, which includes initial attack of the nucleophile onto the S-2 sulfur to form the disulfide **45** after a transfer of the chlorine C-5 atom onto the nitrile. The intermediate **45** can

then cyclize, like before, to afford the isothiazole **42** (Scheme 31). This can be supported by examples in the literature where thiophilic reagents attack first the S-2 atom.[48,51]



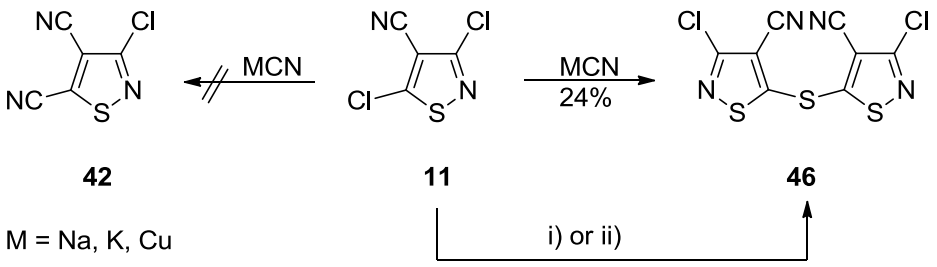
Scheme 31

The high yielding conversion of (dithiazol)ylidene **41** into 3-haloisothiazole-4,5-dicarbonitriles **42** (Halo = Cl) and **43** (Halo = Br) suffers from the drawback of requiring access to the ylidene, although considerable efforts have been made to prepare this ylidene at lower cost. In an attempt to further reduce the cost for the preparation of these isothiazoles we attempted a shorter and more rational synthetic route by displacement of the C-5 isothiazole's halide of 3,5-dihaloisothiazole-4-carbonitriles **11** and **12** which are readily available[32] by cyanide (Scheme 32).[52]



Scheme 32

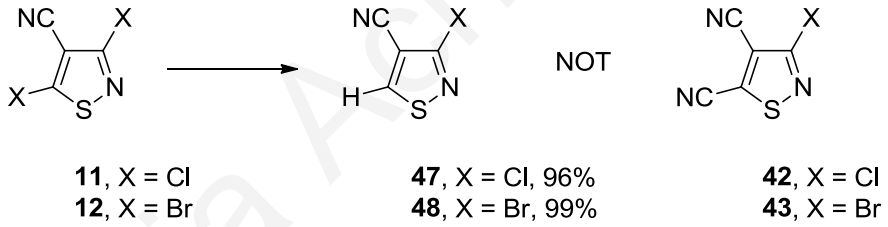
Previous efforts to introduce a nitrile group at the C-5 position of 3,5-dichloroisothiazole-4-carbonitrile **11** using CuCN at 160-250 ^{o}C gave 5,5'-thiobis(3-chloroisothiazole-4-carbonitrile) **46** in 24% yield together with unreacted 3,5-dichloroisothiazole-4-carbonitrile **11** (48%).[53,54] Cyanide, which is a known thiophile,[55-58] presumably attacked the ring sulfur to generate a source of nucleophilic sulfur which then attacks the C-5 position of the isothiazole ring to form the sulfide **46**. Independent synthesis of the sulfide **46** using MSCN (M = Na, K, Cu) or Na_2S led only to the isolation of 5,5'-thiobis(3-chloroisothiazole-4-carbonitrile) **46** in 77 and 46 %, respectively (Scheme 33).[53,54]



Reagents and conditions: i) NaSCN, acetone, 60 ^{o}C, 77%; ii) $Na_2S.10H_2O$, H_2O / MeOH, 45 ^{o}C, 15 min, 46%.

Scheme 33

As such, alternative cyanating agents such as $Zn(CN)_2$, $K_4[Fe(CN)_6]$, Bu_3SnCN, Me_3SiCN were tried under palladium catalysis but none of them gave the desired product. In most cases, the starting material could be recovered. In the case where $Zn(CN)_2$ was used, in the presence of $Pd(OAc)_2$ (1 equiv) and PMHS, the C-5 protodebrominated product, 3-chloroisothiazole-4-carbonitrile **47** was isolated in high yield (96%) (Scheme 34). Similar treatment of 3,5-dibromo **12** gave 3-bromoisothiazole-4-carbonitrile **48** in 99% yield.

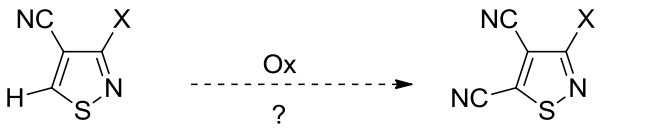


Reagents and conditions: $Zn(CN)_2$ (1 equiv.), $Pd(OAc)_2$ (0.1 equiv.), DPPF (0.01 equiv.), PMHS (few drops), PhMe, 110 ^{o}C

Scheme 34

To the best of our knowledge the preparation of 3-bromoisothiazole-4-carbonitrile **48** had not been reported and while 3-chloroisothiazole-4-carbonitrile **47** has been prepared in good yield (76%) from the protodecarboxylation of 3-chloro-4-cyanoisothiazole-5-carboxylic acid,[36] this route required access to 3-chloroisothiazole-4,5-dicarbonitrile **42**[47] and was considered expensive. As such, we investigated the regioselective hydrodehalogenation of 3,5-dihaloisothiazole-4-carbonitriles **11** (Hal = Cl) and **12** (Hal = Br) with the objective of developing a gram scale and inexpensive route to 3-halo-isothiazole-4-carbonitriles **47** (Hal =

Cl) and **48** (Hal = Br), respectively. The dehalogenated isothiazoles **47** and **48** could then undergo oxidative direct cyanation to afford the desired 5-cyano systems **42** and **43** (Scheme 35).



47, X = Cl
48, X = Br

42, X = Cl
43, X = Br

Scheme 35

A wide variety of hydrodehalogenated systems have been developed.[59,60] In mixed halogen systems the ease of hydrodehalogenation follows the order of I > Br > Cl ≥ F in line with the C-Hal bond dissociation energies.[61-67] Interestingly, there are comparatively few examples of regioselective hydrodehalogenations and typically the halogen most susceptible to nucleophilic displacement hydrodehalogenated first.[68] As such, hydrodehalogenation of 3,5-dichloro and 3,5-dibromoisothiazole-4-carbonitriles **11** and **12** was expected to occur regioselectively at C-5, since the C-5 halogen was by far the most susceptible to nucleophilic displacement.[32,53,69-72]

2.2 Dehalogenation of 3,5-Dibromo- and 3,5-Dichloroisothiazole-4-carbonitriles

2.2.1 C-5 Hydrodebromination of 3,5-Dibromoisothiazole-4-carbonitrile

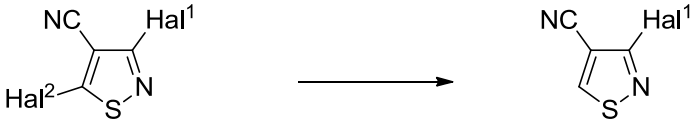
Initially we focused our attention on the 3,5-dibromoisothiazole-4-carbonitrile **12**. Reducing agents such as $NaBH_4$ in MeOH, H_2 or HCO_2H with Pd/C, i-PrOH with Mg, or $SnCl_2$ (DCM) failed to give any product and the starting isothiazole could be recovered while the use of thiourea (EtOH) led to intractable polar products (baseline on TLC). Nevertheless, a successful hydrodebromination was achieved with the use of Zn powder (2 equiv) in refluxing AcOH for 1 h and with In powder (2 equiv) in refluxing H_2O for 24 h or in refluxing HCO_2H for 2 h affording 3-bromoisothiazole-4-carbonitrile **48** in moderate yields 40, 53 and 40%, respectively. In all cases hydrogen sulfide (H_2S) was detected indicating reductive cleavage of the isothiazole ring. The reaction conditions were partially optimized with respect to the metal and its equivalents, the solvent (hydrogen source) and the reaction temperature.

Lowering the reaction temperature to *ca.* 15 ^oC and performed without heating, reduced the formation of H_2S and subsequently the hydrodebromination of 3,5-dibromoisothiazole-4-carbonitrile **12** but this required the addition of at least 5 equivalents of either Zn or In powder to get good product yields. Reducing the equivalents led to longer reaction times and in most cases unreacted isothiazole could be recovered even after 24 h. While increasing the equivalents of Zn (10 equiv) improved the reaction times, the product yields dropped significantly. At elevated temperatures, the product yields dropped and a strong odour of H_2S could be detected. In this regard, switching from acetic (mp 16.5 ^oC, pK_a 4.76) to formic acid (mp 8.4 ^oC, pK_a 3.75) was superior, as the latter not only was a better source of hydrogen[68] but also had a lower melting point facilitating its use at these lower reaction temperatures. On switching to formic acid the reaction times and product yields improved significantly (Table 2).

Interestingly, switching to the significantly stronger trifluoroacetic acid (pK_a 0.65) led to predominantly unreacted isothiazole even after extended reaction times. It has been reported previously that use of strong acids with either Zn (or to hydrodehalogenate) can fail owing to the extremely rapid rates of hydrogen evolution.[73] On scaling the reaction of 3,5-dibromoisothiazole-4-carbonitrile **12** (200 mg, 0.75 mmol) with either Zn or In (5 equiv) in formic acid, the advantageous yields seen with the use of In powder on the smaller scales became negligible 74 *vs* 78%, respectively. In light of the relative costs of Zn and In we

subsequently carried out the hydrodebromination reaction on a 1 g scale only using Zn powder to get the target 3-bromoisothiazole-4-carbonitrile **48** in 70% yield without the need for chromatography.

Table 2 Reaction of 3,5-dihaloisothiazole-4-carbonitriles **11-12** (0.25 mmol) with Zn or In (5 equiv.) in neat acid (1 mL) at 10-25 °C.



11, 12 **47, 48**

Hal^1	Hal^2	Metal	Acid	Time (h)	Yield (%)
Br	Br	Zn	AcOH	24	59
Br	Br	Zn	HCO_2H	0.17	66
Br	Br	Zn	TFA	24	[a]
Cl	Cl	Zn[b]	HCO_2H	1	15
Br	Br	In	AcOH	22	67
Br	Br	In	HCO_2H	3.50	93
Br	Br	In	HCO_2H	5.50	78[c]
Cl	Cl	In	HCO_2H	24	Traces
Br	Br	Zn	HCO_2H	0.15	74[c]
Br	Br	Zn	HCO_2H	0.33	70[d]

[a] Incomplete, complex reaction, mainly starting isothiazole.
[b] 7.5 equiv. (on a 1 g scale yield rose to 23%).
[c] 200 mg scale based on starting isothiazole / acid (3 mL).
[d] 1 g scale based on starting isothiazole / acid (15 mL).

The best conditions Zn or In (5 equiv), formic acid, 10-25 °C were then applied to the 3,5-dichloro analogue. Interestingly, 3,5-dichloroisothiazole-4-carbonitrile **11** treated with Zn powder (5 equiv) failed to give a complete reaction even after 24 h. The reaction finished within 2 h when additional Zn (2.5 equiv) was added but the desired product was isolated in low yield (15%) and a strong odour of H_2S was noticeable indicating reductive cleavage of the isothiazole ring. When In (5 equiv) was used, almost no reaction was observed. Indium has a

lower reduction potential than zinc [-0.763 (Zn) *vs* -0.338 V (In)] and is considered to be a more selective reagent.[74]

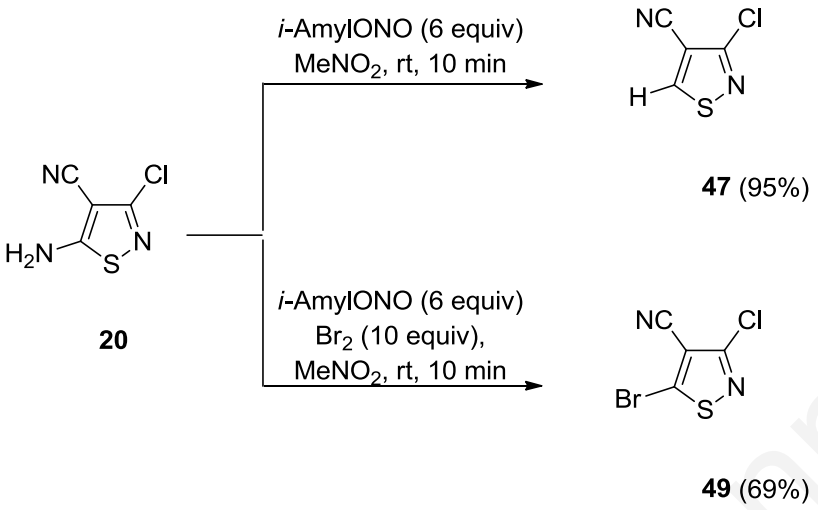
Presumably, the bond dissociation energy[75] of the C-Cl (397), C-Br (280) and C-S (272 kJ/mol) bonds played a role in the release of H_2S. In the presence of a chlorine atom at C-5 and thus a significantly stronger bond, reductive ring cleavage presumably became competitive. In light of this we searched for an alternative route to 3-chloroisothiazole-4-carbonitrile **47** by either Sandmeyer hydrodeamination of 5-amino-3-chloroisothiazole-4-carbonitrile **20** or by Sandmeyer hydrodehalogenation of either 5-bromo or 5-iodo substituted 3-chloroisothiazole-4-carbonitriles.

2.3 Alternative Synthesis of 3-Chloroisothiazole-4-carbonitrile

2.3.1 Sandmeyer Reactions of 5-Amino-3-chloroisothiazole-4-carbonitrile 20

5-Amino-3-chloroisothiazole-4-carbonitrile **20** can be readily prepared and isolated chromatography free by treating 3,5-dichloroisothiazole-4-carbonitrile **11** with dry ammonia in THF.[32] Sandmeyer chemistry could afford the desired 3-chloroisothiazole-4-carbonitrile **47** either directly *via* a hydrodeamination, or indirectly *via* a halodeamination followed by hydrodehalogenation. Reaction of 5-amino-3-chloroisothiazole-4-carbonitrile **20** with isoamyl nitrite (6 equiv) in $MeNO_2$ at *ca.* 20 ^oC for 10 min, gave the desired 3-chloroisothiazole-4-carbonitrile **47** in 95% yield (Scheme 36). When MeCN was used as the solvent, the reaction at *ca.* 20 ^oC gave the desired product in 65% (20 min reaction) while at reflux the product was isolated in 96% yield (10 min).

The Sandmeyer iododeamination of 5-amino-3-chloroisothiazole-4-carbonitrile **20** using isoamyl nitrite and iodine was reported earlier.[36] Similar treatment of 5-amino-3-chloroisothiazole-4-carbonitrile **20** with isoamyl nitrite (6 equiv) and dibromine (10 equiv) in nitromethane, gave 5-bromo-3-chloroisothiazole-4-carbonitrile **49** in 69% yield together with traces of 3-chloroisothiazole-4-carbonitrile **47** (Scheme 36). The use of less isoamyl nitrite or less dibromine led to more hydrodeamination product and lower yields of the halodeaminated isothiazole. With access to both the 5-bromo and the 5-iodo 3-chloroisothiazole-4-carbonitriles **49** and **21** the above hydrodehalogenation conditions could be compared directly against the series I *vs* Br *vs* Cl.

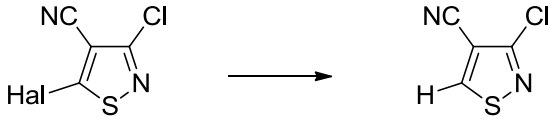


Scheme 36

2.4 Dehalogenation of Dihaloisothiazoles

Hydrodehalogenation of either 5-bromo or 5-iodo 3-chloroisothiazole-4-carbonitriles **49** and **21** in neat formic acid with Zn powder (5 equiv) gave 3-chloroisothiazole-4-carbonitrile **47** in 77 and 51% yields, respectively. The latter hydrodeiodination gave a strong odour of H_2S indicating isothiazole ring cleavage and possibly accounted for the moderate yield of product. This could be owed to a possible exothermic reaction and as such, the reaction was repeated with less Zn (3 equiv) over a 25 min period, however, no improvement in the yield was observed (56%). Although, reaction with Zn (3 equiv) in AcOH gave a fast reaction (40 min) and 86% yield of the desired product. The analogous reactions with In powder (5 equiv) took slightly longer but gave the hydrodebrominated and deiodinated products in comparable and better yields, 75 and 86% yields, respectively (Table 3).

Table 3 Reaction of 5-halo-3-chloroisothiazole-4-carbonitriles **11, 21, 49** (0.25 mmol) with Zn or In in HCO_2H (1 mL) at 10-25 °C.



11, 21, 49 **47**

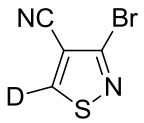
Hal	Metal (equiv)	Time (h)	Yield (%)
Cl	Zn (7.5)	2	15
Br	Zn (5)	0.67	77
I	Zn (5)	0.25	51
I	Zn (3)	0.42	56
I	Zn (3)[a]	0.67	86
Cl	In (5)	24	traces
Br	In (5)	5.5	75
I	In (5)	1	86

[a] AcOH was used instead of HCO_2H.

2.5 Synthesis of 5-Deuterioisothiazole and Proposed Mechanism

There are many examples of reductions using Zn/AcOH[76-82] and the hydrogen transferred is considered to be that of the hydroxyl acid.[83-85] However, in the analogous case of Zn/HCO_2H there was some ambiguity.[86] Formic acid is a known hydrogen source and there are examples to support that both hydrogens, formyl and hydroxyl, can be transferred.[87-90]

In light of the above we investigated the reaction of 3,5-dibromoisothiazole-4-carbonitrile **12** with Zn powder (5 equiv) and various commercial deuterated formic acids DCO_2H and HCO_2D in an effort to elucidate which hydrogen or deuterium, formyl or hydroxyl, transferred to the isothiazole (Table 4). Initially, 3,5-dibromoisothiazole-4-carbonitrile **12** treated with zinc (5 equiv) and commercially available deuterated formic acid DCO_2D was shown to afford 3-bromo-5-deuterioisothiazole-4-carbonitrile **50** (Figure 1) in good yield (71%).



50

Figure 1. 3-Bromo-5-deuterioisothiazole-4-carbonitrile

Mass spectrometry (EI) of the crude product (prior recrystallization) indicated the parent ions peaks at *m/z* 189 (86), 190 (8), 191 (90) and 192 Da (5%). The absence of a peak at *m/z* 188 Da suggested no or very little 3-bromoisothiazole-4-carbonitrile **48** was present. ^{1}H and ^{13}C NMR spectroscopy showed no signal for H-5, and the $^{1}J_{CD}$ 29.4 Hz splitting could be observed. Furthermore, in the FTIR the ν(C-H) 3100 cm^{-1} stretch of 3-bromoisothiazole-4-carbonitrile **48** was replaced by the ν(C-D) 2315 cm^{-1} stretch of 3-bromo-5-deuterio-isothiazole-4-carbonitrile **50**. With pure samples of both 3-bromoisothiazole-4-carbonitrile **48** and 3-bromo-5-deuterioisothiazole-4-carbonitrile **50** we subsequently investigated the use of DCO_2H and HCO_2D.

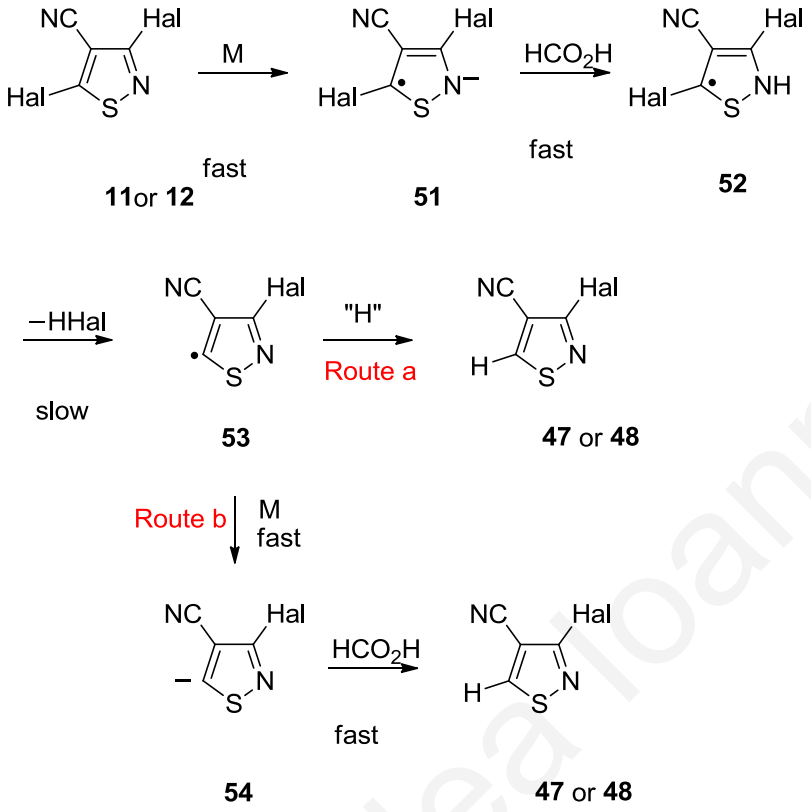
Treating 3,5-dibromoisothiazole-4-carbonitrile **12** with Zn (5 equiv) and HCO_2D gave 3-bromo-5-deuterioisothiazole-4-carbonitrile **50** in 60% yield, identical to that described above with no significant trace of the non-deuterated isothiazole **48**. However, when the reaction was repeated using DCO_2H instead of HCO_2D, 3-bromoisothiazole-4-carbonitrile **48** was the only product (58%) with no significant trace of the deuterated isothiazole observed. In both cases ^{1}H, ^{13}C NMR and FTIR spectroscopy and EI mass spectrometry studies on the reaction products were carried out prior to recrystallization. Furthermore, control studies revealed that pure samples of 3-bromo-5-deuterioisothiazole-4-carbonitrile **50** and 3-bromoisothiazole-4-carbonitrile **48** treated with HCO_2H and DCO_2D, respectively at *ca.* 20 ^{o}C for 1 h (with and without Zn dust) did not suffer any hydrogen-deuterium exchange (by MS and NMR).

Table 4 Parent ion isotopic ratios for products of the Zn mediated hydrodebromination of 3,5-dibromoisothiazole-4-carbonitrile **12** (0.25 mmol) with formic acids (1 mL) at 20 °C.

Formic Acid	*m/z* (Da) / Relative Intensities (%)				
HCO_2H	188 (97.29)	189 (6.12)	190 (100)	191 (6.23)	192 (0)
DCO_2D	188 (3.69)	189 (99.69)	190 (8.78)	191 (100)	192 (6.31)
HCO_2D	188 (5.60)	189 (99.36)	190 (11.59)	191 (100)	192 (6.31)
DCO_2H	188 (97.92)	189 (6.12)	190 (100)	191 (6.24)	192 (0)

The above results, suggested that the hydrogen transferred from the formic acid to the isothiazole originated only from the hydroxyl and not the formyl group. Formally, this could be considered a protodehalogenation but may be misleading. Furthermore, in reviewing the literature we find the terms hydro and protodehalogenation used rather indiscriminately.[91,92]

Several mechanisms can be proposed: Single electron transfer from zinc to isothiazole can form the radical anion **51** and subsequent protonation by the formic acid can give radical **53**. This radical could either accept another electron from the Zn to form anion **54** that protonates to afford the observed product *i.e.* protodehalogenation (Route B),[93,94] or the radical **53** could simply take a "nascent" hydrogen (Route A) (Scheme 37). In the latter case this would imply that all the available "nascent hydrogen" was either H in the case of DCO_2H or D when HCO_2D was used.

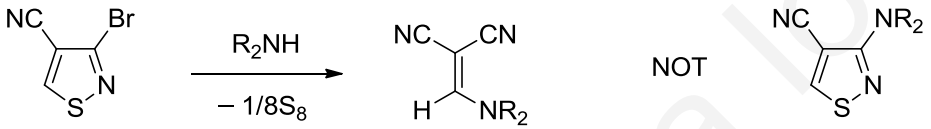


Scheme 37

Our understanding of "nascent hydrogen" is hydrogen chemisorbed onto the surface of the zinc that can be transferred to chemisorbed neighboring isothiazole. Formic acid can undergo reduction by zinc to give hydrogen and formate chemisorbed onto the zinc surface. Intuitively, the transferability of the hydroxyl hydrogen must be superior to that of the formyl hydrogen based on the relative O-H (428 kJ/mol) and C-H (338 kJ/mol) bond dissociation energies (BDE's).[75] The possibility, however, that the formic acid dissociates to give both formyl and hydroxyl hydrogens cannot be eliminated, since there could be a rapid exchange of chemisorbed hydrogen species (H or D) with the formic acid protons (H^+ or D^+) in the bulk solvent. As such this apparent protodehalogenation may in fact be a hydrodehalogenation.

2.6 Chemistry of 3-Bromoisothiazole-4-carbonitrile

With the 3-bromoisothiazole-4-carbonitrile **48** in hand we examined the nucleophilic displacement of the C-3 bromide using various nucleophiles. Treating the 3-bromoisothiazole **48** with either sodium methoxide in methanol at 70 ^{o}C for 4 h led to a complex reaction mixture while treatment with thiophenol and DBU or Hünig's base in benzene led to decomposition. When 3-bromoisothiazole-4-carbonitrile **48** was treated with excess dialkylamines in EtOH at reflux, a clean reaction was obtained with a main product; however, rather than obtaining the 3-aminoisothiazole **55** the ring opened amino-ylidenemalononitriles **56-57** were obtained in good yields, together with elemental sulfur (80%) (Scheme 38).



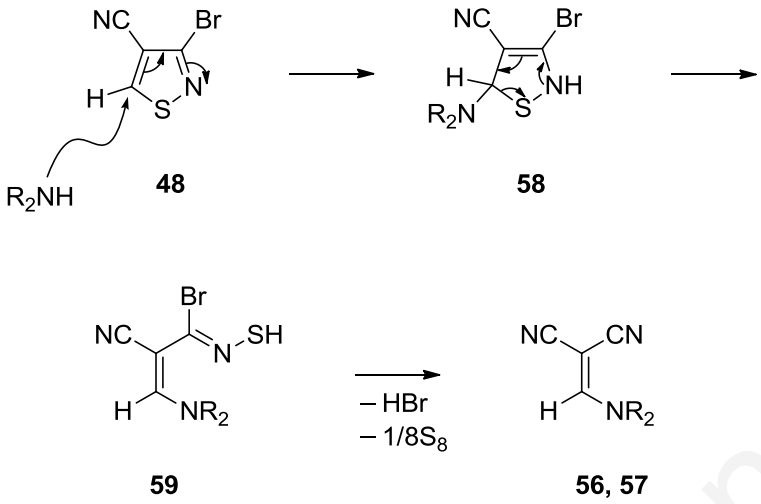
48

56, 69% (NR_2 = Morpholino)
57, 85% (NR_2 = Piperidino)

55

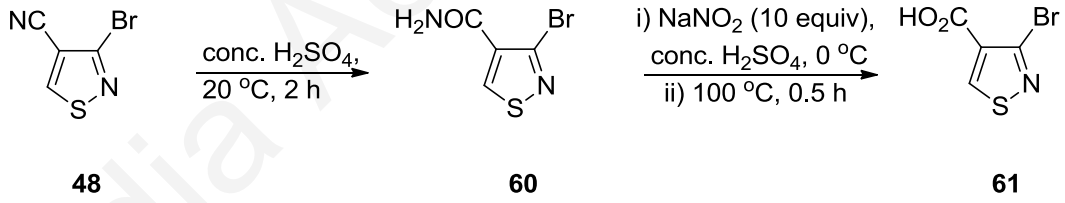
Scheme 38

This was not completely unexpected; isothiazoles are more prone to nucleophilic attack at C-5 and also at the ring sulfur rather than at C-3.[95] As such, we suspect the amines attack the isothiazole at C-5 to give adduct **58**, which subsequently fragments to the sulfide that presumably loses elemental sulfur through a sulfur chain extension mechanism.[96] Direct attack by the amine on the ring sulfur could be dismissed owing to the absence of bis(amino)sulfide in the reaction mixture and the isolation of significant amounts of elemental sulfur (80%) (Scheme 39).



Scheme 39

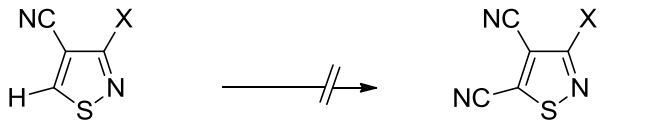
Attempts to brominate 3-bromoisothiazole-5-carbonitrile **48** at C-5 using NBS or Br_2 (2 equiv) in AcOH or in CCl_4 at 60 ^oC, failed to give any reaction even after 24 h. Nevertheless, under acidic conditions, concentrated sulfuric acid at *ca.* 20 ^oC for 2 h, the cyano suffered hydration to give the expected 3-bromoisothiazole-4-carboxamide **60** in 70% yield. The latter was reacted with $NaNO_2$ (10 equiv) in H_2SO_4 at 100 ^oC[37] to give after 0.5 h the 3-bromoisothiazole-4-carboxylic acid **61** in 92% yield (Scheme 40).



Scheme 40

2.7 Direct Cyanation Attempts

While there are many examples on cyanation of activated aromatic halides, very little exist in the literature about direct cyanation through transition-metal catalyzed C-H bond activation.[97-99] Conditions such as trimethylsilyl cyanide or potassium hexacyanoferrate in the presence of a palladium and copper catalysts were tried but failed to give any reaction, while the starting material could be recovered intact (Scheme 41).



47, X = Cl
48, X = Br

42, X = Cl
43, X = Br

Conditions: i) $K_4[Fe(CN)_6]$ (1.5 equiv), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (3 mol%), O_2, DMSO, 130 ^oC, 12 h; ii) TMSCN, $Cu(OAc)_2$ (1 equiv), MeCN, air, 82 ^oC, 12 h

Scheme 41

2.8 Summary

A regioselective dehalogenation on 3,5-dihaloisothiazole-4-carbonitriles using Zinc dust in formic acid, was achieved affording 3-haloisothiazole-4-carbonitriles in good yields. Use of deuterated formic acids (DCO_2D and HCO_2D) afforded the 3-bromo-5-deuterioisothiazole-4-carbonitrile **50** in good yield while use of DCO_2H gave only 3-bromoisothiazole-4-carbonitrile **48**. During ongoing studies on the utility of the versatile isothiazole building blocks 3,5-dichloroisothiazole-4-carbonitrile **11** and 3,5-dibromoisothiazole-4-carbonitrile **12**, we developed conditions for the regiospecific C-5 hydrodehalogenations that gave 3-haloisothiazole-4-carbonitriles **47** (Hal = Cl) and **48** (Hal = Br). Unfortunately, attempts for direct cyanation at C-5 position failed to give any desired product.

CHAPTER 3

Silver Mediated Palladium Catalyzed Direct C-H Arylation of 3-Bromoisothiazole-4-carbonitrile

Sections

3.1 Introduction

After the regiospecific C-5 hydrodehalogenation study of the 3,5-dichloro- and 3,5-dibromoisothiazole-4-carbonitriles **11** and **12**, the desired 3-chloro- and 3-bromo-isothiazole-4-carbonitriles **47** and **48** could be prepared in large scale without the need for chromatography. This gave the opportunity for further functionalization of the system. Combining the 3-haloisothiazole-4-carbonitriles with Pd catalyzed C-H direct arylations, a new route to 5-arylisothiazole-4-carbonitriles that are important due to their cytotoxicity[100] and antiviral activity [100,101] was feasible. To date aryl-substituted isothiazoles have been prepared by either treating arylylidenemalononitriles with S_2Cl_2[26,35,100] or by arylating haloisothiazoles using Suzuki, Stille or Negishi reactions.[35,36,72] However, the former has limitations due to harsh reaction conditions that often lead to chlorination of electron rich aryls and the latter requires often expensive reagents, such as organometallic reagents. In this chapter, we demonstrate for the first time the efficient silver mediated Pd catalyzed direct C-5 arylation of 3-bromoisothiazole-4-carbonitrile **48** using readily available iodoarenes.

Pd-catalyzed direct C-H arylation overcomes the need for expensive organometallic reagents.[102] The reaction has been demonstrated on a wide range of heteroarenes using cheap aryl halides.[103-109] While many publications appear in the literature about direct C-H arylation of thiazoles,[102,106,110-115] there have been no reported examples of Pd catalyzed direct arylation of isothiazoles.

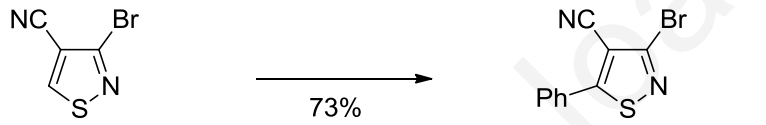
3.2 Optimization Studies

Initially, 3-bromoisothiazole-4-carbonitrile **48** was treated with either chloro-, bromo- or iodobenzene (PhI) in the presence of a Pd catalyst $Pd(dppf)Cl_2$.DCM (20 mol%) and base in MeCN at *ca.* 82 ^oC. Surprisingly, the use of inorganic bases such as KF, CsF, K_2CO_3, Cs_2CO_3, Na_2CO_3 and organic bases such as pyridine and *i*-Pr_2NEt failed to work. In light of this, we investigated the use of silver (I) salts, which are effective additives in both oxidative[116-118] and non-oxidative arylations.[113,119-126]

The addition of $AgNO_3$ assisted the Pd-catalyzed arylation of allyltrimethylsilanes,[127,128] vinylsilanes,[128] while Ag_2O promoted the Pd-catalyzed cross coupling reactions of silanols,

silanediols and silanetriols)[129] as well the reaction between aryl and alkenyl halides with terminal alkynes.[130] Silver(I) fluoride (AgF) served as both an activator of the electrophilic substitution reaction and as the oxidant of Pd(0), and in combination with Cu(II) salts aided the arylation of acetanilides.[124] Furthermore, AgF was used as base for the arylation of thiophenes and thiazoles.[111,132-134]

In light of the above, we treated 3-bromoisothiazole-4-carbonitrile **48** with PhI (1.2 equiv), AgF (2 equiv), Pd(dppf)Cl_2.DCM (20 mol%), and Ph_3P as ligand (10 mol%) in MeCN at *ca.* 82 ^oC for 2 h and obtained the 5-phenylisothiazole **62** in 73% yield (Scheme 42).



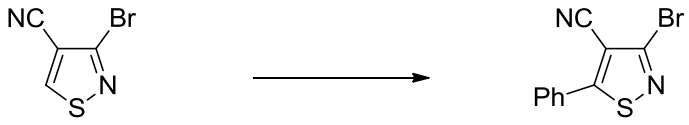
48 **62**

Reagents and Conditions: PhI (1.2 equiv), AgF (2 equiv), Pd(dppf)Cl_2.DCM (20 mol%), Ph_3P (10 mol%), MeCN, 82 ^oC, 2 h

Scheme 42

The conditions were subsequently optimized with respect to catalyst, ligand and base (Table 5). Of the catalysts screened, Pd$(Ph_3P)_2Cl_2$ gave the highest yield (88%) in the shortest time (20 min) and was chosen for further optimization. In contrast $Pd_2(dba)_3$ gave a complex reaction mixture, while Pd$(OAc)_2$, and $(MeCN)_2PdCl_2$ gave the desired product in only moderate yields and required longer reaction times.

Table 5 Reaction of 3-bromoisothiazole-4-carbonitrile **48** (0.25 mmol) with PhI, $Pd(Ph_3P)_2Cl_2$, AgF and Ph_3P in MeCN at ca. 82 °C



48 **62**

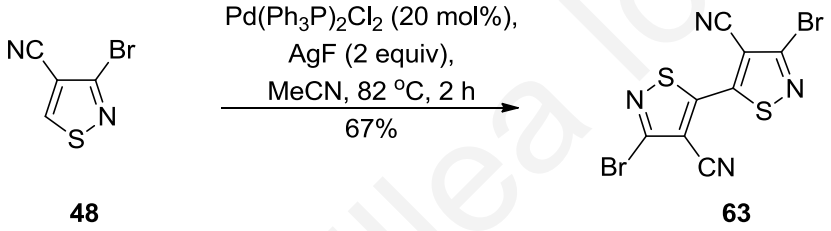
AgF (equiv)	$Pd(Ph_3P)_2Cl_2$ (mol %)	Ph_3P (mol %)	PhI (equiv)	Time (h)	Yield **62** (%)
1	20	10	1.2	24	[a]
2	20	10	1.2	0.33	88
2	20	10	1	2.50	60
2	20	10	1.5	0.17	84
2	20	0	1.2	1	73
2	20	0	1.5	0.50	86
2	20	0	2	0.17	86
2	10	10	1.2	7	62[b]
2	10	10	1.5	5	80
2	10	10	2	3	73
2	5	10	1.2	12	72[b]
2	5	10	1.5	11	60[c]
3	20	10	1.2	0.17	63[d]
3	20	10	2	0.08	78
3	10	10	2	0.10	83
3	5	10	2	0.13	85
3	1	10	2	0.50	17
3	10	10	1.5	0.12	91[b]
3	5	10	1.5	0.17	93[b]

[a] Incomplete reaction. [b] Traces of dimer **63** (TLC). [c] Dimer **63** (15%) was also isolated. [d] Dimer **63** (14%) was also isolated.

On holding constant the catalyst, $Pd(Ph_3P)_2Cl_2$ (20 mol%), both the reaction time and product yield were affected by varying the equivalents of PhI; the highest yields (88 and 84%) were achieved with 1.2 and 1.5 equiv of PhI over a 20 and 10 min period, respectively. In the absence of additional ligand, the product can still be formed in good yield by increasing the PhI equivalents. Switching the ligand to dppf (10 mol%) led to a longer reaction (7 h) and a 67% yield, while the use of JohnPhos (10 mol%) gave only traces of product after 4 h. The catalyst loading was then investigated to find the minimum needed for the reaction to succeed. Reducing the catalyst loading to 10 mol% with 1.2 equiv of PhI, led to longer reaction times (7 h), moderate product yields (60%) and gave traces of 3,3'-dibromo-5,5'-biisothiazole-4,4'-dicarbonitrile **63** presumably owing to a competing oxidative C-5 dimerization. The formation of the latter can be suppressed by increasing the PhI to 1.5 or 2 equiv which led to shorter

reaction times (5 and 3 h, respectively) and the isolation of 5-phenylisothiazole **62** in 80 and 73% yields, respectively. Further attempts to reduce the catalyst loading to 5 mol%, again led to increased reaction times, lower product yields and dimer formation.

3,3'-Dibromo-5,5'-biisothiazole-4,4'-dicarbonitrile **63** was isolated as colorless plates, mp 286 ^{o}C (PhCl). Elemental analysis and mass spectrometry supported a molecular formula of $C_8Br_2N_4S_2$. Infrared spectroscopy supported the presence of nitrile functionality ν(C≡N) 2230 cm^{-1} and ^{13}C NMR spectroscopy gave only 4 carbon resonances indicating a symmetrical molecule. Treating 3-bromoisothiazole-4-carbonitrile **48** with AgF (2 equiv) and $Pd(Ph_3P)_2Cl_2$ (20 mol%) in the absence of PhI gave the 5,5'-biisothiazole **63** in 67% yield (Scheme 43).



48 **63**

Scheme 43

The formation of a dimer **63** in the absence of ArI implied that direct palladation of isothiazole **48** by a Pd(II) species was possible and as such the silver salt serves as an oxidant to support a Pd(II)/Pd(IV) catalytic cycle. This hypothesis also agreed with the observation that Br remained intact during the catalysis.

Control reactions revealed that the presence of both the Pd catalyst and the AgF was needed for the reaction to work, while the use of Ph_3P was not. Attempts to decrease the catalyst loading to 5 mol% led to longer reaction time (12 h) and a drop in yield (51%).

With these partially optimized arylation conditions, the need for AgF was further investigated. In our hands, the use of other silver (I) reagents such as AgBr, $AgNO_3$, Ag_2O, Ag_2SO_4, $AgBF_4$, $AgSbF_6$, AgOTf and AgOAc proved to be ineffective in the arylation reaction of 3-bromoisothiazole-4-carbonitrile **48** with PhI. Nevertheless, Ag_2CO_3, was effective with 20 mol% catalyst giving the desired 3-bromo-5-phenylisothiazole-4-carbonitrile **62** in good

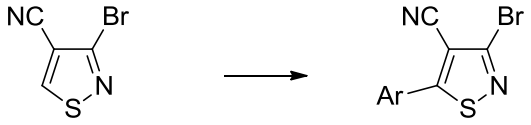
yields (68-73%) together with some amount of dimer **63**. However, attempts to decrease the catalyst loading to 10 or 5 mol% using 2 or 3 equiv of Ag_2CO_3 led to only traces of phenylated product. As such, further optimizations were restricted to the use of AgF.

Screening the AgF equivalents needed for the reaction, revealed that 1 equiv was insufficient to drive the reaction to completion within 24 h, while the use of 3 equiv led to fast reaction times (10 min), a reduced yield of the desired 3-bromo-5-phenylisothiazole-4-carbonitrile **62** (63%) and an increased yield of dimer **63** (14%). Fortunately, the formation of the dimer could be suppressed by increasing the amount of PhI. As such, when PhI (2 equiv) and AgF (3 equiv) were used the reaction finished in 5 min affording the desired product in 78% yield with no dimer byproduct. This last result was promising and under these conditions the Pd catalyst loading was reduced from 10 to 5 mol%. Successfully, the desired product was isolated in high yield (85%) in very short reaction time (8 min). Reducing the catalyst loading to 1 mol%, gave low yields of the desired product, while decreasing the PhI to 1.5 equiv using 10 and 5 mol% catalyst loading, led to fast reactions and very high yields of the desired product but traces of the dimer were also present.

3.3 Analogues Synthesis

The best conditions were applied to a variety of iodoarenes providing a range of 5-aryl and 5-heteroaryl-isothiazole-4-carbonitriles (Table 6). The reactions worked well with aryl derivatives bearing both electron releasing (*e.g.*, entries 2-6) and withdrawing (*e.g.*, entries 7-9) groups. Furthermore, the existence of a second halide (Cl or Br) on the iodoarenes did not affect the reaction and showed that reaction was haloselective (entries 19-23). In most cases iodohetero-arenes worked equally well (entries 11-13,17-22), but in some cases dimer was formed (entries 14-16). Comparitively poor yields were obtained for 4-amino-3-nitroiodobenzene (entries 10) and the 7-iodoindoles (16 and 23) and presumably these reactions would require additional optimisation to maximise the product yields.

Table 6 Reaction of the 3-bromoisothiazole **48** (0.25 mmol) with ArI (2 equiv), $Pd(Ph_3P)_2Cl_2$ (5 mol%), AgF (3 equiv), Ph_3P (10 mol%) in MeCN at ca. 82 °C



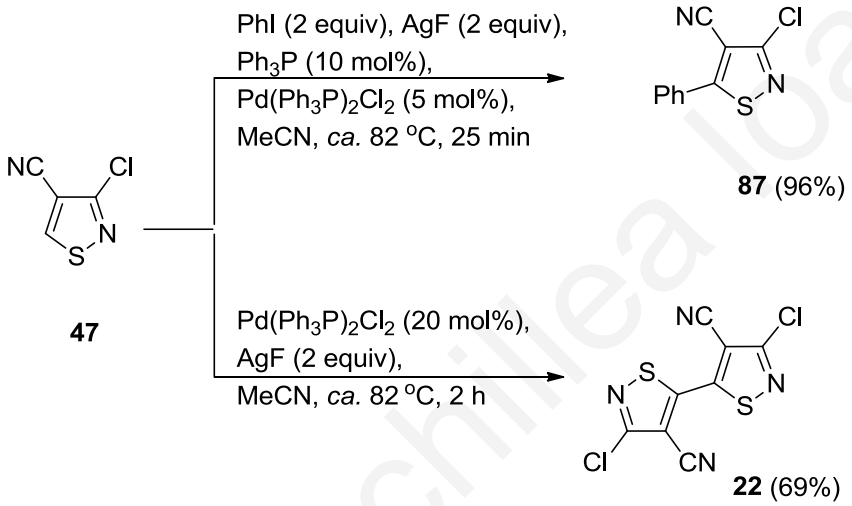
48 **64-86**

Entry	Ar	time (h)	yield **64-86** (%)	yield **63** (%)
1	4-Tol	3.50	**64** (82)	-
2	2-$MeOC_6H_4$	7	**65** (89)	-
3	3-$MeOC_6H_4$	3	**66** (91)	-
4	4-$MeOC_6H_4$	2.50	**67** (81)	-
5	2,4-$(MeO)_2C_6H_3$	4	**68** (73)	-
6	4-HOC_6H_4	4	**69** (79)	-
7	2-$O_2NC_6H_4$	0.67	**70** (89)	-
8	3-$O_2NC_6H_4$	0.67	**71** (83)	-
9	4-$O_2NC_6H_4$	0.50	**72** (98)	-
10	4-H_2N-3-$O_2NC_6H_3$	0.17	**73** (41)[a]	-
11	Pyrid-2-yl	20	**74** (74)	-
12	Pyrid-3-yl	5	**75** (92)	-
13	Pyrid-4-yl	20	**76** (95)	-
14	Pyrazinyl	2	**77** (72)	16
15	Indol-5-yl	3	**78** (66)	20
16	Indol-7-yl	2	**79** (52)	28
17	Thien-2-yl	0.33	**80** (93)	-
18	Thien-3-yl	0.67	**81** (92)	-
19	3-BrC_6H_4	1.50	**82** (97)	-
20	2-Cl-Pyrid-4-yl	6	**83** (78)	-
21	2-Br-Pyrid-4-yl	4	**84** (87)	-
22	7-Cl-Quinolin-4-yl	1.50	**85** (94)	-
23	5-Br-Indol-7-yl	20	**86** (34)[b]	-

[a] Reaction finished immediately but 24% of ArI was recovered. [b] Yield based on 43% recovered starting isothiazole **48**.

The best conditions for the direct arylation of 3-bromoisothiazole-4-carbonitrile **48** were also used with the 3-chloroisothiazole **47**. The chemistry was subtly different. Treating 3-chloro-isothiazole-4-carbonitrile **47** with PhI (2 equiv) in the presence of AgF (3 equiv), Ph_3P (10 mol%) and $Pd(Ph_3P)_2Cl_2$ (5 mol%) in MeCN at *ca.* 82 °C gave after 15 min 3-chloro-5-phenylisothiazole-4-carbonitrile **87** in moderate yield (58%) and traces of 3,3′-dichloro-5,5′-biisothiazole-4,4′-dicarbonitrile **22**. In light of the above study we rationalized that decreasing

the AgF to 2 equiv, could help avoid the competing oxidative dimerization and indeed obtained in 25 min the desired product **87** in excellent yield (96%) with no traces of dimer. The influence of the 3-halogen was surprising since it was not near the reaction site, but presumably chlorine being more electronegative than bromine would make the C-5 hydrogen marginally more acidic and this may play a role. Finally by applying the conditions used for the dimerization of the bromo analogue [$Pd(Ph_3P)_2Cl_2$ (20 mol%), AgF (2 equiv)], onto 3-chloroisothiazole-4-carbonitrile **47**, the 3,3′-dichloro-5,5′-biisothiazole-4,4′-dicarbonitrile **22** was isolated in 69% yield after 2 h (Scheme 44).



Scheme 44

3.4 Summary

In conclusion, 3-bromoisothiazole-4-carbonitrile **48** readily undergoes Pd catalyzed direct CH arylation at C5 with a range of cheap, commercially available iodoarenes in the presence of AgF to give twenty four 5-aryl and heteroarylisothiazole-4-carbonitriles in good yields. Furthermore, treating 3-bromoisothiazole-4-carbonitrile **48** with AgF and Pd catalyst led to oxidative dimerization affording 3,3'-dibromo-5,5'-biisothiazole-4,4'-dicarbonitrile **63**. Similarly, phenylation at C-5 and oxidative C-5 dimerization were demonstrated for 3-chloroisothiazole-4-carbonitrile **47** affording the chloro phenylated and dimerized analogues **87** and **22** in 96 and 69% yields, respectively.

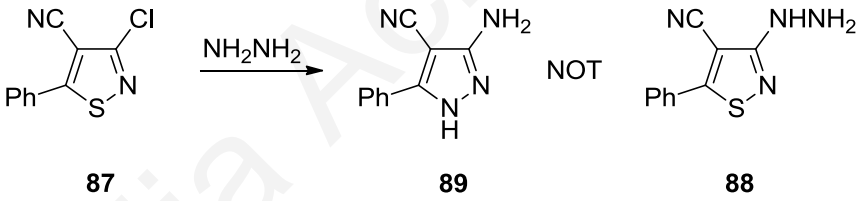
CHAPTER 4

The Conversion of Isothiazole into Pyrazole with Hydrazine

Sections

4.1 Introduction

Pyrazoles (1,2-diazoles) rarely occur in nature, however they are structural components of many biologically active compounds. Important commercial pyrazole products include Sildenafil (Viagra),[135] Lonazolac,[136,137] Difenamizole,[138] Mepirizole,[139] Phenidone,[140] and bicyclic pyrazolidinone LY 186826.[141] Synthetic methods for the preparation of monocyclic pyrazoles are well documented[142-145] and a common synthetic strategy involves the reaction of 1,3-dicarbonyl compounds or their equivalents with hydrazine. Heterocycles that can behave as 1,3-dicarbonyl equivalents can therefore be transformed into pyrazoles on treatment with hydrazines.[145] Recently a former member of the group tried to prepare 3-hydrazino-5-phenylisothiazole-4-carbonitrile **88** from 3-chloro-5-phenylisothiazole-4-carbonitrile **87** using neat anhydrous hydrazine but obtained in quantitative yield 3-amino-5-phenylpyrazole-4-carbonitrile **89** (Scheme 45).[36] This pyrazole, first prepared by treating [2-methoxy(phenyl)methylene]-malononitrile with hydrazine monohydrate,[146] when in solution is in a dynamic solvent dependent prototropic equilibrium[147-150] with isomer 5-amino-3-phenylpyrazole-4-carbonitrile. No attempts to differentiate between prototropic isomers were made.



87 **89** **88**

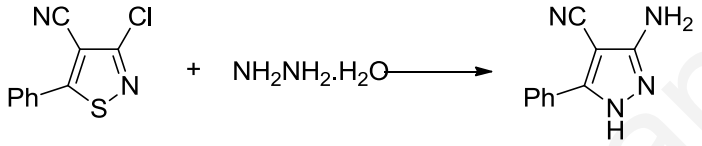
Scheme 45

The analogous transformation of isoxazoles into pyrazoles using arylhydrazines[151-167] or alkylhydrazines[168] is well documented. Furthermore, the transformations of isoxazolium salts,[169] isoxazolidin-2-yl,[170] isoxazolidin-5-ones,[171] isoxazol-4-one oximes[172,173] and isoxazole-4,5-diones [174] into pyrazoles have been reported. While there are several reports on the analogous conversion of isothiazolium salts into pyrazoles,[25,175-177] there is only one report on the transformation of isothiazoles into pyrazoles using arylhydrazines.[178] In this chapter an extended study on the transformation of substituted isothiazoles into pyrazoles on treatment with hydrazine is described.

4.2 Hydrazine Equivalents Needed for the Transformation

In an early effort to avoid the need for excess neat anhydrous hydrazine, the use of hydrazine monohydrate with a co-solvent to improve solubility was studied (Table 7).

Table 7 Reaction of 3-chloro-5-phenylisothiazole-4-carbonitrile **87** (0.230 mmol) with $NH_2NH_2.H_2O$ in different solvents (1 mL).



87 **89**

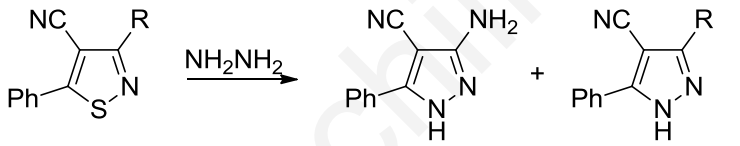
$NH_2NH_2.H_2O$ (equiv.)	Solvent	Temperature (^oC)	Time (h)	Yield (%)
10	DMSO	20	5.5	50
15	DMSO	20	5	51
25	DMSO	20	1	65
100	DMSO	20	1	72
100	DMF	20	1	60
100	EtOH	20-80	1	87
150	DMSO	20	0.5	89
200	DMSO	20	0.5	92

The use of either DMF or DMSO as co-solvent was satisfactory for the room temperature conversion of 3-chloro-5-phenylisothiazole-4-carbonitrile **87** into the pyrazole **89**, while the use of ethanol required heating to reflux owing to poor solubility of the starting isothiazole. Of the three co-solvents investigated, DMSO gave the cleanest reaction mixtures (by TLC), however, there remained a need for a large excess (>100 equiv.) of hydrazine monohydrate to obtain short reaction times and high product yields. By comparison neat anhydrous hydrazine gave the cleanest reaction mixtures and since the absence of a co-solvent also facilitated isolation of pyrazole product all further studies were conducted using neat anhydrous hydrazine.

4.3 Modification of Substituents at C-3

A structural comparison of the pyrazole product and the starting isothiazole indicated that cleavage of the C-R bond at the isothiazole C-3 position must occur during the transformation. As such the leaving group ability of the C-3 substituent was investigated (Table 8). The reaction times of the 3-halo derivatives (**87** R = Cl, **62** R = Br, **23** R = I) decreased in accordance with the nucleofugality of the halide. However, when the C-3 substituent was methoxy, hydroxyl or alkylamino, which are by comparison poor nucleofuges, new major pyrazole products **96-99** were isolated that retained the C-3 substituent together with some of the 3-aminopyrazole **89**. The conversion of 3,5-diphenylisothiazole-4-carbonitrile **95**, which has no leaving group at C-3 (R = Ph), into 3,5-diphenylpyrazole-4-carbonitrile **100** (83%) required harsh conditions (150 ^{o}C, sealed tube).

Table 8 Reaction of 5-phenyl-3-substituted-isothiazole-4-carbonitrile **23, 62, 87, 90-95** (0.230 mmol) with anhydrous hydrazine (2 mL) at *ca.* 20 ^{o}C under a $CaCl_2$ drying tube.



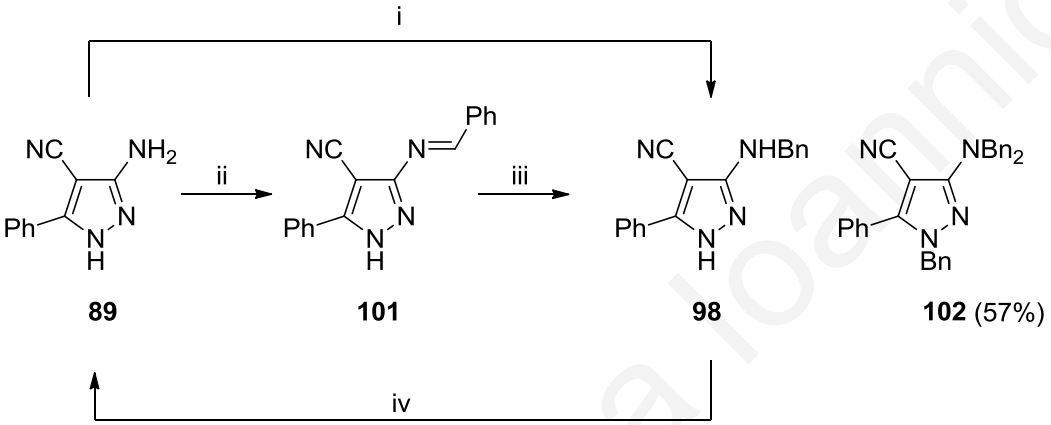
23, 62, 87, 90-95 **89** **96-100**

	R	Time (min)	Yields (%) **89**	**96-100**
87	Cl	15	99	0
62	Br	10	100	0
23	I	5	98	0
90	MeO	15	48	**96** (52)
91	HO	30	3	**97** (97)
92	H_2N	20	93	-
93	BnNH	4.5 h	33	**98** (67)
94	*N*-Morpholino	36 h	55	**99** (40)
94	*N*-Morpholino	30 (80 ^{o}C)	44	**99** (56)
95	Ph	24 h (150 ^{o}C)[a]	0	**100** (83)

[a] Sealed tube.

Interestingly the major product of the reaction between 3-benzylamino-5-phenylisothiazole-4-carbonitrile **93** and hydrazine was 3-benzylamino-5-phenylpyrazole-4-carbonitrile **98** (67%). To the best of our knowledge the 3-benzylaminopyrazole **98** has not previously been reported

and in our hands its preparation *via* direct regiocontrolled *N*-benzylation of the 3-amino-5-phenylpyrazole-4-carbonitrile **89** using benzyl bromide and KOH, led to a complex mixture from which the desired product **98** could be isolated in low yield (33%) together with the tribenzylated pyrazole **102** (57%). Nevertheless a two step benzylation *via* the imine[179] **101** followed by treatment with $NaBH_4$ in MeOH gave the *N*-benzylaminopyrazole **98** in a good overall yield of 72% (Scheme 46).



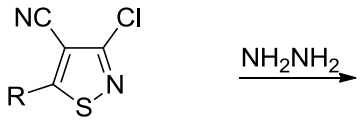
Reagents and conditions: i) $PhCH_2Br$ (1 equiv.), KOH (12 equiv.), DMF, 20 ^oC, 15 min, 33%; ii) PhCHO (36 equiv. = 1 mL), 20 ^oC, 2 h, 72%; iii) $NaBH_4$ (2 equiv.), MeOH, 0-20 ^oC, Ar, 10 min, 100%; iv) H_2O-MeOH (5%), 20 ^oC, 15 min, 99%.

Scheme 46

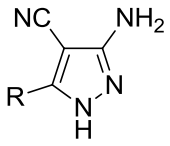
4.4 Modification of Substituents at C-5

The transformation of isothiazole into pyrazole required that C-N bond formation occurs at the isothiazole C-5 carbon. This carbon, known to be highly electrophilic[32,35,180] was a probable site for initial attack by hydrazine and as such both steric and electronic factors that influence the C-5 position could affect the ring transformation. To investigate this, a series of 3-chloro-5-substituted isothiazole-4-carbonitriles bearing steric and/or electronic constraints at C-5 were treated with anhydrous hydrazine to examine their effect on reaction time and pyrazole yields (Table 9).

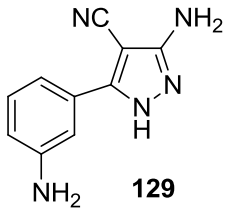
Table 9 Reaction of 3-chloro-5-substituted isothiazole-4-carbonitriles **11, 20, 87, 103-119** (0.230 mmol) in anhydrous hydrazine (2 mL) at *ca.* 20 °C under a $CaCl_2$ drying tube.



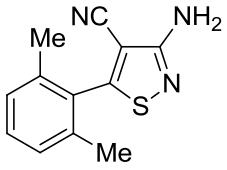
11, 20, 87, 103-119



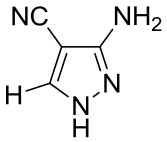
89, 120-136



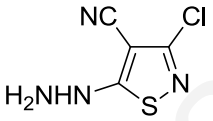
129



130



133



114

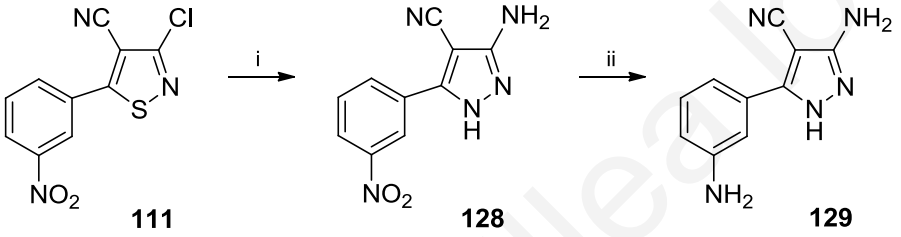
	R	Time (h)	Yields (%) **89, 120-136**	**114, 129-130, 133**
87	Ph	0.25	**89** (99)	-
103	3-MeC_6H_4	0.33	**120** (97)	-
104	2-$MeOC_6H_4$	3	**121** (95)	-
105	3-$MeOC_6H_4$	3-2.5	**122** (100)	-
106	4-$MeOC_6H_4$	4	**123** (94)	-
107	3-Thienyl	1	**124** (94)	-
108	2-ClC_6H_4	0.25	**125** (90)	-
109	3-ClC_6H_4	0.25	**126** (89)	-
110	4-ClC_6H_4	0.50	**127** (86)	-
111	3-$NO_2C_6H_4$	1	**128** (72)	**129** (28)
112	2,6-$(Me)_2C_6H_3$	8	-	**130** (70)
113	*N*-Morpholino	1	**131** (82)	-
20	NH_2	0.08	**132** (84)	-
114	$NHNH_2$	24	nr[a]	-
114	$NHNH_2$	0.75 (110 °C)	**132** (86)	**133** (13)
115	PhNH	24	nr[a]	-
115	PhNH	1 (110 °C)	**134** (91)	-
116	BnNH	24	nr[a]	-
116	BnNH	0.33 (110 °C)	**135** (92)	-
117	MeO	0.05	**136** (65)	**114** (30)
118	PhO	0.08	-	**114** (85)
119	PhS	0.08	-	**114** (90)
11	Cl	0.08	-	**114** (100)

[a] nr = no reaction.

Electron rich aryl and thien-3-yl substituents at C-5 (*e.g.*, isothiazoles **103-107**) led to long reaction times (1-4 h) while comparatively electron poor aryl substituents (*e.g.*, isothiazoles **108-111**) led to short reaction times (15-30 min). More interestingly the isothiazole **112**

bearing the sterically demanding 2,6-dimethylphenyl substituent at C-5 reacted slowly (8 h) with anhydrous hydrazine to give 3-amino-5-(2,6-dimethylphenyl)isothiazole-4-carbonitrile **130** in good yield (70%). Tentatively this 3-aminoisothiazole is derived from the 3-hydrazinyl derivative (see below, Tables 11-14), although all our efforts to isolate this were not successful. The data supported that the C-5 substituent influenced the reaction both sterically and electronically and tentatively supported that hydrazine initially attacked the isothiazole C-5 position. This was further supported when the C-5 substituent could act as a leaving group. Isothiazoles with poor leaving groups at C-5 such as the 5-morpholino, 5-anilino- and 5-benzylaminoisothiazoles **113**, **115** and **116** gave the expected morpholino, anilino and benzylamino substituted pyrazoles **131**, **134** and **135** respectively in good yield, however, where the C-5 isothiazole substituent was a better nucleofuge (*e.g.*, PhO, PhS and Cl substituted isothiazoles **118, 119, 11**) only the 5-hydrazinylisothiazole **114** was obtained quickly and in good yield. Several examples of the replacement of leaving groups (*e.g.*, halogen,[32,181,182] OEt,[183] SR,[181,184] and SO_2R,[185]) at the isothiazole C-5 position by hydrazine monohydrate are known and the displacement of phenoxy groups by hydrazine from heteroarenes, (*e.g.*, from [1,2,4]dithiazolo-[1,5-*b*][1,2,4]dithiazoles,[186] acridines[187]and phthalazines[188]), has been previously reported. The data collected, suggested that the conversion of 5-amino-3-chloroisothiazole-4-carbonitrile **20** into 3,5-diaminopyrazole-4-carbonitrile **132** at ambient temperatures probably does not proceed *via* initial displacement of the C-5 amine by hydrazine to give the intermediate hydrazinylisothiazole **114**. Nevertheless under more forcing conditions (110 ^{o}C), a pure sample of 3-chloro-5-hydrazinylisothiazole-4-carbonitrile **114** treated with anhydrous hydrazine gave 3,5-diaminopyrazole-4-carbonitrile **132** (86%) together with some reduced 3-aminopyrazole-4-carbonitrile **133** (13%). Heating (*ca.* 200 ^{o}C) a pure sample of the 5-hydrazinylisothiazole **114** gave a very complex mixture (by TLC) which was not pursued further. Interestingly a colorless DMSO solution of pure 3-chloro-5-hydrazinylisothiazole-4-carbonitrile **114** on standing in the presence of daylight turns blue in color. TLC indicated the formation of an unidentified highly polar (baseline) blue colored product together with starting isothiazole **114**. This light sensitivity was confirmed when a fresh solution kept in the dark gave no color change. The identification of this product was outside of the scope of the present study.

Furthermore, while the methoxyphenyl, chlorophenyl and thienyl substituents were unaffected by the hydrazine treatment, the reaction of 3-chloro-5-(3-nitrophenyl)-isothiazole-4-carbonitrile **111** with anhydrous hydrazine gave a second product, 5-(3-anilino)-3-chloropyrazole-4-carbonitrile **129**. Hydrazine in the presence of a transition metal catalyst is well known to reduce nitro to amino groups.[189,190] A pure recrystallized sample of 3-amino-5-(3-nitrophenyl)pyrazole-4-carbonitrile **128** treated with hydrazine and KOH in MeOH at *ca.* 20 ^{o}C for 4 d in the absence of any transition metal catalyst gave the (3-anilino)pyrazole **129** in 97% yield. Interestingly the reduction of the nitro group could be avoided with the use of hydrazine monohydrate in DMSO at *ca.* 20 ^{o}C for 40 min which converted the isothiazole **111** into the desired 3-nitrophenylpyrazole-4-carbonitrile **128** in 90% yield (Scheme 47).



111 **128** **129**

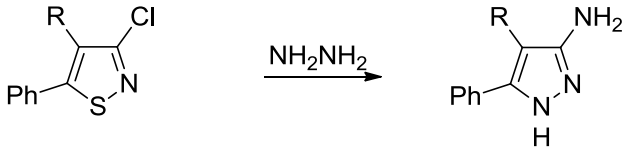
Reagents and conditions: i) **111** (0.19 mmol), $NH_2NH_2.H_2O$ (0.5 mL, 20 ^{o}C, DMSO (1.5 mL), 40 min, 90%; ii) **128** (0.19 mmol), NH_2NH_2 (2 equiv.), KOH (3 equiv.), MeOH, 4 d, 20 ^{o}C, 97%.

Scheme 47

4.5 Varying the Isothiazole C-4 Substituent with a Nucleofuge at C-3

The isothiazole C-4 nitrile could be involved in the isothiazole into pyrazole transformation. As such several isothiazoles with a variety of C-4 substituents (**137** R = H, **138** R = Br, **139** R = Ph and **140** R = NH_2) were subjected to anhydrous hydrazine to elucidate the influence of the C-4 substituents (Table 10).

Table 10 Reaction of 3-chloro-5-phenyl-4-substituted-isothiazoles **87, 137-140** (0.230 mmol) in anhydrous hydrazine (2 mL) under a $CaCl_2$ drying tube.



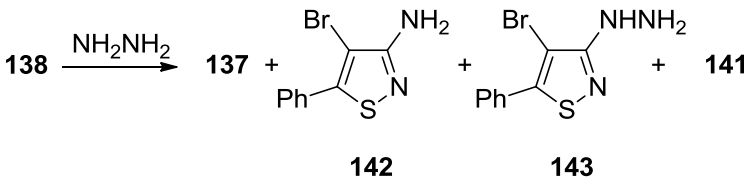
87, 137-140 **89, 141**

	R	Temp. (°C)	Time (h)	Yields (%)
87	CN	20	0.25	**89** (99)
137	H	20	7	**141** (70)
137	H	200[a]	0.5	**141** (72)
138	Br	20	27	complex [b]
139	Ph	20	24	complex [c]
140	NH_2	20	24	v. complex
140	NH_2	200[a]	48	v. complex

[a] Sealed tube.
[b] Refer to Table 11.
[c] Refer to Table 14.

3-Chloro-5-phenylisothiazole **137** was converted cleanly into the corresponding 3-amino-5-phenylpyrazole **141** (70%), but required a long reaction time (7 h) compared to the 4-carbonitrile derivative **87**. Introducing the reaction mixture (sealed tube) into a preheated Wood's metal bath at 200 °C gave a substantially shorter reaction time (0.5 h) and comparable yield (72%). This supported that the C-4 nitrile was not essential for the ring transformation to occur but tentatively assisted the reaction by enhancing the electrophilicity of the isothiazole C-5 position. The 4-bromo- and 4-phenylisothiazoles **138** and **139** gave complex reaction mixtures which were studied further (Tables 11-14), while 4-amino-3-chloro-5-phenylisothiazole **140** gave a reaction mixture that was too complex to analyze.

Table 11 Reaction of 4-bromo-3-chloro-5-phenylisothiazole **138** (0.230 mmol) with anhydrous hydrazine (2 mL) under a $CaCl_2$ drying tube.



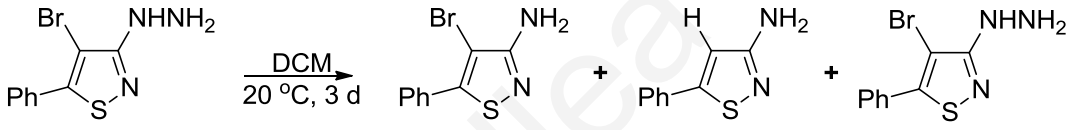
Temp. (°C)	Time (h)	Yields (%) 137	142	143	141
20	27	11	29	18	26
20-110	2.5	34	25	14	20
110	0.5	20	55	16	7
150[a]	5 min	0	5	82	6
200[a]	3 min	0	0	86	4

[a] Sealed tube.

At *ca.* 20 °C, 4-bromo-3-chloro-5-phenylisothiazole **138** required 27 h to be consumed by anhydrous hydrazine and the reaction gave four products but not 3-amino-4-bromo-5-phenylpyrazole. The first and fourth products isolated by chromatography were 3-chloro-5-phenylisothiazole **137** in which chemoselective protodehalogenation had occurred at C-4 and the corresponding 3-amino-5-phenylpyrazole **141**. Unlike the reduction of the nitro group (Scheme 3) the use of hydrazine monohydrate in DMSO failed to prevent the protodehalogenation at C-4. Hydrazine is known to reduce alkyl and aryl halides.[189] Surprisingly, the second and third products were 3-amino-4-bromo-5-phenylisothiazole **142** and 4-bromo-3-hydrazino-5-phenylisothiazole **143**. Since arylhydrazines are known to suffer autoreductive conversion to give anilines[191] it was possible that the 3-aminoisothiazole **142** was derived from the 3-hydrazinylisothiazole **143**. While 3-hydrazinyl benzoisothiazole was reported,[192] monocyclic 3-hydrazinylisothiazoles are not known and only a few unsubstituted 5-hydrazinyl monocyclic isothiazoles have been reported,[32,181-185,193,194] together with only two reports of trisubstituted 4-hydrazinyl-isothiazoles.[195,196] To our delight, performing the reaction at high temperature in a preheated (200 °C) Wood's metal bath for a short duration (3 min) followed by a rapid quench in crushed ice gave 4-bromo-3-hydrazino-5-phenylisothiazole **143** in high yield (86%). This allowed for a careful study of the novel 4-bromo-3-hydrazino-5-phenylisothiazole **143**.

A 2D silica TLC stability study showed that the 3-hydrazinylisothiazole **143** was unstable and converted into the 3-aminoisothiazole **142**. Furthermore a degassed DCM solution of 3-hydrazinylisothiazole **143** under an argon or air atmosphere after 3 d led to a 64-62% conversion of 3-hydrazinylisothiazole **143** into 3-amino-4-bromo-5-phenylisothiazole **142** (56-49%) and 3-aminoisothiazole **144** (43-51%). After 3 d under a pure O_2 atmosphere a similar quantity of the 3-hydrazinylisothiazole **143** was consumed (60%), however, a significantly improved yield of 3-amino-4-bromo-5-phenylisothiazole **142** (89%) together with a significantly reduced amount of the protodebrominated 3-aminoisothiazole **144** (11%) were obtained (Table 12).

Table 12 Stability of the 3-hydrazinylisothiazole **143** (0.074 mmol) in DCM (1 mL) under various atmospheres at *ca.* 20 °C for 3 d.



143 **142** **144** **143**

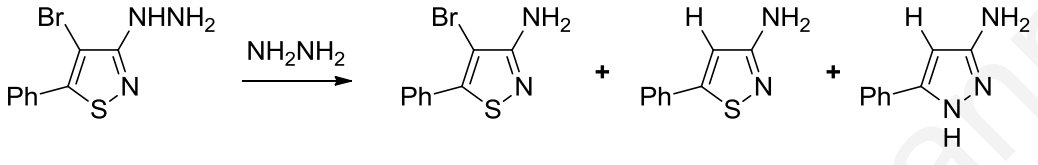
Atmosphere	Yields (%)[a]		
	142	**144**	**143**
Ar	56	43	36
Air	49	51	38
O_2	89	11	40

[a] Yields based on recovered 3-hydrazinylisothiazole **143**.

Interestingly treating 4-bromo-3-hydrazino-5-phenylisothiazole **143** with neat anhydrous hydrazine under an air atmosphere at *ca.* 20 °C for only 35 min gave a clean conversion to 3-amino-4-bromo-5-phenylisothiazole **142** (96%). Although when the reaction was repeated in neat degassed anhydrous hydrazine under an argon atmosphere the conversion (**143** → **142**) was incomplete after 1 d. Suprisingly under a pure oxygen atmosphere the reaction was still slow but after 25 h the conversion (**143** → **142**) was complete and high yielding (98%). Furthermore, on prolonged reaction times (2 d) at *ca*. 20 °C or under reflux (110 °C) the reaction mixture became more complex and both the protodebrominated 3-amino-5-

phenylisothiazole **144** and the 3-amino-5-phenylpyrazole **141** could be isolated. Prolonged heating (6 d) at 110 °C gave 3-amino-5-phenylpyrazole **141** as the major product (81%) (Table 13).

Table 13 Reaction of the 3-hydrazinylisothiazole **143** (0.100 mmol) with anhydrous hydrazine (1 mL) under an atmosphere of air protected from moisture by a $CaCl_2$ drying tube.

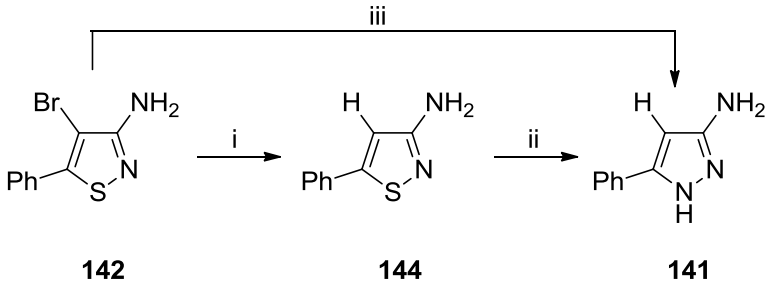


143 **142** **144** **141**

Temp. (°C)	Time (d)	Yields (%) **142**	**144**	**141**
20	35 min	96	0	0
20	1[a]	91[b]	0	0
20	2	26	45	20
20	25 h[c]	98	0	0
110	1	0	39	55
110	6	0	9	81

[a] Degassed hydrazine under an argon atmosphere.
[b] Based on (29-30%) recovered 3-hydrazinylisothiazole **143**.
[c] Under an oxygen atmosphere.

Attempts to directly obtain a high yield of 3-amino-5-phenylisothiazole **144** from 4-bromo-3-hydrazino-5-phenylisothiazole **143** were not successful (Table 13). Nevertheless, treating 3-amino-4-bromo-5-phenylisothiazole **142** with anhydrous hydrazine at *ca.* 20 °C for 35 h gave only the protodebrominated 3-amino-5-phenylisothiazole **144** in high yield (90%). Heating either 3-amino-4-bromo- or 3-amino-5-phenylisothiazole **142** & **144** with anhydrous hydrazine at 110 °C for 4 and 5 d respectively gave 3-amino-5-phenylpyrazole **141** in 80% (8% recovered starting isothiazole **144**) and 81% yields respectively (Scheme 48).



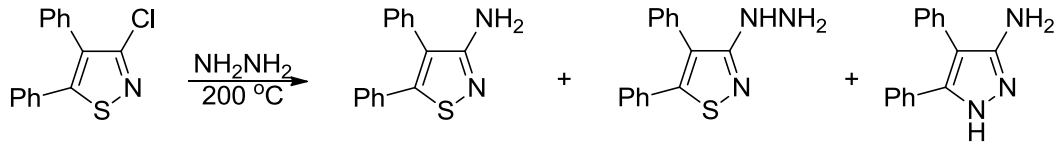
142 **144** **141**

Reagents and conditions: i) N_2H_4, 20 ^oC, 35 h, 90%; ii) N_2H_4, 110 ^oC, 4 d, 80%; iii) N_2H_4, 110 ^oC, 5 d, 81%.

Scheme 48

The reaction of 3-chloro-4,5-diphenylisothiazole **139** with anhydrous hydrazine at 20 ^oC gave a complex reaction mixture (Table 14), but the product distribution was simplified when the reaction was performed in a sealed tube at 200 ^oC (Wood's metal bath) for 20 min, giving mainly 3-hydrazino-4,5-diphenylisothiazole **146** in good yield (77%) together with some unreacted starting isothiazole **139**. Prolonged heating (35 min) gave two new products, 3-amino-4,5-diphenylisothiazole **145** and 3-amino-4,5-diphenylpyrazole **147** (Table 14). Extending the heating period to 2 h led to an increase in the formation of 3-aminoisothiazole **145** and the 3-amino-4,5-diphenylpyrazole **147** at the expense of 3-hydrazino-4,5-diphenylisothiazole **146**.

Table 14 Reaction of 3-chloro-4,5-diphenylisothiazole **139** (0.185 mmol) with anhydrous hydrazine (2 mL) in a sealed tube at 200 °C.



139 **145** **146** **147**

Time (min)	Yields (%) 145	146	147
20	0	77 (87)[a]	0
35	39	40	21
2 h	60	0	33

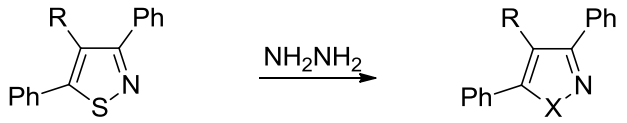
[a] Yield based on recovered 3-chloro-4,5-diphenylisothiazole **139**.

The stability of the 3-hydrazino-4,5-diphenylisothiazole **146** was investigated further. Rather surprisingly, DCM solutions of 3-hydrazino-4,5-diphenylisothiazole **146** under air, argon and oxygen atmospheres for 3 d at *ca.* 20 °C, gave no reaction products and the 3-hydrazino-4,5-diphenylisothiazole **146** was quantitatively recovered unchanged. This stability was in stark contrast with that of the 4-bromo-3-hydrazino-5-phenylisothiazole **143** (Table 12). While this difference in stability remains to be explained the formation of the 3-hydrazinylisothiazoles **143** and **146** under thermodynamically driven conditions (200 °C) provides a rather precarious yet novel route to these previously unreported 3-hydrazino functionalized isothiazoles. The analogous attempts to prepare 3-hydrazino-5-phenylisothiazole-4-carbonitrile **88** from 3-chloro-5-phenylisothiazole-4-carbonitrile **87** only afforded pyrazole **89**.

4.6 Varying the Isothiazole C-4 Substituent without a Nucleofuge at C-3

When the substituent at the isothiazole C-3 position was not a leaving group the conversion into pyrazole proceeded only under relatively very harsh conditions; no reactions were observed at room temperature (Table 15).

Table 15 Reaction of 3,5-diphenyl-4-substituted isothiazoles **95, 148-151** (0.230 mmol) in anhydrous hydrazine (2 mL) in a sealed reaction tube.



95, 148-151 **100, 148, 152**

	R	Temp. (°C)	Time (d)	Yields (%)
95	CN	150	1	**100** (X = NH, R = CN) (83)
148	H	200	7	nr[a]
149	Br	200	2.5 h	**148** (X = S, R = H) (100)
150	Ph	200	7	nr[a]
151	NH_2	150	20	**152** (X = NH, R = NH_2) (20)[b]

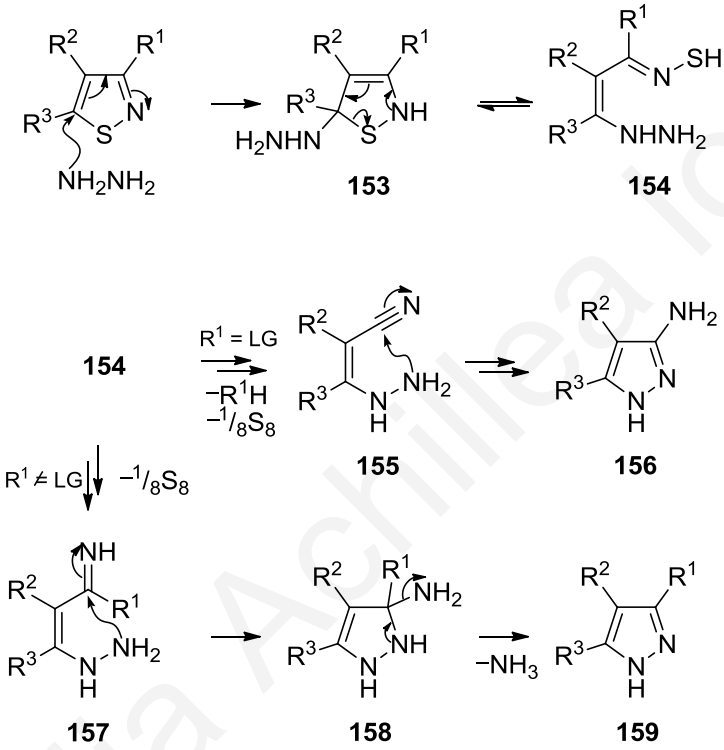
[a] nr = no reaction.
[b] Based on 49% recovered 4-amino-3,5-diphenylisothiazole **151**.

4-Bromo-3,5-diphenylisothiazole **149** suffered only quantitative protodebromination to afford 3,5-diphenylisothiazole **148** which showed no further reaction with anhydrous hydrazine. Prolonged heating in a sealed tube or the use of a CEM Discover microwave reactor at 200 °C for 20 min failed to convert or consume either 3,5-diphenyl- or 3,4,5-triphenyl- isothiazoles **148** and **150**, respectively. These examples identified one of the limits for the isothiazole into pyrazole conversion using neat anhydrous hydrazine. The high yield conversion of the 4-cyano isothiazole **95** was presumably owed to the powerful electron withdrawing effect of the nitrile which provided some activation for the isothiazole into pyrazole conversion, although at the reaction temperature (150 °C) and based on the isolation of 3-hydrazinyl-isothiazoles **143** and **146** the initial site of attack by hydrazine could in this case be the isothiazole C-3 position (see Scheme 50 below).

4.7 Mechanistic rationale

In light of the above, rational mechanisms could be proposed to explain the formation of the pyrazoles depending on the leaving ability of the isothiazole C-3 substituent (Scheme 49). Initially hydrazine could attack the highly electrophilic isothiazole C-5[32,35,180] to afford the 2,5-dihydroisothiazole **153** that could be in equilibrium with its ring opened form **154**. When

R^1 was a good leaving group (*e.g.*, R^1 = Cl), loss of R^1H and sulfur could give the hydrazinyl acrylonitrile **155**. Intramolecular cyclization and subsequent tautomerization would afford the 3-aminopyrazole **156**. The intramolecular cyclization of 3-hydrazinyl acrylonitriles into 3-aminopyrazoles has been reported to be rapid and independent of *E*/*Z* alkene geometry.[197,198] Where R^1 was not or was a poor leaving group the ring opened intermediate **154** could lose sulfur to afford the hydrazinyl enimine **157**, which could suffer intramolecular cyclization to give the 1,3-dihydropyrazole **158** and ultimately the fully aromatic pyrazole **159**.

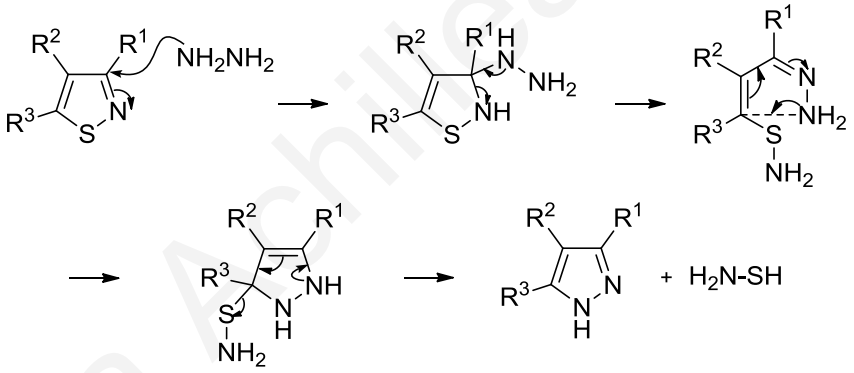


Scheme 49

The reaction mixtures showed no elemental sulfur as would be expected since anhydrous hydrazine was known to reduce sulfur rapidly to hydrogen sulfide which then can form $(N_2H_4)_2.H_2S$ and $N_2H_4.H_2S$ salts with the excess hydrazine.[199] Indeed the reaction mixtures gave a strong odour of hydrogen sulfide [WARNING TOXIC] and its presence was confirmed using Accuro pump fitted with a hydrogen sulfide Dräger tube which tested positive. It was not clear whether hydrogen sulfide was formed directly from the reaction or from elemental sulfur which could have originated from the reaction mixture. However, nucleophilic attack on isothiazole in the absence of a good nucleofuge at C-5 is normally expected to occur on the ring sulfur.[200,201] Since this possibility cannot be eliminated based on the observed

experimental data, initial nucleophilic attack at sulfur could also be the initiation point for this ring transformation, although the failure to convert 3-chloro-5-(2,6-dimethylphenyl)-isothiazole-4-carbonitrile **112** into the corresponding pyrazole suggested that when the isothiazole C-5 position was sterically hindered then attack at C-3 was preferential to attack at the ring sulfur.

Furthermore, in light of the initial formation and isolation of 3-hydrazinylisothiazoles **143** and **146** during the high temperature reactions with anhydrous hydrazine an alternative mechanism must be considered for the high temperature (150 ^{o}C) ring transformation of 3,5-diphenyl-isothiazole-4-carbonitrile **95** into 3,5-diphenylpyrazole-4-carbonitrile **100**. In this case, hydrazine could initially attack the isothiazole C-3 carbon and a ring opening - ring closure sequence ultimately releasing the observed pyrazole and possibly a species equivalent to thiohydroxylamine (Scheme 50).[202]



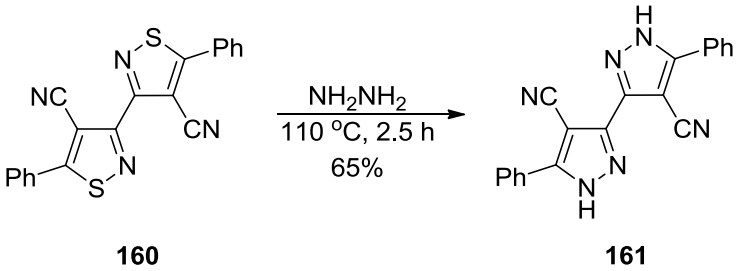
Scheme 50

Regardless of which pathways are proposed this ring transformation clearly belongs to the Addition Nucleophilic Ring Opening Ring Closing ANRORC family.[203]

4.8 Conversion of Biisothiazoles into Bipyrazoles

The conversion of isothiazoles into pyrazoles using neat anhydrous hydrazine could be extended without complication to the known 5,5′-diphenyl-3,3′-biisothiazole-4,4′-dicarbo-nitrile **160** which was readily transformed into 5,5′-diphenyl-3,3′-bi(1*H*-pyrazole)-4,4′-dicarbonitrile **161** in 65% yield (Scheme 51). Similar treatment of 5,5′-bi(3-chloroisothiazole-

4-carbonitrile) with hydrazine, however, gave only a complex reaction mixture from which no products could be isolated and characterized. Many bipyrazoles are known, and several 3,3′- and 5,5′-bipyrazoles have shown interesting biological activities.[204-206]

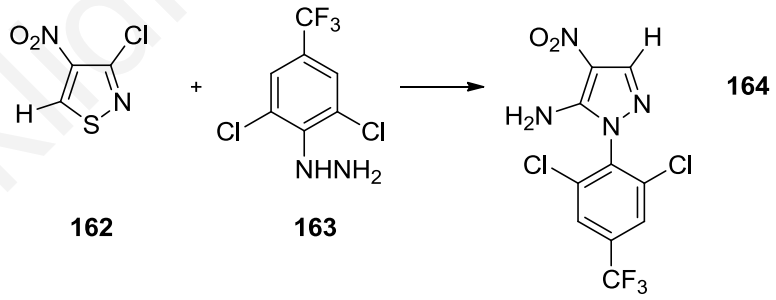


160 **161**

Scheme 51

4.9 Methylhydrazine

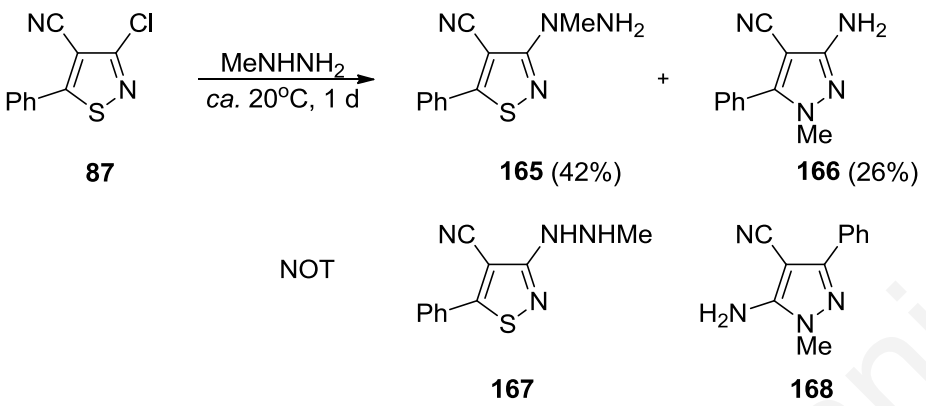
The conversion of isothiazoles into pyrazoles has been shown to proceed with hydrazine, both in its hydrated and anhydrous form. Only one example currently exists where the conversion has been achieved with a substituted hydrazine. 3-Chloro-4-nitroisothiazole **162** was converted into 5-amino-1-(2,6-dichloro-4-trifluoromethylphenyl)-4-nitropyrazole **164** using 2,6-dichloro-4-trifluoromethyl-phenylhydrazine **163** (Scheme 52).[178] Assuming the initial attack occurred at the isothiazole C-5 position then the arylhydrazine appeared to have attacked *via* its *β*-nitrogen. A logical extension of our current study was therefore to investigate the action of methylhydrazine on isothiazoles.



162 **163** **164**

Scheme 52

3-Chloro-5-phenylisothiazole-4-carbonitrile **87** treated with methylhydrazine at *ca.* 20 °C for 1 d gave two products, 3-(1-methylhydrazino)-5-phenylisothiazole-4-carbonitrile **165** in 42% and 3-amino-1-methyl-5-phenylpyrazole-4-carbonitrile **166** in 27% yield (Scheme 53).

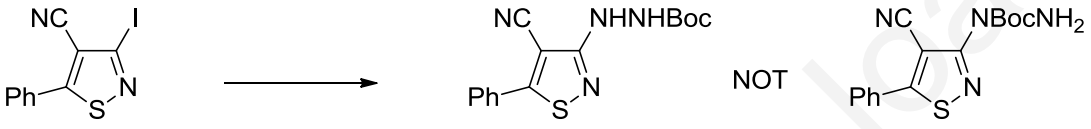


Scheme 53

The structural elucidation of the reaction products was complicated owing to the possibility of alternative isomeric structures isothiazole **167** and pyrazole **168**. Nevertheless, the two possible isothiazole isomers **165** and **167** could be tentatively differentiated by their ^{1}H NMR spectra. The 1,2-disubstituted unsymmetrical hydrazine **167** was expected to show two separate NH resonances which should integrate in a ratio of 1:1, while the 1,1-disubstituted hydrazine **165** should show only one NH_2 resonance the integration of which should show two protons. The ^{1}H NMR of the isolated isothiazole gave a single broad peak at 4.02 ppm the integration of which showed two protons and supported the structure to be isothiazole **165**. Fortunately the two possible pyrazole isomers had both been previously prepared independently with no ambiguity in their reported structures. These two pyrazoles had significantly different melting points, 3-amino-1-methyl-5-phenylpyrazole-4-carbonitrile **166** (mp 158 ^{o}C)[207] and 5-amino-1-methyl-3-phenylpyrazole-4-carbonitrile **168** (mp 134 ^{o}C, from H_2O).[208] The isolated pyrazole (mp 158 ^{o}C from EtOH) matched the melting point of the reported pyrazole **166**. Both products clearly indicated a preference for the methylhydrazine to attack through the α-nitrogen bearing the methyl substituent which was unlike the preference of the arylhydrazine that preferred to attack through the β-nitrogen.

4.10 Synthesis of *tert*-Butyl 3-(4-Cyano-5-phenylisothiazol-3-yl)carbazate

As mentioned earlier, attempts to prepare the desired 3-hydrazinyl-5-phenylisothiazole-4-carbonitrile **88** were unsuccessful. An alternative strategy to access 3-hydrazinyl-5-phenyl-isothiazole-4-carbonitrile involved preparing the title compound *via* modified Buchwald C-N coupling conditions.[209-211] As such, the reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile **23**[36] with *tert*-butyl carbazate in the presence of copper iodide and cesium carbonate as base, together with 1,10-phenanthroline as the ligand, in dry DMF at 80 ^{o}C gave the Boc protected 3-hydrazinyl-5-phenylisothiazole-4-carbonitrile **169** (Scheme 54).

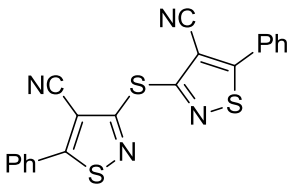


23 **169** **170**

Reagents and conditions: $BocNHNH_2$, CuI, Cs_2CO_3, 1,10-phen, DMF, 80 ^{o}C, 0.5 h, 70%

Scheme 54

Elemental analysis supported an empirical formula of $C_{15}H_{16}N_4O_2S$ and LREI gave a weak parent ion of *m/z* 316 Da (1%) with a major ion at 216 Da (100%) corresponding to the loss of the Boc group. IR spectroscopy supports the presence of the amino [ν(N-H) 3350w & 3239w cm^{-1}], cyano [ν(C≡N) 2216w cm^{-1}] and the carbonyl [ν(C=O) 1722s cm^{-1}] functionalities. Despite this data, two possible isomers could still be formed whereby coupling occurred *via* the carbazate *β* or *α* nitrogens to give either isothiazoles 2 or 3, respectively. ^{1}H NMR spectroscopy, showed two separate NH resonances at δ_H 6.83 and 6.64 ppm that integrated in a ratio of 1:1, tentatively supporting isothiazole **169** to be the correct product. The alternative isomer *tert*-butyl 2-(4-cyano-5-phenylisothiazol-3-yl)carbazate **170** should exhibit a single NH resonance in the ^{1}H NMR spectrum with an integration supporting two hydrogens.[209] Although the compound was successfully synthesized and characterized, there was a problem repeating this chemistry since in all the attempts to isolate the target molecule in quantities, a new product was observed as the only product and this appeared to be the sulfide **171** (Figure 2).



171

Figure 2. Structure of the sulfide

4.11 Summary

The use of hydrazine to convert isothiazoles into pyrazoles has been investigated with respect to substitution patterns on the isothiazole at C-3, C-4 and C-5. The data tentatively suggests that in the absence of steric hindrance the hydrazine attacks initially the isothiazole C-5 carbon and that this is followed by ring opening and subsequent ring closure to give pyrazoles. When the isothiazole C-5 substituent is not a good nucleofuge and the C-3 substituent is a good nucleofuge the use of high temperatures and short reaction times can lead to the formation of 3-hydrazinylisothiazoles. When both the C-3 and C-5 substituents are not leaving groups the isothiazoles can be transformed into pyrazoles only under harsh conditions and the presence of a nitrile at C-4 assists this transformation. The isothiazole into pyrazole conversion can be extended to methylhydrazine which preferentially attacks through its α-nitrogen. Furthermore, in an attempt to independently synthesize 3-hydrazino isothiazole, the *N*-Boc protected isothiazole *tert*-butyl 3-(4-cyano-5-phenylisothiazol-3-yl)carbazate, was synthesized.

PART 2

CHAPTER 5

Palladium Catalyzed C-C Coupling Reactions of 3,5-Dichloro-4*H*-1,2,6-thiadiazin-4-one

Sections

5.1 Introduction

In this chapter the chemistry of 3,5-dichloro-1,2,6-thiadiazinone **24** is investigated. Suzuki-Miyaura, Stille and Sonogashira palladium-catalyzed C-C coupling reactions were applied for the first time onto dichlorothiadiazinone **24** to give symmetrical 3,5-bis-arylated, heteroarylated and alkynylated thiadiazinones.

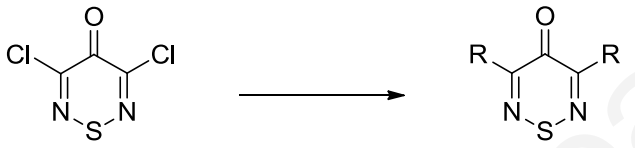
Palladium catalyzed C-C coupling reactions have widely been used for the synthesis of alkylated and/or arylated arenes and heteroarenes.[13,212,213] Interestingly, while there are many electron rich symmetrical dihalo heterocyclic systems that participate in palladium catalyzed C-C coupling reactions to give in one pot bis-arylated/alkylated systems, there are relatively few examples of electron poor symmetrical dihalohetero-arenes *e.g.*, 1,2,5-thiadiazoles,[214] 1,3,4-thiadiazoles,[215] pyridines,[216-219] and pyrimidines.[220,221]

5.2 Suzuki Reaction on 3,5-Dichloro-1,2,6-thiadiazin-4-one 24

Owing to the facile displacement of chloride by a wide variety of nucleophiles the initial attempts at Suzuki-Miyaura coupling of the dichlorothiadiazinone **24** focused on protocols that were non-aqueous with the hope of limiting base catalyzed hydrolysis of the heterocycle. Similar anhydrous protocols worked well for the C-5 selective Suzuki-Miyaura reactions of highly reactive 3,5-dichloroisothiazole-4-carbonitrile **11**.[35] Nevertheless when the dichlorothiadiazinone **24** was reacted with phenylboronic acid (2.2 equiv) and $Pd(OAc)_2$ (5 mol%) in organic solvents (PhH, PhMe, DCM, MeCN, 1,4-dioxane, THF) and inorganic [M_2CO_3 (M = Li, Na, K, Cs), $KHCO_3$, KF, KOH, K_3PO_4] or organic (Et_3N, *i*-Pr_2NEt, pyridine) bases together with phase-transfer agents (18-C-6, Adogen 464®, Aliquat 336®, $BnEt_3NI$, $BnEt_3NCl$,) only mixtures of unreacted dichlorothiadiazinone **24**, mono- and bisphenylated thiadiazines were isolated after 24 h. In light of this, we switched to biphasic systems and fortunately this led to complete consumption of the dichlorothiadiazinone **24**. We screened a range of solvents (PhH, PhMe, DCM, 1,4-dioxane, DME, MeCN, THF, DMA, DMF,), bases [KOH, M_2CO_3, $MHCO_3$, MF (M = Na, K, Cs)] and catalysts [($Pd(Ph_3P)_4$, $Pd(OAc)_2$, $(Ph_3P)_2PdCl_2$, $(PhCN)_2PdCl_2$, $(MeCN)_2PdCl_2$, $(dba)_3Pd_2$, [1,1'-(Ph_2P)ferrocene]$PdCl_2$.DCM)]. The best conditions required the use of $PhB(OH)_2$ (2.2-3 equiv), $Pd(Ph_3P)_4$ (5 mol%) and Na_2CO_3 (2 equiv) in either 1,4-dioxane/H_2O (5:3) or

benzene/H_2O (5:3) at 20-100 ^oC. The concentration of the reaction mixture proved to be important: high concentrations (*e.g.*, 0.8 mL for 0.27 mmol of **24**) led to faster and cleaner reaction. Using the best conditions 12 analogues were synthesized that tested both steric and electronic limits (Table 16).

Table 16 Reaction of dichlorothiadiazinone **24** (0.273 mmol) with $RB(OH)_2$ (2.2 equiv), $Pd(Ph_3P)_4$ (5 mol%), Na_2CO_3 (2 equiv) in dioxane/H_2O (0.5:0.3 mL) at 20-100 ^oC.



24 **172-184**

entry	$RB(OH)_2$ (equiv)	time (min)	yields (%)
1	$PhB(OH)_2$ (2.2)	20	**172** (91)
2	2-Tol$B(OH)_2$ (2.2)	30	**173** (94)
3	3-Tol$B(OH)_2$ (2.2)	30	**174** (91)
4	4-Tol$B(OH)_2$ (2.2)	15	**175** (99)
5	2,6-$Me_2C_6H_3B(OH)_2$ (2.2)	40	[a]
6	2-$MeOC_6H_4B(OH)_2$ (2.2)	15	**176** (87)
7	3-$MeOC_6H_4B(OH)_2$ (2.2)	15	**177** (88)
8	4-$MeOC_6H_4B(OH)_2$ (2.2)	15	**178** (86)
9	2-$ClC_6H_4B(OH)_2$ (2.2)	40	**179** (80)
10	3-$ClC_6H_4B(OH)_2$ (2.2)	40	**180** (81)
11	4-$ClC_6H_4B(OH)_2$ (2.2)	40	**181** (89)
12	3-$O_2NC_6H_4B(OH)_2$ (2.2)	30	**182** (54)
13	3-$O_2NC_6H_4B(OH)_2$ (3)	30	**182** (64)
14	3-$O_2NC_6H_4B(OH)_2$ (4)	30	**182** (66)
15	Thien-3-yl$B(OH)_2$ (2.2)	15	**183** (98)
16	Thien-2-yl$B(OH)_2$ (2.2)	75	**184** (42)
17	Thien-2-yl$B(OH)_2$ (3)	60	**184** (90)
18	Pyrid-3-yl$B(OH)_2$ (2.2)	60	[a]
19	Pyrid-4-yl$B(OH)_2$ (2.2)	60	[a]
20	$MeB(OH)_2$ (2.2)	30	[a]

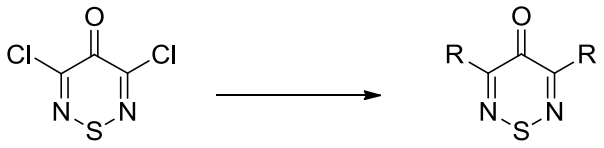
[a] Consumption of the starting material, no product.

In most cases 2-substituted phenylboronic acids reacted equally well with the 3- and 4-substituted analogues, indicating that there was little steric effect, however, when the more sterically demanding 2,6-dimethylphenylboronic acid was used no product was obtained (Table 16, entry 5). In the case of 3-nitrophenyl analogue the yield was low and could not be significantly improved by increasing the quantity of the boronic acid from 2.2 to 4 equiv (entries 12-14). The other electron poor 3- and 4-pyridylboronic acids gave only intractable polar products (baseline on TLC) (entries 18 and 19). The reaction with methyl-boronic acid was also unsuccessful (entry 20). Fortunately, both the 2- and 3-thienylboronic acids reacted to give the expected bisthienyl substituted thiadiazinones **183** and **184**, although the former required additional equivalents to give high yields (entry 17). This was not surprising considering the ease with which thien-2-ylboronic acid suffers protodeboronation.[222-224]

5.3 Stille Reaction on 3,5-Dichloro-1,2,6-thiadiazin-4-one 24

The Stille coupling of dichlorothiadiazinone **24** with phenyl, fur-2-yl, thien-2-yl and *N*-methylpyrrol-2-yl tributyl stannanes in the presence of $Pd(Ph_3P)_2Cl_2$ (5 mol%) in MeCN gave the expected products in very high yields. Other stannyl reagents such as thiazol-2-yl, vinyl, propynyl and tributylstannyl led to either decomposition or no reaction (Table 17).

Table 17 Reaction of dichlorothiadiazinone **24** (0.273 mmol) with $RSnBu_3$, $Pd(Ph_3P)_2Cl_2$ (5 mol %) in MeCN (1 mL) at 20-82 °C.

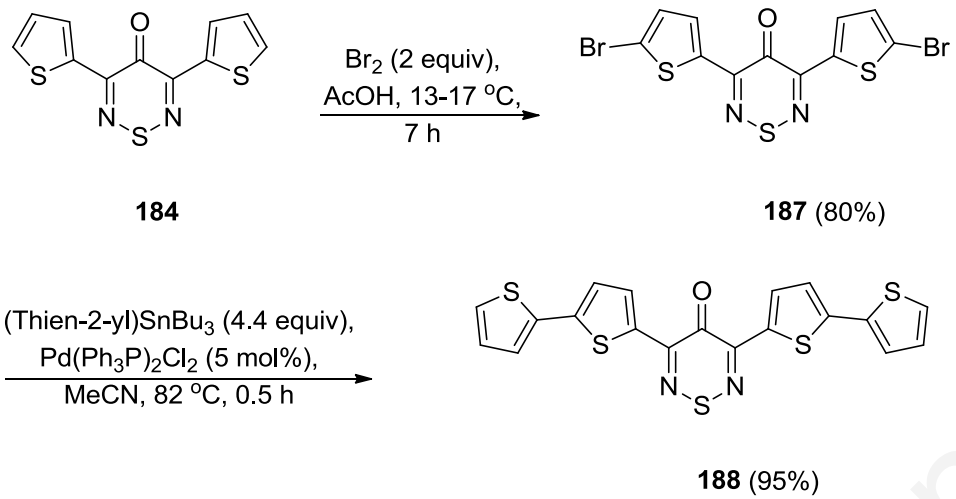


24 **172, 184, 185-186**

entry	R	$RSnBu_3$ (equiv)	time (h)	yields (%)
1	Ph	2.2	2.5	**172** (95)
2	Fur-2-yl	2.2	0.75	**185** (92)
3	Thien-2-yl	2.2	1	**184** (92)
4	*N*-Me-pyrrol-2-yl	2.2	1	**186** (93)
5	Thiazol-2-yl	2.2	20	*a*
6	Vinyl	2.2	4	*a*
7	Propynyl	3	4	*b*
8	Bu_3Sn	3	24	*b*

a Consumption of the starting material, no product.
b Recovered starting material.

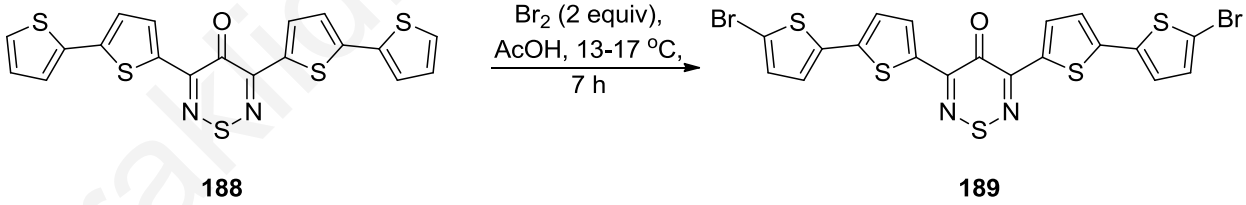
Having access to a high yielding synthesis of 3,5-di-(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one **184** and in light of our on-going goal for the incorporation of thiadiazine into conjugated polymers, we proceeded to synthesize oligothiophene 1,2,6-thiadiazin-4-one **188**. Oligo- and polythiophenes are shown to be important as advanced electronic and photonic materials, such as organic TFT's, liquid crystals, photovoltaic cells, etc.[225-228]



Scheme 55

Bromination of bis(thien-2-yl) 1,2,6-thiadiazin-4-one **184** using 2 equiv of either Br_2 or NBS in AcOH at low temperature (13-15 ^{o}C) gave the 3,5-di(5-bromothien-2-yl)-4*H*-1,2,6-thiadiazin-4-one **187** in 80% yield. The latter underwent the Stille conditions developed earlier using 2-tributylstannyl thiophene in refluxing MeCN to afford the tetrathiophene **188** in very high yield (95%).

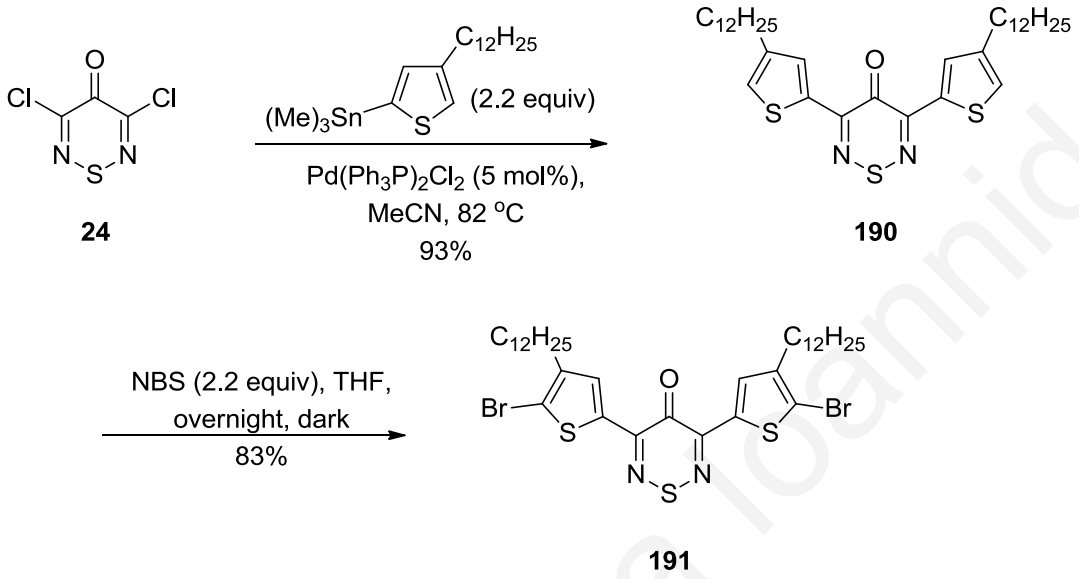
Attempts to make the hexathiophene thiadiazinone, failed due to the low solubility of the synthesized 3,5-bis(5'-bromo-[2,2'-bithiophen]-5-yl)-4*H*-1,2,6-thiadiazin-4-one **189** (Scheme 56) in acetonitrile even in high dilution conditions (50 mg, 10 mL). Some product, although in low yield, was observed when Biphenyl was used as a solvent.



Scheme 56

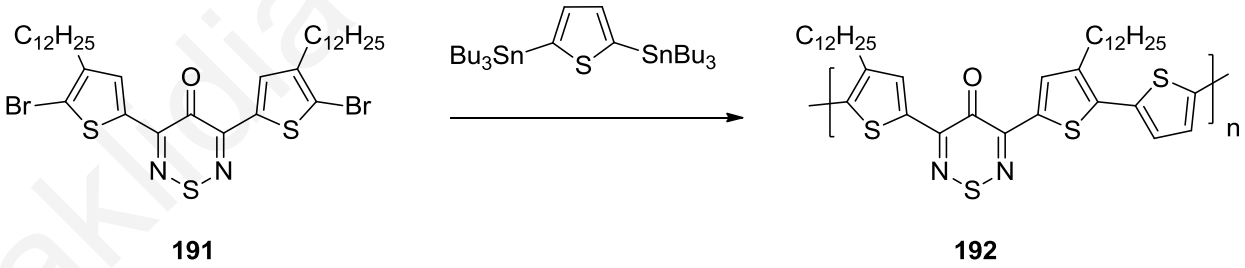
As such, a more soluble oligothiophene thiadiazinone was desired. Using the Stille conditions, the 3-dodecyldithienyl-1,2,6-thiadiazinone **190** was prepared using (4-dodecylthiophen-2-yl)trimethylstannane. The reaction proceeded very well giving the bis-thiophene **190** in high

yield. The latter underwent bromination using NBS to give the bis-bromo product **191** in high yield (Scheme 57).



Scheme 57

The bis-bromo compound **191** was then given to collaborators in CUT (Cyprus University of Technology) where it was copolymerized with 2,5-bis(tributylstannyl)thiophene to give a deep purple-colored polymer **192** (Scheme 58) which is now under study. The UV-vis spectrum of the polymer **192** is shown below (Figure 3).



Scheme 58

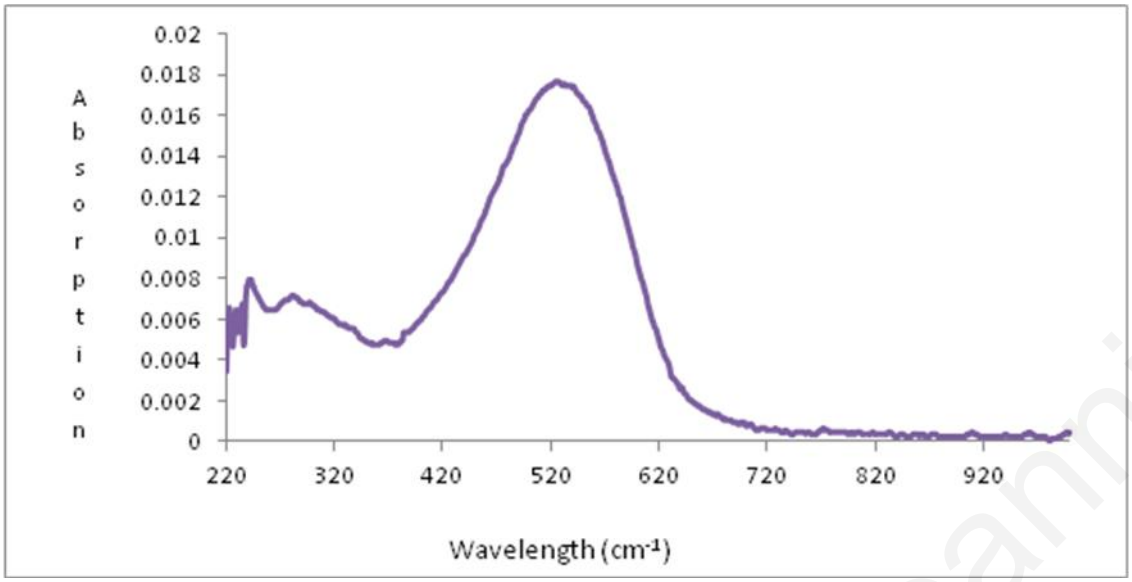
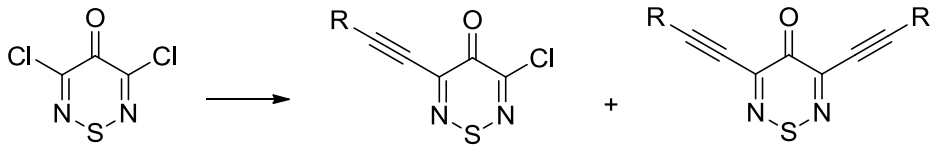


Figure 3. *UV-vis spectrum of the thiadiazinone polymer **192***

5.4 Sonogashira Reaction on 3,5-Dichloro-1,2,6-thiadiazin-4-one 24

Attempts to carry out the Sonogashira reaction between the dichlorothiadiazinone **24** and phenylacetylene, included the examination of the solvent (PhH, PhMe, 1,4-dioxane, THF, DMF, DCM, MeCN) and organic base (Et_3N, Hünig's, lutidine, pyridine) using 5 mol% of a palladium source [$Pd(Ph_3P)_4$, $(dba)_3Pd_2$, $Pd(OAc)_2$, $(PhCN)_2PdCl_2$, $(MeCN)_2PdCl_2$, $(Ph_3P)_2PdCl_2$ and [1,1'-(Ph_2P)ferrocene]-$PdCl_2$.DCM)] and CuI (10 mol%) at rt. The best yield of bisacetylene **193** (73%) was obtained using MeCN, Et_3N (4 equiv), $(Ph_3P)_2PdCl_2$ (5 mol%) and CuI (10 mol%) at rt (Table 18, entry 1). Using these conditions the 3,5-bis(thien-3-ylacetylene) derivative **194** was synthesized in 69% yield at 20-80 ^oC. While 3-pyridinyl acetylene gave the 3,5-bis(pyrid-3-ylacetylene) **195** in 68% yield, the 2-pyridinyl acetylene led to a very complex reaction mixture even at higher temperature (80 ^oC). Use of the ferrocenyl acetylene (3 equiv) gave mixtures of the mono- and di-substituted thiadiazin-4-ones **196** and **197** in 10 and 17% yields, respectively, while use of TMS-acetylene led to decomposition of the starting material (Table 18).

Table 18 Reaction of dichlorothiadiazinone **24** (0.273 mmol) with acetylene (2.2 equiv), Et_3N (4 equiv), CuI (10 mol%), $Pd(Ph_3P)_2Cl_2$ (5 mol%) in MeCN.



24 **196** **193-195, 197**

entry	R	time (min)	yields (%)
1	Ph	10	**193** (73)
2	Thien-3-yl	30	**194** (69)
3	Pyrid-2-yl	30	[a]
4	Pyrid-3-yl	45	**195** (68)
5	Ferrocenyl	180	**196** (10), **197** (17)
6	TMS	60	[b]

[a] Complex reaction mixture
[b] Decomposition

5.5 Summary

In conclusion, the dichlorothiadiazinone **24** underwent Pd catalyzed Suzuki-Miyaura, Stille and Sonogashira C-C coupling reactions to afford symmetrical bis-arylated, heteroarylated and alkynylated systems, respectively. The synthesis of thiophene-thiadiazinone oligomers together with the first thiadiazinone polymer, were achieved.

CHAPTER 6

Reactions of 3-Chloro-5-halo(pseudohalo)-4*H*-1,2,6-thiadiazin-4-ones

Sections

6.1 Introduction

The two chlorine atoms that 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** bears, have exactly the same reactivity owing to the perfect symmetry of the system. As such, the differentiation of the two is impossible and all the C-C coupling reactions tried on the system, were affording mixtures of mono and bis-coupled products. In a continuation of our studies on the scaffold thiadiazinone **24** we proceeded to investigate the synthesis of non-symmetrical 3,5-bis-heteroarylated thiadiazinones by modifying the initial chlorine substituent to bromine, iodine and triflate, targeting chemoselective chemistry.

6.2 Initial study

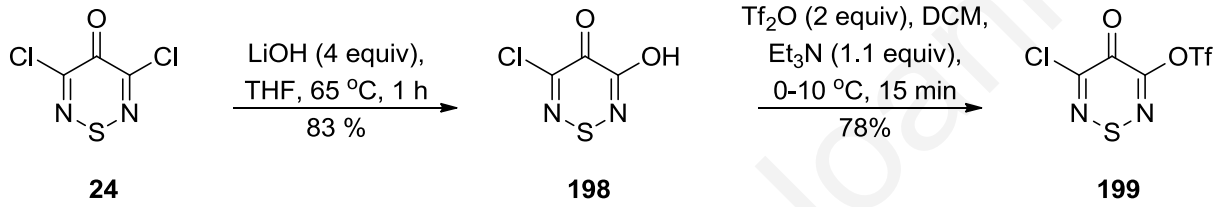
A search in the literature revealed that chemistry can be efficient with symmetrical dihaloheteroarenes that are electron poor (*e.g.*, 1,3,4-thiadiazoles,[229,230] pyridines,[231-236] and pyrimidines[237,238]). In some cases (*e.g.*, 2,6-dihalopyridine) the selective displacement of only one halogen using the Stille protocol required the presence of a large excess of the substrate to prevent the formation of the bis-coupled product,[239] while the Sonogashira reaction of 3,5-dibromopyridine, gave mixtures of mono- and bis-ethynylated derivatives.[240]

Attempts to synthesize 3-aryl-5-chlorothiadiazinone starting from 3,5-dichloro-1,2,6-thiadiazin-4-one **24** using our typical Suzuki-Miyaura or Stille conditions[241] with only 1 equiv of arylboronic acid or arylstannyl reagent, gave only mixtures of mono- and bis-arylated systems, despite varying the reaction solvent, temperature and catalysts. As such, an alternative pathway was proposed that required access to non-symmetrical 3,5-dihalo or 3-halo-5-(pseudohalo)thiadiazinones, which could favor chemoselective Pd catalyzed C-C coupling reactions. Pd catalyzed C-C coupling reactions of "non-symmetrical" mixed dihalo systems 2-bromo-6-chloropyridine[242] and 2-bromo-5-chlorothiophene[243-247] occur chemoselectively at the more reactive bromine.

Initial attempts to exchange selectively one halide with KBr or KI in acetone (Finkelstein reaction)[248] failed and only the starting dichlorothiadiazinone **24** was recovered. Nevertheless, thiadiazinone **24** could be converted into 3-chloro-5-trifluoromethanesulfonyl-4*H*-1,2,6-thiadiazin-4-one **199** in two steps (Scheme 59) and this in turn could be readily converted into the 3-bromo-5-chloro- and the 3-chloro-5-iodothiadiazinones **200** and **201**, respectively (Scheme 60).

6.3 Synthesis of Non-symmetrical Dihalo Thiadiazinones

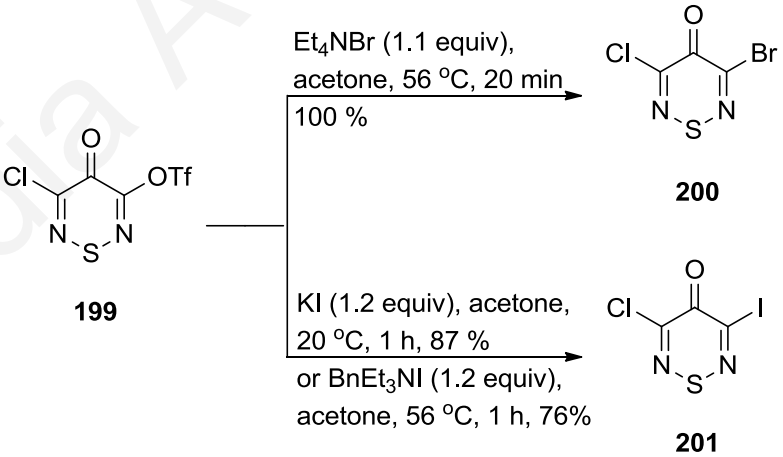
3,5-Dichloro-4*H*-1,2,6-thiadiazin-4-one **24** treated with LiOH (4 equiv) in dry THF heated at *ca.* 65 ^{o}C for 1 h gave 3-chloro-5-hydroxy-4*H*-1,2,6-thiadiazin-4-one **198** directly in 83% yield. The reaction of the alcohol **198** with trifluoromethanesulfonic anhydride (Tf_2O) (2 equiv) in the presence of Et_3N (1.1 equiv) in DCM at *ca.* 0-10 ^{o}C for 15 min gave the 3-chloro-5-triflate-1,2,6-thiadiazin-4-one **199** in 78% yield (Scheme 59).



24 **198** **199**

Scheme 59

By treating the triflate **199** with Et_4NBr (1.1 equiv) in acetone at *ca.* 56 ^{o}C for 20 min, 3-bromo-5-chloro-4*H*-1,2,6-thiadiazin-4-one **200** was obtained in 100% yield, while treatment with KI (1.2 equiv) or $BnEt_3NI$ (1.2 equiv) in acetone at rt and 56 ^{o}C for 1 h gave 3-chloro-5-iodo-4*H*-1,2,6-thiadiazin-4-one **201** in 87 and 76% yields, respectively (Scheme 60).



199 **200** **201**

Scheme 60

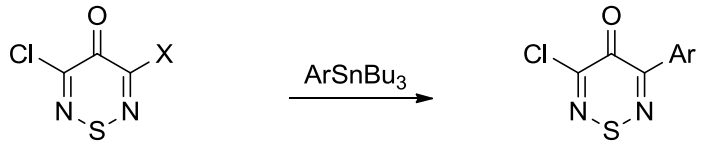
6.4 Stille Reaction

Initially, a screen was pursued of Stille reaction conditions for the mono arylation of the dihalo and pseudohalo thiadiazinones **24, 199-201** using 2-(tributylstannyl)thiophene (1 equiv) and $Pd(Ph_3P)_2Cl_2$ (5 mol%) at rt varying the solvents (*e.g.*, THF, PhH, PhMe and MeCN). 2-(Tributylstannyl)thiophene was used instead of the tributylphenyltin, because the dihalo-, 3-chloro-5-phenyl- and 3,5-diphenylthiadiazinones co-run on TLC. From the solvents screened, PhH gave the fastest and cleanest reaction mixtures, while in MeCN the starting thiadiazinones were insoluble at rt and required heating to *ca.* 50 ^{o}C to solubilize but this led to mixtures of mono and bisthienylated thiadiazinones. The use of THF led to a very fast but complex reaction mixtures (by TLC) while in the case of the PhMe a small amount (4%) of the bis-thienylated product was also isolated.

Of the four thiadiazinones screened, the dichlorothiadiazinone **24** gave mixtures of mono- and bis-thienylated products, while the chloroiodothiadiazinone **201** gave a complex reaction mixture from which no desired product was detectable (by TLC). Fortunately, the bromochloro- and the chlorotriflate- thiadiazinones **200** and **199** reacted chemoselectively with 2-(tributylstannyl)thiophene to give 3-chloro-5-thien-2-yl-4*H*-1,2,6-thiadiazin-4-one **202** in 83 and 85% yields, respectively.

Since the Stille reaction of the 2-(tributylstannyl)thiophene with the triflate thiadiazinone **199** was significantly faster than that of the bromochlorothiadiazinone **200** (2 h *vs* 2 d) we subsequently chose the triflate thiadiazinone **199** as the starting material for the synthesis of a series of chloro monoaryl thiadiazinones (Table 19) that could later be modified into a series of mixed biaryl thiadiazinones (Table 20).

Table 19 Reaction of the 3-chloro-5-halo(pseudohalo)-1,2,6-thiadiazinones **24, 199-201** (0.22 mmol) with $ArSnBu_3$ (1 equiv), $Pd(Ph_3P)_2Cl_2$ (5 mol%), in PhH (2 mL) at rt.



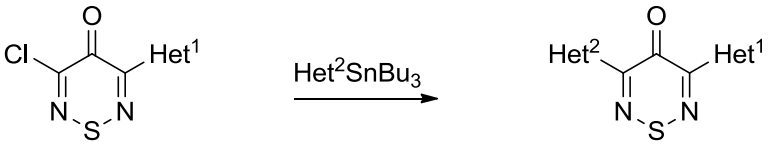
24, 199-201 **202-204**

X	Ar	time (h)	yield (%)
Cl	Thien-2-yl	48	[a]
Br	Thien-2-yl	44	**202** (83)
I	Thien-2-yl	0.5	[b]
OTf	Thien-2-yl	2	**202** (85)
OTf	Fur-2-yl	0.8	**203** (76)
OTf	*N*-Me-pyrrol-2-yl	0.08	**204** (94)
OTf	Ph	4	[a]

[a] Mixture of mono and bi arylated thiadiazinones.
[b] Complex reaction mixture.

Disappointingly, attempts to perform a one-pot Stille mediated two step mixed arylation failed. Nevertheless, unsymmetrical biheteroaryl thiadiazinones were prepared in high yields by reacting the isolated 3-chloro-5-heteroaryl thiadiazinones **202-204** with heteroaryltin and $Pd(Ph_3P)_2Cl_2$ (5 mol%) in MeCN at *ca.* 82 ^oC (Table 20).

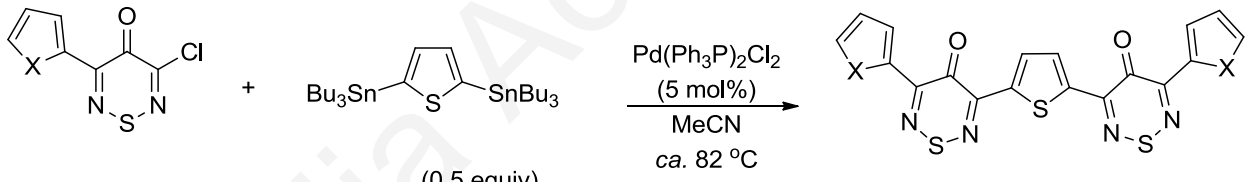
Table 20 Reaction of the 3-chloro-5-heteroarylthiadiazin-4-ones **202-204** (0.22 mmol) with $ArSnBu_3$ (1.2 equiv), $Pd(Ph_3P)_2Cl_2$ (5 mol%), in MeCN (2 mL) at *ca.* 82 °C.



202-204 **205-207**

Het^1	Het^2	time (min)	yield (%)
Thien-2-yl	Fur-2-yl	20	**205** (88)
Thien-2-yl	*N*-Me-pyrrol-2-yl	45	**206** (88)
Fur-2-yl	Thien-2-yl	20	**205** (78)
Fur-2-yl	*N*-Me-pyrrol-2-yl	20	**207** (100)
N-Me-pyrrol-2-yl	Thien-2-yl	45	**206** (100)
N-Me-pyrrol-2-yl	Fur-2-yl	15	**207** (94)

Furthermore, by reacting either the 3-chloro-5-(thien-2-yl)- or the 3-chloro-5-(*N*-methylpyrrol-2-yl)thiadiazin-4-ones **202** or **204** with 2,5-bis(tributylstannyl)thiophene the potentially useful **208** and **209** were synthesized in 76 and 92% yields, respectively (Scheme 61).



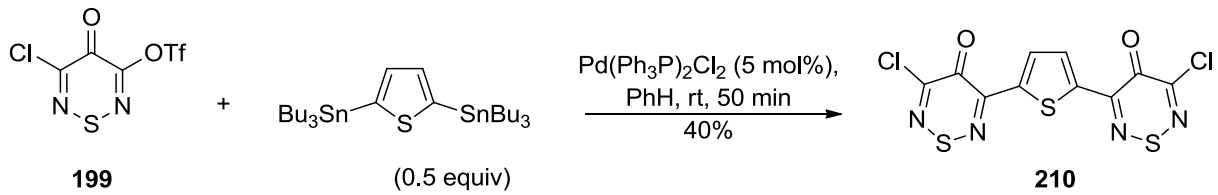
202, X = S
204, X = NMe

(0.5 equiv)

208, X = S, 76%
209, X = NMe, 92%

Scheme 61

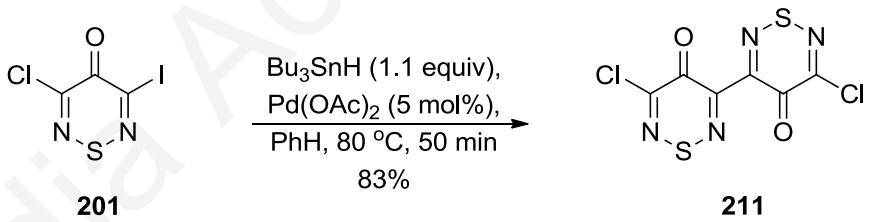
An alternative synthesis of compounds **208** and **209** was also targeted by building first 5,5'-(thiophene-2,5-diyl)bis(3-chloro-4*H*-1,2,6-thiadiazin-4-one) **210** but the synthesis of this from 2,5-bis(tributylstannyl)thiophene and the 3-chloro-5-triflate thiadiazinone **199** was low yielding (40%) and as such this route was abandoned (Scheme 62).



Scheme 62

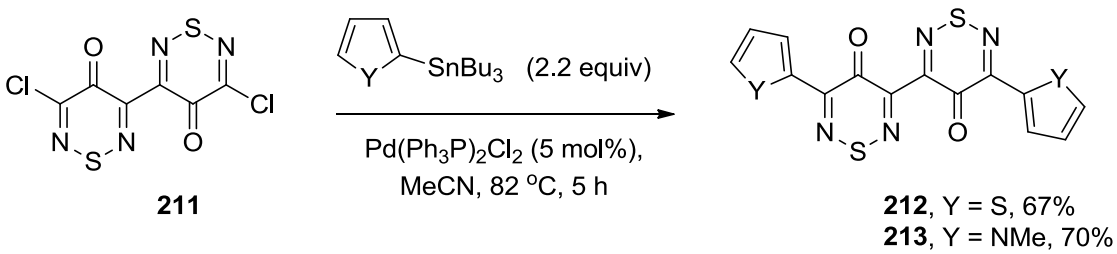
6.5 Synthesis of Thiadiazinone Dimer

We also tried to make 5,5'-dichloro-4*H*,4'*H*-[3,3'-bi-(1,2,6-thiadiazine)]-4,4'-dione **211** from the dihalo-thiadiazinones **24**, **200** and **201** *via* the Ullmann reaction, but the use of copper powder,[249] led to complex reaction mixtures (by TLC) and the use of $Pd(OAc)_2$[36] gave only decomposition. Nevertheless, Bu_3SnH in the presence of a Pd catalyst and KOAc was known to react with iodoarenes to give the tributyltin-arenes but in the absence of base these reactions often afford some biaryls.[250,251] In light of this, 3-chloro-5-iodo-4*H*-1,2,6-thiadiazin-4-one **201** was treated with Bu_3SnH (1.1 equiv) and $Pd(OAc)_2$ (5 mol%) in PhH heated at reflux, and after 50 min the desired 5,5'-dichloro-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione **211** was isolated in 83% yield (Scheme 63). Similar treatment of the dichloro- and bromochloro-thiadiazinones **24** and **200** gave only recovered starting materials.



Scheme 63

The dimer **211** reacted readily with either 2-(tributylstannyl)thiophene or 1-methyl-2-(tributylstannyl)pyrrole (2.2 equiv) and $Pd(Ph_3P)_2Cl_2$ (5 mol%) in MeCN heated to reflux to give 5,5'-di(thiophen-2-yl)-4*H*,4'*H*-[3,3'-bi-(1,2,6-thiadiazine)]-4,4'-dione **212** and 5,5'-di(*N*-meth-ylpyrrol-2-yl)-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione **213** in 67 and 70% yields, respectively (Scheme 64).



Scheme 64

6.6 Summary

In conclusion, desymmetrization of dichlorothiadiazinone **24** *via* modified Finkelstein reaction conditions gave triflate-, bromo-, and iodo-substituted chlorothiadiazinones **199**, **200** and **201** respectively. Both the triflate and the bromochlorothiadiazinones suffered chemoselective Stille couplings to give 3-chloro-5-heteroaryl thiadiazinones **202-204**, while treatment of the chloroiodothiadiazinone **201** with Bu_3SnH and $Pd(OAc)_2$ gave the dimer dichlorobithiadiazinone **211**. Manipulation of the above gave the π-extended oligomers **208**, **209**, **212** and **213** that could find use in optoelectronic applications.

CHAPTER 7

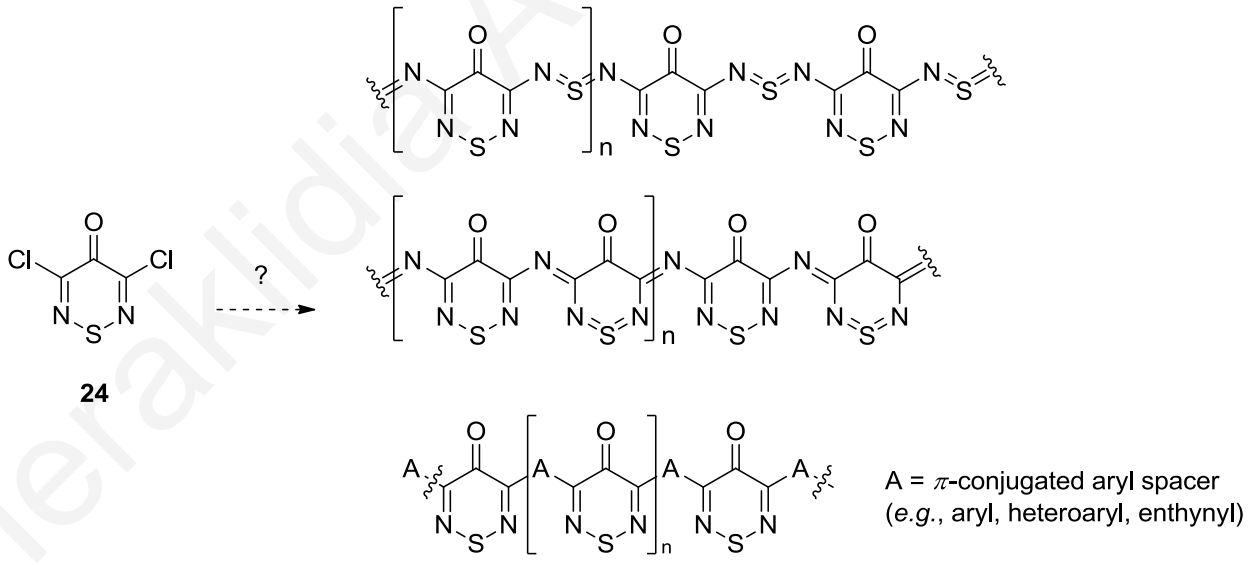
Modification of C-4 Position of 3,5-Disubstituted 4*H*-1,2,6-Thiadiazin-4-ones

Sections

7.1 Introduction

While many 5-substituted derivatives of 3-chloro-4*H*-1,2,6-thiadiazin-4-ones have high fungicidal activity,[252-255] this usefulness has not prompted extensive studies and the known chemistry of the dichlorothiadiazines **24** and **26** remains limited. The chlorines in **24** and **26** can be successively displaced by a range of nucleophiles, the second requiring more vigorous conditions.[38,43-45] To the best of our knowledge there are no reports on the direct intermolecular condensation on the C-4 carbonyl of the dichlorothiadiazinone **24**. The only examples about modification of the C-4 carbonyl are those of bidentate bisnucleophiles reacting with thiadiazinones **24** and **26** (see Introduction schemes 25, 27).[43-46]

In Chapters 5 and 6, we have demonstrated that C-C coupling reactions can be applied onto 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** to form both symmetrical and non-symmetrical 1,2,6-thiadiazin-4-ones.[241,256] This development in the chemistry of the dichlorothiadiazinone **24** potentially could lead to the construction of novel π-conjugated oligomers and polymers (Scheme 65). π-Conjugated polymers of thiadiazines have been proposed by both Woodward[257] and Rees [39,40,43] as stable alternatives to the superconductor poly(sulfur nitride) $(SN)_x$.



Scheme 65

The optical/electrical properties of such oligomers or polymers could be moderated by manipulation of the thiadiazine C-4 position. In this chapter we describe our efforts to moderate the C-4 position of the model compound 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-one **172** together with some related chemistry of 3,5-dithien-2-yl-4*H*-1,2,6-thiadiazin-4-one **184**.

7.2 Addition Reactions

Both 3,5-diphenyl- and 3,5-dithien-2-yl-4*H*-1,2,6-thiadiazin-4-ones **172** and **184** were prepared in multigram quantities (up to 5g) *via* Suzuki-Miyaura or Stille coupling reactions starting from 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** as described in chapter 5.[241] Our study on the chemistry of the C-4 position began with the formal addition of hydrogen and methane across the carbonyl. The mild reduction of the diphenylthiadiazinone **172** using $NaBH_4$ (2 equiv) in dry MeOH gave 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ol **214** in 90% yield in only 5 min, however, owing to the poor solubility of the dithienylthiadiazinone **184** in MeOH the analogous reduction of the latter required a 1:1 mixture of MeOH and DCM (Table 21).

Table 21 Addition reactions of 3,5-diaryl-4*H*-1,2,6-thiadiazin-4-ones **172** and **184**.

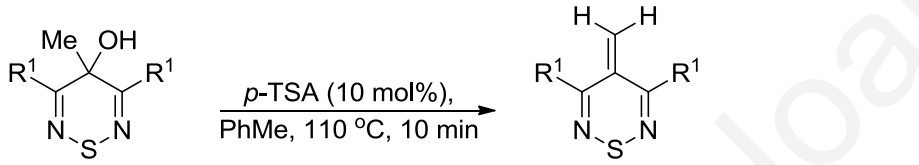
172 (R^1 = Ph) **214-217**
184 (R^1 = Thien-2-yl)

R^1	Conditions	Time (min)	R^2	Yields (%)
Ph	$NaBH_4$ (2 equiv), MeOH, 50 ^oC	5	H	**214** (97)
Thien-2-yl	$NaBH_4$ (2 equiv), MeOH/DCM (1:1), 50 ^oC	15	H	**215** (98)
Ph	MeLi (4 equiv), THF, 0-10 ^oC	60	Me	**216** (90)
Thien-2-yl	MeLi (4 equiv), THF, 0-10 ^oC	60	Me	**217** (79)

Addition of methane could also be achieved by treating 3,5-diphenyl- and 3,5-dithien-2-ylthiadiazinone **172** and **184** with MeLi in dry THF at 0-10 ^oC, to give after 1 h 4-methyl-3,5-

diphenyl- and 4-methyl-3,5-dithien-2-yl-4*H*-1,2,6-thiadiazin-4-ols **216** and **217** in high yields, respectively (Table 21).

Attempts to chlorodehydroxylate or prepare the triflate of 4-methyl-3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ol **216**, using $SOCl_2$ or Tf_2O/Et_3N, respectively gave only the dehydrated (3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane **218**. In light of this facile dehydration the diphenyl- and dithienylthiadiazinols **216-217** were treated with catalytic *p*-TSA (10 mol%) in PhMe at *ca.* 110 ^{o}C for 10 min to afford the corresponding ylidenes **218** and **219** in high yields (Scheme 66).

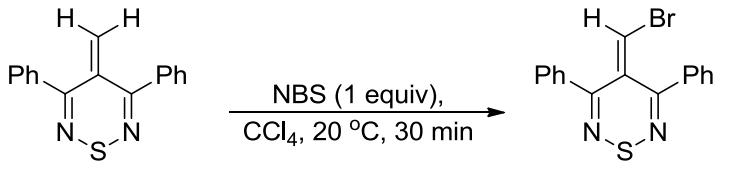


216 (R^1 = Ph)
217 (R^1 = thien-2-yl)

218 (R^1 = Ph, 90%)
219 (R^1 = thien-2-yl, 96%)

Scheme 66

Interestingly, during the attempted chlorodehydroxylation of 4-methyl-3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ol **216** with neat $SOCl_2$ we observed traces of a compound that gave a molecular ion of *m/z* 298 Da with a chlorine isotope pattern tentatively corresponding to a chlorodehydration. As such we investigated the possibility of further halogenating the (thiadiazinylidene)methanes. The attempted chlorination of the (diphenylthiadiazinylidene) methane **218** using $SOCl_2$ gave mixtures and was abandoned. Neverthesless, treating (3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane **218** with NBS (1 equiv) in CCl_4 at *ca.* 20 ^{o}C, gave bromo(3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane **220** in 80% yield (Scheme 67). The analogous reactions with NCS and NIS at *ca.* 20 ^{o}C gave only recovered starting material while at *ca.* 70 ^{o}C the former gave again recovered starting material and the latter gave a complex reaction mixture (TLC) and no trace of the target compound. The analogous reaction of (dithienylthiadiazinylidene)methane **219** led to mainly unreacted starting material and a polar baseline.



218 **220** (80%)

Scheme 67

Further attempts to bis halogenate by either treating the methylene **218** or the monobromoylidene **220** with additional NBS (2 and 3 equiv.) in either CCl_4 or with Br_2 in AcOH led to complex mixtures but no trace of the dibrominated product (by TLC), as such this was not pursued further.

7.3 Preparation of Dihalo(thiadiazin-4-ylidene)methanes

Fortunately, the dihalomethane thiadiazines **221** and **222** could be prepared *via* the Appel reaction.[258] Treating the diphenylthiadiazinone **172** with Ph_3P in CCl_4 or CBr_4 at elevated temperatures in a sealed tube and prolonged heating gave the desired dichloro(3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane **221** and dibromo(3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane **222**, respectively. In the case of the CCl_4 reaction, heating at *ca.* 140 °C under microwave irradiation (MW 250 W, 70 PSI) was the best choice for small scale reactions (up to 0.75 mmol), giving a short reaction time (1 h) (95%) while with CBr_4, heating with microwave irradiation at *ca.* 140 °C (MW 250 W, 68 PSI) led to lower yields (70%) and the best yield was obtained when a sealed tube was used for 7 h at 150 °C (91%) (Scheme 68).

172 **221** (Hal = Cl)
222 (Hal = Br)

Reagents and Conditions: Hal = Cl, Ph_3P (4 equiv), CCl_4, MW (250 W), 140 °C (70 PSI), 1 h, 95%; Hal = Br, Ph_3P (4 equiv), CBr_4 (2 equiv), PhH, MW (250 W), 140 °C (68 PSI), 1 h, 70% or sealed tube, 150 °C, 7 h, 91%.

Scheme 68

The dibromomethane **222** proved to be stable under several reducing conditions: H_2 over Pd/C in EtOH or $NaBH_4$ in MeOH, and In (0) in AcOH but the use of Zn in HCO_2H[259] led to decomposition of the starting material. Furthermore, the dichloromethane **221** and dibromomethane **222** were stable in the presence of nucleophiles, such as morpholine for 2 d at 100 ^oC, *o*-phenylenediamine in EtOH heated at reflux for 2 d and thiophenol in refluxing PhMe for 2 d. This limited reactivity of the dihalomethanes **221** and **222** could be owed to steric effect shielding from the phenyl groups.

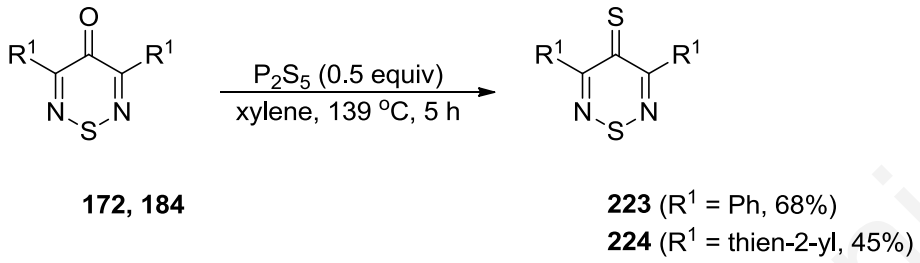
7.4 Preparation of (Thiadiazin-4-ylidene)malononitriles from 3,5-Diphenyl- and 3,5-Dithien-2-yl Thiadiazinones 172 and 184

Prior attempts to condense malononitrile and the dichlorothiadiazinone **24** to prepare the dicyanomethylene **26** had failed and this was tentatively owed to the high reactivity of the chlorine substituents at C-3 and C-5. With the 3,5-diphenyl- and 3,5-dithien-2-yl thiadiazinones **172** and **184** in hand the C-3 and C-5 positions were now blocked and the analogous condensation was reexamined. Treatment of either diphenyl- or dithienylthiadiazinones **172** and **184** with malononitrile in the presence of bases such as Et_3N, pyridine, *t*-BuLi or *n*-BuLi/diisopropylamine in THF or the use of Lewis acids $TiCl_4$ in PhH or ammonium acetate in Ac_2O, or simply refluxing the mixture in Ac_2O afforded only recovered starting thiadiazinones. Furthermore, the thiadiazinones **172** and **184** were unreactive towards a series of reagents like TCNE, TCNEO, MeI, ethyl diazoacetate and the Wittig reagent (cyanomethyl)triphenylphosphonium chloride with NaH in THF. Nevertheless, the ylidenemalononitriles could be prepared from the more reactive thiones **223-224**.

7.5 Preparation of Thiadiazine-4-thiones

Alternative routes to ylidenemalononitriles involve cycloaddition of TCNE or tetracyanoethylene oxide (TCNEO) to thiones[47,260,261] and fortunately, the thiadiazine-4-thiones could be readily prepared. The reaction of thiadiazinones **172** and **184** with of P_2S_5 (0.5 equiv) in xylenes heated at *ca.* 139 ^oC for 5 h gave the desired 3,5-diphenyl- and 3,5-dithien-2-yl-4*H*-1,2,6-thiadiazine 4-thiones **223** and **224** in about 70% and 45% yields, respectively (1 g scales) (Scheme 69). Interestingly, the analogous reactions with Lawesson's reagent (LR) (0.5 equiv) in dry toluene or xylenes heated at *ca.* 110 ^oC and 139 ^oC,

respectively for 12 h led to complex mixtures containing mainly unreacted starting thiadiazinones (by TLC).



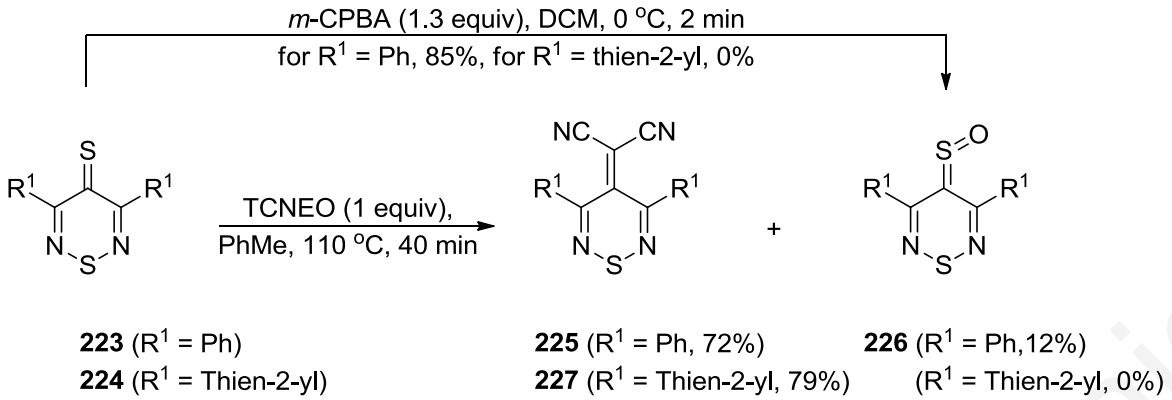
172, 184

223 (R^1 = Ph, 68%)
224 (R^1 = thien-2-yl, 45%)

Scheme 69

7.6 Preparation of (Thiadiazin-4-ylidene)malononitriles from Thiones

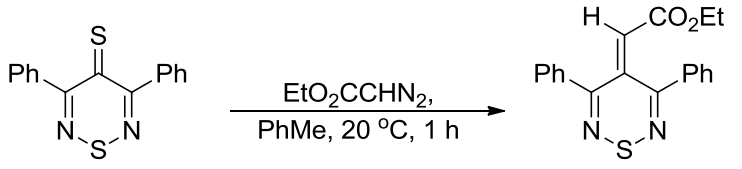
3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-thione **223** treated with TCNE (1 equiv) in PhCl heated to *ca.* 132 °C for 12 h gave 2-(3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile **225** in a moderate (36%) yield together with two purple colored minor side products that could not be separated or characterized. The reaction of the dithienylthiadiazinethione **224** with TCNE, however, led to a complex reaction mixture and this was not altogether surprising since TCNE was known to react with thiophenes to give tricyanovinyl substituted thiophenes at C-2 [262] and in rare cases Diels-Alder adducts can form.[263,264] In light of this, we then reacted both diphenyl and dithienylthiadiazine-4-thiones **223** and **224** with TCNEO (1.2 equiv) in PhMe heated to *ca.* 110 °C for 40 min and obtained the desired ylidenemalononitriles **225** and **227** in 72 and 79% yields, respectively (Scheme 70). Interestingly, the reaction between 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-thione **223** and TCNEO also gave *3*,5-diphenyl-4*H*-1,2,6-thiadiazine-4-thione oxide **226** as a minor side product in 12% yield (Scheme 70). The sulfine **226** could be prepared directly and in high yield (85%) by treating the diphenylthiadiazinethione **223** with *m*-CPBA (1.3 equiv) at *ca.* 0 °C for 2 min, however, the analogous reaction with the dithienylthiadiazin-4-thione **224** gave only decomposition (by TLC), and this was probably owed to the ability of *m*-CPBA to oxidize the electron rich thiophenes.[265]



Scheme 70

The mechanistic rationale for the reactions between TCNE and TCNEO with thiones to give ylidenemalononitriles and also in the latter case the sulfine have been previously reported for 1,2,3-dithiazole-5-thione.[47,261] Briefly, both reagents cycloadd to the thione, TCNE *via* [2+2] and TCNEO *via* [2+3] cycloadditions. The adducts then fragment *via* retrocycloadditions tentatively losing in the first case thiocarbonyl cyanide and in the second case carbonyl cyanide and elemental sulfur, leaving behind the desired ylidenemalononitriles. It has been postulated that sulfine **226** forms by direct attack of the thione onto the TCNEO oxygen leading to an effective oxygen transfer and generation of TCNE as a reaction side product.[261]

In light of this success, we extended the [2+3] cycloaddition chemistry of the thiadiazine-thiones by reacting both the diphenyl- and dithienylthiadiazinethiones **223** and **224** with ethyl diazoacetate (1.5 equiv) in PhMe at *ca.* 20 °C for 1 h and isolated ethyl 2-(3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)acetate **228** in 97% yield from the former (Scheme 71) but failed to obtain a product from the dithienyl analogue. This could be owed to the known reactivity of thiophenes with ethyl diazoacetate that can lead to competing cyclopropanation reactions.[266]



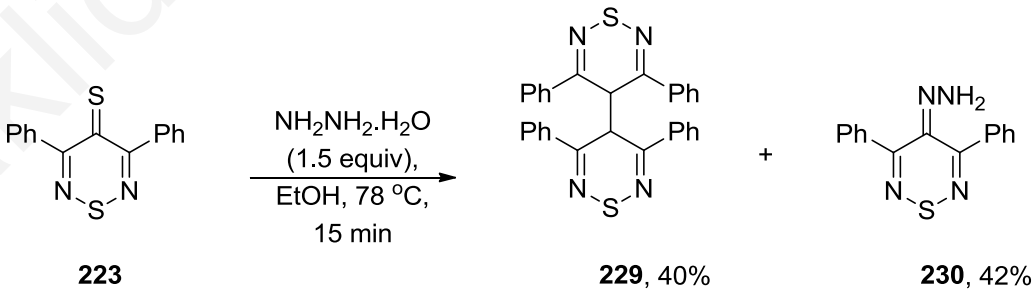
223 **228** (97%)

Scheme 71

7.7 Reaction of Thiadiazine-4-thiones with Hydrazine

Finally we considered the preparation of [(thiadiazin-4-ylidene)amino]arenes by treating either 3,5-diphenyl- and 3,5-dithien-2-yl-4*H*-1,2,6-thiadiazin-4-ones and thiones with primary anilines [*e.g.*, $PhNH_2$ in EtOH at reflux or neat $PhNH_2$] but were unable to isolate any desired products. In light of this, the thiadiazinones and thiadiazine-thiones were treated with the more nucleophilic hydrazine. While the thiadiazinones were again unreactive, 3,5-diphenyl-thiadiazin-4-thione **223** reacted with hydrazine monohydrate (1.5 equiv) in EtOH at *ca.* 78 ^{o}C for 20 min to give an unknown **229** and 4-hydrazono-3,5-diphenyl-4*H*-1,2,6-thiadiazine **230** in 40 and 42% yields, respectively (Scheme 72).

The unknown compound **229** was isolated as yellow plates mp 262-263 ^{o}C (from cyclohexane). Microanalysis of the compound gave C, 71.4; H, 4.7; N, 11.1% and mass spectrometry of compound **229** indicated a MW of 251 Da which could probably be the M^{+}-1. However, the ^{1}H-NMR showed a singlet at 6.02 ppm integrating only 1 proton while the aromatic region integrated 10 protons. The ^{13}C-NMR showed 6 peaks of which one, was an sp^3 (CH) carbon at 25.4 ppm splitting into a double-doublet (*J* 138.8 and 5 Hz) in the coupled ^{13}C-NMR. The UV/vis spectroscopy showed a λ_{max} at 397 nm (log ε 3.71) which indicated less extensive conjugation in comparison with the starting thione **223**. The above data suggested that the structure of the unknown was 3,3',5,5'-tetraphenyl-4*H*,4'*H*-4,4'-bi(1,2,6-thiadiazine) **229** which however has a molecular weight of 502 Da. Further attempts to observe the molecular weight using MALDI-TOF showed only a very weak peak at 502 while the major peak was the 251.



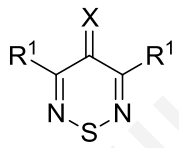
223 **229**, 40% **230**, 42%

Scheme 72

7.8 Comparison of Selected Spectroscopic Data of Thiadiazinylidenes

With a range of 4*H*-1,2,6-thiadiazin-4-ylidenes in hand that varied at C-4, the absorption properties in the UV/vis absorption spectra could be compared. This comparison can yield qualitative information about optical band gaps that can be used in the design of oligomers or polymers needed for further materials studies. On comparing the 3,5-diphenylthiadiazines it was clear that the replacement of oxygen by either sulfur or carbon substituents shifted the longest wavelength absorption to the red (Table 22). On switching the C-4 oxygen for $C(CN)_2$ red shifts of 97 and 157 nm were observed for the diphenyl and dithienylthiadiazinylidenes, respectively.

Table 22 Longest wavelength absorption in the UV/vis spectra of thiadiazinylidenes.



Compound No.	R^1	X	λ_{max} (DCM) /nm (log ε)	^{13}C (ppm) $C(X)_2$
172	Ph	O	348 (3.28)	-
221	Ph	CCl_2	358 (3.19)	121.2
222	Ph	CBr_2	361 (3.19)	91.9
218	Ph	CH_2	392 (2.84)	117.3
223	Ph	S	416 (3.37)	-
225	Ph	$C(CN)_2$	445 (3.07)	79
184	thien-2-yl	O	327 (3.74)	-
219	thien-2-yl	CH_2	395 (3.59)	114.8
224	thien-2-yl	S	454 (3.15)	-
227	thien-2-yl	$C(CN)_2$	484 (3.29)	78.6

The ^{13}C NMR data of ylidenemalononitriles **225** and **227** also indicated that a considerable negative charge was located on the central carbon of the malononitrile group [δ_C $C(CN)_2$ **225** (R^1 = Ph) 79.0 ppm and **227** (R^1 = thien-2-yl) 78.6 ppm] indicating the presence of a considerable push–pull effect,[34] the 'push' originating presumably from the electron rich arenes at C-3 and C-5 and also from the thiadiazine ring sulfur. The above data tentatively support that electron transfer occurred from the 3,5-diaryl substituents to the thiadiazine ring

and that modifications at the C-4 positions strongly affect the properties of these 3,5-diarylthiadiazinylidenes.

7.9 Summary

We have succesfully demonstrated a series of reactions taking place at C-4 position of 3,5-biaryl-1,2,6-thiadiazinones **172** and **184**. The carbonyl group appeared to be difficult to modify but nevertheless by converting it into the most reactive thiones **223**-**224**, condensations and addition reactions could be addressed affording the desired products in high yields.

PART 3

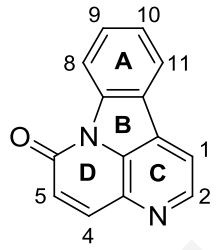
CHAPTER 8

Synthesis of Ethyl Canthinone-1-carboxylates

Sections

8.1 Introduction

Canthin-6-one **231** (6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one) (Figure 4), first isolated in 1952 by Haynes,[267] is the parent of the 120 member plus canthinone alkaloid family which includes over 40 naturally occurring analogues.[268-274] Selected canthin-6-one alkaloids have interesting biological properties including antiparasitic activity against *Trypanosoma cruzi* (Chagas disease),[275,276] and *Plasmodium falciparum* (malaria),[277-279] antibacterial[280,281] and antifungal[282-284] properties. Furthermore, some canthinones are cytotoxic against several strains of cancer cells[277,278,285-291] and act as vasodilators since they can inhibit cAMP phosphodiesterase,[292,293] while 1-methoxycanthinone is a potent anti-HIV agent.[290]



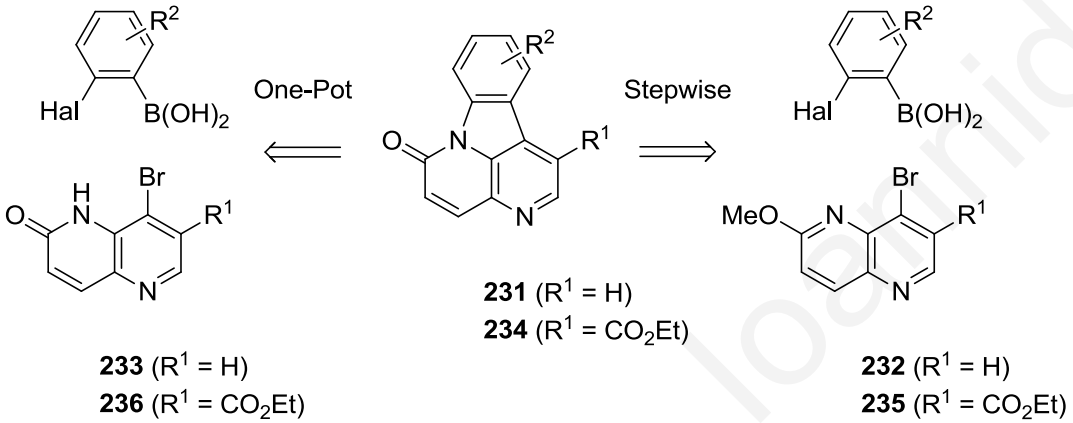
231

Figure 4. Structure and chemical numbering of canthin-6-one.

Owing to this broad range of biological activity there is continued demand for syntheses that provide functionalized canthinones efficiently. Canthinones bearing carboxylate groups are of particular value since modification of the carboxylate group can lead to a wide variety of other functionalities. We note that there are several reports on the preparation of canthinone-2-carboxylates,[294-300] but only two reports on canthinone-5-carboxylates[301-302] and one report each on canthinone-1,2-dicarboxylates[303] and 1,2,5-tricarboxylates.[296] No specific routes to canthinone-1-carboxylates have been reported and we therefore considered preparing a series of this class of canthinones.

The "classical" approach to synthesize canthinones relies on the sequential construction of rings *C* and *D* starting from indoles or construction of the *D* ring starting from *β*-carbolines.[295-298, 300-314.] Recently, a former member of the group demonstrated both a rapid one-pot and stepwise "non-classical" convergent synthesis of canthinones **231** (R^1 = H) that required access to available 4-bromo-6-methoxy-1,5-naphthyridine **232** (R^1 = H), 4-bromo-5,6-

dihydro-1,5-naphthyrid-6-one **233** (R^1 = H) and 2-haloarylboronic acids.[315] The synthesis involved construction of ring *B* *via* transition metal catalyzed intermolecular C-C and intramolecular C-N bond formation. By varying the 2-haloarylboronic acids the construction of analogues bearing substitution on ring *A* was achieved (Scheme 73).



Scheme 73

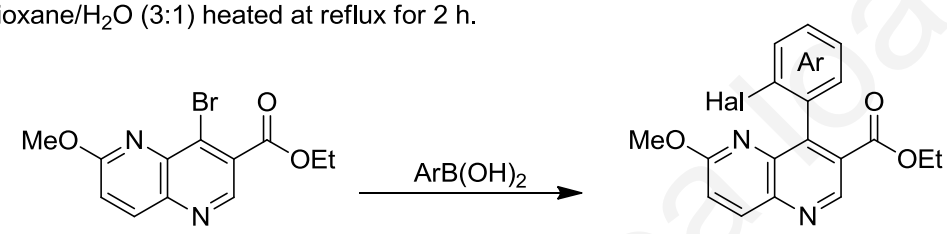
In this chapter, the preparation of 10 new canthinone-1-carboxylates including the first examples of aza-canthinone analogues starting from ethyl 4-bromo-6-methoxy-1,5-naphthyridine-3-carboxylate **235** (R^1 = CO_2Et) *via* the stepwise protocol is described.

The stepwise synthesis of the desired ethyl canthinone-1-carboxylates **234** (R^1 = CO_2Et) required the known ethyl 4-bromo-6-methoxy-1,5-naphthyridine-3-carboxylate **235** which can be prepared in multigram quantities (3-5 g) in three steps from commercially available 6-methoxypyridin-3-amine.[316] Attempts to access the one-pot procedure required access to the unknown ethyl 4-bromo-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate **236**, however, this route could not be realized because a clean demethylation of the bromonaphthyridine **235** using either TMSCl/NaI in MeCN, aq. HBr in dioxane at reflux, or BBr_3 in DCM 0 ^oC to *ca.* 20 ^oC failed.

8.2 Suzuki-Miyaura Coupling Reactions of the Bromonaphthyridines

With ethyl 4-bromo-6-methoxy-1,5-naphthyridine-3-carboxylate **235** in hand, the stepwise synthetic protocol was followed. As such, the Suzuki-Miyaura coupling of a variety 2-haloarylboronic acids (1.8 equiv) with the bromonaphthyridine **235** using Pd(dppf)Cl_2·DCM (5 mol%) as catalyst and K_2CO_3 (2 equiv) as base in aqueous dioxane/H_2O (3:1) heated to reflux for *ca.* 2 h gave 8-(2-haloaryl)-2-methoxynaphthyridines **237**-**248** in high yields (Table 23).

Table 23 Reaction of the bromonaphthyridine **235** (1.2 mmol) with $ArB(OH)_2$ (1.8 equiv) in the presence of K_2CO_3 (2 equiv), Pd(dppf)Cl_2.DCM (5 mol%) in dioxane/H_2O (3:1) heated at reflux for 2 h.



235 **237-248**

Entry	$ArB(OH)_2$	Yields (%)
1	2-Br$C_6H_4B(OH)_2$	**237** (98)
2	2-Cl$C_6H_4B(OH)_2$	**238** (90)
3	2,3-$Cl_2C_6H_3B(OH)_2$	**239** (99)
4	2,4-$Cl_2C_6H_3B(OH)_2$	**240** (86)
5	2-Cl-4-$F_3CC_6H_3B(OH)_2$	**241** (92)
6	2-Cl-4-Me$C_6H_3B(OH)_2$)	**242** (84)
7	2-Cl-4-MeO$C_6H_3B(OH)_2$	**243** (90)
8	2-Cl-4-F$C_6H_3B(OH)_2$	**244** (89)
9	2,5-$Cl_2C_6H_3B(OH)_2$	**245** (92)
10	2-Cl-5-$F_3CC_6H_3B(OH)_2$	**246** (92)
11	2-Cl-6-F$C_6H_3B(OH)_2$	*a*
12	2-Cl-6-MeO$C_6H_3B(OH)_2$	*a*
13	2-Cl-Pyrid-3-yl$B(OH)_2$	**247** (64)
14	3-Cl-Pyrid-4-yl$B(OR)_2$ *b*	**248** (62)

a No reaction, starting bromonaphthyridine **235** recovered.
b 3-Cl-Pyrid-4-yl$B(OR)_2$ = pinacol ester.

Typically the reactions came to completion with only a minimal quantity of biphenyl by-products present (by TLC). The ethyl 4-(2-haloaryl)-6-methoxy-1,5-naphthyridine-3-carboxylates **237**-**248** were isolated by dry flash chromatography (Hexane/*t*-BuOMe, 4:1) as viscous

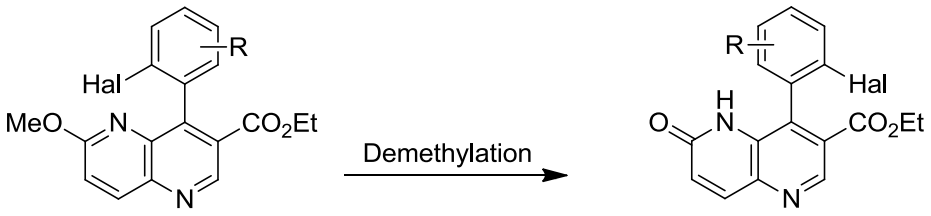
yellow oils that were in nearly all cases crystallized from pentane. Furthermore, electron impact (EI) mass spectrometry of these naphthyridines indicated only very weak or non-visible parent ions owing to a very facile fragmentation of the 2-halogen on the 4-aryl substituent, leading to the *m/z* (M^+-Hal) ion as the base peak.

The Suzuki-Miyaura coupling also tolerated the use of the heterocyclic 2-chloropyrid-3-ylboronic acid (entry 12) and 3-chloropyrid-4-ylboronic acid pinacol ester (entry 14) which afforded the corresponding pyridylnaphthyridines **247** and **248** in 64 and 62% yields, respectively, with no sign of bipyridyl byproducts. Sterically demanding 2,6-disubstituted arylboronic acids, however, led to the quantitative recovery of the starting bromonaphthyridine **235** (entries 11 and 12).

8.3 Demethylation of 4-Aryl-6-methoxy-1,5-naphthyridines

Demethylation of the ethyl 4-(2-haloaryl)-6-methoxy-1,5-naphthyridine-3-carboxylates **237-248** to afford the desired ethyl 4-(2-haloaryl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylates **249-260** was achieved using TMSCl/NaI[317] in refluxing MeCN heated to reflux for about 1-2 h (Table 24).

Table 24 Demethylation of the naphthyridines **237-248** (0.5 mmol) with TMSCl (5 equiv), NaI (3 equiv) in the MeCN (1 mL) at reflux for 1-2 h.



237-248 **249-260**

Entry	Hal	R	Yields (%)
1	Br	H	**249** (70)
2	Cl	H	**250** (81)
3	Cl	3-Cl	**251** (92)
4	Cl	4-Cl	**252** (83)
5	Cl	4-F_3C	**253** (80)
6	Cl	4-Me	**254** (74)
7	Cl	4-MeO	**255** (89)
8	Cl	4-F	**256** (98)
9	Cl	5-Cl	**257** (97)
10	Cl	5-F_3C	**258** (92)
11	Cl	3-aza	**259** (87)
12	Cl	4-aza	**260** (67)

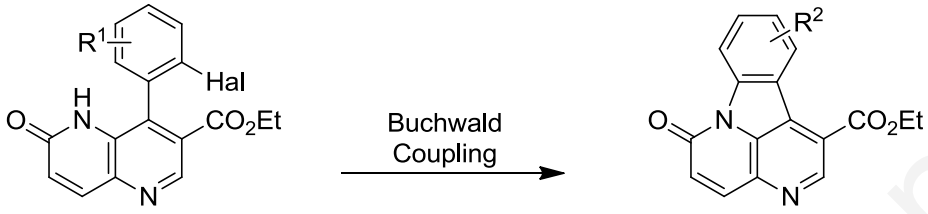
Earlier attempted demethylations using aqueous HCl in dioxane at reflux that had previously worked well for the non-ester analogues,[315] or BBr_3 resulted in complex reaction mixtures (TLC). Interestingly, the TMSCl/NaI demethylation conditions were selective and differentiated between the naphthyridine and anisidine methoxy groups (entry 7). The naphthyridones **249-260** were isolated using dry flash chromatography (*t*-BuOMe, 100%), and recrystallized from the same solvent. ^{1}H NMR spectroscopy of the products showed the absence of the naphthyridine methoxy signals (*ca.* 3.7 ppm) and the formation of a broad exchangeable signals at 8.0-8.6 ppm attributed to the naphthyridone amide NH. The presence of the amide was also supported by FTIR spectroscopy which showed new amide carbonyl stretching frequencies *v*(NH-C=O) 1659-1697 cm^{-1}. With the naphthyridones **249-260** accessible formation of the central *B* ring could be pursued *via* a copper catalyzed Buchwald cyclization.

8.4 Synthesis of Ethyl Canthinone-1-carboxylate 261 and its Analogues

Treating ethyl 4-(2-bromophenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate **249** with our typical Buchwald conditions [CuI (5 mol%), DMEDA (10 mol%), Cs_2CO_3 (2 equiv), water (2 equiv) in refluxing dioxane, 1 h][315] gave the ethyl canthinone-1-carboxylate **261** in 85% yield (Table 25, entry 1). However, these conditions were not successful with the 2-chlorophenyl analogue **250** that gave only traces of product even after 24 h (entry 2). The reaction could, however, be driven to completion when additional CuI/DMEDA (a total of 30 mol% with respect to CuI) was added to the reaction mixture affording after 18 h the canthinone **261** in moderate yield of (48%) (entry 3). By premixing various ratios of CuI and DMEDA in dioxane/H_2O (1 mL) we found that a ratio of CuI (10 mol%)/DMEDA (60 mol%) added to the reaction mixture of starting material and base in dioxane/H_2O (1 mL), significantly improved the product yield and shortened the reaction time, affording the desired canthinone **261** in 84% yield in only 9 h (entry 4). Further increases in the ratio of CuI/DMEDA, 1:8 and 1:10, did not improve the yields but did shorten the reaction times further, 82%/3.5 h and 83%/3 h, respectively. Keeping the ratio of CuI/DMEDA at 1:6, and reducing the quantity of CuI (5 mol%) led to a very slow reaction which gave only traces of product after 24 h (TLC). In a further attempt to improve the cyclization, DMEDA was replaced with the ligand *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (DMCDA) which was known to be particularly effective for C-N coupling of chloro-substituted substrates.[318] As such, when a dioxane/H_2O (1 mL) solution of the 2-chlorophenyl analogue **250** (R^1 = H) and Cs_2CO_3 (2 equiv) was treated with a premix of CuI (10 mol%)/DMCDA (60 mol%) and heated to reflux for 2 h, the cyclization was completed affording the canthinone **261** in 74% yield (entry 5). These conditions also worked well for most of the remaining 2-chlorophenyl derivatives (entries 8-10, 15 and 16). The exceptions were the 2,3-dichlorophenyl analogue **251** (R^1 = 3-Cl) (entries 6 and 7) which gave no reaction even with 30 mol% CuI and the 2-chloro-4-methoxyphenyl, 2-chloro-4-fluorophenyl, 2-chloropyrid-3-yl and 3-chloropyrid-4-yl analogues, **255** (R^1 = 4-MeO), **256** (R^1 = 4-F), **259** (R^1 = 3-aza) and **260** (R^1 = 4-aza) which required a CuI catalyst loading of at least 20 mol% to reach completion (entries 11-14 and 17-20) (Table 25). Worthy of note was the cyclization of the two pyridyl analogues **259** and **260** that afforded, to the best of our knowledge, the first azacanthinones **269** and **270** in 69 and 56% yields, respectively (entries 18 and 20). The failure to cyclize the 2,3-dichlorophenyl

analogue **251** was surprising since the analogous non ester substituted canthinone was readily prepared.[315]

Table 25 Cyclization of the naphthyridones **249-260** (0.13 mmol) with CuI, Ligand, Cs_2CO_3 (2 equiv) and water (2 equiv) in refluxing dioxane (2 mL).



249-260 **261-270**

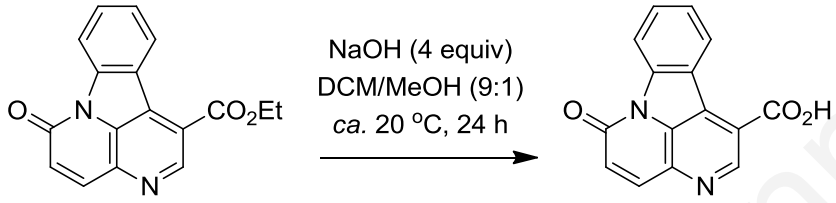
Entry	Hal	CuI (mol%)	Ligand (mol%)	Time (h)	R^2	Yields (%)
1	Br	5	DMEDA (10)	1	H	**261** (85)
2	Cl	5	DMEDA (10)	24	H	[a]
3	Cl	30	DMEDA (60)	18	H	**261** (48)
4	Cl	10	DMEDA (60)	9	H	**261** (84)
5	Cl	10	DMCDA (60)	2	H	**261** (74)
6	Cl	10	DMCDA (60)	24	8-Cl	[b]
7	Cl	30	DMCDA (180)	24	8-Cl	[b]
8	Cl	10	DMCDA (60)	4	9-Cl	**262** (85)
9	Cl	10	DMCDA (60)	1	9-F_3C	**263** (90)
10	Cl	10	DMCDA (60)	12	9-Me	**264** (80)
11	Cl	10	DMCDA (60)	24	9-MeO	[a]
12	Cl	20	DMCDA (120)	24	9-MeO	**265** (73)
13	Cl	10	DMCDA (60)	24	9-F	[a]
14	Cl	20	DMCDA (120)	24	9-F	**266** (70)
15	Cl	10	DMCDA (60)	1.5	10-Cl	**267** (89)
16	Cl	10	DMCDA (60)	4.3	10-F_3C	**268** (95)
17	Cl	10	DMCDA (60)	24	8-aza	[a]
18	Cl	20	DMCDA (120)	4	8-aza	**269** (69)
19	Cl	10	DMCDA (60)	24	9-aza	[a]
20	Cl	20	DMCDA (120)	4	9-aza	**270** (56)

[a] Incomplete reaction.

[b] No reaction, starting material recovered even after 24 h.

Having demonstrated a route to the ethyl canthinone-1-carboxylates **261-270** we showed that the ester group of the ethyl canthinone-1-carboxylate **261** could be readily hydrolyzed (Scheme 74). Treating a DCM/MeOH (9:1) solution of the ethyl canthinone-1-carboxylate **261**

with NaOH (4 equiv) at *ca.* 20 °C for 24 h[319] afforded a precipitate assumed to be the sodium carboxylate. Acidification of the reaction mixture using 10% HCl followed by extraction with EtOAc afforded the orange 6-oxo-6*H*-indolo[3,2,1-*de*]-[1,5]naphthyridine-1-carboxylic acid **271** in excellent yield.



261 **271** (99%)

Scheme 74

8.5 Summary

Starting from the known ethyl 4-bromo-6-methoxy-1,5-naphthyridine-3-carboxylate **235** a series of eight ethyl canthinone-1-carboxylates **261-268** were prepared bearing various substituents on the A ring, together with the 8-aza and 9-aza analogues **269** and **270** that constitute two members of previously unknown ring systems. The synthetic route that was used involved three key steps: first the Suzuki-Miyaura arylation of the 4-bromonaphthyridine **235** to afford the ethyl 4-aryl-6-methoxy-1,5-naphthyridine-3-carboxylates **237-248**, then the TMSCl/NaI mediated demethylation to afford the ethyl 4-(2-haloaryl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylates **249-260** and finally the copper catalyzed Buchwald cyclization to afford the target ethyl canthinone-1-carboxylates **261-270**. The biological properties of these compounds are now being pursued by collaborators in France and Italy.

CHAPTER 9

Experimental

Sections

9.1 Introduction

DCM, CCl_4, MeOH, 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 hydrazine was prepared by distillation of hydrazine monohydrate from KOH under argon and stored over 4Å molecular sieves. Potassium salts K_2CO_3 and KF were powdered and vacuum dried at 130 ^oC / 2 Torr. All chemicals were commercially available except those whose synthesis is described. Anhydrous Na_2SO_4 was used for drying organic extracts and 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).[320] A CEM Discover Microwave Reactor was used for microwave experiments. Melting points were determined using a PolyTherm-A, Wagner & Munz, Koefler - Hotstage Microscope apparatus or were determined using a TA Instruments DSC Q1000 with samples hermetically sealed in aluminium pans under an argon atmosphere; using heating rates of 5 ^oC/min (DSC mp listed by *onset* and *peak* values). 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 recorded on a Shimadzu 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 recorded on a Bruker Avance 300 and 500 machine (at 300 and 75 and 500 and 125 MHz respectively). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. CH assignments are made based on DEPT 135 or APT experiments. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GCMS with direct inlet probe. 3,5-Dichloroisothiazole-4-carbonitrile **11**, 3,5-dibromoisothiazole-4-carbonitrile **12** and 5-amino-3-chloroisothiazole-4-carbonitrile **20**,[32] 3-chloro-5-iodoisothiazole-4-carbonitrile **21**,[36] 3-iodo-5-phenylisothiazole-4-carbonitrile **23**, 3-methoxy-5-phenylisothiazole-4-carbonitrile **90**,[321] 3-hydroxy-5-phenylisothiazole-4-carbonitrile **91**, 3-amino-5-phenylisothiazole-4-carbonitrile **92** and 3-benzylamino-5-phenylisothiazole-4-carbonitrile **93** and 3,5-diphenylisothiazole-4-carbonitrile **95**,[36] 3-*N*-

morpholino-5-phenylisothiazole-4-carbonitrile **94**,[101.]3-chloro-5-(*m*-tolyl)isothiazole-4-carbonitrile **103**, 3-chloro-5-(2-methoxyphenyl)isothiazole-4-carbonitrile **104**, 3-chloro-5-(3-methoxyphenyl)isothiazole-4-carbonitrile **105**, 3-chloro-5-(4-methoxyphenyl)isothiazole-4-carbonitrile **106**, 3-chloro-5-(3-thienyl)isothiazole-4-carbonitrile **107**, 3-chloro-5-(2-chlorophenyl)isothiazole-4-carbonitrile **108**, 3-chloro-5-(3-chlorophenyl)isothiazole-4-carbonitrile **109**, 3-chloro-5-(4-chlorophenyl)isothiazole-4-carbonitrile **110** and 3-chloro-5-(3-nitrophenyl)isothiazole-4-carbonitrile **111**,[36] 3-chloro-5-hydrazinylisothiazole-4-carbonitrile **114**, 3-chloro-5-(*N*-phenylamino)isothiazole-4-carbonitrile **115**, 3-chloro-5-methoxyisothiazole-4-carbonitrile **117**, 3-chloro-5-phenoxyisothiazole-4-carbonitrile **118** and 3-chloro-5-(phenylthio)isothiazole-4-carbonitrile **119**,[32.] 4-bromo-3-chloro-5-phenylisothiazole **138**, 3-chloro-4,5-diphenylisothiazole **139**, 4-amino-3-chloro-5-phenylisothiazole **140**, 3,5-diphenylisothiazole **146**, 4-bromo-3,5-diphenylisothiazole **149**, 3,4,5-triphenylisothiazole **150**, 4-amino-3,5-diphenylisothiazole **69** and 3-amino-4,5-diphenylisothiazole **151**, [37] 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24**,[38] TCNE,[322] TCNEO[323] and ethyl 4-bromo-6-methoxy-1,5-naphthyridine-3-carboxylate **235**[316] were prepared according to literature procedures.

9.2 Compounds related to Chapter 2

3-Bromoisothiazole-4-carbonitrile 48

To a mixture of 3,5-dibromoisothiazole-4-carbonitrile **12** (67 mg, 0.25 mmol) and Zn dust (81.7 mg, 1.25 mmol) at *ca.* 10 ^{o}C was added cold (*ca.* 15 ^{o}C) HCO_2H (1 mL) and stirred for 10 min at 10-15 ^{o}C. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (5 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed *in vacuo* to afford the *title compound* **48** (31 mg, 66%) as colorless long needles, mp 47.5–48.5 ^{o}C (from pentane) DSC (onset) 54.0 ^{o}C (peak) 54.9 ^{o}C, R_f 0.33 (Hexane/DCM, 1:1); (found: C, 25.6; H, 0.5; N, 14.8. C_4HBrN_2S requires C, 25.4; H, 0.5; N, 4.8%); λ_{max}(DCM)/nm 264 (log ε 4.05); ν_{max}/cm^{-1} 3100m (Ar CH), 2241m (C≡N), 1487m, 1352w, 1323s, 1144m, 1026m, 868s, 831s, 804m, 764m; δ_H(300 MHz; $CDCl_3$) 9.16 (1H, s, *H*-5); δ_C(75 MHz; $CDCl_3$) 158.2 (d), 139.2 (s), 113.2 (s), 111.5 (s); *m/z* (EI) 190 (M^++2, 100%), 188 (M^+, 97), 139 (25), 137 (25), 109 (7), 83 (82), 58 (10), 51 (14), 45 (36). Similarly, treating 3,5-dibromoisothiazole-4-carbonitrile **12** (1 g, 3.6 mmol), with Zn powder (1.22 g, 18.7 mmol) in HCO_2H (15 mL) gave the title compound **48** (493 mg, 70%) as colorless needles identical to that described above.

3-Chloroisothiazole-4-carbonitrile 47; Typical procedure (Table 1)

To a mixture of 3,5-dichloroisothiazole-4-carbonitrile **11** (45 mg, 0.25 mmol) and Zn dust (123 mg, 1.88 mmol) at *ca.* 10 ^{o}C was added cold (*ca.* 15 ^{o}C) HCO_2H (1 mL) and stirred for 1 h at 10-15 ^{o}C. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (5 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed *in vacuo* to afford the title compound **47** (5.5 mg, 15%) as colorless long needles, mp 50-51 ^{o}C (from pentane) (lit.,[36] 50-51 ^{o}C), R_f 0.33 (Hexane/DCM, 1:1) identical to an authentic sample.

Sandmeyer reactions

3-Chloroisothiazole-4-carbonitrile 47 from 5-amino-3-chloroisothiazole-4-carbonitrile 20

To a mixture of isoamyl nitrite (5.1 mL, 37.8 mmol) in $MeNO_2$ (5 mL) at *ca.* 20 ^{o}C, a solution of 5-amino-3-chloroisothiazole-4-carbonitrile **20** (1 g, 6.3 mmol) in $MeNO_2$ (5 mL) was added and the reaction mixture was stirred for 10 min. After the reaction was finished (TLC), the mixture was diluted with DCM (50 mL) and extracted with water (50 mL). The organic phase

was dried (Na_2SO_4), filtered, adsorbed onto silica and chromatographed (DCM) to afford the title compound **47** (870 mg, 96%) as colorless needles, mp 50-51 ^oC (from pentane) (lit.,[36] 50-51 ^oC), R_f 0.33 (Hexane/DCM, 1:1) identical to an authentic sample.

5-Bromo-3-chloroisothiazole-4-carbonitrile 49

To a mixture of isoamyl nitrite (2.55 mL, 18.9 mmol) and Br_2 (1.6 mL, 31 mmol) in $MeNO_2$ (2 mL) at *ca.* 20 ^oC, a solution of 5-amino-3-chloroisothiazole-4-carbonitrile **20** (0.5 g, 3.1 mmol) in $MeNO_2$ (2 mL) was added and the reaction mixture was stirred for 10 min. After the reaction was finished (TLC), the mixture was diluted with DCM (50 mL), washed with $Na_2S_2O_3$ (500 mg, 32 mmol) and extracted with water (50 mL). The organic phase was dried (Na_2SO_4), filtered, adsorbed onto silica and chromatographed (Hexane) to afford the *title compound* **49** (486 mg, 69%) as colorless plates, mp 94.5-95.5 ^oC (from cyclohexane), R_f 0.56 (Hexane/DCM, 1:1); (found: C, 21.6; H, <0.1; N, 12.5. C_4BrClN_2S requires C, 21.5; H, 0.0; N, 12.5%); λ_{max}(DCM)/nm 250 (log ε 4.06), 263 (4.08), 268 inf (4.04); ν_{max}/cm^{-1} 2237m (C≡N), 1495s, 1331s, 1090w, 970m, 816s, 793m; δ_C(75 MHz; $CDCl_3$) 151.0 (s), 147.3 (s), 113.5 (s), 110.1 (s); *m/z* (EI) 226 (M^++4, 10%), 224 (M^++2, 38), 222 (M^+, 30), 173 (31), 171 (86), 163 (11), 161 (11), 143 (M^+-Br, 22), 108 (20), 82 (82), 71 (52), 69 (23), 57 (32), 55 (18), 51 (20), 49 (53).

Hydrodehalogenation of mixed dihaloisothiazoles 49 and 21

3-Chloroisothiazole-4-carbonitrile 47 from 5-bromo-3-chloroisothiazole-4-carbonitrile 49

To a mixture of 5-bromo-3-chloroisothiazole-4-carbonitrile **49** (56 mg, 0.25 mmol) and Zn dust (81.7 mg, 1.25 mmol) at *ca.* 10 ^oC was added cold (*ca.* 15 ^oC) HCO_2H (1 mL) and stirred for 40 min at *ca.* 10-15 ^oC. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (5 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed *in vacuo* to afford the *title compound* **47** (28 mg, 77%) as colorless long needles, mp 50-51 ^oC (from pentane) (lit.,[36] 50-51 ^oC), identical to an authentic sample.

3-Chloroisothiazole-4-carbonitrile 47 from 5-iodo-3-chloroisothiazole-4-carbonitrile 21

To a mixture of 5-iodo-3-chloroisothiazole-4-carbonitrile **21** (68 mg, 0.25 mmol) and Zn dust (81.7 mg, 1.25 mmol) at *ca.* 10 ^{o}C was added cold (*ca.* 15 ^{o}C) HCO_2H (1 mL) and stirred for 15 min at 10-15 ^{o}C. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (5 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed *in vacuo* to afford the *title compound* **47** (18.5 mg, 51%) as colorless long needles, mp 50-51 ^{o}C (from pentane) (lit.,[36] 50-51 ^{o}C) identical to an authentic sample.

Reactions with deuterated formic acids

3-Bromo-5-deuterioisothiazole-4-carbonitrile 50

To a mixture of 3,5-dibromoisothiazole-4-carbonitrile **12** (67 mg, 0.25 mmol) and Zn dust (81.7 mg, 1.25 mmol) at *ca.* 10 ^{o}C was added cold (*ca.* 15 ^{o}C) DCO_2D (1 mL) and stirred at 10-15 ^{o}C. After the reaction was finished (TLC) the mixture was filtered and the filtrate extracted with DCM (20 mL) and water (10 mL). The organic phase was dried (Na_2SO_4), filtered and the volatiles removed *in vacuo* to afford the *title compound* **50** (34 mg, 71%) as colorless long needles, mp 46-46.5 ^{o}C (from pentane) DSC (onset) 53.9 ^{o}C (peak) 54.8 ^{o}C, R_f 0.33 (Hexane/DCM, 1:1); (found: C, 25.3; H, 1.0; N, 14.6. C_4DBrN_2S requires C, 25.3; H, 1.1; N, 14.7%); λ_{max}(DCM)/nm 263 (log ε 4.36); ν_{max}/cm^{-1} 2315m (Ar CD), 2239m (C≡N), 1476s, 1354w, 1346w, 1315s, 1034m, 1016m, 986m, 804s, 766s; δ_C(125 MHz; $CDCl_3$) 158.0 (t, $^{1}J_{CD}$ 29.8, *C*-5), 139.3 (s), 113.1 (s), 111.5 (s); *m/z* (EI) 191 (M^++2, 90%), 189 (M^+, 86), 139 (28), 137 (30), 110 (9), 84 (100), 82 (49), 58 (22), 52 (20), 46 (57). Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **12** with DCO_2D gave the title compound **50** (28.5 mg, 60%) as colorless needles, mp 46-46.5 ^{o}C (from pentane) identical to that described above.

3-Bromoisothiazole-4-carbonitrile 48 from DCO_2H reaction

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **12** (67 mg, 0.25 mmol) with Zn dust (81.7 mg, 1.25 mmol) and DCO_2H (1 mL), gave the title compound **48** as colorless needles, mp 47.5–48.5 ^{o}C (from pentane), identical to that described above.

Reactions of 3-bromoisothiazole-4-carbonitrile 48

***2*-(Morpholinomethylene)malononitrile 56 (Typical Procedure)**

A stirred mixture of 3-bromoisothiazole-4-carbonitrile **48** (25 mg, 0.13 mmol) and morpholine (45 μL, 0.52 mmol) in EtOH (1 mL) was heated at *ca.* 78 ^{o}C until no starting material remained (TLC). The reaction mixture was adsorbed onto silica and chromatographed (Hexane) to afford elemental sulfur (3.3 mg, 80%) as yellow needles, mp 114-115 ^{o}C, R_F 0.76 (Hexane). Further elution (Hexane/DCM, 1:4) gave the title compound **56** (15 mg, 71%) as beige flakes, mp 138-140 ^{o}C (from EtOH/pentane) [lit.,[324] 149-150 ^{o}C (from EtOH)], R_F 0.43 (DCM/t-BuOMe, 9:1); ν_{max}/cm^{-1} 2982w, 2874w, 2208m and 2197m (C≡N), 1632s (C=C), 1466w, 1454m, 1439m, 1375w, 1354m, 1310w, 1285w, 1250m, 1119s, 1080w, 1026m, 1011m, 974w, 937w, 870s, 779w; δ_H(300 MHz; $CDCl_3$) 7.02 (1H, s, C-*H*), 3.95 (2H, br s, NCH_2), 3.79 (4H, dd *J* 4.9, 4.7, OCH_2), 3.49 (2H, br s, NCH_2); *m/z* (EI) 163 (M^+, 47%), 105 (37), 91 (7), 78 (80), 57 (39), 51 (9), 42 (100).

2-(Piperidin-1-ylmethylene)malononitrile 57

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (25 mg, 0.13 mmol) with piperidine (51 μL, 0.52 mmol) afforded elemental sulfur (3.7 mg, 87%) as yellow needles, mp 114-115 ^{o}C; R_F 0.76 (hexane) and then the title compound **57** (18 mg, 84%) as light orange needles, mp 85.5-86.5 ^{o}C (from EtOH/pentane) [lit.,[325] 90-91 ^{o}C (from EtOAc/pentane)], R_F 0.84 (DCM/*t*-BuOMe, 9:1); ν_{max}/cm^{-1} 2947w, 2208m and 2195m (C≡N), 1618s (C=C), 1470w, 1441w, 1362m, 1346m, 1269w, 1256w, 1217w, 1179w, 1098w, 1024m, 997w, 968w, 945w, 854w, 764m; δ_H(300 MHz; $CDCl_3$) 6.96 (1H, s, =C-*H*), 3.86 (2H, br s, NCH_2), 3.43 (2H, br s, NCH_2), 1.73 (6H, br s, 3 × CH_2); *m/z* (EI) 161 (M^+, 100%), 146 (13), 132 (32), 120 (26), 106 (32), 94 (11), 83 (73), 78 (43), 67 (13), 57 (29), 41 (65).

3-Bromoisothiazole-4-carboxamide 60

A mixture of 3-bromoisothiazole-4-carbonitrile **48** (25 mg, 0.13 mmol) in c. H_2SO_4 (1 mL) was stirred at *ca.* 20 ^{o}C for 2 h until no starting material remained (TLC). After the reaction was finished, the reaction mixture was poured onto crushed ice and extracted with *t*-BuOMe (2 × 50 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated *in vacuo* to afford the *title compound* **60** (15 mg, 70%) as colorless needles, mp 138-141 ^{o}C (from PhH), R_f 0.47 (*t*-BuOMe); (found: C, 23.3; H, 1.4; N, 13.4. $C_4H_3BrN_2OS$ requires C, 23.2; H, 1.5; N,

13.5%); λ_{max}(DCM)/nm 228 (log ε 3.44), 258 (3.96); ν_{max}/cm^{-1} 3381w (NH), 3289w, 3188w, 3102w, 1655s (C=O), 1612m, 1506m, 1406m, 1344w, 1294m, 1140w, 1120m, 1003m, 864w, 822w, 812w, 779w; δ_H(300 MHz; DMSO-d_6) 9.32 (1H, s, *H*-5), 7.96 (1H, br s, N*H*), 7.59 (1H, br s, N*H*); δ_C(75 MHz; DMSO-d_6) 162.4 (s), 153.4 (d), 136.1 (s), 133.8 (s); *m/z* (EI) 208 (M^++2, 58%), 206 (M^+, 59), 192 (99), 190 (100), 164 (3), 162 (3), 127 (15), 113 (5), 111 (9), 85 (20), 83 (22), 57 (32), 52 (9), 44 (65).

3-Bromoisothiazole-4-carboxylic acid 61

To a stirred solution of 3-bromoisothiazole-4-carboxamide **60** (86 mg, 0.41 mmol) in c. H_2SO_4 (2 mL) at 0 ^oC, was added in 3 equal portions $NaNO_2$ (285 mg, 4.1 mmol). The reaction mixture was then heated at *ca.* 100 ^oC until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC and was poured onto crushed ice to afford a colorless precipitate. The precipitate was filtered, washed (H_2O) and dried *in vacuo* to give the *title compound* **61** (79.4 mg, 92%) as pale beige plates, mp 195-197 ^oC (from PhH), R_f 0.44 (*t*-BuOMe); (found: C, 23.2; H, 0.7; N, 6.5. $C_4H_2BrNO_2S$ requires C, 23.1; H, 1.0; N, 6.7%); λ_{max}(DCM)/nm 228 (log ε 3.49), 260 (3.93); ν_{max}/cm^{-1} 3113w, 2947w, 2907w, 2733w, 2602w, 2536w, 1713 (C=O), 1483m, 1435w, 1418w, 1354m, 1333w, 1217s, 1015s, 887m, 849w, 835m; δ_H(300 MHz; DMSO-d_6) O*H* missing, 9.60 (1H, s, *H*-5); δ_C(75 MHz; DMSO-d_6) 161.2 (s), 159.2 (s), 137.3 (s), 129.6 (s); *m/z* (EI) 209 (M^++2, 94%), 207 (M^+, 96), 192 (100), 190 (95), 128 (6), 113 (6), 111 (9), 85 (19), 83 (29), 82 (18), 57 (57), 52 (12), 45 (63).

9.3 Compounds related to Chapter 3

3-Bromo-5-phenylisothiazole-4-carbonitrile 62

To a stirred solution of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) in MeCN (1 mL) at *ca.* 20 ^{o}C, AgF (63 mg, 0.5 mmol), Ph_3P (6.5 mg, 10 mol%), and iodobenzene (33 μL, 0.3 mmol) were added. To this mixture $Pd(Ph_3P)_2Cl_2$ (8.8 mg, 5 mol%) was then added and the mixture was heated at *ca.* 82 ^{o}C until no starting material remained (TLC). The reaction mixture was left to cool to *ca.* 20 ^{o}C and adsorbed onto silica. Chromatography (Hexane/DCM, 3:2) gave the title compound **62** (49.5 mg, 90%) as colorless needles, mp 93-94 ^{o}C (from cyclohexane, lit.,[35] 93-94 ^{o}C) identical to an authentic sample.

3-Bromo-5-*p*-tolylisothiazole-4-carbonitrile 64

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 4-iodotoluene (65.4 mg, 0.3 mmol) gave the *title compound* **64** (57 mg, 82%) as colorless plates, mp 107.5–109.5 ^{o}C (from cyclohexane), R_f 0.4 (Hexane/DCM, 1:1); (found: C, 47.5; H, 2.5; N, 9.9. $C_{11}H_7BrN_2S$ requires C, 47.3; H, 2.5; N, 10.0%); λ_{max}(DCM)/nm 229 (log ε 3.95), 285 (4.27), 296 inf (4.23); ν_{max}/cm^{-1} 2953w, 2924w and 2853w (Ar CH), 2232m (C≡N), 1611m, 1524w, 1487s, 1458w, 1391m, 1337s, 1317w, 1240m, 1194w, 1130w, 1036s, 966w, 951w, 833s, 820s, 797s; δ_H(300 MHz; $CDCl_3$) 7.69 (2H, d, *J* 7.7, Ph *H*), 7.37 (2H, d, *J* 7.7, Ph *H*), 2.47 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 176.5 (s), 143.3 (s), 139.7 (s), 130.5 (d), 127.2 (d), 124.5 (s), 112.9 (s), 107.8 (s), 21.6 (*C*H$_3$); *m/z* (EI) 280 (M^++2, 100), 278 (M^+, 95), 266 (8), 264 (8), 199 (76), 184 (10), 172 (52), 155 (31), 140 (24), 134 (13), 128 (14), 113 (11), 101 (7), 91 (21), 77 (11), 65 (32), 51 (18).

3-Bromo-5-(2-methoxyphenyl)isothiazole-4-carbonitrile 65

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 2-iodoanisole (70.2 mg, 0.3 mmol) gave the *title compound* **65** (65 mg, 89%) as colorless needles, mp 160–162 ^{o}C (from cyclohexane), R_f 0.29 (Hexane/DCM, 1:1); (found: C, 44.8; H, 2.3; N, 9.6. $C_{11}H_7BrN_2OS$ requires C, 44.8; H, 2.4; N, 9.5%); λ_{max}(DCM)/nm 229 (log ε 3.85), 284 (4.02), 292 inf (3.95), 331 (3.87); ν_{max}/cm^{-1} 2968w, 2941w, 2878w, 2839w, 2220w (C≡N), 1601w, 1578w, 1503m, 1476m, 1462m, 1435m, 1393w, 1331s, 1300m, 1290w, 1259s, 1231w, 1219w, 1188w, 1159m, 1128m, 1055w, 1016s, 941w, 831s, 804w; δ_H(300 MHz;

$CDCl_3$) 8.39 (1H, d, *J* 7.9, Ph *H*), 7.54 (1H, dd, *J* 7.8, 7.8, Ph *H*), 7.16 (1H, dd, *J* 7.6, 7.6, Ph *H*), 7.09 (2H, d, *J* 8.3, Ph *H*), 4.06 (3H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 169.9 (s), 156.6 (s), 138.5 (s), 133.4 (d), 127.3 (d), 121.6 (d), 117.0 (s), 114.3 (s), 111.5 (d), 106.6 (s), 55.8 (O*C*H$_3$); *m/z* (EI) 296 (M^++2, 53%), 294 (M^+, 50), 215 (100), 200 (29), 187 (34), 182 (63), 171 (23), 155 (16), 146 (29), 137 (21), 128 (20), 120 (35), 114 (35), 77 (21), 69 (23), 63 (29), 51 (21).

3-Bromo-5-(3-methoxyphenyl)isothiazole-4-carbonitrile 66

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 3-iodoanisole (70.2 mg, 0.3 mmol) gave the *title compound* **66** (67 mg, 91%) as colorless plates, mp 112.5–114.5 ^oC (from cyclohexane), R_f 0.29 (Hexane/DCM, 1:1); (found: C, 44.7; H, 2.3; N, 9.4. $C_{11}H_7BrN_2OS$ requires C, 44.8; H, 2.4; N, 9.5%); λ_{max}(DCM)/nm 228 (log ε 3.77), 246 (3.71), 280 (3.86), 314 inf (3.42); ν_{max}/cm^{-1} 3013w, 2974w, 2941w, 2835w, 2232w (C≡N), 1605w, 1576m, 1508m, 1487m, 1479m, 1464w, 1456w, 1425w, 1389w, 1337s, 1288s, 1269w, 1206s, 1173s, 1103w, 1053s, 1028w, 970w, 876m, 864m, 793s, 760m; δ_H(300 MHz; $CDCl_3$) 7.46 (1H, dd, *J* 7.9, Ph *H*), 7.33-7.29 (2H, m, Ph *H*), 7.11 (1H, d, *J* 8.1, Ph *H*), 3.88 (3H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 176.3 (s), 160.4 (s), 139.8 (s), 131.0 (d), 128.2 (s), 119.7 (d), 118.2 (d), 112.7 (s), 112.4 (d), 108.5 (s), 55.6 (O*C*H$_3$); *m/z* (EI) 296 (M^++2, 96%), 294 (M^+, 100), 267 (28), 265 (29), 185 (22), 171 (28), 158 (12), 146 (16), 128 (8), 114 (17), 108 (11), 92 (10), 77 (11), 69 (11), 63 (17), 51 (8).

3-Bromo-5-(4-methoxyphenyl)isothiazole-4-carbonitrile 67

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 4-iodoanisole (70.2 mg, 0.3 mmol) gave the *title compound* **67** (60 mg, 81%) as colorless needles, mp 131–131.5 ^oC (from cyclohexane), R_f 0.29 (Hexane/DCM, 1:1); (found: C, 44.8; H, 2.3; N, 9.4. $C_{11}H_7BrN_2OS$ requires C, 44.8; H, 2.4; N, 9.5%); λ_{max}(DCM)/nm 230 (log ε 3.41), 288 (3.29), 319 (3.57); ν_{max}/cm^{-1} 2922w, 2849w, 2226w (C≡N), 1601s, 1572w, 1526w, 1489s, 1462w, 1439w, 1398m, 1335s, 1314m, 1265s, 1238w, 1186s, 1123w, 1038s, 1020m, 951w, 831s, 797w, 764w; δ_H(300 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.6, Ph *H*), 7.04 (2H, d, *J* 8.7, Ph *H*), 3.89 (3H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 176.1 (s), 162.8 (s), 139.7 (s), 129.0 (d), 119.7 (s), 115.2 (d), 113.2 (s), 107.0 (s), 55.6 (O*C*H$_3$); *m/z* (EI) 296 (M^++2, 100%), 294 (M^+, 97), 281 (17), 279 (17), 253 (11), 251 (11), 171 (28), 146 (12), 114 (12), 108 (8), 77 (6), 69 (7), 63 (12), 51 (6).

3-Bromo-5-(2,4-dimethoxyphenyl)isothiazole-4-carbonitrile 68

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 1-iodo-2,4-dimethoxybenzene (79.2 mg, 0.3 mmol) gave the *title compound* **68** (60 mg, 73%) as colorless needles, mp 226–227 ^{o}C (from cyclohexane/EtOH), R_f 0.18 (Hexane/DCM, 1:1); (found: C, 44.4; H, 2.7; N, 8.5. $C_{12}H_9BrN_2O_2S$ requires C, 44.3; H, 2.8; N, 8.6%); λ_{max}(DCM)/nm 236 (log ε 3.73), 288 inf (3.58), 293 (3.61), 341 (3.97); ν_{max}/cm^{-1} 2982w, 2940w, 2847w, 2218m (C≡N), 1612m, 1578w, 1514w, 1481s, 1437w, 1427w, 1395m, 1321s, 1300w, 1271s, 1236w, 1217s, 1182w, 1138m, 1038m, 1016s, 947m, 826s, 816s, 799m; δ_H(500 MHz; CD_2Cl_2) 8.42 (1H, d, *J* 8.9, Ph *H*-6), 6.80 (1H, dd, *J* 8.9, 2.3, Ph *H*-5), 6.68 (1H, d, *J* 8.9, 1.3, Ph *H*-3), 4.09 (3H, s, OCH_3), 3.96 (3H, s, OCH_3); δ_C(125 MHz; CD_2Cl_2) 165.0 (s), 159.3 (s), 128.9 (d), 117.9 (s), 115.7 (s), 113.4 (s), 111.2 (s), 110.3 (s), 107.3 (d), 98.7 (d), 56.3 (O*C*H$_3$), 56.2 (O*C*H$_3$); *m/z* (EI) 326 (M$^+$+2, 90%), 324 (M$^+$, 100), 311 (8), 309 (8), 283 (10), 281 (10), 245 (58), 230 (13), 217 (21), 212 (47), 201 (19), 187 (12), 174 (12), 163 (10), 159 (11), 133 (8), 100 (7), 88 (8), 75 (7), 69 (23), 63 (12), 51 (8).

3-Bromo-5-(4-hydroxyphenyl)isothiazole-4-carbonitrile 69

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 4-iodophenol (66 mg, 0.3 mmol) gave the *title compound* **69**(55.3 mg, 79%) as colorless plates, mp 163–166 ^{o}C (from cyclohexane), R_f 0.14 (DCM); (found: C, 42.6; H, 1.7; N, 9.8. $C_{10}H_5BrN_2OS$ requires C, 42.7; H, 1.8; N, 10.0%); λ_{max}(DCM)/nm 231 (log ε 3.99), 288 inf (3.98), 313 (4.15); ν_{max}/cm^{-1} 3229br & w (OH), 2232w (C≡N), 1603m, 1585m, 1524w, 1493s, 1435m, 1393m, 1371m, 1360w, 1337m, 1287m, 1248m, 1219m, 1179s, 1130w, 1119w, 1032m, 1009w, 953w, 835s, 818s, 779m; δ_H(300 MHz; $CDCl_3$) 7.70 (2H, d, *J* 8.5, Ph *H*), 7.00 (2H, d, *J* 8.7, Ph *H*), 6.06 (1H, br s, O*H*); δ_C(75 MHz; $CDCl_3$) 176.3 (s), 159.5 (s), 139.8 (s), 129.2 (d), 119.6 (s), 116.8 (d), 113.4 (s), 106.8 (s); *m/z* (EI) 282 (M$^+$+2, 97%), 280 (M$^+$, 100), 254 (7), 252 (6), 201 (13), 173 (26), 157 (42), 146 (13), 143 (13), 114 (9), 102 (9), 88 (10), 65 (21), 63 (10), 51 (6).

3-Bromo-5-(2-nitrophenyl)isothiazole-4-carbonitrile 70

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 1-iodo-2-nitrobenzene (74.7 mg, 0.3 mmol) gave the *title compound* **70** (69 mg, 89%) as light yellow plates, mp 144.5–146.5 ^{o}C (from cyclohexane), R_f 0.14 (Hexane/DCM, 1:1); (found: C, 38.6; H, 1.4; N, 13.5. $C_{10}H_4BrN_3O_2S$ requires C, 38.7; H, 1.3; N, 13.6%); λ_{max}(DCM)/nm 232 (log ε 3.91), 250 (3.99), 266 (4.02); ν_{max}/cm^{-1} 3092w, 3073w, 3059w, 2855w, 2234w (C≡N), 1572w, 1518s, 1472m, 1391w, 1341s, 1236m, 1148w, 1092w, 1024w, 961w, 854m, 822m, 795m; δ_H(300 MHz; $CDCl_3$) 8.29 (1H, dd, *J* 7.6, 1.8, Ph *H*), 7.87-7.77 (2H, m, Ph *H*), 7.54 (1H, dd, *J* 7.0, 2.1, Ph *H*); δ_C(75 MHz; $CDCl_3$) 172.5 (s), 147.3 (s), 138.4 (s), 134.0 (d), 132.6 (d), 132.1 (d), 126.0 (d), 121.9 (s), 113.1 (s), 111.1 (s); *m/z* (EI) 311 (M^++2, 20%), 309 (M^+, 19), 237 (6), 235 (7), 230 (9), 186 (16), 184 (22), 183 (13), 182 (100), 150 (17), 114 (24), 104 (18), 102 (52), 90 (12), 76 (19), 75 (10), 63 (9), 51 (8).

3-Bromo-5-(3-nitrophenyl)isothiazole-4-carbonitrile 71

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 1-iodo-3-nitrobenzene (74.7 mg, 0.3 mmol) gave the *title compound* **71** (64 mg, 83%) as colorless needles, mp 148–149 ^{o}C (from cyclohexane), R_f 0.14 (Hexane/DCM, 1:1); (found: C, 38.7; H, 1.2; N, 13.5. $C_{10}H_4BrN_3O_2S$ requires C, 38.7; H, 1.3; N, 13.6%); λ_{max}(DCM)/nm 232 (log ε 3.91), 250 (3.99), 266 (4.16); ν_{max}/cm^{-1} 3075w (Ar CH), 2232w (C≡N), 1614w, 1530s, 1504m, 1476m, 1458w, 1387w, 1352s, 1335s, 1288w, 1246w, 1105w, 1047m, 966w, 912w, 887m, 810m, 789m; δ_H(300 MHz; $CDCl_3$) 8.52 (1H, s, Ph *H*), 8.40 (1H, d, *J* 8.1, Ph *H*), 8.08 (1H, d, *J* 7.7, Ph *H*), 7.78 (1H, dd, *J* 7.9, 7.9, Ph *H*); δ_C(75 MHz; $CDCl_3$) 172.8 (s), 148.2 (s), 139.6 (s), 132.4 (d), 130.8 (d), 128.0 (s), 126.0 (d), 122.0 (d), 111.4 (s), 109.5 (s); *m/z* (EI) 311 (M^++2, 61%), 309 (M^+, 60), 265 (12), 263 (13), 253 (10), 251 (10), 184 (100), 172 (10), 158 (28), 157 (21), 140 (19), 139 (15), 120 (14), 114 (56), 113 (12), 100 (14), 99 (17), 93 (17), 88 (14), 82 (16), 76 (27), 75 (24), 74 (19), 69 (30), 63 (17), 51 (18).

3-Bromo-5-(4-nitrophenyl)isothiazole-4-carbonitrile 72

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 1-iodo-4-nitrobenzene (74.7 mg, 0.3 mmol) gave the *title compound* **72** (76 mg, 98%) as colorless plates, mp 135.5–136.5 ^{o}C (from cyclohexane), R_f 0.14 (Hexane/DCM, 1:1); (found: C, 38.7; H, 1.2; N, 13.4. $C_{10}H_4BrN_3O_2S$ requires C, 38.7; H, 1.3; N, 13.6%); λ_{max}(DCM)/nm 228 (log ε 3.67), 288 (4.14); ν_{max}/cm^{-1} 3096w (Ar CH), 2922w, 2851w, 2235w (C≡N), 1595w, 1572w,

1514s, 1481w, 1470w, 1391w, 1337s, 1310w, 1244w, 1179w, 1105w, 1053w, 1036w, 1009w, 853m, 837m, 818m; δ_H(300 MHz; $CDCl_3$) 8.42 (2H, d, *J* 8.9, Ph *H*), 7.95 (2H, d, *J* 8.9, Ph *H*); δ_C(75 MHz; $CDCl_3$) 173.6 (s), 150.0 (s), 140.8 (s), 133.1 (s), 129.0 (d), 125.5 (d), 112.4 (s), 110.7 (s); *m/z* (EI) 311 (M^++2, 100%), 309 (M^+, 96), 281 (29), 279 (28), 265 (7), 263 (7), 253 (20), 251 (19), 185 (12), 184 (97), 183 (10), 172 (14), 158 (29), 157 (17), 146 (12), 145 (12), 140 (16), 139 (12), 120 (13), 114 (47), 76 (14), 69 (20), 63 (11), 51 (10).

5-(4-Amino-3-nitrophenyl)-3-bromoisothiazole-4-carbonitrile 73

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 4-iodo-2-nitroaniline (79.2 mg, 0.3 mmol) gave the *title compound* **73** (33.4 mg, 41%) as orange needles, mp 254–257 ^oC (from cyclohexane), R_f 0.42 (DCM); (found: C, 36.8; H, 1.5; N, 17.3. $C_{10}H_5BrN_4O_2S$ requires C, 36.9; H, 1.6; N, 17.2%); λ_{max}(DCM)/nm 230 (log ε 4.29), 270 (4.24), 333 (4.35), 401 (3.71); ν_{max}/cm^{-1} 3455w and 3337m (NH_2), 2234w (C≡N), 1632m, 1603w, 1557m, 1497s, 1468w, 1425w, 1396m, 1368w, 1356w, 1323m, 1256s, 1236m, 1188m, 1082w, 1043m, 1016w, 989w, 968w, 901w, 885w, 818m, 779w; δ_H(300 MHz; DMSO-d_6) 8.55-8.53 (1H, m, Ph *H*), 8.10 (2H, br s, NH_2), 7.79-7.74 (1H, m, Ph *H*), 7.19-7.14 (1H, m, Ph *H*); δ_C(75 MHz; DMSO-d_6) 174.5 (s), 148.2 (s), 139.5 (s), 133.7 (d), 129.9 (s), 125.1 (d), 120.7 (d), 113.5 (s), 113.3 (s), 105.9 (s); *m/z* (EI) 326 (M^++2, 100%), 324 (M^+, 98), 309 (12), 307 (10), 280 (19), 278 (19), 268 (11), 266 (12), 253 (19), 251 (20), 201 (12), 199 (39), 172 (26), 171 (21), 155 (15), 145 (23), 139 (11), 128 (13), 120 (11), 114 (11), 113 (10), 91 (14), 88 (11), 76 (9), 63 (19), 52 (34).

3-Bromo-5-(pyridin-2-yl)isothiazole-4-carbonitrile 74

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 2-iodopyridine (61.5 mg, 0.3 mmol) gave the *title compound* **74** (63 mg, 95%) as colorless plates, mp 132.5-135 ^oC (from cyclohexane/DCM), R_f 0.11 (DCM); (found: C, 40.6; H, 1.4; N, 15.8. $C_9H_4BrN_3S$ requires C, 40.6; H, 1.5; N, 15.8%); λ_{max}(DCM)/nm 229 (log ε 3.23), 272 inf (3.35), 294 (3.61), 335 inf (2.82); ν_{max}/cm^{-1} 2957w, 2926w, 2853w, 2230w (C≡N), 1734w, 1580w, 1522w, 1456s, 1437m, 1393w, 1377w, 1329s, 1288m, 1260m, 1233w, 1155w, 1101w, 1059w, 1038s, 991m, 966w, 885w, 827m, 800m, 783s; δ_H(300 MHz; CD_2Cl_2) 8.67 (1H, d, *J* 4.5, Py *H*), 8.25 (1H, d, *J* 7.9, Py *H*), 7.96 (1H, dd, *J* 7.9, 7.7, Py *H*), 7.49 (1H, dd, *J* 7.5, 5.1, Py *H*); δ_C(75 MHz; CD_2Cl_2) 176.9 (s), 150.8 (d), 146.6 (s), 139.5 (s), 138.4 (d), 127.1 (d),

120.7 (d), 113.3 (s), 107.1 (s); *m/z* (EI) 267 (M^++2, 32%), 265 (M^+, 33), 205 (8), 187 (12), 186 (100), 149 (9), 97 (9), 85 (12), 83 (11), 79 (100), 78 (96), 71 (16), 69 (19), 57 (26), 51 (36).

3-Bromo-5-(pyridin-3-yl)isothiazole-4-carbonitrile 75

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 3-iodopyridine (61.5 mg, 0.3 mmol) gave the *title compound* **75** (61 mg, 95%) as colorless needles, mp 121–123 ^oC (from cyclohexane), R_f 0.11 (DCM); (found: C, 40.7; H, 1.6; N, 15.6. $C_9H_4BrN_3S$ requires C, 40.6; H, 1.5; N, 15.8%); λ_{max}(DCM)/nm 227 (log ε 4.26), 276 (4.69); ν_{max}/cm^{-1} 3028w (Py CH), 2228w (C≡N), 1585m, 1566w, 1539w, 1504w, 1477m, 1456w, 1412m, 1391w, 1358w, 1341w, 1327m, 1250m, 1194w, 1186w, 1134w, 1057w, 1026m, 1016w, 955w, 826s, 804s, 783w; δ_H(300 MHz; $CDCl_3$) 8.98 (1H, s, Py *H*-2), 8.82 (1H, d, *J* 4.7, Py *H*), 8.24 (1H, d, *J* 7.7, Py *H*), 7.69 (1H, dd, *J* 6.3, 6.3, Py *H*-5); δ_C(75 MHz; $CDCl_3$) 173.3 (s), 152.7 (d), 147.9 (d), 139.4 (s), 135.5 (d), 124.5 (d), 123.6 (s), 112.7 (s), 109.5 (s); *m/z* (EI) 267 (M^++2, 48%), 265 (M^+, 47), 186 (100), 159 (16), 154 (16), 142 (7), 127 (14), 115 (6), 100 (13), 93 (8), 88 (10), 78 (16), 75 (17), 69 (16), 51 (23).

3-Bromo-5-(pyridin-4-yl)isothiazole-4-carbonitrile 76

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 4-iodopyridine (61.5 mg, 0.3 mmol) gave the *title compound* **76** (77 mg, 95%) as colorless needles, mp 113–115 ^oC (from cyclohexane/DCM), R_f 0.11 (DCM); (found: C, 40.7; H, 1.5; N, 15.6. $C_9H_4BrN_3S$ requires C, 40.6; H, 1.5; N, 15.8%); λ_{max}(DCM)/nm 228 (log ε 3.73), 272 (4.06); ν_{max}/cm^{-1} 3040w and 3015w (Ar CH), 2922w, 2235w (C≡N), 1597m, 1551w, 1518m, 1487m, 1454w, 1435w, 1412s, 1385w, 1342s, 1325s, 1242m, 1225w, 1098w, 1074m, 1038s, 995w, 974w, 833s, 818s, 783m; δ_H(500 MHz; CD_2Cl_2) 8.85 (2H, br s, Py *H*), 7.63 (2H, d, *J* 5.8, Py *H*); δ_C(125 MHz; CD_2Cl_2) 173.4 (s), 151.6 (d), 140.2 (s), 134.2 (s), 121.0 (d), 112.1 (s), 110.2 (s); *m/z* (EI) 267 (M^++2, 72%), 265 (M^+, 74), 186 (100), 159 (32), 154 (17), 132 (12), 115 (12), 101 (13), 100 (17), 88 (27), 78 (29), 75 (33), 69 (28), 63 (13), 58 (12), 51 (86).

3-Bromo-5-(pyrazinyl)isothiazole-4-carbonitrile 77

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with iodopyrazine (62 mg, 0.3 mmol) gave the *title compound* **77** (48 mg, 72%) as colorless needles, mp 125.5-126.5 ^oC (from cyclohexane/DCM), R_f 0.14 (DCM/Hexane, 4:1); (found: C, 36.1; H, 1.1; N, 21.0. $C_8H_3BrN_4S$ requires C, 36.0; H, 1.1; N, 21.0%); λ_{max}(DCM)/nm 230

(log ε 3.88), 268 (3.88), 296 (4.36); ν_{max}/cm^{-1} 3065w (Ar CH), 2232w (C≡N), 1530w, 1450m, 1412m, 1379w, 1335m, 1296m, 1250m, 1171m, 1074w, 1030s, 1013s, 966m, 858m, 833s, 787m; δ_H(500 MHz; CD_2Cl_2) 9.48 (1H, s, Ar *H*), 8.80 (1H, d, *J* 2.2, Ar *H*), 8.71 (1H, br s, Ar *H*); δ_C(125 MHz; CD_2Cl_2) 173.3 (s), 147.7 (d), 145.0 (d), 142.3 (s), 141.2 (d), 139.9 (s), 112.5 (s), 108.0 (s); *m/z* (EI) 267 (M^++1, 86%), 265 (M^+, 95), 187 (12), 186 (93), 183 (19), 159 (33), 154 (17), 139 (8), 115 (11), 108 (14), 100 (10), 93 (11), 88 (19), 83 (11), 82 (11), 78 (20), 75 (18), 69 (24), 51 (52).

3-Bromo-5-(indol-5-yl)isothiazole-4-carbonitrile 78

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 5-iodo-1*H*-indole (72.9 mg, 0.3 mmol) gave the *title compound* **78** (50 mg, 66%) as colorless needles, mp 233–235 ^{o}C (from cyclohexane/EtOH), R_f 0.43 (DCM/Hexane, 4:1); (found: C, 47.5; H, 1.9; N, 13.9. $C_{12}H_6BrN_3S$ requires C, 47.4; H, 2.0; N, 13.8%); λ_{max}(DCM)/nm 230 (log ε 4.03), 275 (4.19), 327 (4.01); ν_{max}/cm^{-1} 3308bw (NH), 3105w (Ar CH), 2228w (C≡N), 1748w, 1611m, 1520m, 1501m, 1466s, 1450w, 1425m, 1393s, 1350w, 1341m, 1313s, 1246w, 1171w, 1144w, 1103m, 1072w, 1028s, 955w, 914w, 887m, 874m, 826s, 810s, 793m; δ_H(500 MHz; CD_2Cl_2) 11.12 (1H, br s, N*H*), 8.03 (1H, br s, Ar *H*), 7.52-7.45 (2H, m, Ar *H*), 7.29 (1H, br s Ar *H*), 6.54 (1H, br s, Ar *H*); δ_C(125 MHz; CD_2Cl_2) 178.5 (s), 138.9 (s), 138.1 (s), 128.2 (s), 127.2 (d), 120.0 (d), 119.9 (d), 118.1 (s), 113.4 (s), 112.7 (d), 106.0 (s), 102.5 (d); *m/z* (EI) 305 (M^++2, 97%), 303 (M^+, 100), 197 (29), 191 (10), 180 (66), 166 (14), 153 (15), 139 (12), 116 (12), 112 (12), 89 (24), 88 (11), 63 (18), 51 (7).

3-Bromo-5-(indol-7-yl)isothiazole-4-carbonitrile 79

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 7-iodoindole (73 mg, 0.3 mmol) gave the *title compound* **79** (39 mg, 52%) as colorless needles, mp 174-176 ^{o}C (from cyclohexane/DCM), R_f 0.43 (DCM/Hexane, 4:1); (found: C, 47.4; H, 1.9; N, 13.8. $C_{12}H_6BrN_3S$ requires C, 47.4; H, 2.0; N, 13.8%); λ_{max}(DCM)/nm 233 (log ε 5.0), 266 (4.92), 350 (4.76); ν_{max}/cm^{-1} 3364w (NH), 2928w, 2853w, 2236w (C≡N), 1601w, 1584w, 1522w, 1485w, 1437w, 1414w, 1389w, 1337s, 1273w, 1258w, 1217w, 1179w, 1107w, 1088m, 1072w, 978w, 932w, 907w, 883w, 849w, 799s; δ_H(300 MHz; CD_2Cl_2) 8.63 (1H, br s, N*H*), 7.87 (1H, d, *J* 7.9, Ar *H*), 7.49 (1H, d, *J* 7.5, Ar *H*), 7.38 (1H, br s, Ar *H*), 7.28 (1H, dd, *J* 7.7, 7.5, Ar *H*), 6.71 (1H, br s, Ar *H*); δ_C(75 MHz; CD_2Cl_2) 174.8 (s), 140.1

(s), 132.6 (s), 130.2 (s), 129.9 (s), 127.8 (s), 126.2 (d), 125.5 (d), 123.2 (d), 120.6 (d), 112.8 (s), 111.0 (s), 104.1 (d); *m/z* (EI) 305 (M^++2, 100%), 303 (M^+, 97), 224 (50), 223 (10), 197 (19), 180 (58), 166 (8), 153 (12), 139 (9), 112 (16), 99 (9), 89 (18), 63 (9), 51 (6).

3-Bromo-5-(thien-2-yl)isothiazole-4-carbonitrile 80

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 2-iodothiophene (63 mg, 0.3 mmol) gave the title compound **80** (63 mg, 93%) as colorless plates, mp 134-135 ^oC (from cyclohexane, lit.,[36] 134-135 ^oC) identical to an authentic sample.

3-Bromo-5-(thien-3-yl)isothiazole-4-carbonitrile 81

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 3-iodothiophene (63 mg, 0.3 mmol) gave the *title compound* **81** (62 mg, 92%) as colorless plates, mp 135-138 ^oC (from cyclohexane), R_f 0.58 (Hexane/DCM, 1:1); (found: C, 35.6; H, 1.0; N, 10.4. $C_8H_3BrN_2S_2$ requires C, 35.4; H, 1.1; N, 10.3%); λ_{max}(DCM)/nm 228 (log ε 3.91), 282 (4.24), 291 inf (4.22); ν_{max}/cm^{-1} 3100w and 3077w (Ar CH), 2230w (C≡N), 1522m, 1503w, 1479w, 1427w, 1377w, 1358w, 1327m, 1207w, 1103w, 1043m, 991w, 901w, 862w, 822w, 785s; δ_H(300 MHz; $CDCl_3$) 8.11 (1H, br s, thienyl C-2-*H*), 7.54 (1H, br s, thienyl C-*H*), 7.48 (1H, d, *J* 5.1, thienyl C-*H*); δ_C(75 MHz; $CDCl_3$) 170.1 (s), 139.5 (s), 128.6 (d), 127.6 (s), 127.4 (d), 125.6 (d), 113.0 (s), 107.4 (s); *m/z* (EI) 272 (M^++2, 100%), 270 (M^+, 86), 191 (63), 164 (11), 147 (84), 139 (7), 133 (14), 127 (17), 120 (13), 94 (10), 88 (11), 82 (14), 69 (28), 58 (18), 51 (7).

3-Bromo-5-(3-bromophenyl)isothiazole-4-carbonitrile 82

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 3-bromoiodobenzene (84.9 mg, 0.3 mmol) gave the *title compound* **82** (83 mg, 97%) as colorless plates, mp 107.5–109.5 ^oC (from cyclohexane), R_f 0.59 (Hexane/DCM, 1:1); (found: C, 34.9; H, 1.1; N, 8.1. $C_{10}H_4Br_2N_2S$ requires C, 34.9; H, 1.2; N, 8.1%); λ_{max}(DCM)/nm 230 (log ε 3.46), 238 inf (3.37), 277 (3.68); ν_{max}/cm^{-1} 3075w and 3053w (Ar CH), 2236w (C≡N), 1558w, 1508m, 1472m, 1406w, 1387m, 1335s, 1310w, 1269w, 1240w, 1099w, 1076w, 1040s, 993w, 970w, 962w, 905m, 837m, 793s; δ_H(300 MHz; $CDCl_3$) 7.85 (1H, s, Ph *H*-2), 7.72 (2H, d, *J* 7.9, Ph *H*-4 & 6), 7.45 (1H, dd, *J* 7.9, 7.9, Ph *H*-5); δ_C(75 MHz; $CDCl_3$) 174.5 (s), 140.0 (s), 135.2 (d), 131.4 (d), 130.3 (d), 128.9 (s), 125.9 (d), 123.9 (s), 112.3 (s), 109.2 (s); *m/z* (EI)

346 (M^++4, 46%), 344 (M^++2, 100), 342 (M^+, 48), 265 (21), 264 (11), 263 (21), 185 (12), 184 (84), 157 (14), 140 (10), 126 (9), 120 (12), 114 (17), 99 (12), 76 (24), 75 (27), 63 (8), 51 (13).

3-Bromo-5-(2-chloropyridin-4-yl)isothiazole-4-carbonitrile 83

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 2-chloro-4-iodopyridine (71.8 mg, 0.3 mmol) gave the *title compound* **83** (58 mg, 78%) as colorless plates, mp 95–96 ^oC (from cyclohexane), R_f 0.17 (Hexane/DCM, 1:1); (found: C, 36.1; H, 0.9; N, 13.9. $C_9H_3BrClN_3S$ requires C, 36.0; H, 1.0; N, 14.0%); λ_{max}(DCM)/nm 228 (log ε 3.85), 270 (4.14); ν_{max}/cm^{-1} 3048w (Ar CH), 2237w (C≡N), 1587s, 1535w, 1501m, 1462s, 1373m, 1335s, 1312w, 1242w, 1142m, 1094m, 1053s, 988w, 966w, 885m, 856w, 833s, 806m; δ_H(300 MHz; CD_2Cl_2) 8.62 (1H, d, *J* 5.1, Py *H*-6), 7.66 (1H, s, Py *H*-3), 7.59 (1H, d, *J* 5.1, Py *H*-5); δ_C(75 MHz; CD_2Cl_2) 171.9, 153.5, 151.8 (Py *C*H), 140.7, 137.3, 122.2 (Py *C*H), 120.3 (Py *C*H), 112.0, 111.1; *m/z* (EI) 303 (M^++4, 26%), 301 (M^++2, 100), 299 (M^+, 71), 266 (31), 264 (32), 263 (17), 220 (19), 185 (20), 184 (20), 158 (11), 100 (9), 88 (8), 85 (11), 76 (11), 75 (11), 69 (10), 51 (12).

3-Bromo-5-(2-bromopyridin-4-yl)isothiazole-4-carbonitrile 84

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 2-bromo-4-iodopyridine (85.2 mg, 0.3 mmol) gave the *title compound* **84** (75 mg, 87%) as colorless plates, mp 113.5–114.5 ^oC (from cyclohexane/DCM), R_f 0.17 (Hexane/DCM, 1:1); (found: C, 31.5; H, 0.8; N, 12.1. $C_9H_3Br_2N_3S$ requires C, 31.3; H, 0.9; N, 12.2%); λ_{max}(DCM)/nm 228 (log ε 4.09), 271 (4.23); ν_{max}/cm^{-1} 3069w and 3044w (Ar CH), 2235w (C≡N), 1584m, 1530w, 1504w, 1458s, 1371m, 1333s, 1304w, 1240w, 1138m, 1088m, 1049s, 986w, 964w, 885m, 845m, 833s, 802m, 764m; δ_H(300 MHz; $CDCl_3$) 8.62 (1H, d, *J* 5.1, Py *H*-6), 7.78 (1H, s, Py *H*-3), 7.62 (1H, d, *J* 5.1, Py *H*-5); δ_C(75 MHz; $CDCl_3$) 171.1 (s), 151.8 (d), 143.8 (s), 140.6 (s), 136.4 (s), 125.4 (d), 119.8 (d), 111.6 (s), 110.7 (s); *m/z* (EI) 347 (M^++4, 15%), 345 (M^++2, 27), 343 (M^+, 14), 266 (38), 264 (36), 185 (14), 158 (9), 133 (6), 132 (7), 100 (6), 94 (5), 76 (9), 69 (7), 51 (8).

3-Bromo-5-(7-chloroquinolin-4-yl)isothiazole-4-carbonitrile 85

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 7-chloro-4-iodoquinoline (86.9 mg, 0.3 mmol) gave the *title compound* **85** (82 mg, 94%) as colorless needles, mp 170.5–172 ^{o}C (from cyclohexane/EtOH), R_f 0.15 (DCM); (found: C, 44.7; H, 1.4; N, 11.9. $C_{13}H_5BrClN_3S$ requires C, 44.5; H, 1.4; N, 12.0%); λ_{max}(DCM)/nm 232 (log ε 4.36), 247 (4.03), 274 inf (3.81); ν_{max}/cm^{-1} 3080w (Ar CH), 2924w, 2853w, 2230w (C≡N), 1605m, 1574m, 1558w, 1551w, 1508m, 1483m, 1418m, 1387w, 1366w, 1337m, 1294w, 1254w, 1242w, 1190w, 1169w, 1130m, 1074m, 1055m, 989w, 961w, 885s, 858w, 841w, 818s, 802m, 773w; δ_H(300 MHz; $CDCl_3$) 9.08 (1H, d, *J* 4.2, Ar *H*), 8.26 (1H, s, Ar *H*), 7.78 (1H, d, *J* 8.9, Ar *H*), 7.65 (1H, d, *J* 8.9, Ar *H*), 7.49 (1H, d, *J* 4.1, Ar *H*); δ_C(75 MHz; $CDCl_3$) 171.4 (s), 150.7 (d), 149.0 (s), 139.7 (s), 137.0 (s), 132.7 (s), 129.7 (d), 129.6 (d), 125.2 (d), 122.8 (s), 121.7 (d), 113.5 (s), 111.1 (s); *m/z* (EI) 353 (M^++4, 29%), 351 (M^++2, 100), 349 (M^+, 78), 272 (20), 270 (54), 243 (38), 235 (60), 208 (21), 163 (6), 135 (13), 100 (9), 99 (22), 75 (13), 74 (13), 69 (6), 63 (6), 51 (5).

3-Bromo-5-(5-bromoindol-7-yl)isothiazole-4-carbonitrile 86

Similar treatment of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) with 5-bromo-7-iodoindole (96 mg, 0.3 mmol) gave the *title compound* **86** (32 mg, 34%) as yellowish plates, mp 174.5–176.5 ^{o}C (from cyclohexane/EtOH), R_f 0.67 (DCM); (found: C, 37.6; H, 1.3; N, 10.8. $C_{12}H_5Br_2N_3S$ requires C, 37.6; H, 1.3; N, 11.0%); λ_{max}(DCM)/nm 230 (log ε 3.46), 270 (3.25), 350 (2.91); ν_{max}/cm^{-1} 3366m (NH), 2228w (C≡N), 1576m, 1518m, 1485m, 1462w, 1429w, 1406w, 1393w, 1329m, 1314s, 1269w, 1252w, 1217w, 1128w, 1101m, 1074w, 976m, 943w, 883m, 862w, 847m, 797m, 768s; δ_H(500 MHz; CD_2Cl_2) 8.0 (1H, s, Ar *H*), 7.55 (1H, d, *J* 1.4, Ar *H*), 7.41 (1H, dd, *J* 2.9, 2.9, Ar *H*), 6.68 (1H, dd, *J* 3.0, 2.1, Ar *H*); δ_C(125 MHz; CD_2Cl_2) 172.8 (s), 139.9 (s), 131.3 (d), 131.2 (s), 127.3 (d), 127.25 (d), 125.1 (d), 112.9 (s), 112.1 (s), 112.0 (s), 110.5 (s), 103.5 (s); *m/z* (EI) 385 (M^++4, 50%), 384 (M^++2, 13), 383 (M++1, 100), 382 (M^+, 8), 304 (7), 302 (7), 224 (11), 223 (69), 196 (10), 195 (7), 169 (5), 152 (17), 112 (14), 98 (10), 63 (5).

3,3'-Dibromo-5,5'-biisothiazole-4,4'-dicarbonitrile 63

To a stirred solution of 3-bromoisothiazole-4-carbonitrile **48** (47 mg, 0.25 mmol) in MeCN (1 mL) at *ca.* 20 ^{o}C, AgF (63 mg, 0.5 mmol) was added. To this mixture $Pd(Ph_3P)_2Cl_2$ (35 mg, 0.05 mmol) was then added and the mixture was heated at *ca.* 82 ^{o}C until no starting material

remained (TLC). The reaction mixture was left to cool to *ca.* 20 °C and adsorbed onto silica. Chromatography (DCM/hexane, 3:2) gave the *title compound* **63** (63 mg, 67%) as yellowish plates, mp (DSC onset) 286 °C (from PhCl), R_f 0.33 (Hexane/DCM, 1:1); (found: C, 25.5; N, 14.7. $C_8Br_2N_4S_2$ requires C, 25.6; N, 14.9%); λ_{max}(DCM)/nm 229 (log ε 4.6), 293 (4.9); ν_{max}/cm^{-1} 2230w (C≡N), 1458s, 1327s, 1269w, 1040s, 887w, 800s; δ_C(75 MHz; CD_2Cl_2) 159.1 (s), 138.6 (s), 112.5 (s), 111.4 (s); *m/z* 378 (M^++4, 43%), 377 (M^++3, 9), 376 (M^++2, 100), 374 (M+, 47), 297 (8), 295 (8), 271 (7), 269 (7), 253 (8), 251 (7), 233 (6), 216 (20), 190 (8), 169 (5), 146 (9), 139 (26), 137 (25), 126 (11), 120 (11), 108 (28), 100 (13), 94 (50), 88 (10), 82 (29), 70 (24), 64 (34), 58 (12).

3-Chloro-5-phenylisothiazole-4-carbonitrile 87

To a stirred solution of 3-chloroisothiazole-4-carbonitrile **47** (36 mg, 0.25 mmol) in MeCN (1 mL) at *ca.* 20 °C, AgF (63 mg, 0.5 mmol), Ph_3P (6.5 mg, 10 mol%), and iodobenzene (55 μL, 0.5 mmol) were added. To this mixture $Pd(Ph_3P)_2Cl_2$ (8.8 mg, 5 mol%) was then added and the mixture was heated at *ca.* 82 °C until no starting material remained (TLC). The reaction mixture was left to cool to *ca.* 20 °C and adsorbed onto silica. Chromatography (Hexane/DCM, 3:2) gave the title compound **87** (63.6 mg, 96%) as colorless needles, mp 87-88 °C (from cyclohexane, lit.,[35] 87-88 °C) identical to an authentic sample.

3,3'-Dichloro-5,5'-biisothiazole-4,4'-dicarbonitrile 22

To a stirred solution of 3-chloroisothiazole-4-carbonitrile **47** (36 mg, 0.25 mmol) in MeCN (1 mL) at *ca.* 20 °C, AgF (63 mg, 0.5 mmol) was added. To this mixture $Pd(Ph_3P)_2Cl_2$ (35 mg, 0.05 mmol) was then added and the mixture was heated at *ca.* 82 °C until no starting material remained (TLC). The reaction mixture was left to cool to *ca.* 20 °C and adsorbed onto silica. Chromatography (DCM/Hexane, 3:2) gave the title compound **22** (63 mg, 67%) as colorless needles, mp 243-244 °C (from PhH, lit.,[36] 244-245 °C) identical to an authentic sample.

9.4 Compounds related to Chapter 4

3-Amino-5-phenylpyrazole-4-carbonitrile 89 (see Table 7)

To a stirred mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **87** (50 mg, 0.23 mmol) in DMSO (1 mL), protected with $CaCl_2$ drying tube at *ca*. 20 ^oC, hydrazine monohydrate (1.9 mL, 0.046 mol) was added. The reaction mixture was kept at this temperature until no starting material remained (by TLC) and was then poured onto crushed ice and extracted (Et_2O). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Hexane/Et_2O, 3*:*7) gave the title compound **89** (39 mg, 92%) as a white powder, mp 194-195 ^oC (lit.,[146] 200 ^oC) (from EtOH/H_2O) identical to an authentic sample.

3-Amino-5-phenylpyrazole-4-carbonitrile 89 (Table 8)

A mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **87** (50 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), protected with $CaCl_2$ drying tube was stirred at *ca.* 20 ^oC until no starting material remained (TLC). The reaction mixture was then poured onto crushed ice. The precipitate which formed was collected by filtration to afford the title compound **89** (42 mg, 99%) as a white powder, mp 194-195 ^oC (lit.,[146] 200 ^oC) (from EtOH/H_2O) identical to that described above.

3-Amino-5-phenylpyrazole-4-carbonitrile 89 (from 3-bromoisothiazole 62)

Similar treatment of 3-bromo-5-phenylisothiazole-4-carbonitrile **62** (61 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) gave the title compound **89** (42 mg, 100%) as a white powder, mp 194-195 ^oC (lit.,[146] 200 ^oC) (from EtOH/H_2O) identical to that described above.

3-Amino-5-phenylpyrazole-4-carbonitrile 89 (from 3-iodoisothiazole 23)

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **23** (72 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) gave the title compound **89** (41 mg, 98%) as a white powder, mp 194-195 ^oC (lit.,[146] 200 ^oC) (from EtOH/H_2O) identical to that described above.

3-Methoxy-5-phenyl-1*H*-pyrazole-4-carbonitrile 96

A mixture of 3-methoxy-5-phenylisothiazole-4-carbonitrile **90** (46 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), protected with a $CaCl_2$ drying tube, was stirred at *ca.* 20 ^oC until no starting material remained (TLC). The reaction mixture was then poured onto crushed ice

and extracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 1:1) gave the *title compound* **96** (25 mg, 52%) as colorless needles, mp 181-182 ^{o}C (from EtOH); (found: C, 66.4; H, 4.6; N, 21.0. $C_{11}H_9N_3O$ requires C, 66.3; H, 4.6; N, 21.1%); λ_{max}(EtOAc)/nm 262 (log ε 2.97); ν_{max}/cm^{-1} 3183w (NH_2), 3119w, 3017w, 2961w (Ar CH), 2853w (Ph CH), 2818w (Ph CH), 2232m (C≡N), 1589w, 1568w, 1537s, 1512s, 1493m, 1458w, 1444w, 1418s, 1331w, 1258w, 1196w, 1158w, 1142m, 1131m, 1040w, 1011m, 961w, 920w, 777m, 751w, 725s, 713m; δ_H(300 MHz; DMSO-d_6) 13.33 (1H, br s, N*H*), 7.81-7.70 (2H, m, Ph C*H*), 7.62-7.46 (3H, m, Ph C*H*), 3.95 (3H, s, CH_3); δ_C(75 MHz; DMSO-d_6) 164.5 (s), 147.2 (s), 130.4 (d), 129.3 (d), 126.7 (s), 126.2 (d), 114.0 (s), 74.1 (s), 56.45 (*C*H_3); *m/z* (EI) 199 (M^+, 100%), 198 (M^+-1, 53), 170 (38), 156 (7), 142 (12), 127 (50), 115 (11), 104 (75), 100 (29), 77 ($C_6H_5^+$, 83), 63 (15), 51 (58). Further elution (EtOAc, 100%) gave 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **89** (20 mg, 48%) as a white powder, mp 194-195^{o}C (lit.,[13] 200 ^{o}C) (from EtOH/H_2O) identical to an authentic sample.

3-Hydroxy-5-phenyl-1*H*-pyrazole-4-carbonitrile 97

Similar treatment of 3-hydroxy-5-phenylisothiazole-4-carbonitrile **91** (47 mg, 0.23 mmol) with anhydrous hydrazine gave after chromatography (Hexane/Et_2O, 7:3) the *title compound* **97** (41 mg, 97%) as colorless needles, mp 141.5-143.5 ^{o}C (from pentane/EtOH); (found: C, 64.8; H, 3.9; N, 22.6. $C_{10}H_7N_3O$ requires C, 64.9; H, 3.8; N, 22.7%); λ_{max}(MeOH)/nm 237 (log ε 4.42), 260 inf (4.41), 296 inf (4.26), 312 inf (4.12), 326 inf (3.87); ν_{max}/cm^{-1} 3333w & br (OH), 2957w (Ph CH), 2924m (Ph CH), 2853w (Ph CH), 2203w (C≡N), 1643m, 1589m, 1514w, 1485m, 1449w, 1433w, 1377w, 1275w, 1123w, 1098w, 1072w, 1030w, 970w, 918w, 860w, 797w, 766w, 743w, 725s; δ_H(300 MHz; DMSO-d_6) (1 peak missing) 13.28 (1H, br s, N*H* or O*H*), 7.76-7.61 (5H, m, Ph C*H*); δ_C(300 MHz; DMSO-d_6) 173.8 (s), 168.6 (s), 131.7 (d), 129.7 (d), 128.1 (s), 126.9 (d), 113.4 (s), 93.0 (s); *m/z* (EI) 185 (M^+, 24), 128 (42), 121 (11), 104 (30), 91 (50), 86 (67), 77 ($C_6H_5^+$, 100), 57 (38), 51 (41).

3-(*N*-Benzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile 98

Similar treatment of 3-benzylamino-5-phenylisothiazole-4-carbonitrile **93** (67 mg, 0.23 mmol) with anhydrous hydrazine gave after chromatography (Hexane/Et_2O, 7:3) the *title compound* **98** (34 mg, 54%) as pale yellow plates, mp 206-208 ^{o}C (from EtOH); (found: C, 74.4; H, 5.1; N, 20.4. $C_{17}H_{14}N_4$ requires C, 74.4; H, 5.1; N, 20.4%); λ_{max}(MeOH)/nm 209 (log ε 3.20), 237

(3.11); ν_{max}/cm^{-1} 3360m (NH), 3184w, 3150w, 3105w, 3086w (Ph CH), 3055w (Ph CH), 3028w (Ph CH), 2951w, 2918w, 2884w, 2837w, 2803w, 2218s (C≡N), 1587m, 1570s, 1524m, 1495m, 1466w, 1452m, 1429w, 1350m, 1327w, 1306w, 1234w, 1196w, 1161w, 1130w, 1080m, 1058w, 1030w, 986w, 959w, 916w, 837w, 797w, 770m, 731s; δ_H(300 MHz; DMSO-d_6) 12.62 (1H, br s, N*H*), 7.78 (2H, d, *J* 7.2, Ph *H*), 7.51-7.30 (8H, m, Ph *H* and N*H*), 7.25-7.21 (1H, m, Ph *H*), 4.40 (2H, d, *J* 6, CH_2); δ_C[75 MHz; DMSO-d_6 with Cr(acac)$_3$] (1 peak missing) 156.2 (s, w & br), 150.95 (s, w & br), 139.45 (s), 129.5 (d), 129.0 (d), 128.3 (d), 127.3 (d), 126.9 (d), 125.9 (d), 116.0 (s), 70.0 [s, w & br], 46.2 (*C*H$_2$); *m/z* (EI) 274 (M$^+$, 24%), 197 (M$^+$-C_6H_5, 8), 170 (4), 127 (6), 104 (4), 91 ($C_6H_5CH_2^+$, 100), 77 ($C_6H_5^+$, 12), 51 (7). Further elution (Et$_2$O, 100%) gave 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **89** (14 mg, 33%) as a white powder, mp 194-195 ^{o}C (lit.,[13] 200 ^{o}C) (from EtOH/H$_2$O) identical to an authentic sample.

3-Morpholino-5-phenyl-1*H*-pyrazole-4-carbonitrile 99

A mixture of 3-morpholino-5-phenylisothiazole-4-carbonitrile **94** (62 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was heated to *ca.* 80 ^{o}C until no starting material remained (TLC). The reaction mixture was allowed to cool to *ca*. 20 ^{o}C, poured onto crushed ice and extracted (Et$_2$O). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Et$_2$O/Hexane, 7:3) gave the *title compound* **99** (35 mg, 59%) as colorless needles, mp 184.5-185 ^{o}C (from EtOH); (Found: C, 66.2; H, 5.5; N, 21.9. $C_{14}H_{14}N_4O$ requires C, 66.1; H, 5.55; N, 22.0%); λ_{max}(MeOH)/nm 207 (log ε 3.15), 211 (3.11), 235 (3.04), 254 inf (2.98); ν_{max}/cm^{-1} 3214w&br (NH), 2960w (Ph CH), 2917w (Ph CH), 2860w and 2832w (CH$_2$), 2218s (C≡N), 1565m, 1512s, 1495s, 1456m, 1436w, 1377m, 1305m, 1287m, 1281m, 1264w, 1239w, 1151m, 1121s, 1072w, 1052w, 1045w, 1030w, 968s, 917s, 858w, 844m, 777s; δ_H(300 MHz; CD_2Cl_2) 7.75-7.71 (2H, m, Ph *H*), 7.53-7.50 (3H, m, Ph *H*), 3.82 (4H, dd, *J* 4.8, CH_2N), 3.42 (4H, dd, *J* 5.6, 4.1, CH_2O); δ_C(75 MHz; DMSO-d_6) (1 peak missing) 160.1 (s, w & br), 148.1 (s, w & br), 129.9 (s), 129.1 (d), 128.3 (s), 126.4 (d), 116.4 (s), 76.4 [s, w & br], 65.5 (*C*H$_2$O), 48.0 (*C*H$_2$N); *m/z* (EI) 254 (M$^+$, 91%), 239 (35), 223 (17), 196 (67), 169 (23), 140 (10), 127 (15), 104 (100), 77 ($C_6H_5^+$, 48), 57 (29). Further elution (Et$_2$O, 100%) gave 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **89** (16 mg, 38%) as a white powder, mp 194-195 ^{o}C (lit.,[13] 200 ^{o}C) (from EtOH/H$_2$O) identical to an authentic sample.

3,5-Diphenyl-1*H*-pyrazole-4-carbonitrile 100

A mixture of 3,5-diphenylisothiazole-4-carbonitrile **95** (45 mg, 0.23 mmol) and anhydrous hydrazine in a sealed tube, was introduced into a preheated Wood's metal bath at 150 ^{o}C and was stirred until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca*. 20 ^{o}C, poured onto crushed ice and extracted (EtOAc). The organic extracts were combined, dried and evaporated to afford the title compound **100** (26 mg, 83%) as colorless needles, mp 220.5-221.5 ^{o}C (lit.,[326] 230 ^{o}C) (from EtOH); λ_{max}(*t*-BuOMe)/nm 208 (log ε 3.42), 248 (3.45); ν_{max}/cm^{-1} 3181 br & w (NH), 3024w (Ph CH), 2228m (C≡N), 1564w, 1486m, 1450w, 1444m, 1431w, 1402w, 1319w, 1297w, 1279w, 1254w, 1137m, 1074m, 1027w, 1002w, 964s, 918w, 777s, 733m, 717s; δ_H(300 MHz; $CDCl_3$) 10.82 (1H, br s, N*H*), 7.92-7.89 (4H, m, Ph *H*), 7.55-7.48 (6H, m, Ph *H*); δ_C(75 MHz; DMSO-d_6) 153.1 (s), 148.6 (s), 130.9 (d), 129.3 (d), 126.6 (d), 115.8 (s), 109.4 (s), 85.4 (s); *m/z* (EI) 245 (M^+, 100%), 216 (10), 189 (6), 142 (4), 122 (5), 115 (6), 104 (7), 94 (7), 77 ($C_6H_5^+$, 21), 63 (5), 51 (13).

3-(Benzylideneamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile 101 (see Scheme 46)

A mixture of 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **89** (50 mg, 0.27 mmol) and PhCHO (1 mL, 9.72 mmol) was stirred at *ca*. 20 ^{o}C until no starting material remained (TLC). The reaction mixture was diluted with Et_2O and extracted with saturated solution of sodium bisulfate to remove unreacted benzaldehyde. The organic extracts were combined, dried and evaporated to give the *title compound* **101** (53 mg, 72%) as yellow plates, mp 174-175 ^{o}C (from EtOH); (found C, 74.9; H, 4.4; N, 20.5. $C_{17}H_{12}N_4$ requires C, 75.0; H, 4.4; N, 20.6%); λ_{max} (*t*-BuOMe)/nm 205 (log ε 4.35), 228 (4.22), 263 (4.18); ν_{max}/cm^{-1} 3202w & br (NH), 3119w (Ph CH), 3059w (Ph CH), 3030w (Ph CH), 2232m (C≡N), 1620s, 1599w, 1574m, 1493m, 1458m, 1429w, 1348w, 1314w, 1296w, 1275w, 1213m, 1159w, 1111m, 1078w, 1001w, 984w, 972m, 922w, 876w, 849w, 800w, 777w, 760s; δ_H(300 MHz; DMSO-d_6) 14.05 (s, 1H, N*H*), 9.08 (s, 1H, N=C*H*), 8.01 (d, 2H, *J* 6.9, Ph *H*), 7.88 (d, 2*H*, *J* 6.9, Ph *H*), 7.68-7.50 (m, 6H, *J* 7.2, Ph *H*); δ_C(75 MHz; DMSO-d_6) 163.7 (d), 147.7 (s), 134.9 (s), 134.5 (s), 132.7 (s), 130.1 (d), 129.4 (d), 129.2 (d), 129.0 (d), 126.2 (d), 125.6 (d), 114.7 (s), 83.2 (s); *m/z* (EI) 272 (M^+, 11%), 271 (M^+-1, 11), 184 (15), 172 (51), 155 (5), 128 (11), 115 (12), 104 (11), 91 ($PhCH_2^+$, 100), 77 ($C_6H_5^+$, 20), 65 (14).

1-Benzyl-3-(dibenzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile 102 (see Scheme 46)

To a stirred mixture of 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **89** (50 mg, 0.27 mmol) and potassium hydroxide (182 mg, 3.24 mmol) in DMF (2 mL) at *ca.* 20 ^{o}C, benzyl bromide (32 μL, 0.27 mmol) was added. The reaction mixture was held at this temperature until no starting material remained (TLC). The mixture was diluted with EtOAc and extracted (H_2O). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 7:3) gave 3-(*N*-benzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile **98** (24 mg, 33%), mp 206-208 ^{o}C (from EtOH), identical to that described above. Further elution (EtOAc, 100%) gave the *title compound* **102** as colorless needles (23 mg, 57%), mp 118.5-120.5 ^{o}C (from EtOH); (found C, 81.9; H, 5.7; N, 12.2. $C_{31}H_{26}N_4$ requires C, 81.9; H, 5.8; N, 12.3%); λ_{max}(EtOAc)/nm 253 (log ε 3.52); ν_{max}/cm^{-1} 3077w (Ph CH), 3042w (Ph CH), 2854w, 2217m (C≡N), 1607w, 1586w, 1527m, 1495w, 1474m, 1453m, 1451m, 1436w, 1400w, 1367m, 1359m, 1324w, 1288w, 1266w, 1228w, 1211w, 1180w, 1154w, 1140w, 1098w, 1074w, 1041w, 1030w, 1016w, 1003w, 968w, 936w, 919w, 904w, 846w, 833w, 779s, 758s, 749s, 731m, 719m; δ_H(300 MHz; $CDCl_3$) 7.99-7.97 (2H, d, *J* 6, Ph *H*), 7.49-7.18 (16H, m, Ph *H*), 7.10-7.03 (2H, m, Ph *H*), 5.11 (2H, s, NC*H*$_2$Ph), 4.28 [4H, s, N(C*H*$_2$Ph)$_2$]; δ_C(75 MHz; $CDCl_3$) (1 peak missing) 154.9 (s), 151.6 (s), 136.1 (s), 135.7 (s), 131.1 (s), 129.1 (d), 128.9 (d), 128.7 (d), 128.6 (d), 127.9 (d), 127.8 (d), 127.0 (d), 126.3 (d), 115.1 (s), 84.1 (s), 57.3 (*C*H$_2$), 51.5 (*C*H$_2$); *m/z* (EI) 454 (M$^+$, 9%), 363 (M$^+$-PhCH$_2$, 7), 199 (40), 170 (9), 143 (7), 116 (8), 91 (PhCH$_2^+$, 100), 77 ($C_6H_5^+$, 6), 74 (14), 65 (19).

3-(*N*-Benzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile 98 (See Scheme 46)

To a stirred mixture of 3-(benzylideneamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile **101** (30 mg, 0.11 mmol) in MeOH (2 mL) under argon at *ca*. 0 ^{o}C, $NaBH_4$ (68.2 mg, 0.22 mmol) was added in one portion. The reaction left to warm to *ca*. 20 ^{o}C until no starting material remained (TLC). The reaction mixture was diluted with EtOAc and extracted (H_2O). The organic extracts were combined, dried and evaporated to afford the *title compound* **98** (30 mg, 100%) as pale yellow plates, mp 206-208 ^{o}C (from EtOH), identical to that described above.

3-Amino-5-phenyl-1*H*-pyrazole-4-carbonitrile 89 (see Scheme 46)

In a suspension of 3-(*N*-benzylamino)-5-phenyl-1*H*-pyrazole-4-carbonitrile **98** (30 mg, 0.11 mmol) in H_2O at *ca*. 20 ^{o}C, MeOH (176 μL, 5%) was added. The reaction mixture held at this temperature until no starting material remained (TLC) and was then diluted with H_2O and

extracted with EtOAc. The organic extracts were combined, dried and evaporated to afford the title compound **89** (20 mg, 99%), as a white powder, mp 194-195 ^{o}C (lit.,[146] 200 ^{o}C) (from EtOH/H_2O) identical to an authentic sample.

3-Amino-5-*m*-tolyl-1*H*-pyrazole-4-carbonitrile 120

A mixture of 3-chloro-5-*m*-tolylisothiazole-4-carbonitrile **103** (54 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), protected with a $CaCl_2$ drying tube, was stirred at *ca.* 20 ^{o}C until no starting material remained (TLC). The reaction mixture was poured onto crushed ice and exracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 7:3) gave the *title compound* **120** (44 mg, 97%) as colorless needles, mp 194.5-195.5 ^{o}C (from EtOH); (found: C, 66.6; H, 5.0; N, 28.2. $C_{11}H_{10}N_4$ requires C, 66.6; H, 5.1; N, 28.3%); λ_{max}(MeOH)/nm 209 (log ε 2.76), 231 (2.52), 255 (2.45); ν_{max}/cm^{-1} 3365w and 3299w (NH_2), 3279w, 3206m and 3184m (NH), 3139w, 3101w, 3060w, 3050w and 3012w (Ph CH), 2959w and 2912w (CH_3), 2226s (C≡N), 1646m, 1575m, 1534s, 1506m, 1483m, 1398w, 1344w, 1168w, 1082m, 1017w, 984w, 898w, 882w, 854m, 786s, 747s, 727s; δ_H(300 MHz; DMSO-d_6) 12.18 (1H, s, N*H*), 7.63-7.55 (2H, m, Ph C*H*), 7.39-7.29 (1H, br m, Ph C*H*), 7.24-7.16 (1H, br m, Ph C*H*), 6.44 (2H, br s, NH_2), 2.34 (3H, s, CH_3); δ_C(75 MHz; DMSO-d_6) 154.7 (s, w & br), 150.0 (s, w & br), 137.9 (d), 131.9 (s, w & br), 129.3 (s, w & br), 128.7 (d), 126.2 (d), 122.8 (d), 116.2 (s), 69.6 (s), 21.1 (*C*H_3); *m/z* (EI) 199 (M^++1, 16), 198 (M^+, 100%), 197 (M^+-1, 16), 180 (9), 170 (4), 155 (8), 142 (4), 115 (3), 91 (2), 77 (1).

3-Amino-5-(2-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile 121

Similar treatment of 3-amino-5-(2-methoxyphenyl)isothiazole-4-carbonitrile **104** (58 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **121** (47 mg, 95%) as pale yellow plates, mp 179-180 ^{o}C (lit.,[327] 192 ^{o}C) (from EtOH); (found: C, 61.7; H, 4.8; N, 26.1. $C_{11}H_{10}N_4O$ requires C, 61.7; H, 4.7; N, 26.1%); λ_{max}(MeOH)/nm 213 (log ε 3.13), 259 (2.83), 287 inf (2.73); ν_{max}/cm^{-1} 3413w (NH_2), 3326w and 3295w (NH), 3186w (Ph CH), 2211m (C≡N), 1636m, 1602w, 1587m, 1558m, 1524m, 1484m, 1457m, 1449w, 1432w, 1307w, 1269m, 1251m, 1187w, 1167w, 1120w, 1071m, 1023m, 969m, 945w, 807w, 768s, 752m, 706m; δ_H(300 MHz; DMSO-d_6) tautomeric mixture of isomers 12.43 (1H, br s, N*H*), 12.11 (1H, br s, N*H*), 7.50-7.35 (4H, m, Ph C*H*), 7.20-7.10 (2H, m, Ph C*H*), 7.10-6.95 (2H, m, Ph C*H*), 6.27 (2H, br s, NH_2), 5.50 (2H, br s, NH_2), 3.80 (6H, s, CH_3); δ_C(75 MHz; DMSO-d_6)

156.6 (s), 153.8 (s, w & br), 149.4 (s, w & br), 130.7 (s, w & br), 129.6 (s, w & br), 120.6 (d), 115.8 (s), 111.8 (d), 73.5 (s, w & br), 73.50 (s, w & br), 55.4 (O*C*H$_3$); *m/z* (EI) 214 (M$^+$, 100%), 198 (5), 185 (11), 171 (9), 155 (4), 144 (11), 129 (6), 116 (11), 101 (5), 89 (11), 77 ($C_6H_5^+$, 5), 63 (4).

3-Amino-5-(3-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile 122

Similar treatment of 3-amino-5-(3-methoxyphenyl)isothiazole-4-carbonitrile **105** (58 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the *title compound* **122** (44 mg, 90%) as colorless needles, mp 132-133 ^{o}C (from EtOH); (found: C, 61.6; H, 4.7; N, 26.0. $C_{11}H_{10}N_4O$ requires C, 61.7; H, 4.7; N, 26.1%); λ_{max}(MeOH)/nm 219 (log ε 3.21), 255 (2.89), 290 inf (2.66); ν_{max}/cm^{-1} 3428w (NH$_2$), 3349w, 3218w (NH), 3165w (Ph CH), 2962w, 2936w, 2914w and 2833w (CH$_3$), 2211s (C≡N), 1637s, 1614m, 1604m, 1597m, 1583m, 1520s, 1462m, 1430m, 1350m, 1316w, 1287m, 1275w, 1230s, 1183w, 1144w, 1106w, 1091w, 1049s, 1000m, 991m, 892m, 880w, 849m, 789m, 783m, 762w, 733m; δ_H(300 MHz; DMSO-d$_6$) 12.21 (1H, s, N*H*), 7.38-7.34 (3H, m, Ph C*H*), 6.97 (1H, br s, Ph C*H*), 6.49 (2H, br s, N*H*$_2$), 3.78 (3H, s, OC*H*$_3$); δ_C(75 MHz; DMSO-d$_6$) 159.3 (s), 154.6 (s), 149.8 (s), 133.4 (s), 129.8 (d), 117.9 (d), 116.3 (s), 114.1 (d), 110.9 (d), 69.5 (s), 55.0 (O*C*H$_3$); *m/z* (EI) 214 (M$^+$, 100%), 199 (3), 185 (22), 171 (12), 158 (6), 142 (14), 129 (6), 116 (12), 107 (8), 102 (4), 89 (11), 88 (7), 77 ($C_6H_5^+$, 7), 63 (7), 51 (4).

3-Amino-5-(4-methoxyphenyl)-1*H*-pyrazole-4-carbonitrile 123

Similar treatment of 3-amino-5-(4-methoxyphenyl)isothiazole-4-carbonitrile **106** (58 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **123** (42 mg, 94%) as colorless needles, mp 170.5-171.5 ^{o}C (lit.,[328] 183-186 ^{o}C) (from EtOH); (found: C, 61.6; H, 4.6; N, 26.1. $C_{11}H_{10}N_4O$ requires C, 61.7; H, 4.7; N, 26.1%); λ_{max}(MeOH)/nm 207 (log ε 3.01), 262 (2.84); ν_{max}/cm^{-1} 3464w, 3427w (NH$_2$), 3362w, 3321w (NH), 3179w (Ph CH), 2219w and 2206m (C≡N), 1653w, 1627m, 1613m, 1587w, 1532s, 1509w, 1502w, 1489m, 1482m, 1434m, 1292m, 1261s, 1253s, 1189m, 1159w, 1138w, 1065w, 1024m, 1011w, 968w, 829s, 803w, 780w, 737m, 714w; δ_H(300 MHz; DMSO-d$_6$) 12.08 (1H, s, N*H*), 7.74-7.72 (2H, d, *J* 8.4, Ph C*H*), 7.05-7.02 (2H, d, *J* 8.1, Ph C*H*), 6.41 (2H, s, N*H*$_2$), 3.79 (3H, s, OC*H*$_3$); δ_C(75 MHz; DMSO-d$_6$) 159.6 (s), 154.7 (s), 149.8 (s), 127.1 (d), 124.7 (s), 116.4 (s), 114.2 (d), 69.3 (s), 55.2 (O*C*H$_3$); *m/z* (EI) 214 (M$^+$, 100%), 199 (30), 185 (3), 171 (17), 157 (3), 143 (6), 129 (3), 116 (8), 114 (5), 107 (4), 89 (7), 77 ($C_6H_5^+$, 3), 63 (4).

3-Amino-5-(thien-3-yl)-1*H*-pyrazole-4-carbonitrile 124

Similar treatment of 3-amino-5-(thien-3-yl)isothiazole-4-carbonitrile **107** (52 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the *title compound* **124** (41 mg, 94%) as colorless needles, mp 224.5-225.5 ^{o}C (from EtOH); (found: C, 50.5; H, 3.2; N, 29.4. $C_8H_6N_4S$ requires C, 50.5; H, 3.2; N, 29.4%); λ_{max}(MeOH)/nm 210 (log ε 3.05), 263 (2.93); ν_{max}/cm^{-1} 3419w and 3341w (NH_2), 3226w (NH), 3163w, 3111w, 3028w, 2966w (Ph CH), 2898w (Ph CH), 2838w (Ph CH), 2213s (C≡N), 1634s, 1596m, 1559w, 1521s, 1456m, 1379m, 1339m, 1272w, 1081w, 1003s, 891m, 860m, 814w, 784s, 723s; δ_H(300 MHz; $CDCl_3$/drop of DMSO-d_6) (1 peak missing), 7.75 (1H, s, thienyl C*H*), 7.45 (1H, d, *J* 4.8, thienyl C*H*), 7.24-7.22 (1H, m, thienyl C*H*), 4.86 (2H, s, NH_2); δ_C(75 MHz; DMSO-d_6) 154.1 (s), 146.7 (s), 133.5 (s), 126.9 (d), 125.5 (d), 121.9 (d), 116.3 (s), 69.4 (s); *m/z* (EI) 190 (M^+, 100%), 161 (14), 148 (9), 134 (12), 121 (3), 108 (3), 95 (4), 90 (4), 76 (3), 63 (4).

3-Amino-5-(2-chlorophenyl)-1*H*-pyrazole-4-carbonitrile 125[329]

Similar treatment of 3-amino-5-(2-chlorophenyl)isothiazole-4-carbonitrile **108** (59 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **125** (42 mg, 87%) as colorless needles, mp 184-189 ^{o}C (from EtOH); (found: C, 55.0; H, 3.1; N, 25.7. $C_{10}H_7N_4Cl$ requires C, 54.9; H, 3.2; N, 25.6%); λ_{max}(MeOH)/nm 212 (log ε 3.15), 228 inf (2.94), 267 inf (2.44); ν_{max}/cm^{-1} 3198m (NH_2), 3183m (NH), 3173w and 3166w and 3159w (Ph CH), 2225m (C≡N), 1647w, 1636w, 1624w, 1582w, 1565m, 1555w, 1532m, 1528m, 1500m, 1490w, 1473w, 1465w, 1457w, 1437w, 1395w, 1324w, 1282w, 1259w, 1254w, 1168w, 1104w, 1081m, 1058m, 1045w, 986m, 972w, 879, 851w, 830w, 788m, 777w, 769w, 755s, 729s, 720s; δ_H(300 MHz; DMSO-d_6) 12.215 (1H, s, NH), 7.58-7.45 (4H, m, Ph CH), 6.45 (2H, s, NH_2); δ_C(75 MHz; DMSO-d_6) 153.5 (s), 149.8 (s), 132.1 (s), 131.45 (d), 130.5 (d), 129.7 (d), 129.2 (s), 127.1 (d), 115.1 (s), 72.9 (s); δ_C(75 MHz; DEPT-135, DMSO-d_6) 131.45 (Ph CH), 130.5 (Ph CH), 129.7 (Ph CH), 127.1 (Ph CH); *m/z* (EI) 218 (M^+, 100%), 220 (32), 189 (6), 183 (M^+-Cl, 5), 176 (11), 155 (17), 126 (27), 114 (8), 100 (23), 87 (8), 77 ($C_6H_5^+$, 22), 63 (15), 51 (25).

3-Amino-5-(3-chlorophenyl)-1*H*-pyrazole-4-carbonitrile 126

Similar treatment of 3-amino-5-(3-chlorophenyl)isothiazole-4-carbonitrile **109** (59 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the *title compound* **126** (45 mg, 90%) as colorless needles, mp 211-212 ^{o}C (from EtOH); (found: C, 55.0; H, 3.3; N, 25.6. $C_{10}H_7N_4Cl$ requires C, 54.9; H, 3.2; N, 25.6%); λ_{max}(MeOH)/nm 256 (log ε 3.18), 275 inf (3.06); ν_{max}/cm^{-1} 3362w (NH_2), 3303w (NH), 3295w, 3199m, 3169m, 3140w, 3127w and 3095w (Ph CH), 3069w (Ph CH), 3048w (Ph CH), 2227s (C≡N), 1642m, 1582m, 1565m, 1532s, 1500m, 1474m, 1437w, 1423w, 1406w, 1396w, 1343w, 1314w, 1168w, 1104w, 1082m, 987m, 907w, 879m, 811w, 787s, 777m, 744m, 728s; δ_H(300 MHz; DMSO-d_6) 12.37 (1H, s, N*H*), 7.79-7.74 (2H, m, Ph C*H*), 7.53-7.44 (2H, m, Ph C*H*), 6.5 (2H, s, NH_2); δ_C(75 MHz; DMSO-d_6) 155.2 (s), 147.9 (s), 133.5 (s), 131.5 (s), 130.8 (d), 128.5 (d), 125.1 (d), 124.1 (d), 116.0 (s), 70.1 (s); *m/z* (EI) 218 (M^+, 100%), 220 (33), 189 (12), 176 (7), 162 (20), 153 (6), 1127 (26), 114 (13), 99 (24), 85 (18), 77 ($C_6H_5^+$, 23), 63 (18), 57 (53).

3-Amino-5-(4-chlorophenyl)-1*H*-pyrazole-4-carbonitrile 127

Similar treatment of 3-amino-5-(4-chlorophenyl)isothiazole-4-carbonitrile **110** (59 mg, 0.23mmol) with anhydrous hydrazine (2 mL) gave the title compound **127** (46 mg, 92%) as colorless needles, mp 209-212 ^{o}C (lit.,[330] 212 ^{o}C) (from EtOH); (found: C, 55.0; H, 3.2; N, 25.5. $C_{10}H_7N_4Cl$ requires: C, 54.9; H, 3.2; N, 25.6%); λ_{max}(MeOH)/nm 209 (log ε 3.11), 238 inf (3.07), 257 (3.13); ν_{max}/cm^{-1} 3344w (NH_2), 3296w, 3201m (NH), 3138w and 3122w and 3071w and 3045w (Ph CH), 2958w, 2917w, 2849w, 2223s (C≡N), 1647w, 1605w, 1582w, 1531s, 1489s, 1424w, 1420w, 1383w, 1347w, 1341w, 1173w, 1139w, 1097m, 1086m, 1016w, 967w, 825s, 817m, 769m, 733s; δ_H(300 MHz; DMSO-d_6) 12.24 (1H, s, N*H*), 7.82-7.79 (2H, m, Ph C*H*), 7.55-7.52 (2H, m, Ph C*H*), 6.54 (2H, s, NH_2); δ_C(75 MHz; DMSO-d_6) 154.7 (s), 148.8 (s), 133.1 (d), 130.9 (d), 128.8 (d), 127.2 (d), 116.1 (s), 69.4 (s); *m/z* (EI) 220 (M^++2, 13%), 218 (M^+, 39), 189 (4), 176 (4), 153 (4), 126 (12), 111 (16), 99 (14), 85 (29), 77 ($C_6H_5^+$, 11), 71 (47), 63 (6), 57 (91).

3-Amino-5-(3-nitrophenyl)-1*H*-pyrazole-4-carbonitrile 128[328] **and 3-amino-5-(3-aminophenyl)-1*H*-pyrazole-4-carbonitrile 129**

Similar treatment of 3-amino-5-(3-nitrophenyl)isothiazole-4-carbonitrile **111** (61 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave two products. Chromatography (Hexane/Et_2O, 3:2) gave the title compound **128** (38 mg, 72%) as yellow plates, mp 251-252 ^{o}C (from

EtOH); (found C, 52.5, H, 3.0, N, 30.6. $C_{10}H_7N_5O_2$ requires C, 52.4; H, 3.1; N, 30.6%); λ_{max}(MeOH)/nm 234 (log ε 3.08), 254 (3.10); ν_{max}/cm^{-1} 3460w (NH_2), 3428w, 3396w, 3360w, 3207w (Ph CH), 2924w (Ph CH), 2854w (Ph CH), 2213m (C≡N), 1652m, 1627m, 1616m, 1597w, 1576w, 1532m, 1516m, 1511m, 1498m, 1351s, 1110w, 1072w, 998w, 900w, 893w, 879w, 822w, 798w, 792w, 748w, 736w, 715s; δ_H(300 MHz; DMSO-d_6) 12.42 (1H, s, N*H*), 8.61 (1H, dd, *J* 1.7, 1.65, Ph C*H*), 8.23 (2H, m, Ph C*H*), 7.76 (1H, t, *J* 8.1, Ph C*H*), 6.65 (2H, s, N*H*$_2$); δ_C(75 MHz; DMSO-d_6) 154.9 (s), 148.1 (s), 147.7 (s), 133.5 (s), 131.5 (d), 130.5 (d), 123.1 (d), 119.7 (d), 115.8 (s), 69.6 (s); *m/z* (EI) 229 (M^+, 100%), 183 (18), 156 (13), 141 (4), 129 (21), 114 (14), 101 (7), 99 (4), 77 ($C_6H_5^+$, 7), 63 (4). Further elution (Et_2O, 100%) gave *3-amino-5-(3-aminophenyl)-1*H*-pyrazole-4-carbonitrile* **129** as colorless needles (13 mg, 28 %), mp > 300 ^oC (from EtOH); (found: C, 60.4; H, 4.5; N, 35.2. $C_{10}H_9N_5$ requires C, 60.3; H, 4.55; N, 35.2%); λ_{max}(MeOH)/nm 207 (log ε 2.55), 265 (3.17); ν_{max}/cm^{-1} 3447m, 3330m (NH_2), 3250m, 3210m (NH), 2918w (Ph CH), 2851w (Ph CH), 2209s (C≡N), 1647s, 1636s, 1596s, 1517s, 1463m, 1448m, 1437m, 1333w, 1307w, 1265w, 1242w, 1074m, 1014w, 1008w, 926w, 900w, 878w, 797m, 727s; δ_H(300 MHz; DMSO-d_6) 12.18 (1H, s, N*H*), 7.08 (1H, t, *J* 7.6, Ph C*H*), 6.97 (1H, s, Ph C*H*), 6.91 (1H, d, *J* 7.5, Ph C*H*), 6.59 (1H, d, J 7.5, Ph C*H*), 6.11 (2H, s, N*H*$_2$), 5.22 (2H, s, C_6H_4 N*H*$_2$); δ_C(75MHz; DMSO-d_6) 148.8 (s), 131.7 (s), 129.1 (d), 128.7 (d), 128.6 (d), 116.1 (d), 114.5 (s), 113.4 (s), 111.0 (s), 71.0 (s); *m/z* (EI) 199 (M^+, 100%), 170 (19), 155 (10), 143 (14), 116 (9), 99 (6), 89 (7), 77 ($C_6H_5^+$, 4), 63 (6), 57 (5).

3-Chloro-5-(2,6-dimethylphenyl)isothiazole-4-carbonitrile 112

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **11** (100 mg, 0.56 mmol), 2,6-dimethylphenylboronic acid (226 mg, 1.51 mmol), KF (179 mg, 3.07 mmol), $Pd(OAc)_2$ (6 mg, 5 mol%) and 18-crown-6 (74 mg, 0.28 mmol, 0.5 equiv.) in dry and degassed DMF (2 mL) under an argon atmosphere, was heated to *ca.* 110 ^oC, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC, diluted with DCM and washed with H_2O. The organic layer was separated, dried and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1) gave the *title compound* **112** (42 mg, 30%) as colorless needles, mp 73-74 ^oC (from cyclohexane); (found: C, 58.2; H, 3.5; N, 11.3. $C_{12}H_9ClN_2S$ requires C, 58.0; H, 3.6; N, 11.3%); λ_{max}(DCM)/nm 228 (log ε 2.71), 268 (2.59), 298 (2.46); ν_{max}/cm^{-1} 2235w, 1514w, 1507w, 1463w, 1448w, 1420w, 1388w, 1381w, 1344m, 1309w, 1226w, 1169w, 1104w, 1043w, 833m, 811w, 779s, 737w, 723w, 705w; δ_H(300 MHz; $CDCl_3$) 7.35-7.30 (1H,

m, Ph C*H*), 7.2-7.18 (2H, m, Ph C*H*), 2.18 (6H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 176.9 (s), 150.5 (s), 136.1 (s), 130.9 (d), 128.2 (d), 125.7 (s), 110.8 (s), 109.4 (s), 20.2 (*C*H_3); *m/z* (EI) 250 (M^++2, 27%), 248 (M^+, 71), 233 (4), 213 (M^+-Cl, 100), 206 (6), 186 (36), 169 (10), 159 (9), 153 (12), 147 (7), 140 (17), 127 (16), 115 (20), 103 (12), 93 (27), 77 ($C_6H_5^+$, 50), 63 (31), 51 (35).

3-Amino-5-(2,6-dimethylphenyl)-1*H*-isothiazole-4-carbonitrile 130

A mixture of 3-chloro-5-(2,6-dimethylphenyl)isothiazole-4-carbonitrile **112** (61 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), protected with a $CaCl_2$ drying tube, was stirred at *ca.* 20 °C until no starting material remained (TLC). The reaction mixture was poured onto crushed ice and extracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 7:3) gave the *title compound* **130** (39 mg, 70%) as pale yellow crystals, mp 145 °C (from EtOH/H_2O); (found: C, 62.9; H, 4.8; N, 18.4. $C_{12}H_{11}N_3S$ requires C, 62.9; H, 4.8; N, 18.3%); λ_{max} (*t*-BuOMe)/nm 206 (log ε 3.99), 305 (3.92); ν_{max}/cm^{-1} 3408m and 3320w (NH_2), 3215w (NH), 2920w (CH_3), 2230m (C≡N), 1641m, 1551s, 1486m, 1464w, 1429w, 1396w, 1382w, 1313w, 1261w, 1227w, 1165w, 1117w, 1096w, 1037w, 964w, 892w, 843m, 776s, 743m, 725m; δ_H(300 MHz; DMSO-d_6) 7.35-7.30 (1H, m, Ph C*H*-4), 7.24-7.21 (2H, m, Ph C*H*-3 & 5), 6.96 (2H, br s, NH_2), 2.13 (6H, s, CH_3); δ_C(75 MHz; DMSO-d_6) 173.7 (s), 164.9 (s), 136.15 (s), 129.95 (d), 127.8 (d), 127.3 (s), 112.7 (s), 96.5 (s), 19.6 (*C*H_3); *m/z* (EI) 229 (M^+, 100%), 214 (8), 211 (10), 197 (6), 186 (18), 172 (8), 160 (9), 140 (8), 127 (9), 115 (10), 77 ($C_6H_5^+$, 8), 63 (5).

3-Chloro-5-(*N*-morpholino)isothiazole-4-carbonitrile 113

In a stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **11** (0.5 g, 2.8 mmol) in EtOH (50 mL) at *ca*. 20 °C, protected with a $CaCl_2$ drying tube, morpholine (0.49 g, 5.60 mmol) was added and the reaction mixture stirred at this temperature until no starting material remained (TLC). The precipitate which formed was collected by filtration to afford the *title compound* **113** (577 mg, 90%) as colorless needles, mp 129-129.5 °C (from cyclohexane); λ_{max}(DCM)/nm 229 (log ε 2.0), 280 (1.9); ν_{max}/cm^{-1} 2978w, 2914w, 2870w, 2210m (C≡N), 1558s, 1537s, 1506w, 1483s, 1466w, 1441m, 1387w, 1354w, 1341w, 1308m, 1294s, 1275m, 1250w, 1117s, 1065w, 1057w, 982m, 951s, 903w, 800m, 789m; δ_H(300 MHz; $CDCl_3$) 3.87-3.84 (4H, t, *J* 5.1, CH_2O), 3.60-3.57 (4H, t, J 4.9, CH_2N); δ_C(75 MHz; $CDCl_3$) 179.4 (s), 150.3

(s), 113.9 (s), 85.8 (s), 65.5 (*C*H_2O), 49.5 (*C*H_2N); *m/z* (EI) 231 (M^++2, 38%), 229 (M^+, 100), 214 (10), 194 (6), 171 (85), 164 (12), 144 (25), 109 (84), 82 (16), 57 (34).

3-Amino-5-(*N*-morpholino)-1*H*-pyrazole-4-carbonitrile 131

Similar treatment of 3-chloro-5-(*N*-morpholino)isothiazole-4-carbonitrile **113** (53 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **131** as colorless needles, mp 98.5-99.5 ^oC (from EtOH); (found C, 49.7; H, 5.8; N, 36.3. $C_8H_{11}N_5O$ requires C, 49.7; H, 5.7; N, 36.3%); λ_{max}(*t*-BuOMe)/nm 210 (log ε 3.08), 232 inf (2.72), 259 inf (2.10); ν_{max}/cm^{-1} 3381m, 3337w, 3275w, 3219w, 3177m, 3024w, 2951w, 2876w and 2832w (CH_2), 2207s (C≡N), 1668s, 1624s, 1607s, 1541s, 1520m, 1493s, 1445m, 1369m, 1335w, 1317w, 1310w, 1288w, 1269w, 1254m, 1186w, 1138w, 1115s, 1074w, 1047w, 1026m, 999w, 912s, 853w, 777w, 731m; δ_H(300 MHz; DMSO-d_6); 11.07 (1H, s, N*H*), 6.12 (2H, s, NH_2), 3.66 (4H, br s, CH_2N), 3.12 (4H, br s, CH_2O); δ_C(75 MHz; DMSO-d_6) 168.6 (s), 154.2 (s), 116.35 (s), 65.5 (*C*H_2O), 62.0 (s), 47.9 (*C*H_2N); *m/z* (EI) 193 (M^+, 73%), 178 (26), 162 (11), 149 (5), 135 (100), 122 (3), 108 (28), 92 (8), 80 (16), 79 (18), 66 (27), 57 (9).

3,5-Diamino-1*H*-pyrazole-4-carbonitrile 132

A mixture of 5-amino-3-chloroisothiazole-4-carbonitrile **20** (37 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at *ca*. 20 ^oC for 5 min until no starting material remained (TLC). The reaction mixture was poured onto crushed ice and the aqueous mixture was then evaporated. The residue obtained was passed through a short pad (2 cm) of silica that was then washed well with *t*-BuOMe. Removal of the volatiles gave the title compound **132** (24 mg, 84%) as colorless needles, mp 170-171 ^oC, (lit.,[331] 169-170 ^oC) (from EtOH); λ_{max}(*t*-BuOMe)/nm 276 (log ε 3.41); ν_{max}/cm^{-1} 3236w, 3212w and 3050w (NH), 1683m, 1666s, 1648m, 1631w, 1544s, 1437w, 1367m, 1289m, 1253s, 1117m, 1049m, 984w; δ_H(300 MHz; DMSO-d_6) 8.94 (1H, s, N*H*), 4.13 (2H, s, NH_2); δ_C(75 MHz; DMSO-d_6) 175.2 (s), 169.5 (s), 168.9 (s), (1 peak missing); *m/z* (EI) 123 (M^+, 12%), 97 (M^+-CN, 11), 83 (11), 74 (9), 69 (14), 57 (30), 55 (21).

3-Amino-1*H*-pyrazole-4-carbonitrile 133

A mixture of 3-chloro-5-hydrazinoisothiazole-4-carbonitrile **114** (40 mg, 0.23 mmol) in anhydrous hydrazine (2 mL), was stirred at *ca*. 110 °C until no starting material remained (TLC). The reaction mixture was allowed to cool to *ca*. 20 °C, poured onto crushed ice and extracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 1:1) gave 3,5-diamino-1*H*-pyrazole-4-carbonitrile **132** (25 mg, 86%) as colorless needles, mp 170-171 °C, (lit.,[331] 169-170 °C) (from EtOH), identical to that described above. Further elution (EtOAc, 100%), gave 3-amino-1*H*-pyrazole-4-carbonitrile **133** (3 mg, 13%) as a colorless powder, mp 173-174 °C (lit.,[332] 172 °C); δ_H(300 MHz; DMSO-d_6) 12.05 (1H, s, N*H*), 7.64 (2H, br & w, NH_2), 6.30 (1H, s, C*H*), identical to an authentic sample.

3-Amino-5-(*N*-phenylamino)-1*H*-pyrazole-4-carbonitrile 134

A mixture of 3-chloro-5-(*N*-phenylamino)isothiazole-4-carbonitrile **115** (54 mg, 0.23 mmol) and anhydrous hydrazine (2 mL), was stirred at *ca*. 110 °C until no starting material remained (TLC). The reaction mixture was allowed to cool to *ca*. 20 °C and was poured onto crushed ice. The aqueous mixture was then evaporated and the residue obtained was passed through a short pad (2 cm) of silica that was then washed well with *t*-BuOMe. Removal of the volatiles gave the title compound **134** (41 mg, 91%) as pink plates, mp 195-196 °C (lit.,[333] 205 °C) (EtOH/cyclohexane); λ_{max}(*t*-BuOMe)/nm 206 (log ε 3.54), 222 inf (3.43), 263 (3.49), 367 (1.73); ν_{max}/cm^{-1} 3463w, 3374w and 3304w (NH_2), 3202w, 3142w (Ph CH), 2214m (C≡N), 1624m, 1605m, 1582m, 1566m, 1547s, 1499m, 1483m, 1450w, 1395w, 1306w, 1246m, 1178w, 1130w, 1069w, 1051w, 1028w, 995w, 897w, 856w, 839w, 818w, 752m; δ_H(300 MHz; DMSO-d_6) 11.14 (1H, br s, N*H*), 8.31 (1H, br s, N*H*Ph), 7.44 (2H, app d, *J* 5.7, Ph *H*-2 & 6), 7.16 (2H, app t, *J* 7.2, Ph *H*-3 & 5), 6.75 (1H, app t, *J* 7.2, Ph *H*-4), 6.25 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 152.85 (s, br & w), 150.8 (s, br & w), 142.6 (s), 128.4 (d), 119.0 (d), 116.0 (d), 115.2 (s), 63.1 (s, br & w); *m/z* (EI) 199 (M^+, 56%), 170 (11), 169 (12), 144 (16), 129 (4), 117 (6), 104 (4), 98 (6), 92 ($C_6H_6N^+$, 4), 77 ($C_6H_5^+$, 23), 67 (7), 66 (9), 51 (17).

5-(*N*-Benzylamino)-3-chloroisothiazole-4-carbonitrile 116

To a stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **11** (500 mg, 2.80 mmol) in EtOH (20 mL) at *ca*. 0 °C, protected with a $CaCl_2$ drying tube, benzylamine (612 μL, 5.60 mmol) was added. The reaction mixture was allowed to warm to *ca*. 20 °C and stirred for 24 h until

no starting material remained (TLC). The precipitate which formed was collected by filtration to afford the *title compound* **116** (627 mg, 90%) as colorless needles, mp 159.5-161.5 °C (from cyclohexane); λ_{max}(*t*-BuOMe)/nm 228 (log ε 2.93), 269 (3.08); ν_{max}/cm^{-1} 3245m (NH), 3123w, 3008w, 2862w, 2225m (C≡N), 1582s, 1479s, 1454m, 1363m, 1351m, 1339w, 1296m, 1224w, 1072w, 1026s, 991w, 958w, 923w, 858w, 828w, 781m, 756s, 701s; δ_H(300 MHz; $CDCl_3$) 7.44-7.32 (5H, m, Ph *H*), 6.84 (1H, br s, N*H*), 4.39 (2H, d, *J* 5.4, CH_2); δ_C(75 MHz; $CDCl_3$) 179.4 (s), 148.2 (s), 134.0 (s), 129.1 (d), 128.8 (d), 128.0 (d), 112.6 (s), 85.95 (s), 51.3 (*C*H_2); m/*z* (EI) 251 (M^++2, 13%), 249 (M^+, 34), 91 ($PhCH_2^+$, 100), 77 ($C_6H_5^+$, 10), 65 (53), 51 (12).

3-Amino-5-(*N*-benzylamino)-1*H*-pyrazole-4-carbonitrile 135

Similar treatment of 5-(*N*-benzylamino)-3-chloroisothiazole-4-carbonitrile **116** (57 mg, 0.23 mmol) with anhydrous hydrazine (2 mL) gave the title compound **135** (45 mg, 92%) as a colorless powder, mp 142-143 °C (lit.,[330] 142 °C) (from EtOH); λ_{max}(*t*-BuOMe)/nm 236 (log ε 4.50), 250 inf (4.34), 294 inf (3.95), 336 inf (3.61); ν_{max}/cm^{-1} 3395w, 3335w, 3248w (NH), 3175w (Ar CH), 3129w (Ar CH), 2955w (Ar CH), 2922m (Ar CH), 2853w, 2205s (C≡N), 1612s, 1595m, 1560m, 1531m, 1499m, 1452m, 1416w, 1368w, 1348m, 1304w, 1248w, 1213w, 1142w, 1109w, 1080w, 1040w, 1028w, 984w, 804w, 754m, 721m; δ_H(300 MHz; DMSO-d_6) 10.68 (1H, s, N*H*), 7.28-7.19 (5H, m, PhC*H*), 6.30 (1H, s, N*H*), 5.73 (2H, s, NH_2), 4.24 (2H, s, CH_2); δ_C(75 MHz; DMSO-d_6) 155.7 (s), 154.7 (s), 141.3 (s), 128.85 (d), 128.1 (d), 127.3 (d), 116.9 (s), 55.7 (s), 46.7 (*C*H_2); *m/z* (EI) 213 (M^+, 6%), 149 (4), 123 (4), 106 (8), 98 (8), 91 ($PhCH_2^+$, 71), 83 (8), 77 ($C_6H_5^+$, 9), 65 (15), 57 (22).

3-Amino-5-methoxy-1*H*-pyrazole-4-carbonitrile 136

A mixture of 3-amino-5-methoxyisothiazole-4-carbonitrile **117** (45 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at *ca.* 20 °C until no starting material remained (TLC) and then poured onto crushed ice and extracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 1:1) gave 3-chloro-5-hydrazinoisothiazole-4-carbonitrile **114** (12 mg, 30%) as colorless needles, mp 151-152 °C (lit.,[32] 150 °C) (from cyclohexane), identical to an authentic sample. Further elution (EtOAc, 100%) gave the title compound **136** (32 mg, 65%) as colorless needles, mp 173-174 °C, (lit.,[334] 160-161 °C) (from pentane-EtOH); λ_{max}(*t*-BuOMe)/nm 221 (log ε 2.72); ν_{max}/cm^{-1} 3414w and 3337w (NH_2), 3225w, 3115w, 3105w, 3024w, 2992w, 2951w, 2895w and 2812w

(CH_3), 2210s (C≡N), 1634m, 1601w, 1568m, 1516s, 1458w, 1416m, 1368w, 1275w, 1196w, 1136w, 1105m, 1014w, 978w, 799m, 719m; δ_H(300 MHz; DMSO-d_6) 11.06 (1H, br s, N*H*), 6.37 (2H, br s, NH_2), 3.75 (3H, s, CH_3O); δ_C(75 MHz; DMSO-d_6) 162.7 (s), 154.1 (s), 115.4 (s), 60.7 (s), 56.0 (*C*H_3O); *m/z* (EI) 138 (M^+, 100%), 137 (M^+-1, 41), 123 (M^+-CH_3, 18), 109 (20), 93 (12), 81 (12), 67 (43), 66 (38).

3-Chloro-5-hydrazinylisothiazole-4-carbonitrile 114 (*via* 5-phenoxyisothiazole 118)

A mixture of 3-chloro-5-phenoxyisothiazole-4-carbonitrile **118** (54 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at *ca.* 20 °C until no starting material remained (TLC) and then poured onto crushed ice and extracted (DCM). The organic extracts were combined and evaporated to afford the title compound **114** (34 mg, 85%) as colorless needles, mp 151-152 °C (lit.,[32] 150 °C) (from cyclohexane), identical to that described above.

3-Chloro-5-hydrazinylisothiazole-4-carbonitrile 114 (*via* 5-thiophenoxyisothiazole 119)

A mixture of 3-chloro-5-phenoxyisothiazole-4-carbonitrile **119** (58 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at *ca.* 20 °C until no starting material remained (TLC) and then poured onto crushed ice and extracted (DCM). The organic extracts were combined and evaporated to afford the title compound **114** (36 mg, 90%) as colorless needles, mp 151-152 °C (lit.,[32] 150 °C) (from cyclohexane), identical to that described above.

3-Chloro-5-hydrazinylisothiazole-4-carbonitrile 114 (*via* 3,5-dichloroisothiazole 11)

A mixture of 3,5-dichloroisothiazole-4-carbonitrile **11** (41 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at *ca.* 20 °C until no starting material remained (TLC) and then poured onto crushed ice and extracted (DCM). The organic extracts were combined and evaporated to afford the title compound **114** (40 mg, 100%) as colorless needles, mp 151-152 °C (lit.,[32] 150 °C) (from cyclohexane), identical to that described above.

3-Amino-5-phenyl-1*H*-pyrazole 141

A mixture of 3-chloro-5-phenylisothiazole **137** (45 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was stirred at *ca*. 20 °C until no starting material remained (TLC). The reaction mixture was then poured onto crushed ice and extracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (hexane/EtOAc, 7:3) gave the title compound **141** (26 mg, 70%) as colorless needles, mp 124-126 °C (lit.,[335] 125 °C) (from

EtOH); λ_{max}(*t*-BuOMe)/nm 206 (log ε 4.13) 222 inf (3.98), 254 inf (3.74); ν_{max}/cm^{-1} 3327w, 3219m (NH), 3042w (NH_2), 2938w (Ph CH), 1697m, 1649s, 1593s, 1562s, 1501s, 1435w, 1366m, 1281m, 1265m, 1113w, 1016m, 945w, 922w; δ_H(300 MHz; DMSO-d_6) 2 peaks missing, 7.64-7.26 (3H, m, Ph C*H*), 5.77 (1H, s); δ_C(75 MHz; DMSO-d_6) 153.0 (s), 145.4 (s), 132.0 (s), 128.5 (d), 127.2 (d), 124.6 (d), 87.2 (s); m/*z* (EI) 159 (M^+, 17%), 130 (5), 116 (5), 103 (3), 77 ($C_6H_5^+$, 6), 74 (21), 58 (2).

Reaction of 4-bromo-3-chloro-5-phenylisothiazole 138 with anhydrous hydrazine (see Table 11)

A mixture of 4-bromo-3-chloro-5-phenylisothiazole **138** (63 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) was heated to *ca*. 110 ^{o}C until no starting material remained (TLC). The reaction mixture was allowed to cool to *ca*. 20 ^{o}C, poured onto crushed ice and extracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 9*:*1), gave 3-chloro-5-phenylisothiazole **137** (9 mg, 20%) as colorless needles, mp 50-51 ^{o}C (lit.,[37] 50-51 ^{o}C) (from pentane), identical to an authentic sample. Further elution (Hexane/EtOAc, 9*:*1) gave the 3-amino-4-bromo-5-phenylisothiazole **142** (32 mg, 55%) as pale yellow plates, mp 123-124 ^{o}C (lit.,[336] 126 ^{o}C) (from cyclohexane); λ_{max}(DCM)/nm 265 (log ε 4.33); ν_{max}/cm^{-1} 3446w (NH_2), 3286w, 3186w, 3171w, 3051w (Ph CH), 1623m, 1549w, 1498m, 1464w, 1444w, 1416m, 1333w, 1312w, 1080m, 1029w, 942w, 912w, 844s, 822w, 750s; δ_H(300 MHz; $CDCl_3$) 7.64-7.60 (2H, m, Ph C*H*), 7.51-7.46 (3H, m, Ph C*H*), 4.37 (2H, br s, NH_2); δ_C(75 MHz; $CDCl_3$) 162.1 (s), 160.6 (s), 130.4 (s), 130.4 (d), 129.4 (d), 128.6 (d), 94.6 (s); *m/z* (EI) 256 (M^++2, 100%), 254 (M^+, 99), 208 (5), 175 (M^+-Br, 6), 148 (8), 133 (31), 128 (39), 121 (13), 104 (5), 101 (7), 89 (28), 77 ($C_6H_5^+$, 16), 63 (9), 51 (19). Further elution (hexane-EtOAc, 9*:*1) gave *4-bromo-3-hydrazinyl-5-phenylisothiazole* **143** (10 mg, 16%) as colorless needles, mp 135.5-137.5 ^{o}C (from cyclohexane); (found C, 40.1; H, 2.9; N, 15.6. $C_9H_8BrN_3S$ requires C, 40.0; H, 3.0; N, 15.5%); λ_{max}(DCM)/nm 263.3 (log ε 2.76); ν_{max}/cm^{-1} 3300m (NH), 3242m, 3205w, 3058w and 3026w (Ph CH), 1622w, 1559s, 1516s, 1447w, 1343m, 1168w, 1148w, 1080m, 1030m, 974w, 937w, 908w, 858m, 831w, 813w, 743s; δ_H(300 MHz; DMSO-d_6) 7.84 (1H, br s, N*H*), 7.65-7.58 (2H, m, Ph *H*), 7.58-7.50 (3H, m, Ph *H*), 4.72 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) 164.5 (s), 159.0 (s), 130.0 (d), 129.6 (s), 129.2 (d), 127.9 (d), 92.5 (s); *m/z* (EI) 271 (M^++2, 100%), 269 (M^+, 90), 242 (9), 240 (9), 208 (16), 206 (M^+-H_3N_2S, 16), 173 (6), 161 (24), 148 (8), 133 (19), 128 (41), 127

(55), 121 (28), 115 (7), 102 (8), 101 (10), 100 (10), 89 (25), 77 ($C_6H_5^+$, 28), 63 (10). Further elution (EtOAc, 100%), gave 3-amino-5-phenyl-1*H*-pyrazole **141** (2.5 mg, 6%) as colorless needles, mp 124-126 °C (lit.,[335] 125 °C) (from EtOH) identical to that described above.

Stability of 4-bromo-3-hydrazinyl-5-phenylisothiazole 143 (Table 12)

A mixture of 4-bromo-3-hydrazinyl-5-phenylisothiazole **143** and degassed DCM (1 mL) was stirred at *ca*. 20 °C under an argon atmosphere. After 3 d the reaction mixture was adsorbed onto silica. Chromatography (Hexane/EtOAc, 9:1) gave 3-amino-4-bromo-5-phenylisothiazole **142** (11 mg, 56%) as pale yellow plates, mp 123-124 °C (lit.,[336] 126 °C) (from cyclohexane) identical to that described above. Further elution (Hexane/EtOAc, 9:1) gave 3-amino-5-phenylisothiazole **144** (5.6 mg, 43%) as colorless needles, mp 190-192 °C (lit.,[336] 194 °C) (from cyclohexane) λ_{max}(DCM)/nm 264 (log ε 4.41); ν_{max}/cm^{-1} 3300w, 3240w, 3206w (NH_2), 3059w, 3024w (Ph CH), 1701w, 1622m, 1558s, 1518s, 1497m, 1462w, 1441w, 1422w, 1395w, 1342w, 1167w, 1080m, 1030w, 974w, 907w, 858m, 833w, 818w, 750s, 743s, 729w; δ_H(300 MHz; $CDCl_3$) 7.55-7.52 (2H, m, Ph C*H*), 7.42-7.40 (3H, m, Ph C*H*), 6.73 (1H, s, isothiazole *H*-4), 4.66 (2H, s, NH_2); δ_C(75 MHz; $CDCl_3$) 167.2 (s), 165.1 (s), 131.1 (s), 130.3 (s), 129.6 (d), 126.8 (d), 108.9 (s); *m/z* (EI) 176 (M^+, 100%), 159 (2), 148 (2), 134 (5), 128 (47), 121 (5), 102 (10), 89 (10), 77 ($C_6H_5^+$, 12), 74 (16), 63 (5), 51 (8). Further elution (EtOAc, 100%) gave the starting 4-bromo-3-hydrazinyl-5-phenylisothiazole **143** identical to an authentic sample. Similar procedure was followed using an oxygen atmosphere.

Reaction of 4-bromo-3-hydrazinyl-5-phenylisothiazole 143 with anhydrous hydrazine (see Table 13)

A mixture of 4-bromo-3-hydrazinyl-5-phenylisothiazole **143** and anhydrous hydrazine (2 mL) was heated to *ca.* 110 °C until no starting material remained (TLC). The reaction mixture was poured onto crushed ice and extracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 1:1) gave 3-amino-5-phenylisothiazole **144** (16 mg, 39%) as colorless needles, mp 190-192 °C (lit.,[336] 194 °C) (from cyclohexane), identical to that described above. Further elution (EtOAc, 100%) gave 3-amino-5-phenyl-1*H*-pyrazole **141** (18 mg, 50%) as colorless needles, mp 124-126 °C (lit.,[335] 125 °C) (from EtOH) identical to that described above.

Reaction of 3-chloro-4,5-diphenylisothiazole 139 with anhydrous hydrazine (see Table 14)

A stirred mixture of 3-chloro-4,5-diphenylisothiazole **139** (50 mg, 0.185 mmol) and anhydrous hydrazine (2 mL) in a sealed tube, was introduced into a preheated Wood's metal bath at 150 ^{o}C and held at this temperature until no starting material remained (TLC). The mixture was allowed to cool to *ca*. 20 ^{o}C and poured onto crushed ice and extracted (EtOAc). The organic layer separated, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 9:1) gave 3-amino-4,5-diphenylisothiazole **145** (18 mg, 39%) as colorless needles, mp 130-131 ^{o}C, (lit.,[37] 130-131 ^{o}C) (from cyclohexane), identical to an authentic sample. Further elution (Hexane/EtOAc 1:1) gave *3-hydrazinyl-4,5-diphenylisothiazole* **146** as colorless needles, mp 124.5-125.5 ^{o}C (from cyclohexane). (found C, 67.45; H, 5.0; N, 15.75; $C_{15}H_{13}N_3S$ requires: C, 67.4; H, 4.9; N, 15.7%); λ_{max}(DCM)/nm 230 (log ε 3.32), 265 (3.14); ν_{max}/cm^{-1} 3337w, 3294w, 3142w, 1600w, 1576w, 1557w, 1542w, 1495m, 1464w, 1438w, 1357w, 1272w, 1156w, 1080w, 1057w, 986w, 975w, 968w, 874w, 772m, 54s, 735m; δ_H(300 MHz; DMSO-d$_6$) 7.39-6.98 (10H, m, Ph C*H*), 6.98 (1H, s, N*H*), 4.77 (2H, s, N*H*$_2$); δ_C(75 MHz; DMSO-d$_6$) (1 peak missing) 167.0 (s), 161.3 (s), 132.9 (s), 131.6 (d), 130.8 (d), 129.9 (d), 129.8 (d), 129.7 (d), 128.8 (d), 123.0 (s); *m/z* (EI) 267 (M$^+$, 100%), 249 (55), 236 (9), 218 (18), 204 (10), 190 (9), 178 (17), 165 (15), 152 (7), 121 (26), 104 (5), 89 (9), 77 ($C_6H_5^+$, 27), 63 (6), 51 (16). Further elution (EtOAc, 100%) gave 3-amino-4,5-diphenyl-1*H*-pyrazole **147** as colorless needles, mp 144-145 ^{o}C (lit.,[337] 147-148 ^{o}C) (from EtOH); λ_{max}(*t*-BuOMe)/nm 232 (log ε 3.83), 242 inf (3.81), 257 inf (3.79); ν_{max}/cm^{-1} 3360w, 3345w, 3252w, 3163w (NH$_2$), 2903w (Ph CH), 1603w, 1587w, 1568w, 1533w, 1520w, 1501m, 1476w, 1441w, 1425w, 1323w, 1312w, 1244w, 1180w, 1098w, 1072w, 1016m, 964w, 914w, 847w, 835w, 781m, 772m, 746m, 731m; δ_H(300 MHz; DMSO-d$_6$) 11.93 (1H, br s, N*H*), 7.35-7.13 (10H, m, Ph C*H*), 4.55 (2H, br s, N*H*$_2$); δ_C(75 MHz; DMSO-d$_6$) (3 peaks missing) 133.6 (s), 129.1 (d), 128.4 (d), 128.2 (d), 127.35 (d), 127.1 (d), 125.6 (d), 103.4 s, (w & br); *m/z* (EI) 235 (M$^+$, 100%), 218 (4), 206 (5), 190 (9), 178 (10), 165 (14), 152 (6), 139 (3), 128 (6), 117 (7), 104 (14), 89 (11), 77 ($C_6H_5^+$, 24), 63 (10), 51 (21).

3,5-Diphenylisothiazole 148

A stirred mixture of 4-bromo-3,5-diphenylisothiazole **149** (73 mg, 0.23 mmol) and anhydrous hydrazine (2 mL) in a sealed tube, was introduced into a preheated Wood's metal bath at

200 °C and was held at this temperature until no starting material remained (TLC). The reaction mixture was allowed to cool to *ca*. 20 °C and poured onto crushed ice to afford the title compound **148** as a white precipitate, mp 80-81 °C (lit.,[37] 80-81 °C) (from pentane), identical to an authentic sample.

4-Amino-3,5-diphenylpyrazole 152

A mixture of 4-amino-3,5-diphenylisothiazole **151** (50 mg, 0.2 mmol) and anhydrous hydrazine (2 mL) was stirred at *ca*. 150 °C until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 °C, poured onto crushed ice and extracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 1:1) gave the title compound **152** (9.4 mg, 20%, based on recovered starting material) as colorless needles, mp 200-202 °C (lit.,[338] 208 °C) (from EtOH); ν_{max}/cm^{-1} 3229w, 3211w, 3192w, 3055w, 2955w, 2924w, 2853w, 1730w, 1607m, 1587w, 1495m, 1458m, 1439m, 1364w, 1315w, 1294w, 1287w, 1221w, 1177m, 1074m, 1026m, 953s, 914m, 765s; δ_H(300 MHz; DMSO-d$_6$) 12.78 (1H, s, N*H*), 7.76-7.32 (10H, m, Ph C*H*), 4.0 (2H, s, N*H*$_2$); *m/z* (EI) 235 (M$^+$, 100%), 220 (8), 132 (17), 117 (6), 104 (81), 77 (50), 51 (19), identical to an authentic sample.

5,5'-Diphenyl-1*H*,1'*H*-3,3'-bipyrazole-4,4'-dicarbonitrile 161

A mixture of 5,5'-diphenyl-3,3'-biisothiazole-4,4'-dicarbonitrile **160** (50 mg, 0.14 mmol) and anhydrous hydrazine (2 mL) was stirred at *ca.* 110 °C until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 °C, poured onto crushed ice and extracted (EtOAc). The organic extracts were combined, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 7:3) gave the *title compound* **161** (29.5 mg, 65%) as a pale yellow powder, mp > 300 °C (from EtOH); λ_{max}(*t*-BuOMe)/nm 206 (log ε 4.43), 241 (4.32), 263 (4.32); ν_{max}/cm^{-1} 3191m, 3119w, 3026w (Ph CH), 2952w, 2924w, 2237s (C≡N), 1636w, 1559w, 1491w, 1475m, 1398w, 1368w, 1300w, 1279w, 1076m, 1039m, 1015m, 956s, 914w, 799m, 765m, 707m; δ_H(300 MHz; DMSO-d$_6$) 7.92-7.90 (4H, m, Ph C*H*), 7.66-7.59 (6H, m, Ph C*H*); δ_C(75 MHz; DMSO) 149.6 (s), 146.5 (s), 131.4 (d), 130.3 (d), 127.6 (d), 127.3 (s), 115.5 (s), 87.1 (s); *m/z* (EI) 336 (M$^+$, 60%), 307 (4), 280 (6), 251 (4), 194 (3), 177 (8), 149 (18), 127 (9), 104 (10), 89 (6), 77 ($C_6H_5^+$, 36), 64 (9), 57 (11) (Found: M$^+$, 336.1134. $C_{20}H_{12}N_6$ requires *M*, 336.1123).

Reaction of 3-chloro-5-phenylisothiazole 87 with methylhydrazine

A mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **87** (50 mg, 0.23 mmol) and methylhydrazine (1 mL) was stirred at *ca*. 20 ^{o}C until no starting material remained (TLC). The reaction mixture was then poured onto crushed ice and extracted (EtOAc). The organic layer was separated, dried and adsorbed onto silica. Chromatography (Hexane/EtOAc, 1:1) gave *3-(1-methylhydrazinyl)-5-phenylisothiazole-4-carbonitrile* **165** (22 mg, 42%) as yellow needles, mp 129.5-131 ^{o}C (from cyclohexane); (found C, 57.4; H, 4.2; N, 24.3. $C_{11}H_{10}N_4S$ requires C, 57.4; H, 4.4; N, 24.3%); λ_{max}(DCM)/nm 275 (log ε 2.88), 332 (2.19); ν_{max}/cm^{-1} 3324w (NH), 3219w, 3061w (Ph CH), 2975w, 2940w, 2222m (C≡N), 1629m, 1536s, 1502m, 1457w, 1446w, 1430w, 1404m, 1386w, 1337w, 1272m, 1249w, 1195w, 1180w, 1120m, 1080w, 1041m, 1030m, 1001w, 968w, 933m, 915w, 855s, 820m, 755s, 722s; δ_H(300 MHz; $CDCl_3$) 7.73-7.70 (2H, m, Ph C*H*), 7.51-7.49 (3H, m, Ph C*H*), 4.02 (2H, br s, NH_2), 3.32 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 176.3 (s), 168.9 (s), 131.1 (d), 129.3 (d), 128.7 (s), 127.5 (d), 115.2 (s), 94.8 (s), 43.0 (*C*H$_3$); *m/z* (EI) 230 (M$^+$, 100%), 214 (22), 201 (4), 187 (11), 159 (5), 153 (8), 128 (15), 121 (60), 114 (5), 104 (12), 77 ($C_6H_5^+$, 20). Further elution (EtOAc, 100%) gave 3-amino-1-methyl-5-phenyl-1*H*-pyrazole-4-carbonitrile **166** (12 mg, 27%), as colorless needles, mp 158-159 ^{o}C (lit.,[207] 158 ^{o}C) (from EtOH), found C, 66.7; H, 5.1; N, 28.3. $C_{11}H_{10}N_4$ requires C, 66.65; H, 5.1; N, 28.3 %; λ_{max}(EtOAc)/nm 252 (log ε 2.95); ν_{max}/cm^{-1} 3381m, 3311w (NH_2), 3213w (NH), 3034w (Ph CH), 2946w, 2220m (C≡N), 1638m, 1557m, 1533m, 1499m, 1479w, 1448w, 1428w, 1396w, 1314w, 1285w, 1248w, 1153w, 1078w, 1030w, 1002w, 931w, 896w, 854w, 779m, 771m, 741w, 715w, 700s; δ_H(300 MHz; $CDCl_3$) 7.52-7.43 (5H, m, Ph C*H*), 4.07 (2H, s, NH_2), 3.68 (3H, s, CH_3); δ_C(75 MHz; $CDCl_3$) 155.9 (s), 148.0 (s), 130.1 (d), 129.1 (d), 128.8 (d), 126.9 (s), 114.35 (s), 79.1 (s), 37.2 (*C*H$_3$); *m/z* (EI) 198 (M$^+$, 100%), 183 (1), 170 (5), 155 (9), 143 (2), 128 (17), 115 (2), 101 (5), 88 (2), 77 ($C_6H_5^+$, 15), 63 (3), 51 (9).

***tert*-Butyl 3-(4-cyano-5-phenylisothiazol-3-yl)carbazate 169**

A mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **23** (100 mg, 0.32 mmol), *tert*-butyl carbazate (84 mg, 0.64 mmol), CuI (61 mg, 0.32 mmol), Cs_2CO_3 (125.2 mg, 0.38 mmol), and 1,10-phenanthroline (6 mg, 0.03 mmol) in anhydrous DMF (4 mL) was stirred at 80 ^oC for 0.5 h. The reaction mixture was allowed to cool to *ca.* 20 ^oC, diluted with water and extracted with DCM (4 × 25 mL). The organic extracts were combined, adsorbed onto silica and chromatographed (Hexane/DCM, 3:7) to afford the *title compound* **169** (71 mg, 70%) as a colorless solid, mp 129.2-130.2 ^oC (from cyclohexane); (Found: C, 57.0; H, 5.1; N, 17.7. $C_{15}H_{16}N_4O_2S$ requires C, 56.9; H, 5.1; N, 17.7%); ν_{max}/cm^{-1} 3350w, 3239w, 2972w, 2932w, 2216w (C≡N), 1722s (C=O), 1526m, 1501m, 1481m, 1456w, 1395w, 1369m, 1358m, 1275m, 1254m, 1219m, 1157s, 1067w, 1049w, 1036w, 1001w, 964w, 935w, 880w, 847m, 797m, 770s, 758w, 725w; δ_H(300 MHz, CDCl3) 7.73-7.70 (2H, m, Ph C*H*), 7.53-7.47 (3H, m, Ph C*H*), 6.83 (1H, s, N*H*), 6.64 (1H, s, N*H*), 1.49 (9H, s, C*H*3); *m/z* (EI) 316 (M^+, 1%), 260 (35), 242 (16), 216 (M^+ - Boc, 100), 200 (7), 128 (8), 121 (21), 77 (11), 57 (99).

3,3'-Thiobis(5-phenylisothiazole-4-carbonitrile) 171

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **23** (100 mg, 0.32 mmol), *tert*-butyl carbazate (84 mg, 0.64 mmol), CuI (61 mg, 0.32 mmol), Cs_2CO_3 (125.2 mg, 0.38 mmol), and 1,10-phenanthroline (6 mg, 0.03 mmol) in anhydrous DMF (4 mL) gave the *title compound* **171** (88 mg, 70%) as a colorless solid, mp 244-245 ^oC (from cyclohexane), found: C, 59.7; H, 2.5; N, 13.9. $C_{20}H_{10}N_4S_3$ requires C, 59.7; H, 2.5; N, 13.9%; λ_{max}(DCM)/nm 231 (log ε 3.02), 286 (3.22); ν_{max}/cm^{-1} 3057w (Ar CH), 2228m (C≡N) 1512w, 1483s, 1445m, 1377w, 1327m, 1240w, 1194w, 1105w, 1045m, 1024w, 999w, 955w, 916w, 829m, 799w, 756s; δ_H(300 MHz, CDCl3) 7.80-7.77 (2H, m, Ph *H*), 7.61-7.52 (3H, m, Ph *H*); δ_C(75 MHz, CDCl3) 176.4 (s), 158.7 (s), 132. 1 (d), 129.8 (d), 127.5 (d), 127.48 (s), 112.4 (s), 107.3 (s); *m/z* (EI) 401 (M^+, 100%), 184 (6), 159 (10), 141 (8), 127 (17), 121 (16), 114 (9), 90 (11), 77 (22), 57 (13), 51 (11).

9.5 Compounds related to Chapter 5

3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-one 172; Typical Suzuki-Miyaura procedure (Table 16)

A stirred mixture of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol), phenylboronic acid (73.2 mg, 0.60 mmol, 2.2 equiv), K_2CO_3 (75.5 mg, 0.546 mmol, 2 equiv) and $Pd(Ph_3P)_4$ (15.8 mg, 0.0137 mmol, 5 mol%) in dioxane/H_2O (5:3, 0.8 mL) was heated at *ca.* 100 ^oC until no starting material remained (TLC). The reaction mixture was then allowed to cool to rt, diluted with DCM (10 mL), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1) gave the *title compound* **172** (65.1 mg, 91%) as yellow needles, mp 119-120 ^oC (from EtOH), R_f 0.49 (Hexane/DCM, 1:1); (found: C, 67.7; H, 3.8; N, 10.4. $C_{15}H_{10}N_2OS$ requires C, 67.7; H, 3.8; N, 10.5%); λ_{max}(DCM)/nm 237 (log ε 3.06), 248 inf (3.01), 348 (3.28); ν_{max}/cm^{-1} 3053w, 2924w, 2853w, 1624s, 1614s, 1601w, 1489w, 1443m, 1354m, 1285w, 1269m, 1159w, 1101w, 1076w, 1030w, 1001w, 914w, 845w, 808w, 797w; δ_H(500 MHz; $CDCl_3$) 8.16 (4H, d, *J* 6.5, Ph *H*), 7.52-7.46 (6H, m, Ph *H*); δ_C(125 MHz; $CDCl_3$) 165.3 (s), 160.9 (s), 134.5 (s), 131.1 (d), 128.9 (d), 128.3 (d); *m/z* (EI) 266 (M^+, 37%), 135 (100), 103 (26), 91 (7), 77 (26), 63 (3), 51 (12).

3,5-Di(*o*-tolyl)-4*H*-1,2,6-thiadiazin-4-one 173

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with *o*-tolylboronic acid (81.6 mg, 0.60 mmol) gave the *title compound* **173** (75.4 mg, 94%) as yellow needles, mp 144-145 ^oC (from cyclohexane), R_f 0.13 (Hexane/DCM, 7:3); (found: C, 69.2; H, 4.7; N, 9.3. $C_{17}H_{14}N_2OS$ requires C, 69.4; H, 4.8; N, 9.5%); λ_{max}(DCM)/nm 330 (log ε 3.93); ν_{max}/cm^{-1} 3017w, 2988w, 2926w, 1628s, 1616m, 1601w, 1470w, 1452w, 1429w, 1379w, 1341w, 1298w, 1275s, 1260s, 1200w, 1157w, 1117w, 1040w, 997w, 939w, 862w, 851w, 812w; δ_H(500 MHz; $CDCl_3$) 7.42 (2H, d, *J* 8.0, Ph *H*), 7.37 (2H, dd, *J* 7.5, 7.5, Ph *H*), 7.29-7.26 (4H, m, Ph *H*), 2.33 (6H, s, C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 165.8 (s), 163.7 (s), 136.5 (s), 134.6 (s), 130.7 (d), 130.1 (d), 129.0 (d), 125.7 (d), 20.3 (*C*H_3); *m/z* (EI) 294 (M^+, 26%), 169 (12), 149 (100), 116 (55), 89 (17), 77 (4), 69 (5), 63 (5), 51 (4).

3,5-Di(*m*-tolyl)-4*H*-1,2,6-thiadiazin-4-one 174

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with *m*-tolylboronic acid (81.6 mg, 0.60 mmol) gave the *title compound* **174** (73 mg, 91%) as yellow needles, mp 145-147 ^{o}C (from cyclohexane), R_f 0.35 (Hexane/DCM, 7:3); (found: C, 69.3; H, 4.7; N, 9.6. $C_{17}H_{14}N_2OS$ requires C, 69.4; H, 4.8; N, 9.5%); λ_{max}(DCM)/nm 244 (log ε 3.13), 351 (3.46); ν_{max}/cm^{-1} 3024w, 2918w, 1632s, 1624s, 1603w, 1576w, 1487w, 1460w, 1416w, 1331s, 1269s, 1186w, 1180w, 1128w, 1096w, 1047w, 997w, 920w, 891w, 880w, 856w, 822w, 804w, 764s; δ_H(500 MHz; $CDCl_3$) 7.95 (2H, d, *J* 8.0, Ph *H*), 7.36 (2H, dd, *J* 7.8, 7.8, Ph *H*), 7.31 (4H, d, *J* 7.5, Ph *H*), 2.43 (6H, s, C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 165.4 (s), 161.0 (s), 137.9 (s), 134.5 (s), 131.9 (d), 129.4 (d), 128.2 (d), 126.1 (d), 21.5 (*C*H$_3$); *m/z* (EI) 294 (M$^+$, 73%), 149 (100), 146 (15), 117 (43), 91 (24), 65 (11), 51 (4).

3,5-Di(*p*-tolyl)-4*H*-1,2,6-thiadiazin-4-one 175

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with *p*-tolylboronic acid (81.6 mg, 0.60 mmol) gave the *title compound* **175** (79.5 mg, 99%) as yellow needles, mp 202-204 ^{o}C (from cyclohexane), R_f 0.35 (Hexane/DCM, 7:3); (found: C, 69.4; H, 4.8; N, 9.5. $C_{17}H_{14}N_2OS$ requires C, 69.4; H, 4.8; N, 9.5%); λ_{max}(DCM)/nm 201 (log ε 4.80), 358 (4.12); ν_{max}/cm^{-1} 3037w, 2978w, 1626s, 1607m, 1504w, 1462w, 1400w, 1331s, 1306w, 1256m, 1186m, 1136w, 1125w, 1040w, 1020w, 999w, 885w, 833s, 779s, 743m, 729m; δ_H(500 MHz; $CDCl_3$) 8.11 (2H, d, *J* 8.0, Ph *H*), 7.29 (2H, d, *J* 8.5, Ph *H*), 2.44 (6H, s, C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 165.5 (s), 160.4 (s), 141.5 (s), 131.9 (s), 129.0 (d), 128.9 (d), 21.5 (*C*H$_3$); *m/z* (EI) 294 (M$^+$, 35%), 149 (100), 146 (6), 117 (24), 91 (17), 65 (5).

3,5-Di(2-methoxyphenyl)-4*H*-1,2,6-thiadiazin-4-one 176

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 2-methoxyphenylboronic acid (91.3 mg, 0.60 mmol) gave the *title compound* **176** (77.4 mg, 87%) as yellow needles, mp 128.5-129 ^{o}C (from cyclohexane), R_f 0.47 (Hexane/DCM, 1:1); (found: C, 62.4; H, 4.2; N, 8.6. $C_{17}H_{14}N_2O_3S$ requires C, 62.6; H, 4.3; N, 8.6%); λ_{max}(DCM)/nm 322 (log ε 4.02); ν_{max}/cm^{-1} 2961w, 2938w, 2832w, 1649m, 1595m, 1582w, 1497m, 1481m, 1458m, 1439w, 1429w, 1346w, 1298m, 1267s, 1248w, 1234w, 1184w, 1163w, 1119m, 1045w, 1026s, 1001w, 862w, 808m; δ_H(500 MHz; $CDCl_3$) 7.45-7.40 (4H, m, Ph *H*), 7.05 (2H, dd, *J* 7.5, 7.5, Ph *H*), 6.99 (2H, d, *J* 8.0, Ph *H*), 3.84 (6H, s, OC*H*$_3$); δ_C(125 MHz; $CDCl_3$) 163.3 (s), 163.3 (s), 157.2 (s), 131.6 (d), 130.1 (d), 125.0 (s), 120.8 (d), 111.5

(d), 55.9 (O*C*H$_3$); *m/z* (EI) 326 (M$^+$, 41%), 295 (12), 193 (13), 165 (100), 137 (29), 132 (42), 119 (33), 104 (16), 91 (33), 77 (7), 63 (9).

3,5-Di(3-methoxyphenyl)-4*H*-1,2,6-thiadiazin-4-one 177

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 3-methoxyphenylboronic acid (91.3 mg, 0.60 mmol) gave the *title compound* **177** (78.3 mg, 88%) as yellow needles, mp 66-67 ^{o}C (from cyclohexane), R_f 0.55 (Hexane/DCM, 7:3); (found: C, 62.6; H, 4.3; N, 8.6. $C_{17}H_{14}N_2O_3S$ requires C, 62.6; H, 4.3; N, 8.6%); λ_{max}(DCM)/nm 352 (log ε 3.96); ν_{max}/cm^{-1} 2943w, 2832w, 1732m, 1692w, 1626m, 1601m, 1582m, 1489m, 1466w, 1450w, 1429m, 1337m, 1287m, 1275m, 1244s, 1221m, 1200w, 1177m, 1159s, 1128w, 1086w, 1045m, 995w, 943w, 918w, 889w, 860m, 824w, 793w, 760s, 743w, 723m; δ_H(500 MHz; $CDCl_3$) 7.77 (2H, d, *J* 8.0, Ph *H*), 7.71 (2H, s, Ph *H*), 7.38 (2H, dd, *J* 8.0, 8.0, Ph *H*), 7.05 (2H, d, *J* 8.0, Ph *H*), 3.89 (6H, s, OC*H*$_3$); δ_C(125 MHz; $CDCl_3$) 165.3 (s), 160.5 (s), 159.4 (s), 135.7 (s), 129.3 (d), 121.5 (d), 117.5 (d), 113.8 (d), 55.4 (O*C*H$_3$); *m/z* (EI) 326 (M$^+$, 52%), 270 (53), 268 (87), 266 (54), 189 (20), 187 (20), 166 (12), 165 (100), 161 (28), 135 (11), 133 (41), 108 (42), 103 (16), 90 (8), 82 (35).

3,5-Di(4-methoxyphenyl)-4*H*-1,2,6-thiadiazin-4-one 178

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 4-methoxyphenylboronic acid (91.3 mg, 0.60 mmol) gave the *title compound* **178** (76.5 mg, 86%) as yellow needles, mp 169-171 ^{o}C (from cyclohexane), R_f 0.55 (Hexane/DCM, 1:1); (found: C, 62.4; H, 4.1; N, 8.5. $C_{17}H_{14}N_2O_3S$ requires C, 62.6; H, 4.3; N, 8.6%); λ_{max}(DCM)/nm 380 (log ε 4.15); ν_{max}/cm^{-1} 2963w, 2914w, 2841w, 1620s, 1595s, 1572w, 1503m, 1462w, 1441w, 1410w, 1331w, 1306m, 1265w, 1244s, 1180s, 1138m, 1121w, 1032m, 1011w, 995w, 870w, 841s, 827w, 812m, 781m; δ_H(500 MHz; $CDCl_3$) 8.22 (4H, d, *J* 9.0, Ph *H*), 6.97 (4H, d, *J* 8.5, Ph *H*), 3.87 (6H, s, OC*H*$_3$); δ_C(125 MHz; $CDCl_3$) 165.7 (s), 161.8 (s), 159.4 (s), 130.8 (d), 127.5 (s), 113.6 (d), 55.4 (O*C*H$_3$); *m/z* (EI) 326 (M$^+$, 51%), 165 (100), 150 (21), 133 (31), 122 (8), 103 (9), 90 (10), 63 (5).

3,5-Di(2-chlorophenyl)-4*H*-1,2,6-thiadiazin-4-one 179

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 2-chlorophenylboronic acid (93.8 mg, 0.60 mmol) gave the *title compound* **179** (73.4 mg, 80%) as yellow needles, mp 110-112 ^{o}C (from cyclohexane), R_f 0.10 (Hexane/DCM, 7:3); (found: C, 53.7; H, 2.4; N, 8.4. $C_{15}H_8Cl_2N_2OS$ requires C, 53.8; H, 2.4; N, 8.4%); λ_{max}(DCM)/nm 324 (log ε 3.92); ν_{max}/cm^{-1} 3011w, 2926w, 1638s, 1589w, 1503w, 1476w, 1437w, 1425w, 1346w, 1294w, 1273w, 1242w, 1074w, 1055w, 1042w, 999w, 945w, 847w, 802w; δ_H(500 MHz; $CDCl_3$) 7.48-7.47 (4H, m, Ph *H*), 7.41 (2H, dd, *J* 7.5, 7.5, Ph *H*), 7.37 (2H, dd, *J* 7.3, 7.3, Ph *H*); δ_C(125 MHz; $CDCl_3$) 163.5 (s), 162.5 (s), 133.9 (s), 132.7 (s), 131.3 (d), 130.4 (d), 129.9 (d), 126.8 (d); *m/z* (EI) 301 (M^++2-Cl, 35%), 299 (M^+-Cl, 100), 171 (32), 169 (85), 139 (15), 137 (39), 134 (19), 111 (8), 102 (26), 90 (4), 75 (19), 57 (5), 50 (8).

3,5-Di(3-chlorophenyl)-4*H*-1,2,6-thiadiazin-4-one 180

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 3-chlorophenylboronic acid (93.8 mg, 0.60 mmol) gave the *title compound* **180** (74 mg, 81%) as yellow needles, mp 148-149 ^{o}C (from cyclohexane), R_f 0.38 (Hexane/DCM, 7:3); (found: C, 53.8; H, 2.5; N, 8.3. $C_{15}H_8Cl_2N_2OS$ requires C, 53.8; H, 2.4; N, 8.4%); λ_{max}(DCM)/nm 350 (log ε 4.05); ν_{max}/cm^{-1} 3076w, 1624m, 1614m, 1572w, 1493w, 1476w, 1423w, 1414w, 1344w, 1287w, 1258w, 1163w, 1098w, 1082w, 1024w, 999w, 878w, 854w, 822w, 810w, 772s; δ_H(500 MHz; $CDCl_3$) 8.19 (2H, s, Ph *H*), 8.09 (2H, d, *J* 8.0, Ph *H*), 7.48 (2H, d, *J* 8.0, Ph *H*), 7.41 (2H, dd, *J* 8.0, 8.0, Ph *H*) ; δ_C(125 MHz; $CDCl_3$) 164.7 (s), 159.5 (s), 135.7 (s), 134.4 (s), 131.3 (d), 129.5 (d), 129.0 (d), 127.1 (d); *m/z* (EI) 336 (M^++2, 16%), 334 (M^+, 21), 171 (35), 169 (100), 149 (5), 139 (8), 137 (27), 134 (7), 111 (9), 102 (14), 75 (12), 51 (5).

3,5-Di(4-chlorophenyl)-4*H*-1,2,6-thiadiazin-4-one 181

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 4-chlorophenylboronic acid (93.8 mg, 0.60 mmol) gave the *title compound* **181** (81.1 mg, 89%) as yellow needles, mp 220-222 ^{o}C (from cyclohexane), R_f 0.38 (Hexane/DCM, 7:3); (found: C, 53.9; H, 2.4; N, 8.3. $C_{15}H_8Cl_2N_2OS$ requires C, 53.8; H, 2.4; N, 8.4%); λ_{max}(DCM)/nm 356 (log ε 4.20); ν_{max}/cm^{-1} 3071w, 2930w, 1618m, 1591m, 1489w, 1474w, 1396w, 1342w, 1271w, 1180w, 1090m, 1015w, 1001w, 829m, 787s; δ_H(500 MHz; $CDCl_3$) 8.16 (4H, d, *J* 8.5, Ph *H*), 7.44 (4H, d, *J* 8.5, Ph *H*); δ_C(125 MHz; $CDCl_3$) 165.0 (s), 159.6 (s),

137.6 (s), 132.7 (s), 130.4 (d), 128.6 (d); *m/z* (EI) 336 (M^++2, 21%), 334 (M^+, 28), 170 (9), 169 (100), 139 (11), 137 (34), 111 (10), 102 (17), 75 (13).

3,5-Di(3-nitrophenyl)-4*H*-1,2,6-thiadiazin-4-one 182

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 3-nitrophenylboronic acid (136.7 mg, 0.82 mmol) gave the *title compound* **182** (62.3 mg, 64%) as yellow needles, mp 176-177 ^oC (from cyclohexane), R_f 0.53 (Hexane/DCM, 7:3); (found: C, 50.6; H, 2.2; N, 15.8. $C_{15}H_8N_4O_5S$ requires C, 50.6; H, 2.3; N, 15.7%); λ_{max}(DCM)/nm 213 (log ε 4.28), 348 (4.10); ν_{max}/cm^{-1} 3094w, 1634m, 1611w, 1510s, 1476w, 1433w, 1343s, 1283m, 1267w, 1090w, 910w, 903w, 878w, 847w, 812w, 797w, 752w, 727s, 694w; δ_H(500 MHz; $CDCl_3$) 8.81 (2H, s, Ph *H*), 8.31 (2H, d, *J* 8.0, Ph *H*), 8.09 (2H, d, *J* 7.5, Ph H), 7.45 (2H, dd, *J* 8.0, 8.0, Ph *H*); δ_C(125 MHz; $CDCl_3$) 164.4 (s), 158.9 (s), 148.2 (s), 135.3 (s), 134.8 (d), 129.5 (d), 125.9 (d), 124.2 (d); *m/z* (EI) 356 (M^+, 27%), 180 (100), 134 (37), 107 (9), 102 (9), 90 (23), 75 (8), 63 (9), 51 (5).

3,5-Di(thien-3-yl)-4*H*-1,2,6-thiadiazin-4-one 183

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 3-thienylboronic acid (76.7 mg, 0.60 mmol) gave the *title compound* **183** (74.4 mg, 98%) as yellow needles, mp 167-169 ^oC (from cyclohexane), R_f 0.40 (Hexane/DCM, 7:3); (found: C, 47.5; H, 2.1; N, 10.0. $C_{11}H_6N_2OS_3$ requires C, 47.5; H, 2.2; N, 10.1%); λ_{max}(DCM)/nm 373 (log ε 3.08); ν_{max}/cm^{-1} 3136w, 1628m, 1512m, 1460w, 1422w, 1319m, 1258w, 1196w, 1161m, 1119w, 1080w, 939w, 908w, 899w, 883m, 851w, 843w, 822m, 776s, 729m, 721m, 710m; δ_H(500 MHz; $CDCl_3$) 8.89 (2H, d, *J* 3.0, thienyl *H*-2), 7.84 (2H, d, *J* 5.0, thienyl *H*-4 or 5), 7.35 (2H, dd, *J* 4.5, 3.0, thienyl *H*-4 or 5); δ_C(125 MHz; $CDCl_3$) 163.8 (s), 155.4 (s), 136.3 (s), 131.7 (d), 127.7 (d), 125.1 (d); *m/z* (EI) 278 (M^+, 58%), 141 (100), 109 (30), 97 (7), 83 (5), 64 (5), 45 (21).

3,5-Di(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one 184

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 2-thienylboronic acid (104.8 mg, 0.82 mmol) gave the *title compound* **184** (68.3 mg, 90%) as yellow needles, mp 175-177 ^oC (from cyclohexane); R_f 0.42 (Hexane/DCM, 7:3); (found: C, 47.5; H, 2.1; N, 10.1. $C_{11}H_6N_2OS_3$ requires C, 47.5; H, 2.2; N, 10.1%); λ_{max}(DCM)/nm 261

(log ε 4.03), 327 (3.74), 369 inf (4.11), 388 inf (4.30), 406 (4.40), 430 (4.31); ν_{max}/cm^{-1} 3103w, 1614s, 1574w, 1504m, 1450m, 1410s, 1385s, 1350w, 1263m, 1223m, 1080m, 1045m, 997m, 914w, 874m, 853s, 814m, 787w, 739s, 731s, 716s; δ_H(500 MHz; $CDCl_3$) 8.28 (2H, d, *J* 4.0, thienyl *H*-3), 7.64 (2H, d, *J* 5.0, thienyl *H*-5), 7.19 (2H, dd, *J* 4.5, 4.0, thienyl *H*-4); δ_C(125 MHz; $CDCl_3$) 161.3 (s), 154.1 (s), 136.4 (s), 133.2 (d), 132.1 (d), 127.7 (d); *m/z* (EI) 278 (M^+, 49%), 141 (100), 114 (6), 109 (36), 97 (8), 83 (6), 71 (11), 64 (7), 58 (14).

3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-one 172; Typical Stille procedure (Table 17)

To a stirred mixture of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) and $(Ph_3P)_2PdCl_2$ (9.6 mg, 0.0137 mmol) in MeCN (2 mL) at *ca.* 20 ^oC protected with a $CaCl_2$ drying tube, tributylphenyltin (220 mg, 0.60 mmol) was added. The mixture was then heated to *ca.* 100 ^oC until no starting material remained (by TLC). The reaction mixture was then cooled to *ca.* 20 ^oC and adsorbed onto silica. Dry flash chromatography (Hexane/DCM, 7:3) gave the title compound **172** (68 mg, 95%) as yellow needles, identical to that described above.

3,5-Di(fur-2-yl)-4*H*-1,2,6-thiadiazin-4-one 185

Similar treatment of of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 2-(tributylstannyl)furan (224 mg, 0.60 mmol) gave the *title compound* **185** (61 mg, 92%) as yellow needles, mp 167-168 ^oC (from cyclohexane); R_f 0.30 (Hexane/DCM, 7:3); (found: C, 53.6; H, 2.5; N, 11.5. $C_{11}H_6N_2O_3S$ requires C, 53.7; H, 2.5; N, 11.4%); λ_{max}(DCM)/nm 250 (log ε 3.14), 288 (2.70), 319 inf (2.89), 329 (2.96), 381 (3.53), 394 (3.53), 415 (3.48); ν_{max}/cm^{-1} 3165w, 3132w, 3115w, 1628s, 1560m, 1483s, 1439w, 1400m, 1350w, 1306w, 1287m, 1223w, 1213w, 1200w, 1165w, 1142w, 1082w, 1045s, 1016s, 997m, 918w, 883s, 866m, 835m, 785s, 773s; δ_H(500 MHz; $CDCl_3$) 7.88 (2H, d, *J* 3.5, furyl *H*), 7.68 (2H, br s, furyl *H*), 6.62 (2H, dd, *J* 3.3, 1.3, furyl *H*); δ_C(125 MHz; $CDCl_3$) 159.9 (s), 149.7 (s), 147.7 (s), 146.3 (d), 119.9 (d), 112.8 (d); *m/z* (EI) 246 (M^+, 82%), 125 (100), 97 (14), 93 (16), 70 (13), 64 (10), 51 (4).

3,5-Di(*N*-methylpyrrol-2-yl)-4*H*-1,2,6-thiadiazin-4-one 186

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 1-methyl-2-(tributylstannyl)pyrrole (222 mg, 0.60 mmol gave the *title compound* **186** (68 mg, 93%) as yellow needles, mp 171-172 ^oC (from PhH); R_f 0.30 (Hexane/DCM, 7:3); (found: C,

57.4; H, 4.4; N, 20.5. $C_{13}H_{12}N_4OS$ requires C, 57.3; H, 4.4; N, 20.6%); λ_{max}(DCM)/nm 232 (log ε 3.76), 261 (3.98), 407 (4.37), 430 inf (4.24); ν_{max}/cm^{-1} 3121w, 3107w, 2996w, 2949w, 1618s, 1522m, 1485s, 1462m, 1406s, 1362m, 1313m, 1267w, 1223w, 1148w, 1097w, 1061s, 1043w, 903w, 872w, 849w, 822w, 789w, 741s, 733s, 710s; δ_H(500 MHz; $CDCl_3$) 7.59 (2H, dd, *J* 4.0, 2.0, pyrrole *H*-5 or 3), 6.83 (2H, dd, *J* 2.0, 2.0, pyrrole *H*-3 or 5), 6.21 (2H, dd, *J* 4.0, 2.5, pyrrole *H*-4), 3.94 (6H, s, C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 162.5 (s), 152.0 (s), 130.0 (d), 126.8 (s), 119.1 (d), 108.1 (d), 38.3 (N*C*H$_3$); *m/z* (EI) 272 (M$^+$, 87%), 138 (100), 123 (5), 110 (10), 106 (47), 97 (4), 78 (8), 64 (4), 52 (5).

3,5-Bis(5-bromothien-2-yl)-4*H*-1,2,6-thiadiazin-4-one 187

To a stirred mixture of 3,5-di(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one **184** (0.50 g, 1.80 mmol) in glacial AcOH (5 mL) cooled to *ca*. 13-15 ^oC using an ice-water bath, Br_2 (0.57 g, 3.60 mmol) was added and the mixture was kept at *ca*. 15 ^oC for 7 h until no starting material remained (by TLC). The reaction mixture was allowed to warm to *ca*. 20 ^oC and diluted with water and extracted with DCM. The organic layer was separated, dried (Na_2SO_4), evaporated on rotary evaporator with the bath's temperature not exceeding 35 ^oC and then adsorbed onto silica. Dry flash chromatography (Hexane/DCM, 7:3) gave the *title compound* **187** (80%) as yellow needles, mp 200-203 ^oC (from cyclohexane); R_f 0.50 (Hexane/DCM, 7:3) (found: C, 30.4; H, 0.8; N, 6.4. $C_{11}H_4Br_2N_2OS_3$ requires C, 30.3; H, 0.9; N, 6.4%); λ_{max}(DCM)/nm 269 (log ε 3.80), 345 (3.62), 384 inf (3.90), 402 inf (4.11), 421 (4.22), 445 (4.18); ν_{max}/cm^{-1} 3090w, 1604m, 1582m, 1508w, 1439w, 1402s, 1387m, 1055w, 999w, 808s, 783m, 743m; δ_H(500 MHz; CD_2Cl_2) 7.98 (2H, d, *J* 4.0, thienyl *H*), 7.21 (2H, d, *J* 4.0, thienyl *H*); δ_C(125 MHz; CD_2Cl_2) 161.4 (s), 153.4 (s), 137.3 (s), 132.4 (d), 131.3 (d), 122.6 (s); *m/z* (EI) 438 (M$^+$+4, 53%), 436 (M$^+$+2, 89), 434 (M$^+$, 45), 221 (100), 219 (94), 189 (37), 187 (37), 178 (4), 177 (3), 140 (47), 108 (16), 96 (28), 82 (15), 69 (12), 64 (30), 57 (11).

3,5-Bis[(2,2'-bithien)-5-yl]-4*H*-1,2,6-thiadiazin-4-one 188

To a stirred mixture of 3,5-bis(5-bromothien-2-yl)-4*H*-1,2,6-thiadiazin-4-one **187** (0.10 g, 0.23 mmol) and $(Ph_3P)_2PdCl_2$ (37 mg, 0.045 mmol) in MeCN (4 mL) at *ca.* 20 ^oC protected with a $CaCl_2$ drying tube, 2-(tributylstannyl)thiophene (371 mg, 0.99 mmol) was added. The mixture was heated to *ca.* 100 ^oC (reflux) until no starting material remained (by TLC). The reaction mixture was then cooled to *ca.* 20 ^oC and adsorbed onto silica. Dry flash chromatography

(Hexane/DCM, 7:3) gave the *title compound* **188** (95%) as red-brown plates, mp 164-167 ^{o}C (from PhH); R_f 0.70 (Hexane/DCM, 1:1); (found: C, 51.7; H, 2.2; N, 6.5. $C_{19}H_{10}N_2OS_5$ requires C, 51.6; H, 2.2; N, 6.6%); λ_{max}(DCM)/nm 231 (log ε 4.02), 292 (4.12), 358 (3.92), 399 inf (4.08), 451 inf (4.41), 477 (4.53), 498 inf (4.51); ν_{max}/cm^{-1} 3109w, 1616m, 1608m, 1495w, 1431s, 1414m, 1387s, 1356w, 1329w, 1227m, 1161w, 1047m, 997w, 839s, 808s, 783m, 739s; δ_H(500 MHz; $CDCl_3$) 8.14 (2H, d, *J* 4.0, thienyl *H*), 7.36 (2H, d, *J* 3.5, thienyl *H*), 7.31 (2H, d, *J* 4.5, thienyl *H*), 7.25 (2H, d, *J* 4.0, thienyl *H*), 7.06 (2H, dd, *J* 5.0, 4.0, thienyl *H*); δ_C(125 MHz; $CDCl_3$) 161.3 (s), 153.2 (s), 145.1 (s), 136.9 (s), 134.4 (s), 133.0 (d), 128.2 (d), 125.9 (d), 125.0 (d), 124.2 (d); *m/z* (EI) 442 (M$^+$, 100%), 223 (62), 191 (62), 159 (9), 146 (11), 121 (14), 69 (8).

3,5-Bis(5'-bromo-[2,2'-bithiophen]-5-yl)-4*H*-1,2,6-thiadiazin-4-one 189

To a stirred mixture of 3,5-bis[(2,2'-bithien)-5-yl]-4*H*-1,2,6-thiadiazin-4-one **188** (0.50 g, 0.23 mmol) in glacial AcOH (5 mL) cooled to *ca*. 13-15 ^{o}C using an ice-water bath, Br_2 (23.6 μl, 0.46 mmol) was added and the mixture was kept at *ca*. 15 ^{o}C for 7 h until no starting material remained (by TLC). The reaction mixture was allowed to warm to *ca*. 20 ^{o}C and diluted with water and extracted with DCM. The organic layer was separated, dried (Na_2SO_4), evaporated on rotary evaporator with the bath's temperature not exceeding 35 ^{o}C and then adsorbed onto silica. Dry flash chromatography (Hexane/DCM, 7:3) gave the *title compound* **189** (80%) as dark orange powder, mp 276-277 ^{o}C (from PhCl); R_f 0.53 (Hexane/DCM, 7:3) (found: C, 38.1; H, 1.4; N, 4.8. $C_{19}H_8Br_2N_2OS_5$ requires C, 38.0; H, 1.3; N, 4.7%); λ_{max}(DCM)/nm 296 (log ε 2.08), 376 (3.17), 482 (3.72), 500 inf (3.69); ν_{max}/cm^{-1} 3075w (Ar CH), 1616m, 1506w, 1441s, 1427m, 1354w, 1292w, 1275w, 1236m, 1219w, 1171w, 1142w, 1128w, 1076w, 1047w, 972w, 883w, 872w, 806m, 777s, 745w, 729w; The sample was insoluble in common deuterated solvents and NMR data could not be collected. *m/z* (EI) 604 (M$^+$+4, 2%), 602 (M$^+$+2, 9), 600 (M$^+$, 13), 522 (19), 520 (14), 271 (12), 269 (11), 223 (14), 191 (13), 177 (9), 146 (22), 91 (6), 69 (7).

3,5-Bis(4-dodecylthiophen-2-yl)-4*H*-1,2,6-thiadiazin-4-one 190

To a solution of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) in MeCN (2 mL) at rt, were added (4-dodecylthiophen-2-yl)trimethylstannane (249 mg, 0.60 mmol) and $Pd(Ph_3P)_2Cl_2$ (9.6 mg, 0.014 mmol) and the reaction was heated at reflux until no starting material remained (TLC). The reaction mixture was then left to cool at rt, diluted (DCM) and

adsorbed onto silica. Chromatography (Hexane/DCM, 7:3) gave the *title compound* **190** (156 mg, 93%) as yellow needles, mp 65.5-67 ^{o}C (from pentane); R_f 0.70 (Hexane/DCM, 7:3); (found: C, 68.4; H, 8.8; N, 4.5. $C_{35}H_{54}N_2OS_3$ requires C, 68.4; H, 8.9; N, 4.6%); λ_{max}(DCM)/nm 229 (log ε 3.40), 265 (3.59), 356 inf (3.36), 382 (3.65), 399 inf (3.75), 415 (3.82), 439 (3.81); ν_{max}/cm^{-1} 2955w, 2918s, 2851m, 1616m, 1464m, 1412m, 1393w, 1341w, 1250w, 1236w, 1225w, 1200w, 1188w, 1103w, 953w, 876w, 864m, 816w, 791w, 764w; δ_H(500 MHz; $CDCl_3$) 8.11 (1H, s, thienyl *H*), 7,24 (1H, s, thienyl *H*), 2.67-2.62 (2H, m), 1.26 (20H, br s), 0.88 (3H, t, *J* 11.0, C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 161.5 (s), 153.9 (s), 144.2 (s), 136.3 (s), 133.3 (d), 128.6 (d), 31.91, 30.5, 30.4, 29.7, 29.65, 29.6, 29.4, 29.35, 29.3, 22.7, 14.1 (C*H*$_3$); *m/z* (EI) 615 (M^++1, 41%), 614 (M^+, 100), 460 (24), 306 (10), 276 (7), 168 (5), 155 (10), 149 (13), 137 (10), 125 (11), 122 (43), 111 (16), 109 (14), 97 (29), 95 (19), 83 (22), 71 (28), 57 (49).

3,5-Bis(5-bromo-4-dodecylthiophen-2-yl)-4*H*-1,2,6-thiadiazin-4-one 191

To a stirred solution of 3,5-bis(4-dodecylthiophen-2-yl)-4*H*-1,2,6-thiadiazin-4-one **190** (100 mg, 0.16 mmol) in THF (4 mL) at rt was added NBS (64 mg, 0.36 mmol) and stirred in dark overnight. The reaction mixture was then diluted (DCM), washed (H_2O) and dried (Na_2SO_4) to give the *title compound* **191** (103 mg, 83%) as yellow platess, mp 102-104 ^{o}C (from pentane); R_f 0.70 (Hexane/DCM, 7:3); (found: C, 54.5; H, 6.6; N, 3.7. $C_{35}H_{52}Br_2N_2OS_3$ requires C, 54.4; H, 6.8; N, 3.6%); λ_{max}(DCM)/nm 272 (log ε 3.33), 363 (3.23), 415 inf (3.66), 430 (3.75), 455 (3.73); ν_{max}/cm^{-1} 2955w, 2922s, 2851m, 1597s, 1576w, 1535w, 1458m, 1441m, 1422s, 1381m, 1348w, 1339w, 1215w, 1188w, 1123w, 1088w, 1022w, 858m; δ_H(500 MHz; $CDCl_3$) 7.90 (1H, s, thienyl *H*), 2.60 (2H, t, *J* 7.8), 1.62 (2H, t, *J* 7.0), 1.33-1.26 (19H, m), 0.88 (3H, t, *J* 6.7, C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 161.1 (s), 152.8 (s), 143.1 (s), 135.0 (s), 132.3 (d), 119.8 (s), 31.9, 29.7, 29.6, 29.55, 29.5, 29.4, 29.35, 29.2, 22.7, 14.1 (C*H*$_3$); *m/z* (EI) 776 (M^++4, 9%), 774 (M^++2, 50), 772 (M^+, 75), 693 (10), 579 (6), 499 (5), 458 (10), 345 (15), 308 (12), 202 (21), 162 (7), 154 (8), 135 (7), 122 (22), 97 (9), 83 (7), 71 (12), 69 (19), 57 (46).

3,5-Bis(phenylethynyl)-4*H*-1,2,6-thiadiazin-4-one 193; Typical Sonogashira procedure (Table 18)

To a stirred mixture of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol), CuI (5.2 mg, 0.0273 mmol) and $(Ph_3P)_2PdCl_2$ (9.6 mg, 0.0137 mmol) in MeCN (2 mL) at *ca.* 20 °C protected with a $CaCl_2$ drying tube, phenylacetylene (61.3 mg, 0.60 mmol) and Et_3N (151.4 μL, 1.09 mmol) were added. The mixture was then heated to *ca.* 100 °C until no starting material remained (by TLC). The reaction mixture was then cooled to *ca.* 20 °C and adsorbed onto silica. Dry flash chromatography (Hexane/DCM, 7:3) gave the *title compound* **193** (62 mg, 73%) as yellow needles, mp 187-188 °C (1,2-DCE, fridge); R_f 0.38 (Hexane/DCM, 7:3); (found: C, 72.5; H, 3.2; N, 8.8. $C_{19}H_{10}N_2OS$ requires C, 72.6; H, 3.2; N, 8.9%); λ_{max}(DCM)/nm 248 (log ε 3.35), 264 (3.28), 283 inf (3.12), 336 inf (3.29), 382 (3.64), 388 (3.62), 401 (3.63), 420 inf (3.46); ν_{max}/cm^{-1} 2197m (C≡C), 1641s, 1570w, 1493m, 1462w, 1443w, 1349s, 1310w, 1283w, 1212w, 1173w, 1129m, 1069w, 1026w, 996w, 976w, 924w, 915w, 880w, 835m, 763s; δ_H(500 MHz; $CDCl_3$) 7.66 (2H, d, *J* 8.0, Ph *H*), 7.46 (1H, dd, *J* 7.0, 7.0, Ph *H*), 7.40 (1H, dd, *J* 8.0, 7.0, Ph *H*); δ_C(125 MHz; $CDCl_3$) 162.5 (s), 147.9 (s), 132.8 (d), 130.6 (d), 128.6 (d), 120.8 (s), 102.3 (s), 83.7 (s); *m/z* (EI) 314 (M^+, 40%), 159 (100), 127 (53), 115 (8), 100 (10), 88 (3), 76 (6), 63 (4), 51 (4).

3,5-Bis(thien-3-ylethynyl)-4*H*-1,2,6-thiadiazin-4-one 194

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 3-ethynylthiophene (64.8 mg, 0.60 mmol) gave the *title compound* **194** (60.8 mg, 69%) as yellow plates, mp > 300 °C (dec.) (1,2-DCE, fridge); R_f 0.35 (Hexane/DCM, 7:3); (found: C, 72.5; H, 3.2; N, 8.8. $C_{19}H_{10}N_2OS$ requires C, 72.6; H, 3.2; N, 8.9%); λ_{max}(DCM)/nm 257 (log ε 3.38), 346 (3.40), 381 (3.65), 396 (3.63), 405 (3.65), 425 (3.58); ν_{max}/cm^{-1} 3102w, 2922w, 2853w, 2199s (C≡C), 1643s, 1456w, 1362m, 1339m, 1277w, 1227w, 1204w, 1119w, 1001m, 959w, 943w, 868m, 835w, 804m, 781s; δ_H(500 MHz; $CDCl_3$) 7.81 (2H, dd, *J* 2.8, 1.3, thienyl *H*), 7.35 (2H, dd, *J* 5.0, 3.0, thienyl *H*), 7.30 (2H, dd, *J* 5.0, 1.0, thienyl *H*); δ_C(125 MHz; $CDCl_3$) 162.5 (s), 147.8 (s), 133.2 (d), 130.1 (d), 126.1 (d), 120.1 (s), 97.6 (s), 83.8 (s); *m/z* (EI) 326 (M^+, 34%), 165 (100), 133 (80), 121 (13), 107 (5), 94 (6), 69 (9), 63 (5), 58 (11).

3,5-Bis(pyridin-3-ylethynyl)-4*H*-1,2,6-thiadiazin-4-one 195

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with 3-ethynylpyridine (62 mg, 0.60 mmol) gave the *title compound* **195** (58.7 mg, 68%) as yellow/brown plates, mp (dec.) (DCE/EtOH) DSC (onset) 232.2 ^{o}C (peak) 235.0 ^{o}C; R_f 0.30 (^{t}BuOMe); (found: C, 64.7; H, 2.5; N, 17.7. $C_{17}H_8N_4OS$ requires C, 64.6; H, 2.6; N, 17.7%); λ_{max}(DCM)/nm 230 (log ε 3.67), 236 inf (3.66), 245 inf (3.63), 264 inf (3.57), 278 inf (3.54), 327 inf (3.42), 373 inf (3.80), 381 (3.82), 385 inf (3.76), 397 (3.76), 411 inf (3.61); ν_{max}/cm^{-1} 3063w, 2203s (C≡C), 1638s, 1580w, 1560w, 1479s, 1460w, 1416w, 1406m, 1356s, 1331w, 1312w, 1223w, 1188w, 1140w, 1121w, 1045w, 1022m, 989w, 972w, 962w, 833m, 814s; δ_H(500 MHz; $CDCl_3$) 8.88 (2H, s, pyridyl *H*), 8.67 (2H, d, *J* 4.0, pyridyl *H*), 7.95 (2H, ddd, *J* 4.5, 2.0, 2.0, pyridyl *H*), 7.36 (2H, dd, *J* 5.0, 3.0, pyridyl *H*); δ_C(125 MHz; DMSO) 162.4 (s), 152.1 (d), 150.7 (d), 147.0 (s), 139.5 (d), 124.0 (d), 117.3 (s), 95.8 (s), 86.5 (s); *m/z* (EI) 316 (M^+, 49%), 160 (100), 128 (48), 116 (7), 107 (5), 101 (23), 76 (16), 50 (8).

3-Chloro-5-(ethynylferrocenyl)-4*H*-1,2,6-thiadiazin-4-one 196 and 3,5-Bis(ethynyl-ferrocenyl)-4*H*-1,2,6-thiadiazin-4-one 197

Similar treatment of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (50 mg, 0.273 mmol) with ethynylferrocene (124.8 mg, 0.60 mmol) gave after chromatography (Hexane/DCM, 1:1) the *title compound* **196** (69.6 mg, 10%) as purple needles, mp (dec.) onset 159.9 ^{o}C peak 166.4 ^{o}C (DSC) (cyclohexane); R_f 0.40 (Hexane/DCM, 1:1); (found: C, 50.5; H, 2.4; N, 7.8. $C_{15}H_9ClFeN_2OS$ requires C, 50.5; H, 2.5; N, 7.9%); λ_{max}(DCM)/nm 230 (log ε 4.75), 268 (4.82), 357 (4.93), 524 (4.15); ν_{max}/cm^{-1} 3100w, 2195s (C≡C), 1643s, 1485w, 1433w, 1408w, 1321m, 1252w, 1240w, 1126m, 1105w, 1057w, 1036m, 1028w, 1001w, 945m, 847w, 824m, 802s; *m/z* (EI) 358 (M^++2, 43%), 356 (M^+, 100), 293 (4), 266 (7), 235 (32), 210 (11), 183 (5), 178 (28), 156 (10), 152 (10), 146 (21), 121 (39), 114 (30), 97 (19), 56 (36). *Note*: Pure compound **196** was unstable in solution preventing the collection of NMR data. Further elution (Hexane/DCM, 1:2) gave the *title compound* **197** (24.6 mg, 17%) as purple solid, mp (dec.) onset 243.9 ^{o}C peak 253.3 ^{o}C (DSC); R_f 0.33 (Hexane/DCM, 1:1); (found: C, 61.1; H, 3.4; N, 5.2. $C_{27}H_{18}Fe_2N_2OS$ requires C, 61.2; H, 3.4; N, 5.3%); λ_{max}(DCM)/nm 230 (log ε 4.75), 268 (4.82), 357 (4.93), 524 (4.15); ν_{max}/cm^{-1} 2193s (C≡C), 1639m, 1508w, 1435w, 1341m, 1281w, 1246w, 1153w, 1105m, 1053w, 1028w, 999w, 978w, 812s; δ_H(500 MHz; $CDCl_3$) 4.67 (1H, dd, *J* 1.8, 1.8, Cp *H*), 4.41 (1H, dd, *J* 2.0, 2.0, Cp *H*), 4.29 (1H, s, Cp *H*);

δ_C(125 MHz; $CDCl_3$) 162.9 (s), 147.3 (s), 104.8 (s), 81.7 (s), 72.8 (d), 70.7 (d), 70.6 (d), 61.6 (s); *m/z* (EI) 530 (M^+, 100%), 322 (4), 284 (8), 265 (14), 235 (39), 209 (3), 186 (5), 152 (9), 121 (34), 97 (16), 71 (2), 56 (19).

9.6 Compounds related to Chapter 6

3-Chloro-5-hydroxy-4*H*-1,2,6-thiadiazin-4-one 198

To a stirred mixture of 3,5-dichloro-4*H*-1,2,6-thiadiazin-4-one **24** (1.00 g, 5.46 mmol) in THF at rt, was added LiOH (523 mg, 21.8 mmol) and the reaction mixture was refluxed until no starting material remained (TLC). The reaction mixture was diluted with DCM, washed (H_2O), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (t-BuOMe/EtOH, 9:1) gave the *title compound* **198** (743 mg, 83%) as yellow plates, mp 99-100 ^oC (from cyclohexane/drops of DCM), R_f 0.43 (*t*-BuOMe/EtOH, 9:1); (found: C, 21.8; H, 0.7; N, 17.0. $C_3HClN_2O_2S$ requires C, 21.9; H, 0.6; N, 17.0%); λ_{max}(DCM)/nm 230 (log ε 2.62), 277 (2.86), 288 (2.70), 345 (3.21); ν_{max}/cm^{-1} 3530br w and 3416w (OH), 1830w, 1607s (C=O), 1560w, 1503m, 1445w, 1373w, 1317s, 1231w, 1217s, 962w, 874m, 841s; δ_H(500 MHz; $CDCl_3$ + DMSO-d_6) 5.68 (1H, br s, O*H*); δ_C(125 MHz; $CDCl_3$ + DMSO-d_6) 158.4 (s), 157.8 (s), 146.1 (s); *m/z* (EI) 166 (M^++2, 41%), 164 (M^+, 97), 138 (10), 136 (27), 129 (5), 121 (12), 101 (8), 95 (43), 93 (100), 86 (13), 75 (100), 70 (18), 62 (22), 58 (42), 54 (42).

3-Chloro-5-trifluoromethanesulfonoxy-4*H*-1,2,6-thiadiazin-4-one 199

To a stirred mixture of 3-chloro-5-hydroxy-4*H*-1,2,6-thiadiazin-4-one **198** (1.00 g, 6.10 mmol) in DCM at *ca.* 0 ^oC, was added triethylamine (0.93 mL, 6.70 mmol) and trifluoromethanesulfonic anhydride (2 mL, 12.2 mmol) and the reaction mixture was left to warm to *ca.* 10 ^oC until no starting material remained (TLC). Dilution (DCM), adsorption on silica and chromatography (Hexane/DCM, 7:3) gave the *title compound* **199** (1.41 g, 78%) as colorless needles, mp 58-59 ^oC (from pentane), R_f 0.28 (Hexane/DCM, 7:3); (found: C, 16.2; N, 9.5. $C_4ClF_3N_2O_4S_2$ requires C, 16.2; N, 9.4%); λ_{max}(DCM)/nm 298 (log ε 3.01), 321 (3.28); ν_{max}/cm^{-1} 1659m, 1495w, 1423m, 1294w, 1229s, 1217s, 1125s, 1030w, 941m, 862m, 822m; δ_C(125 MHz; $CDCl_3$) 156.0 (s), 154.4 (s), 146.0 (s), 118.3 (q, $^1J_{CF}$ 319.2, *C*F_3); *m/z* (EI) 298 (M^++2, 10%), 296 (26), 227 (4), 204 (4), 147 (5), 143 (42), 121 (5), 119 (5), 115 (24), 95 (12), 93 (34), 74 (26), 69 (100), 54 (10).

3-Bromo-5-chloro-4*H*-1,2,6-thiadiazin-4-one 200

To a stirred solution of 3-chloro-5-trifluoromethanesulfonoxy-4*H*-1,2,6-thiadiazin-4-one **199** (1.00 g, 3.37 mmol) in acetone at rt, was added tetraethylammonium bromide (0.78 g, 3.71 mmol) and the reaction mixture was heated at reflux until no starting material remained (TLC). The reaction mixture was then cooled to rt, diluted (DCM), washed (H_2O), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (Hexane/DCM, 7:3) gave the *title compound* **200** (766 mg, 100%) as yellow needles, mp 103-104 ^oC (from cyclohexane), R_f 0.33 (Hexane/DCM, 7:3); (found: C, 15.9; N, 12.3. C_3BrClN_2OS requires C, 15.8; N, 12.3%); λ_{max}(DCM)/nm 305 inf (log ε 3.03), 328 (3.26); ν_{max}/cm^{-1} 1655s (C=O), 1620w, 1493w, 1254w, 1239w, 1225w, 1211w, 1061w, 1044m, 1024w, 851w, 824w; δ_C(125 MHz; $CDCl_3$) 157.4 (s), 147.8 (s), 143.6 (s); *m/z* (EI) 230 (M^++4, 28%), 228 (M^++2, 100), 226 (M^+, 78), 167 (11), 165 (12), 147 (10), 139 (35), 137 (34), 123 (22), 121 (65), 119 (9), 95 (34), 93 (89), 86 (11), 81 (8), 79 (8), 58 (62), 54 (37).

3-Chloro-5-iodo-4*H*-1,2,6-thiadiazin-4-one 201

To a stirred solution of 3-chloro-5-trifluoromethanesulfonoxy-4*H*-1,2,6-thiadiazin-4-one **199** (1.00 g, 3.37 mmol) in acetone at rt, was added potassium iodide (671 mg, 4.04 mmol) and the reaction mixture was stirred at this temperature until no starting material remained (TLC). The reaction mixture was then diluted (DCM), washed (H_2O), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (Hexane/DCM, 7:3) gave the *title compound* **201** (803 mg, 87%) as yellow needles, mp 113-114.5 ^oC (from cyclohexane), R_f 0.33 (Hexane/DCM, 7:3); (found: C, 13.2; N, 10.3. C_3IClN_2OS requires C, 13.1; N, 10.2%); λ_{max}(DCM)/nm 230 inf (log ε 2.70), 312 inf (3.00), 328 (3.02); ν_{max}/cm^{-1} 1652s (C=O), 1485w, 1477w, 1425w, 1292w, 1242m, 1213m, 1126w, 1059w, 1026m, 943w, 862w, 845w, 824w, 808w; δ_C(125 MHz; $CDCl_3$) 157.5 (s), 143.5 (s), 127.8 (s, *C*-5); *m/z* (EI) 276 (M^++2, 36%), 274 (M^+, 95), 185 (26), 159 (8), 153 (8), 149 (22), 147 (62), 127 (79), 121 (25), 119 (52), 95 (36), 93 (100), 86 (47), 58 (92), 54 (60).

3-Chloro-5-(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one 202; Typical Stille procedure (Table 19)

To a stirred solution of 3-chloro-5-trifluoromethanesulfonoxy-4*H*-1,2,6-thiadiazin-4-one **199** (65.0 mg, 0.22 mmol) in PhH (2 mL) at rt, was added 2-(tributylstannyl)thiophene (70 μL, 0.22 mmol) and $Pd(Ph_3P)_2Cl_2$ (7.7 mg, 0.011 mmol) and the mixture was stirred at this

temperature until no starting material remained (TLC). The reaction mixture was then diluted (DCM) and adsorbed onto silica. Chromatography (Hexane/DCM, 7:3), gave the *title compound* **202** (43 mg, 85%) as yellow needles, mp 123-124 ^{o}C (from cyclohexane), R_f 0.39 (Hexane/DCM, 7:3); (found: C, 36.5; H, 1.2; N, 12.1. $C_7H_3ClN_2OS_2$ requires C, 36.4; H, 1.3; N, 12.1%); λ_{max}(DCM)/nm 259 inf (log ε 2.82), 275 (2.93), 363 (3.29), 380 inf (3.21); ν_{max}/cm^{-1} 3125w, 3105w, 3092w and 3078w (Ar CH), 1657w, 1634s (C=O), 1543w, 1510w, 1481w, 1447w, 1420m, 1406m, 1369m, 1346w, 1298w, 1219m, 1182m, 1175m, 1128w, 1072w, 1053w, 1016m, 974w, 941w, 864m, 841m, 829m; δ_H(500 MHz; $CDCl_3$) 8.29 (1H, dd, *J* 4.0, 1.0, thienyl *H*), 7.69 (1H, dd, *J* 5.0, 1.0, thienyl *H*), 7.20 (1H, dd, *J* 4.8, 4.3, thienyl *H*); δ_C(125 MHz; $CDCl_3$) 159.4 (s), 153.0 (s), 151.2 (s), 135.9 (s), 134.2 (d), 133.4 (d), 128.2 (d); *m/z* (EI) 232 (M^++2, 38%), 230 (M^+, 91), 141 (52), 123 (21), 121 (60), 109 (36), 95 (37), 93 (100), 71 (13), 64 (9), 58 (24).

3-Chloro-5-(fur-2-yl)-4*H*-1,2,6-thiadiazin-4-one 203

Similar treatment of 3-chloro-5-trifluoromethanesulfonoxy-4*H*-1,2,6-thiadiazin-4-one **199** (65.0 mg, 0.22 mmol) with 2-(tributylstannyl)furan (69.3 μL, 0.22 mmol) gave the *title compound* **203** (35.8 mg, 76%) as yellow needles, mp 110-111 ^{o}C (from cyclohexane), R_f 0.28 (Hexane/DCM, 7:3); (found: C, 39.2; H, 1.4; N, 13.0. $C_7H_3ClN_2O_2S$ requires C, 39.2; H, 1.4; N, 13.1%); λ_{max}(DCM)/nm 270 (log ε 2.87), 344 inf (3.31), 354 (3.35), 371 inf (3.24); ν_{max}/cm^{-1} 3144w (Ar CH), 1721w, 1628m (C=O), 1558w, 1485m, 1435w, 1396m, 1337w, 1327w, 1219m, 1183m, 1088w, 1045m, 1022w, 1013w, 932w, 901w, 881w, 849s, 760s; δ_H(500 MHz; $CDCl_3$) 7.88 (1H, d, *J* 3.5, furyl *H*), 7.71 (1H, br s, furyl *H*), 6.63 (1H, dd, *J* 3.5, 1.5, furyl *H*); δ_C(125 MHz; $CDCl_3$) 158.4 (s), 151.2 (s), 148.2 (s), 147.2 (d), 146.9 (s), 121.1 (d), 113.1 (s); *m/z* (EI) 216 (M^++2, 35%), 214 (M^+, 86), 125 (29), 123 (21), 121 (53), 97 (10), 95 (28), 93 (100), 70 (10), 64 (12).

3-Chloro-5-(1-methyl-1*H*-pyrrol-2-yl)-4*H*-1,2,6-thiadiazin-4-one 204

Similar treatment of 3-chloro-5-trifluoromethanesulfonoxy-4*H*-1,2,6-thiadiazin-4-one **199** (65.0 mg, 0.22 mmol) with 1-methyl-2-(tributylstannyl)pyrrole (72.6 μL, 0.22 mmol) gave the *title compound* **204** (47 mg, 94%) as yellow needles, mp 174-176 ^{o}C (from cyclohexane), R_f 0.23 (Hexane/DCM, 7:3); (found: C, 42.4; H, 2.7; N, 18.6. $C_8H_6ClN_3OS$ requires C, 42.2; H, 2.7; N, 18.5%); λ_{max}(DCM)/nm 288 (log ε 3.06), 371 (3.43), 385 inf (3.31); ν_{max}/cm^{-1} 3175w

and 3129w (Ar CH), 1641s (C=O), 1560w, 1526m, 1495m, 1466w, 1437w, 1425m, 1412m, 1398w, 1369w, 1329w, 1267m, 1251w, 1179m, 1094m, 1076m, 1042m, 986w, 895w, 858m, 845m, 816w; δ_H(500 MHz; $CDCl_3$) 7.74 (1H, dd, *J* 4.3, 2.0, pyrrolyl *H*), 7.90 (1H, dd, *J* 2.0, 2.0, pyrrolyl *H*), 6.23 (1H, dd, *J* 4.0, 2.5, pyrrolyl *H*), 3.94 (3H, s, NCH_3); δ_C(125 MHz; $CDCl_3$) 159.4 (s), 150.8 (s), 149.5 (s), 132.1 (d), 125.6 (s), 121.6 (d), 108.9 (d), 38.7 (NCH_3); *m/z* (EI) 229 (M^++2, 29%), 227 (M^+, 76), 138 (56), 123 (12), 121 (22), 110 (16), 106 (100), 105 (35), 95 (15), 93 (43), 78 (14), 64 (6), 55 (5).

3-(Fur-2-yl)-5-(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one 205

To a stirred solution of 3-chloro-5-(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one **202** (50.0 mg, 0.22 mmol) in MeCN (2 mL) at rt, was added 2-(tributylstannyl)furan (83 μL, 0.264 mmol) and $Pd(Ph_3P)_2Cl_2$ (7.7 mg, 0.011 mmol) and the mixture was heated at reflux until no starting material remained (TLC). The reaction mixture was then allowed to cool to rt, diluted (DCM) and adsorbed onto silica. Chromatography (Hexane/DCM, 7:3) gave the *title compound* **205** (50.7 mg, 88%) as yellow needles, mp 141.5-143.5 ^oC (from cyclohexane), R_f 0.39 (Hexane/DCM, 7:3); (found: C, 50.5; H, 2.4; N, 10.6. $C_{11}H_6N_2O_2S_2$ requires C, 50.4; H, 2.3; N, 10.7%); λ_{max}(DCM)/nm 255 (log ε 3.26), 339 inf (3.01), 384 inf (3.56), 399 (3.64), 422 (3.54); ν_{max}/cm^{-1} 3165w, 3136w, 3115w and 3100w (Ar CH), 1624s (C=O), 1560m, 1504w, 1481s, 1408s, 1395s, 1375s, 1335w, 1279w, 1173w, 1147w, 1074w, 1053w, 1042w, 1026m, 997w, 926w, 881m, 870m, 854w, 839w, 822m, 761m; δ_H(500 MHz; $CDCl_3$) 8.26 (1H, dd, *J* 3.8, 1.3, thienyl *H*), 7.94 (1H, dd, *J* 3.5, 0.5, furyl *H*), 7.69 (1H, dd, *J* 2.0, 0.5, furyl *H*), 7.65 (1H, dd, *J* 5.0, 1.0, thienyl *H*), 7.20 (1H, dd, *J* 4.0, 1.0, thienyl *H*), 6.63 (1H, dd, *J* 3.5, 1.5, furyl *H*); δ_C(125 MHz; $CDCl_3$) 160.6 (s), 154.2 (s), 149.6 (s), 147.8 (s), 146.3 (d), 136.2 (s), 133.4 (d), 132.1 (d), 127.7 (d), 119.9 (d), 112.8 (d); *m/z* (EI) 262 (M^+, 89%), 141 (47), 125 (100), 109 (20), 97 (15), 93 (15), 70 (14), 64 (12), 58 (9).

3-(1-Methyl-1*H*-pyrrol-2-yl)-5-(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one 206

Similar treatment of 3-chloro-5-(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one **202** (50.0 mg, 0.22 mmol) with 1-methyl-2-(tributylstannyl)pyrrole (87.1 μL, 0.264 mmol) gave the *title compound* **206** (53.3 mg, 88%) as yellow needles, mp 114.5-115.5 ^oC (from cyclohexane), R_f 0.31 (Hexane/DCM, 7:3); (found: C, 52.3; H, 3.2; N, 15.4. $C_{12}H_9N_3OS_2$ requires C, 52.3; H, 3.3; N, 15.3%); λ_{max}(DCM)/nm 260 (log ε 3.82), 344 inf (3.62), 378 (3.97), 381 (3.98), 420 inf (3.89), 432 (3.91); ν_{max}/cm^{-1} 3152w and 3059w (Ar CH), 2997w, 2945w, 1647w, 1614s

(C=O), 1524w, 1506w, 1489m, 1464w, 1447w, 1410m, 1422m, 1373m, 1366m, 1296m, 1269w, 1242w, 1217w, 1136w, 1096w, 1067m, 1049m, 1034w, 978w, 895w, 872m, 856w, 845w, 837w, 822w; δ_H(500 MHz; $CDCl_3$) 8.19 (1H, d, *J* 4.0, thienyl *H*), 7.77 (1H, dd, *J* 4.0, 1.5, pyrrolyl *H*), 7.59 (1H, d, *J* 5.0, thienyl *H*), 7.17 (1H, dd, *J* 4.3, 4.3, thienyl *H*), 6.87 (1H, br s, pyrrolyl *H*), 6.24 (1H, dd, *J* 3.8, 2.8, pyrrolyl *H*), 3.97 (3H, s, NCH_3); δ_C(125 MHz; $CDCl_3$) 161.9 (s), 153.2 (s), 152.4 (s), 136.8 (s), 132.4 (d), 131.2 (d), 131.0 (d), 127.5 (d), 126.5 (s), 120.5 (d), 108.5 (d), 38.6 (NCH_3); *m/z* (EI) 275 (M^+, 95%), 141 (100), 138 (64), 109 (21), 106 (30), 97 (7), 78 (8), 64 (5), 58 (6).

3-(Fur-2-yl)-5-(1-methyl-1*H*-pyrrol-2-yl)-4*H*-1,2,6-thiadiazin-4-one 207

Similar treatment of 3-chloro-5-(fur-2-yl)-4*H*-1,2,6-thiadiazin-4-one **203** (47 mg, 0.22 mmol) with 1-methyl-2-(tributylstannyl)pyrrole (87.1 μL, 0.264 mmol) gave the *title compound* **207** (57 mg, 100%) as yellow needles, mp 87.5-90.5 ^oC (from cyclohexane), R_f 0.18 (Hexane/DCM, 7:3); (found: C, 55.5; H, 3.5; N, 16.1. $C_{12}H_9N_3O_2S$ requires C, 55.6; H, 3.5; N, 16.2%); λ_{max}(DCM)/nm 257 (log ε 2.88), 323 inf (2.65), 330 (2.67), 378 (3.05), 420 inf (2.91), 429 (2.93); ν_{max}/cm^{-1} 3165w, 3134w and 3113w (Ar CH), 2949w, 1622s, 1611s (C=O), 1562w, 1524m, 1485s, 1466m, 1423m, 1412s, 1391m, 1368w, 1310s, 1279w, 1269w, 1246w, 1217w, 1180w, 1155w, 1146w, 1096w, 1082w, 1067s, 1047m, 1013w, 984w, 930w, 893w, 887w, 872w, 841w, 822w, 789w, 762m; δ_H(500 MHz; $CDCl_3$) 7.83 (1H, dd, *J* 3.5, 0.5, furyl *H*), 7.72 (1H, dd, *J* 4.3, 1.8, pyrrolyl *H*), 7.66 (1H, dd, *J* 1.5, 0.5, furyl *H*), 6.88 (1H, dd, *J* 4.5, 2.3, pyrrolyl *H*), 6.60 (1H, dd, *J* 3.5, 2.0, furyl *H*), 6.25 (1H, dd, *J* 4.5, 2.5, pyrrolyl *H*), 3.96 (3H, s, NCH_3); δ_C(125 MHz; $CDCl_3$) 161.2 (s), 152.5 (s), 149.0 (s), 148.1 (s), 145.7 (d), 131.0 (d), 126.4 (s), 120.4 (d), 118.7 (d), 112.6 (d), 108.5 (d), 38.6 (NCH_3); *m/z* (EI) 259 (M^+, 84%), 208 (7), 138 (49), 130 (6), 125 (100), 110 (10), 106 (40), 105 (19), 97 (11), 95 (9), 93 (12), 78 (8), 70 (12), 64 (10), 51 (5).

5,5'-(Thiophene-2,5-diyl)bis[3-(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one] 208

To a stirred solution of 3-chloro-5-(thien-2-yl)-4*H*-1,2,6-thiadiazin-4-one **202** (50.0 mg, 0.22 mmol) in MeCN (2 mL) at rt, was added 2,5-bis(tributylstannyl)thiophene (60.6 μL, 0.11 mmol) and $Pd(Ph_3P)_2Cl_2$ (7.7 mg, 0.011 mmol) and the mixture was heated to reflux until no starting material remained (TLC). During the reaction, an orange precipitate was formed. The reaction mixture was then allowed to cool to rt, filtered and the solid collected washed with

hexane (10 mL) and then pentane (2 mL) and dried under vacuum to afford the *title compound* **208** (39 mg, 76%), as a red powder, mp DSC (onset) 288.0 ^{o}C (peak) 292.3 ^{o}C; (found: C, 45.6; H, 1.7; N, 11.7. $C_{18}H_8N_4O_2S_5$ requires C, 45.7; H, 1.7; N, 11.9%); λ_{max}(DCM)/nm 268 (log ε 3.48), 383 (3.31), 456 inf (3.48), 475 (3.62), 504 (3.58); ν_{max}/cm^{-1} 3115w (Ar CH), 1622s (C=O), 1506m, 1435w, 1412m, 1376s, 1364m, 1339w, 1329w, 1269m, 1240w, 1223w, 1215w, 1078w, 1047m, 880w, 870w, 854m, 827m, 808w, 765w; δ_H(500 MHz; $CDCl_3$) 8.35 (1H, d, *J* 3.0, thienyl *H*), 8.27 (1H, s, thienyl *H*), 7.74 (1H, d, *J* 4.0, thienyl *H*), 7.25 (1H, dd, *J* 8.0, 4.0, thienyl *H*); δ_C(125 MHz; $CDCl_3$) could not be collected owing to poor solubility; *m/z* (EI) 472 (M^+, 66%), 335 (15), 303 (17), 236 (4), 198 (5), 166 (25), 141 (100), 134 (6), 109 (21), 97 (5), 71 (7), 64 (5), 58 (5).

5,5'-(Thiophene-2,5-diyl)bis[3-(1-methyl-1*H*-pyrrol-2-yl)-4*H*-1,2,6-thiadiazin-4-one] 209

Similar treatment of 3-chloro-5-(1-methyl-1*H*-pyrrol-2-yl)-4*H*-1,2,6-thiadiazin-4-one **204** (50.0 mg, 0.22 mmol) with 2,5-bis(tributylstannyl)thiophene (60.6 μL, 0.11 mmol) gave the *title compound* **209** (47 mg, 92%) as a red solid, mp DSC (onset) 266.4 ^{o}C (peak) 270.9 ^{o}C; (found: C, 51.5; H, 3.0; N, 17.9. $C_{20}H_{14}N_6O_2S_3$ requires C, 51.5; H, 3.0; N, 18.0%); λ_{max}(DCM)/nm 270 (log ε 3.31), 385 inf (3.12), 414 (3.14), 471 inf (3.30), 491 (3.41), 518 (3.39); ν_{max}/cm^{-1} 3123w, 2947w, 1728w, 1678w, 1620m, 1572m, 1524m, 1487m, 1464m, 1423s, 1416s, 1369w, 1341w, 1306m, 1263m, 1227w, 1198w, 1153m, 1094w, 1074m, 1065m, 980w, 895w, 870w, 822w, 781m, 773m; δ_H(500 MHz; $CDCl_3$) 8.16 (1H, br s, pyrrolyl *H*), 7.81 (1H, br s, pyrrolyl *H*), 6.94 (1H, br s, pyrrolyl *H*), 6.26 (1H, br s, pyrrolyl H), 3.98 (3H, s, NCH_3); δ_C(125 MHz; $CDCl_3$) could not be collected owing to poor solubility; *m/z* (EI) 466 (M^+, 100%), 332 (19), 300 (28), 262 (7), 233 (6), 198 (13), 183 (6), 166 (28), 138 (91), 110 (11), 106 (34), 78 (5).

5,5'-(Thiophene-2,5-diyl)bis(3-chloro-4*H*-1,2,6-thiadiazin-4-one) 210

To a stirred mixture of 3-chloro-5-trifluoromethanesulfonoxy-4*H*-1,2,6-thiadiazin-4-one **199** (65.0 mg, 0.22 mmol) in PhH (2 mL) at rt, was added 2,5-bis(tributylstannyl)thiophene (60.6 μL, 0.11 mmol) and $Pd(Ph_3P)_2Cl_2$ (7.7 mg, 0.011 mmol) and the reaction mixture stirred at this temperature until no starting material remained (TLC). The mixture was then diluted (DCM) and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1) gave the *title compound* **210** (16.6 mg, 40%) as yellow plates, mp DSC (onset) 261.2 ^{o}C (peak) 262.6 ^{o}C, R_f 0.36 (Hexane/DCM, 1:1); (found: C, 32.0; H, 0.5; N, 14.7. $C_{10}H_2Cl_2N_4O_2S_3$ requires C, 31.8;

H, 0.5; N, 14.9%); λ_{max}(DCM)/nm 265 inf (log ε 2.99), 291 (3.26), 299 inf (3.24), 318 inf (3.18), 384 inf (3.43), 409 inf (3.60), 422 (3.69), 445 (3.66); ν_{max}/cm^{-1} 2938w, 1630s (C=O), 1520w, 1449w, 1327m, 1180m, 1069w, 988w, 964w, 866w, 849w, 835m; δ_H(500 MHz; $CDCl_3$) 8.15 (1H, s, thienyl *H*); δ_C(125 MHz; $CDCl_3$) 160.0 (s), 151.7 (s), 150.6 (s), 140.9 (s), 131.7 (d); *m/z* (EI) 380 (M^++4, 12%), 378 (M^++2, 41), 376 (M^+, 53), 315 (4), 287 (7), 255 (11), 166 (13), 149 (4), 134 (12), 123 (37), 121 (100), 99 (6), 95 (36), 93 (93), 86 (4), 70 (10), 64 (9), 57 (9).

5,5'-Dichloro-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione 211

To a stirred solution of 3-chloro-5-iodo-4*H*-1,2,6-thiadiazin-4-one **201** (64.9 mg, 0.22 mmol) in PhH (2 mL) was added Bu_3SnH (65 μL, 0.242 mmol) and $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) and the reaction mixture was heated at reflux until no starting material remained (TLC). The reaction mixture was then allowed to cool to rt, diluted (DCM) and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1) gave the *title compound* **211** (27 mg, 83%) as pale yellow needles, mp 121-122 ^oC (cyclohexane), R_f 0.33 (Hexane/DCM, 1:1); (found: C, 24.3; N, 18.9. $C_6Cl_2N_4O_2S_2$ requires C, 24.4; N, 19.0%); λ_{max}(DCM)/nm 285 inf (log ε 2.97), 320 (3.28), 332 (3.25); ν_{max}/cm^{-1} 1665m, 1651s (C=O), 1520w, 1503w, 1269m, 1252w, 1148s, 1045m, 881w, 858m, 843w, 826w, 804m, 762w; δ_C(125 MHz; $CDCl_3$) 158.4 (s), 154.7 (s), 154.3 (s); *m/z* (EI) 298 (M^++4, 8%), 296 (M^++2, 31), 294 (M^+, 42), 235 (6), 233 (15), 207 (9), 205 (21), 177 (7), 175 (15), 166 (4), 123 (14), 121 (38), 95 (37), 93 (100), 84 (9), 70 (5), 64 (4), 58 (19).

5,5'-Di(thien-2-yl)-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione 212

To a stirred solution of 5,5'-dichloro-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione **211** (65.0 mg, 0.22 mmol) in MeCN (2 mL) at rt, was added 2-(tributylstannyl)thiophene (153.7 μL, 0.484 mmol) and $Pd(Ph_3P)_2Cl_2$ (7.7 mg, 0.011 mmol) and the reaction was heated at reflux until no starting material remained (TLC). The reaction mixture was then allowed to cool to rt, diluted (DCM) and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1) gave the *title compound* **212** (57 mg, 67%) as yellow needles, mp DSC (onset) 203.5 ^oC (peak) 204.8 ^oC (from cyclohexane), R_f 0.55 (Hexane/DCM, 1:1); (found: C, 43.2; H, 1.5; N, 14.3. $C_{14}H_6N_4O_2S_4$ requires C, 43.1; H, 1.6; N, 14.4%); λ_{max}(DCM)/nm 269 (log ε 3.35), 378 (3.59), 384 inf (3.57); ν_{max}/cm^{-1} 3102w, 3075w, 1639m, 1618m, 1516w, 1504w, 1481w, 1445m,

1416m, 1408s, 1379m, 1346w, 1260w, 1223w, 1188w, 1094w, 1076w, 1057w, 866m, 853w, 841w, 822m, 800w, 770w; δ_H(500 MHz; $CDCl_3$) 8.32 (1H, dd, *J* 4.0, 1.0, thienyl *H*), 7.69 (1H, dd, *J* 5.0, 1.0, thienyl *H*), 7.20 (1H, dd, *J* 5.0, 4.0, thienyl *H*); δ_C(125 MHz; $CDCl_3$) 161.1 (s), 157.9 (s), 156.0 (s), 136.1 (s), 134.4 (d), 133.5 (d), 128.2 (d); *m/z* (EI) 390 (M^+, 100%), 281 (28), 280 (37), 253 (12), 217 (5), 201 (22), 195 (4), 173 (17), 141 (86), 116 (26), 112 (16), 109 (56), 97 (9), 84 (20), 71 (13), 64 (8), 58 (15).

5,5'-Bis(1-methyl-1*H*-pyrrol-2-yl)-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione 213

Similar treatment of 5,5'-dichloro-4*H*,4'*H*-[3,3'-bi(1,2,6-thiadiazine)]-4,4'-dione **211** (65.0 mg, 0.22 mmol) with 1-methyl-2-(tributylstannyl)pyrrole (160 μL, 0.484 mmol) gave the *title compound* **213** (59 mg, 70%) as orange plates, mp 265-267 ^oC (from PhH), R_f 0.30 (Hexane/DCM, 1:1); (found: C, 50.1; H, 3.1; N, 21.8. $C_{16}H_{12}N_6O_2S_2$ requires C, 50.0; H, 3.2; N, 21.9%); λ_{max}(DCM)/nm 279 (log ε 3.55), 380 (3.60), 401 (3.53); ν_{max}/cm^{-1} 3121w and 3105w (Ar CH), 2951w, 1603s (C=O), 1526m, 1489m, 1464m, 1439w, 1416m, 1406m, 1373w, 1331w, 1314w, 1275m, 1233w, 1184m, 1105w, 1096m, 1065s, 1040w, 893m, 866m, 824m, 783w, 760s; δ_H(500 MHz; DMSO-d_6) 7.46 (1H, dd, *J* 4.0, 1.5, pyrrolyl *H*), 7.26 (1H, dd, *J* 3.0, 1.5, pyrrolyl *H*), 6.20 (1H, dd, *J* 4.0, 2.5, pyrrolyl *H*), 3.94 (3H, s, NCH_3); δ_C(125 MHz; DMSO-d_6) 161.2 (s), 157.0 (s), 152.6 (s), 132.3 (d), 125.1 (s), 120.2 (d), 108.3 (d), 38.0 (NCH_3); *m/z* (EI) 384 (M^+, 72%), 278 (8), 250 (18), 245 (5), 222 (5), 217 (7), 198 (11), 170 (18), 138 (59), 116 (28), 112 (18), 106 (100), 84 (8), 78 (12), 70 (5), 64 (4), 52 (5).

9.7 Compounds related to Chapter 7

3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-ol 214

To a stirred suspension of 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-one **172** (100 mg, 0.376 mmol) in MeOH (4 mL) at *ca.* 20 ^{o}C, was added $NaBH_4$ (28.4 mg, 0.75 mmol) and the mixture was placed to a preheated oil bath at *ca.* 50 ^{o}C until no starting material remained (TLC). The mixture was then diluted (DCM), washed (H_2O) and dried (Na_2SO_4) to give the *title compound* **214** (98 mg, 97%) as yellow flakes, mp 75-77 ^{o}C (from pentane), R_f 0.60 (DCM); (found: C, 67.0; H, 4.6; N, 10.3. $C_{15}H_{12}N_2OS$ requires C, 67.1; H, 4.5; N, 10.4%); λ_{max}(DCM)/nm 240 inf (306), 246 (3.07), 277 inf (2.91), 348 (3.03); ν_{max}/cm^{-1} 3356w, 3310w, 3260w (OH), 3059w (Ar CH), 1703w, 1493w, 1445s, 1385m, 1360s, 1265s, 1234w, 1200m, 1182w, 1157w, 1070s, 1040w, 1020s, 969s, 932m, 910w, 847m; δ_H(500 MHz; $CDCl_3$) 7.99-7.97 (1H, m, Ph *H*), 7.47-7.46 (1H, m, Ph *H*), 6.07 (1H, s, C*H*OH); δ_C(125 MHz; CDCl3) 150.3 (s), 136.6 (s), 130.6 (d), 128.8 (d), 126.8 (d), 52.4 (d, *C*HOH); *m/z* (EI) 268 (M^+, 7%), 267 (M^+-1, 7), 252 (21), 251 (6), 221 (100), 220 (43), 149 (25), 137 (11), 135 (9), 121 (7), 116 (14), 103 (36), 77 (36), 51 (18).

3,5-Dithien-2-yl-4*H*-1,2,6-thiadiazin-4-ol 215

Similar treatment of 3,5-dithien-2-yl-4*H*-1,2,6-thiadiazin-4-one **184** (105 mg, 0.376 mmol) in MeOH/DCM (1:1, 4 mL) gave the *title compound* **215** (103 mg, 98%) as yellow needles, mp 110-112 ^{o}C (from cyclohexane), R_f 0.50 (DCM); (found: C, 47.2; H, 2.8; N, 9.9. $C_{11}H_8N_2OS_3$ requires C, 47.1; H, 2.9; N, 10.0%); λ_{max}(DCM)/nm 269 (log ε 3.23), 285 inf (3.10), 381 (3.33), 389 (3.32), 406 inf (3.19); ν_{max}/cm^{-1} 3480w, 3292brw (OH), 3088w (Ar CH), 1533m, 1425s, 1373w, 1352w, 1287w, 1250w, 1246m, 1088w, 1063m, 1022w, 999s, 926m, 916m, 907w, 856m, 847s, 795w; δ_H(500 MHz; $CDCl_3$) 7.63 (2H, d, *J* 3.5, thienyl *H*), 7.50 (2H, d, *J* 5.0, thienyl *H*), 7.12 (2H, dd, *J* 4.5, 4.5, thienyl *H*-4), 5.91 (1H, s, C*H*OH); δ_C(125 MHz; $CDCl_3$) 146.1 (s), 142.9 (s), 130.6 (d), 127.9 (d), 126.4 (d), 54.0 (d); *m/z* (EI) 280 (M^+, 25%), 263 (6), 233 (2), 171 (8), 142 (35), 127 (4), 115 (6), 112 (6), 110 (100), 97 (5), 84 (17), 71 (8), 64 (11), 58 (11), 49 (12).

4-Methyl-3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ol 216

To a stirred solution of 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-one **172** (100 mg, 0.376 mmol) in THF (4 mL) at *ca.* 0 °C protected from moisture with a $CaCl_2$ drying tube, was added MeLi (0.33 mL, 1.5 mmol) and the mixture was left to come to *ca.* 10 °C until no starting material remained (TLC). The mixture was then diluted (DCM), washed (H_2O), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1) gave the *title compound* **216** (95.6 mg, 90%) as pale yellow needles, mp (DSC) onset 122.9 °C, peak 123.3 °C (from cyclohexane), R_f 0.33 (Hexane/DCM, 1:1); (found: C, 68.2; H, 5.1; N, 9.8. $C_{16}H_{14}N_2OS$ requires C, 68.1; H, 5.0; N, 9.9%); λ_{max}(DCM)/nm 235 (log ε 3.23), 248 inf (3.14), 284 (3.01), 340 (3.03); ν_{max}/cm^{-1} 3333brw (OH), 3055w (Ar CH), 2992w, 1491w, 1439m, 1369m, 1273m, 1179m, 1155w, 1078w, 1057m, 1032w, 1001w, 982w, 947w, 926w, 841w, 818m, 768s, 762s; δ_H(500 MHz; $CDCl_3$) 7.82 (4H, d, *J* 7.5, Ph *H*), 7.42-7.37 (6H, m, Ph *H*), 2.43 (1H, s, O*H*), 1.66 (3H, s, CH_3); δ_C(125 MHz; $CDCl_3$) 155.8 (s), 135.1 (s), 130.1 (d), 129.6 (d), 128.1 (d), 68.4 (s), 19.0 (*C*H_3); *m/z* (EI) 282 (M$^+$, 7%), 267 (2), 263 (2), 239 (5), 179 (31), 160 (4), 146 (7), 136 (100), 109 (9), 104 (27), 85 (4), 77 (20), 71 (6), 57 (8), 51 (9).

4-Methyl-3,5-dithien-2-yl-4*H*-1,2,6-thiadiazin-4-ol 217

Similar treatment of 3,5-dithien-2-yl-4*H*-1,2,6-thiadiazin-4-one **184** (105 mg, 0.376 mmol) gave the *title compound* **217** (103 mg, 98%) as yellow plates, mp 32-34 °C, R_f 0.33 (Hexane/DCM, 1:1); (found: C, 49.1; H, 3.4; N, 9.7. $C_{12}H_{10}N_2OS_3$ requires C, 49.0; H, 3.4; N, 9.5%); λ_{max}(DCM)/nm 277 (log ε 4.23), 354 (3.90), 429 (3.95); ν_{max}/cm^{-1} 3433brw (OH), 3100w and 3076w (Ar CH), 2976w, 1697w, 1647w, 1541m, 1520w, 1418s, 1356m, 1267m, 1229m, 1211w, 1169m, 1078w, 1047s, 976w, 949w, 905w, 851s, 812w, 779w; δ_H(500 MHz; $CDCl_3$) 7.87 (2H, d, *J* 4.0, thienyl *H*), 7.42 (2H, d, *J* 5.0, thienyl *H*), 7.05 (2H, dd, *J* 4.5, 4.5, thienyl *H*-4), 3.04 (1H, s, CO*H*CH_3), 1.62 (1H, s, CH_3); δ_C(125 MHz; $CDCl_3$) 150.4 (s), 139.5 (s), 130.4 (d), 130.1 (d), 127.7 (d), 66.8 (s), 19.9 (*C*H_3); *m/z* (EI) 294 (M$^+$, 49%), 279 (15), 251 (7), 185 (23), 170 (4), 142 (100), 116 (9), 109 (24), 84 (12), 71 (7), 58 (7).

(3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane 218

To a stirred solution of 4-methyl-3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ol **216** (50 mg, 0.18 mmol) in PhMe (2 mL) at *ca.* 20 °C was added *p*-TSA (3.4 mg, 0.018 mmol) and the mixture was heated at *ca.* 110 °C (preheated oil bath) until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 °C, diluted (DCM) and adsorbed onto

silica. Chromatography (Hexane/DCM, 7:3) gave the *title compound* **218** (42.8 mg, 90%) as yellow plates, mp 66.5-67.5 ^{o}C (from cyclohexane), R_f 0.70 (Hexane/DCM, 1:1); (found: C, 72.7; H, 4.7; N, 10.7. $C_{16}H_{12}N_2S$ requires C, 72.7; H, 4.6; N, 10.6%); λ_{max}(DCM)/nm 247 (log ε 3.42), 333 (3.09), 392 (2.84); ν_{max}/cm^{-1} 3053w (Ar CH), 2955w, 2924w, 2853w, 1593w, 1576w, 1531m, 1489m, 1472w, 1441m, 1396w, 1352s, 1277m, 1175m, 1076m, 1028w, 999w, 989m, 968w, 918s, 851w, 841w, 831w, 781s; δ_H(500 MHz; $CDCl_3$) 7.82-7.81 (4H, m, Ph *H*), 7.45-7.43 (6H, m, Ph *H*), 5.59 (2H, s, C*H*$_2$); δ_C(125 MHz; $CDCl_3$) 158.2 (s), 137.2 (s), 130.2 (d), 128.6 (d), 128.5 (s), 127.5 (d), 117.3 (=*C*H$_2$); *m/z* (EI) 264 (M$^+$, 84%), 263 (100), 185 (4), 160 (67), 134 (6), 115 (42), 109 (5), 103 (11), 89 (14), 77 (18), 63 (10), 58 (9), 51 (14).

(3,5-Dithien-2-yl-4*H*-1,2,6-thiadiazin-4-ylidene)methane 219

Similar treatment of 4-methyl-3,5-dithien-2-yl-4*H*-1,2,6-thiadiazin-4-ol **217** (53 mg, 0.18 mmol) gave the *title compound* **219** (47.7 mg, 96%) as orange plates, mp 66.5-67 ^{o}C (from pentane, fridge), R_f 0.70 (Hexane/DCM, 1:1); (found: C, 52.2; H, 2.8; N, 10.1. $C_{12}H_8N_2S_3$ requires C, 52.1; H, 2.9; N, 10.1%); λ_{max}(DCM)/nm 254 inf (log ε 3.44), 273 (3.61), 299 inf (3.39), 382 (3.57), 395 (3.59); ν_{max}/cm^{-1} 3100w and 3075w (Ar CH), 1591w, 1520m, 1504w, 1425s, 1352w, 1337w, 1271w, 1231m, 1055m, 955m, 943w, 926m, 920m, 905w, 851s; δ_H(500 MHz; $CDCl_3$) 7.65 (2H, dd, *J* 3.4, 1.3, thienyl *H*), 7.46 (2H, dd, *J* 5.3, 1.2, thienyl *H*), 7.07 (2H, dd, *J* 5.0, 4.0, thienyl *H*-4), 5.96 (2H, s, C*H*$_2$); δ_C(125 MHz; $CDCl_3$) 149.6 (s), 141.4 (s), 130.3 (d), 128.4 (s), 127.4 (d), 127.3 (d), 114.8 (*C*H$_2$); *m/z* (EI) 276 (M$^+$, 100%), 243 (6), 231 (4), 192 (5), 167 (13), 140 (8), 121 (19), 109 (9), 97 (7), 77 (14), 69 (7), 58 (9).

Bromo(3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane 220

To a stirred solution of (3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane **218** (50 mg, 0.19 mmol) in CCl_4 (2 mL) at *ca.* 20 ^{o}C, was added NBS (33.8 mg, 0.19 mmol) and stirred until no starting material remained. Then the reaction mixture was adsorbed onto silica and chromatography (Hexane/DCM, 7:3) gave the *title compound* **220** (52 mg, 80%) as yellow plates, mp 97.5-98.5 ^{o}C (from pentane, fridge), R_f 0.74 (Hexane/DCM, 7:3); (found: C, 56.0; H, 3.2 N, 8.2. $C_{16}H_{11}BrN_2S$ requires C, 56.0; H, 3.2; N, 8.2%); λ_{max}(DCM)/nm 246 (log ε 3.51), 350 (3.24), 381 inf (3.08), 397 (3.04); ν_{max}/cm^{-1} 3055w (Ar CH), 1574w, 1506w, 1491w, 1443w, 1341m, 1308w, 1281w, 1238w, 1173w, 1161w, 1074w, 1028w, 1007w, 995w, 974w, 922w, 841m, 802w, 793w, 716s; δ_H(500 MHz; $CDCl_3$) 7.98-7.96 (2H, m, Ph *H*), 7.85

(1H, dd, *J* 7.5, 1.3, Ph *H*), 7.48-7.46 (6H, m, Ph *H*), 6.85 (1H, s); δ_C(125 MHz; $CDCl_3$) (1 quaternary missing) 153.2 (s), 152.0 (s), 135.7 (s), 130.8 (d), 130.1 (d), 130.1 (s), 129.0 (d), 128.7 (d), 127.8 (d), 127.4 (d), 110.4 (d, *C*HBr); *m/z* (EI) 344 (M^++2, 11%), 342 (M^+, 11), 263 (778), 185 (6), 160 (100), 133 (11), 131 (17), 116 (17), 114 (21), 109 (13), 89 (9), 77 (18), 65 (6), 51 (12).

Dichloro(3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane 221

3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-one **172** (100 mg, 0.365 mmol), Ph_3P (393.5 mg, 1.50 mmol) and CCl_4 (1 mL) were placed in a MW reactor (250 W) and heated to *ca.* 140 ^oC (70 PSI) for 1 h. The reaction mixture was then allowed to cool to *ca.* 20 ^oC, diluted (DCM) and adsorbed onto silica. Chromatography (Hexane/DCM, 7:3) gave the *title compound* **221** (118.9 mg, 95%) as yellow plates, mp 154-156 ^oC (from pentane), R_f 0.75 (Hexane/DCM, 7:3); (found: C, 57.8; H, 3.0; N, 8.3. $C_{16}H_{10}Cl_2N_2S$ requires C, 57.7; H, 3.0; N, 8.4%); λ_{max}(DCM)/nm 247 (log ε 3.41), 257 inf (3.37), 358 (3.19); ν_{max}/cm^{-1} 3059w (Ar CH), 1574w, 1506w, 1489w, 1443m, 1317m, 1296m, 1246w, 1177w, 1138w, 1076w, 1026w, 928s, 914w, 878s, 843w, 781s, 768s; δ_H(500 MHz; $CDCl_3$) 7.93 (4H, d, *J* 7.5, Ph *H*), 7.50-7.43 (6H, m, Ph *H*); δ_C(125 MHz; $CDCl_3$) 148.1 (s), 134.8 (s), 130.4 (d), 128.9 (d), 127.4 (d), 126.2 (s), 121.2 (s); *m/z* (EI) 336 (M^++4, 4%), 334 (M^++2, 17), 332 (M^+, 26), 299 (13), 297 (36), 294 (33), 262 (27), 215 (6), 196 (35), 194 (100), 185 (36), 183 (56), 159 (11), 152 (6), 148 (20), 139 (9), 130 (18), 121 (6), 113 (23), 109 (9), 103 (6), 77 (22), 63 (12), 51 (18).

Dibromo(3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)methane 222

3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-one **172** (100 mg, 0.365 mmol), Ph_3P (393.5 mg, 1.50 mmol), CBr_4 (249 mg, 0.73 mmol) and dry PhH (1 mL) were placed in a sealed tube and heated to 150 ^oC for 7 h until no starting material remained (TLC). After the reaction was finished, the reaction mixture was diluted with DCM and adsorbed onto silica. Chromatography (Hexane/DCM, 7:3) gave the *title compound* **222** (144.2 mg, 91%) as yellow plates, mp (DSC) onset 151.7 ^oC, peak 153.5 ^oC (from pentane), R_f 0.75 (Hexane/DCM, 7:3); (found: C, 45.6; H, 2.4; N, 6.6. $C_{16}H_{10}Br_2N_2S$ requires C, 45.5; H, 2.4; N, 6.6%); λ_{max}(DCM)/nm 245 (log ε 3.33), 261 (3.38), 361 (3.19); ν_{max}/cm^{-1} 3057w (Ar CH), 1557w, 1508w, 1487w, 1441m, 1315s, 1294m, 1277w, 1175m, 1134m, 1076w, 1032w, 1024w, 1009w, 997w, 920w, 862s, 856m, 779s, 766s; δ_H(500 MHz; $CDCl_3$) 7.96 (4H, d, *J* 7.5, Ph *H*), 7.50-7.42 (6H, m, Ph *H*); δ_C(125 MHz; $CDCl_3$) 149.1 (s), 134.3 (s), 133.6 (s), 130.4 (d), 128.9

(d), 127.6 (d), 91.9 (s); *m/z* (EI) 424 (M^++4, 7%), 422 (M^++2, 17), 420 (M^+, 7), 343 (7), 341 (7), 262 (100), 216 (6), 159 (17), 131 (13), 113 (18), 109 (10), 77 (15), 63 (8), 51 (16).

3,5-Diphenyl-4*H*-1,2,6-thiadiazine-4-thione 223

To a stirred solution of 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-one **172** (100 mg, 0.375 mmol) in xylene (4 mL) was added P_2S_5 (83.5 mg, 0.188 mmol) and the reaction mixture was heated at *ca.* 139 ^oC until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 ^oC, filtered through a pad of silica gel and washed with hexane (30 mL) to remove xylene and then elution with Hexane/DCM (7:3), to give the *title compound* **223** (72 mg, 68%) as yellow needles, mp 109.5-110 ^oC (from pentane/DCM, at *ca.* 0 ^oC), R_f 0.65 (Hexane/DCM, 7:3); (found: C, 63.8; H, 3.5; N, 9.9. $C_{15}H_{10}N_2S_2$ requires C, 63.8; H, 3.6; N, 9.9%); λ_{max}(DCM)/nm 235 inf (log ε 3.43), 253 (3.57), 416 (3.37); ν_{max}/cm^{-1} 3030w (Ar CH), 1578w, 1466w, 1435w, 1425w, 1329m, 1319m, 1290w, 1271w, 1177w, 1152s, 1072w, 1030w, 1001w, 910w, 824m, 773m; δ_H(500 MHz; $CDCl_3$) 7.84 (4H, d, *J* 7.5, Ph *H*), 7.46-7.42 (6H, m, Ph *H*); δ_C(125 MHz; $CDCl_3$) 191.6 (s, *C*=S), 169.0 (s), 137.7 (s), 130.6 (d), 128.3 (d), 127.9 (d); *m/z* (EI) 282 (M^+, 52%), 281 (M^+-1, 100), 204 (4), 179 (8), 141 (5), 135 (13), 121 (22), 103 (41), 89 (15), 77 (19), 76 (19), 63 (6), 51 (12).

3,5-Dithien-2-yl-4*H*-1,2,6-thiadiazine-4-thione 224

Similar treatment of 3,5-dithien-2-yl-4*H*-1,2,6-thiadiazin-4-one **184** (104 mg, 0.375 mmol) gave the *title compound* **224** (50 mg, 45%) as bright green needles, mp 134-136 ^oC (from cyclohexane), R_f 0.75 (Hexane/DCM, 7:3); (found: C, 44.9; H, 2.0; N, 9.5. $C_{11}H_6N_2S_4$ requires C, 44.9; H, 2.1; N, 9.5%); λ_{max}(DCM)/nm 296 (log ε 3.35), 454 (3.15); ν_{max}/cm^{-1} 3088w (Ar CH), 1491w, 1412s, 1391w, 1350s, 1306s, 1260m, 1223w, 1211w, 1161s, 1136w, 1113w, 1078w, 1071w, 1057w, 947w, 914w, 874w, 851m, 839w, 802s; δ_H(500 MHz; $CDCl_3$) 8.29 (2H, dd, *J* 4.0, 1.0, thienyl *H*), 7.56 (2H, dd, *J* 5.0, 1.5, thienyl *H*), 7.15 (2H, dd, *J* 4.5, 4.0, thienyl *H*); δ_C(125 MHz; $CDCl_3$) 181.7 (s, *C*=S), 160.3 (s), 139.1 (s), 133.6 (d), 132.7 (d), 126.9 (d); *m/z* (EI) 294 (M^+, 100%), 293 (93), 261 (5), 210 (4), 185 (12), 147 (7), 141 (26), 139 (25), 127 (12), 115 (14), 109 (80), 95 (24), 71 (16), 69 (18), 58 (14).

2-(3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile 225

To a stirred solution of 3,5-diphenyl-4*H*-1,2,6-thiadiazine-4-thione **223** (100 mg, 0.355 mmol) in PhCl (2 mL) was added TCNE (54.6 mg, 0.426 mmol) and the reaction mixture was heated at *ca.* 132 ^{o}C until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 ^{o}C, diluted (DCM) and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1), gave the *title compound* **225** (35.6 mg, 79%) as yellow needles, mp (DSC) onset 213.2 ^{o}C, peak 214.5 ^{o}C (from pentane/DCM, 0 ^{o}C), R_f 0.40 (Hexane/DCM, 1:1); (found: C, 68.9; H, 3.2; N, 17.7. $C_{18}H_{10}N_4S$ requires C, 68.8; H, 3.2; N, 17.8%); λ_{max}(DCM)/nm 261 (log ε 3.31), 381 (2.91), 445 (3.07); ν_{max}/cm^{-1} 3046w (Ar CH), 2218m (C≡N), 1512s, 1491w, 1477s, 1439s, 1343s, 1277m, 1177w, 1159w, 1103w, 1078w, 1028w, 999w, 966w, 939w, 920w, 837w, 818s, 797m, 775m; δ_H(500 MHz; $CDCl_3$) 7.87 (4H, br s, Ph *H*), 7.59 (6H, br s, Ph *H*); δ_C(125 MHz; $CDCl_3$) 150.4 (s), 142.7 (s), 134.7 (s), 132.1 (d), 129.5 (d), 127.8 (d), 111.8 (s, *C*≡N), 79.0 [s, *C*(C≡N)$_2$]; *m/z* (EI) 314 (M$^+$, 23%), 288 (5), 210 (9), 177 (16), 167 (15), 149 (100), 138 (9), 125 (7), 121 (10), 113 (14), 111 (14), 105 (10), 99 (12), 97 (17), 93 (10), 84 (41), 77 (12), 71 (41), 57 (56), 51 (21). Further elution (DCM) gave a mixture of two purple compounds which could not be separated or characterized.

2-(3,5-Diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile 225 and 3,5-Diphenyl-4*H*-1,2,6-thiadiazine-4-thione oxide 226

To a stirred solution of 3,5-diphenyl-4*H*-1,2,6-thiadiazine-4-thione **223** (100 mg, 0.355 mmol) in PhMe (2 mL) was added TCNEO (61.3 mg, 0.426 mmol) and the reaction mixture was heated at *ca.* 110 ^{o}C until no starting material remained (TLC). The reaction mixture was then allowed to cool to *ca.* 20 ^{o}C, diluted (DCM) and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1), gave the *title compound* **225** (88 mg, 79%) as yellow needles, mp (DSC) onset 213.2 ^{o}C, peak 214.5 ^{o}C (from pentane/DCM, 0 ^{o}C), identical to that described above. Further elution (Hexane/DCM, 1:1) gave the *title compound* **226** (13.2 mg, 12%) as red flakes, mp 124-125.5 ^{o}C (from pentane/EtOH, at *ca.* 0 ^{o}C), R_f 0.50 (Hexane/DCM, 1:1); (found: C, 60.3; H, 3.3; N, 9.3. $C_{15}H_{10}N_2OS_2$ requires C, 60.4; H, 3.4; N, 9.4%); λ_{max}(DCM)/nm 251 (log ε 3.18), 284 (3.02), 426 (2.90); ν_{max}/cm^{-1} 3059w (Ar CH), 1483w, 1437w, 1321m, 1302w, 1269w, 1165w, 1142w, 1082s, 1074m, 1030w, 999w, 986w, 922w, 841w, 793m, 770m; δ_H(500 MHz; $CDCl_3$) 7.95 (2H, d, *J* 7.0, Ph *H*), 7.77-7.75 (2H, m , Ph *H*), 7.56-7.47 (6H, m, Ph *H*); δ_C(125 MHz; $CDCl_3$) 166.0 (s), 153.5 (s), 153.45 (s), 136.2 (s), 135.1 (s), 132.0 (d), 131.1 (d), 129.3 (d), 128.4 (d), 128.0 (d), 127.3 (d); *m/z* (EI) 298 (M$^+$, 100%), 281 (75), 269

(15), 265 (15), 249 (8), 220 (11), 205 (7), 190 (11), 175 (21), 167 (8), 149 (13), 146 (10), 135 (15), 121 (31), 103 (38), 89 (10), 77 (49), 63 (11), 51 (29).

2-(3,5-Dithien-2-yl-4*H*-1,2,6-thiadiazin-4-ylidene)malononitrile 227

Similar treatment of 3,5-dithien-2-yl-4*H*-1,2,6-thiadiazine-4-thione **224** (105 mg, 0.355 mmol) gave the *title compound* **227** (91.5 mg, 79%) as red needles, mp 217-220 ^{o}C (from cyclohexane), R_f 0.25 (Hexane/DCM, 7:3); (found: C, 51.4; H, 1.8; N, 17.1. $C_{14}H_6N_4S_3$ requires C, 51.5; H, 1.9; N, 17.2%); λ_{max}(DCM)/nm 259 inf (log ε 3.45), 281 (3.63), 422 (3.41), 484 (3.29); ν_{max}/cm^{-1} 3111w and 3094w (Ar CH), 2218m (C≡N), 1520m, 1505s, 1452m, 1439m, 1418s, 1348m, 1337w, 1287w, 1248w, 1225w, 1109w, 1057w, 907w, 858m, 851m, 828w, 816m; δ_H(500 MHz; $CDCl_3$) 7.66 (2H, d, *J* 5.0, thienyl *H*), 7.58 (2H, d, *J* 3.5, thienyl *H*), 7.19 (2H, dd, *J* 4.3, 4.3, thienyl *H*-4); δ_C(125 MHz; $CDCl_3$) 142.7 (s), 142.0 (s), 138.0 (s), 133.0 (d), 129.7 (d), 128.0 (d), 111.8 (*C*≡N), 78.6 (s); *m/z* (EI) 326 (M$^+$, 100%), 293 (44), 277 (4), 249 (4), 217 (7), 171 (60), 149 (12), 144 (12), 127 (12), 115 (8), 109 (46), 97 (8), 82 (11), 69 (29), 58 (23).

Ethyl 2-(3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-ylidene)acetate 228

To a stirred solution of 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-thione **223** (100 mg, 0.355 mmol) in PhMe (4 mL) at *ca.* 20 ^{o}C was added ethyl diazoacetate (56 μL, 0.533 mmol) and the reaction mixture was stirred at this temperature until no starting material remained (TLC). The reaction mixture was then diluted with DCM (20 mL) and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1) gave the *title compound* **228** as yellow plates, mp (DSC) onset 82.0 ^{o}C, peak 84.0 ^{o}C (from pentane, at *ca.* 0 ^{o}C), R_f 0.41 (Hexane/DCM, 1:1); (found: C, 67.7; H, 4.9; N, 8.3. $C_{19}H_{16}N_2O_2S$ requires C, 67.8; H, 4.8; N, 8.3%); λ_{max}(DCM)/nm 242 (log ε 3.61), 253 inf (3.58), 276 inf (3.40), 380 (3.39), 385 inf (3.36); ν_{max}/cm^{-1} 3059w (Ar CH), 2982w, 2938w, 2901w, 1703s (C=O), 1599w, 1512w, 1489w, 1472w, 1439m, 1395w, 1368w, 1354m, 1315w, 1267s, 1180w, 1153w, 1123w, 1078w, 1036m, 1007w, 966w, 930w, 876m, 833w, 806w, 776m; δ_H(500 MHz; $CDCl_3$) 7.96 (2H, d, *J* 5.0, Ph *H*), 7.89 (2H, d, *J* 7.0, Ph *H*), 7.48 (3H, br s, Ph *H*), 7.42-7.40 (3H, m, Ph *H*), 3.72 (2H, q, *J* 7.0, C*H*$_2$), 0.93 (3H, t, *J* 7.5, 7.0, C*H*$_3$); δ_C(125 MHz; $CDCl_3$) 165.3 (s), 152.3 (s), 152.2 (s), 137.8 (s), 135.5 (s), 132.1 (s), 130.7 (d), 130.0 (d), 129.0 (d), 128.7 (d), 128.0 (d), 126.0 (d), 116.6 (d, *C*HCO$_2$Et), 60.8

(CH_2), 13.7 (CH_3); *m/z* (EI) 336 (M^+, 21%), 307 (9), 291 (6), 262 (100), 216 (3), 204 (2), 185 (9), 160 (55), 133 (8), 121 (5), 116 (13), 109 (10), 103 (7), 89 (8), 77 (19), 65 (7), 51 (8).

3,3',5,5'-Tetraphenyl-4*H*,4'*H*-4,4'-bi(1,2,6-thiadiazine) 229 and 4-hydrazono-3,5-diphenyl-4*H*-1,2,6-thiadiazine 230

To a stirred solution of 3,5-diphenyl-4*H*-1,2,6-thiadiazin-4-thione **223** (100 mg, 0.355 mmol) in EtOH (4 mL) at *ca.* 20 ^oC was added hydrazine monohydrate (26.7 mg, 0.533 mmol) and the reaction mixture was heated at reflux until no starting material remained (TLC). The reaction mixture was then diluted with DCM (20 mL), washed (H_2O), dried (Na_2SO_4) and adsorbed onto silica. Chromatography (Hexane/DCM, 1:1) gave the *title compound* **229** (35.6 mg, 40%) as yellow plates, mp 262-263 ^oC (from cyclohexane); (found: C, 71.4; H, 4.7; N, 11.1. $C_{30}H_{22}N_4S_2$ requires C, 71.7; H, 4.4; N, 11.1%); λ_{max}(DCM)/nm 239 (log ε 4.03), 265 (4.08), 282 inf (3.79), 330 (3.58), 382 (3.70), 397 (3.71); ν_{max}/cm^{-1} 3059w (Ar CH), 1530w, 1516w, 1491w, 1443m, 1342w, 1323w, 1296m, 1275w, 1261w, 1225w, 1200w, 1179w, 1159w, 1101w, 1076w, 1036w, 1016w, 968w, 922w, 893w, 791m, 768m, 752s; δ_H(500 MHz; $CDCl_3$) 7.59-7.57 (4H, m, Ph *H*), 7.35-7.27 (6H, m, Ph *H*), 6.02 (1H, s); δ_C(125 MHz; $CDCl_3$) 147.7 (s), 136.5 (s), 130.5 (d), 128.4 (d), 126.3 (d), 25.4; *m/z* (EI) 251 (M^+, 100%), 149 (15), 126 (6), 121 (36), 104 (21), 89 (8), 77 (23), 51 (10). Further elution (DCM) gave the *title compound* **230** (41.8 mg, 42%) as orange plates, mp 1324-136 ^oC (from pentane); (found: C, 64.2; H, 4.2; N, 19.9. $C_{15}H_{12}N_4S$ requires C, 64.3; H, 4.3; N, 20.0%); λ_{max}(DCM)/nm 251 (log ε 3.30), 278 (3.10), 345 (3.05), 407 (2.73); ν_{max}/cm^{-1} 3402m (NH_2), 3289w, 3213w, 3053w (Ar CH), 1620w, 1566w, 1508w, 1491m, 1441m, 1352s, 1285w, 1180w, 1157w, 1126w, 1103w, 1076w, 1032w, 991w, 966w, 918w, 841m, 806w; δ_H(500 MHz; $CDCl_3$) 8.05-8.03 (2H, m, Ph *H*), 7.68-7.66 (2H, m, Ph *H*), 7.51-7.44 6, m, Ph *H*), 5.51 (2H, s, NH_2); δ_C(125 MHz; $CDCl_3$) 155.5 (s), 149.5 (s), 135.9 (s), 134.6 (s), 130.7 (d), 130.4 (d), 130.2 (s), 129.0 (d), 128.4 (d), 128.2 (d), 127.1 (d); *m/z* (EI) 280 (M^+, 100%), 264 (20), 135 (56), 132 (14), 119 (12), 108 (9), 103 (36), 91 (8), 77 (36), 74 (38), 65 (8), 51 (16).

9.8 Compounds related to Chapter 8

Ethyl 4-(2-bromophenyl)-6-methoxy-1,5-naphthyridine-3-carboxylate 237; Typical procedure (see Table 23, entry 1)

Ethyl 4-bromo-6-methoxy-1,5-naphthyridine-3-carboxylate **235** (310 mg, 1 mmol), K_2CO_3 (279 mg, 2 equiv), Pd(dppf)Cl_2·DCM (41 mg, 0.05 mmol) and 2-bromophenylboronic acid (264 mg, 1.8 mmol) were dissolved in dioxane/H_2O (3:1) (2 mL). The stirred mixture was heated to reflux (preheated oil bath) and refluxed for 2 h until the reaction was finished (TLC), before it was allowed to cool to *ca.* 20 °C. It was diluted (DCM, 20 mL), dried (Na_2SO_4), filtered and adsorbed onto silica gel. Dry flash chromatography (Hexane/*t*-BuOMe, 4:1) gave the *title compound* **237** (378 mg, 98%) as colorless cubes mp 80-81 °C (DCM/pentane), R_f 0.60 (Hexane/*t*-BuOMe, 8:2); (found: C, 55.7; H, 3.8; N, 7.3. $C_{18}H_{15}BrN_2O_3$ requires C, 55.8; H, 3.9; N, 7.2%); λ_{max}(DCM)/nm 231 (log ε 4.01), 264 (3.14), 333 (3.36); ν_{max}/cm^{-1} 1703s, 1612m, 1498m, 1402m, 1338m, 1255m, 1110m, 840m, 748s; δ_H(500 MHz; CD_2Cl_2) 9.28 (1H, s, Naph *H*-2), 8.27 (1H, d, *J* 9.0, Naph *H*-7), 7.69 (1H, d, *J* 7.9, Ar *H*), 7.40 (1H, ddd, *J* 7.4, 7.4, 1.3, Ar *H*), 7.30 (1H, ddd, *J* 8.5, 7.6, 1.7, Ar *H*), 7.21 (1H, dd, *J* 7.6, 1.6, Ar *H*), 7.17 (1H, d, *J* 9.2, Ar *H*), 4.15 (2H, q, *J* 7.1, OCH_2), 3.70 (3H, s, OCH_3), 1.05 (3H, t, *J* 7.1, CH_3); δ_C(125 MHz; CD_2Cl_2) 166.0 (s), 162.7 (s), 148.5 (d), 147.3 (s), 144.3 (s), 140.4 (d), 140.0 (s), 138.5 (s), 132.2 (d), 130.9 (d), 129.4 (d), 126.9 (d), 126.3 (s), 123.2 (s), 118.3 (d), 61.8 (O*C*H_2), 54.0 (O*C*H_3), 13.9 (*C*H_3); *m/z* (EI) 308 (M^++1, 21%), 307 (M^+-Br, 100), 279 (75), 247 (8), 236 (12), 191 (14), 164 (12).

4-(2-Chlorophenyl)-6-methoxy-1,5-naphthyridine-3-carboxylate 238

(307 mg, 90%) as colorless plates, mp 67-69 °C (pentane), R_f 0.60 (Hexane/*t*-BuOMe, 8:2); (found: C, 63.2; H, 4.4; N, 8.1. $C_{18}H_{14}ClN_2O_3$ requires C, 63.1; H, 4.4; N, 8.2%); λ_{max}(DCM)/nm 236 (log ε 4.03), 261 (3.63), 270 (3.61), 282 inf (3.49), 327 (3.49), 339 (3.46); ν_{max}/cm^{-1} 2992w, 2941w, 1705s (C=O), 1612m, 1562w, 1501m, 1479w, 1464w, 1433w, 1402s, 1366m, 1339s, 1321s, 1290m, 1261s, 1256m, 1223m, 1206m, 1180w, 1134m, 1113m, 1059w, 1034s, 1018m, 999w, 932w, 868w, 843s, 812w, 775m, 760m; δ_H(500 MHz; CD_2Cl_2) 9.28 (1H, s, Naph *H*-2), 8.27 (1H, d, *J* 9.0, Naph *H*-7), 7.50 (1H, dd, *J* 7.7, 1.4, Ar *H*), 7.39 (1H, ddd, *J* 7.5, 7.5, 1.8, Ar *H*), 7.36 (1H, ddd, *J* 7.5, 7.5, 1.5, Ar *H*), 7.24 (1H, dd, *J* 7.3, 1.9, Ar *H*), 7.17 (1H, d, *J* 9.2, Naph *H*-8), 4.15 (2H, q, *J* 7.1, OCH_2), 3.70 (3H, s, OCH_3), 1.05 (3H,

t, *J* 7.2, C*H*$_3$); δ_C(125 MHz; CD_2Cl_2) 166.1 (s), 162.8 (s), 148.5 (d), 145.8 (s), 144.2 (s), 140.4 (d), 140.1 (s), 136.3 (s), 133.3 (s), 131.1 (d), 129.4 (d), 129.1 (d), 126.6 (s), 126.3 (d), 118.3 (d), 61.8 (O*C*H$_2$), 54.0 (O*C*H$_3$), 13.9 (*C*H$_3$); *m/z* (EI) 308 (MH^+-Cl, 20%), 307 (M^+-Cl, 100), 280 (14), 279 (68), 264 (17), 247 (12), 236 (8), 226 (7), 219 (8), 201 (5), 191 (10), 165 (5), 164 (11), 113 (5).

Ethyl 4-(2,3-dichlorophenyl)-6-methoxy-1,5-naphthyridine-3-carboxylate 239

(373 mg, 99%) as colorless cubes, mp 107-108 ºC (pentane), R_f 0.30 (Hexane/*t*-BuOMe, 8:2); (found: C, 57.5; H, 3.9; N, 7.3. $C_{18}H_{14}Cl_2N_2O_3$ requires C, 57.3; H, 3.7; N, 7.4%); λ_{max}(DCM)/nm 232 (log ε 3.94), 261 (3.32), 269 (3.28), 327 (3.27), 339 (3.25); ν_{max}/cm^{-1} 3046w (Ar CH), 2990w, 2941w, 1713s (C=O), 1612m, 1499s, 1479w, 1450w, 1402m, 1371w, 1339m, 1323s, 1277m, 1261m, 1225m, 1180w, 1144m, 1117m, 1038m, 1018m, 991w, 941w, 848m, 816m, 789m, 773w; δ_H(300 MHz; CD_2Cl_2) 9.30 (1H, s, Naph *H*-2), 8.27 (1H, d, *J* 9.3, Naph *H*-7), 7.57 (1H, dd, *J* 7.8, 1.8, Ar *H*), 7.31 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.18 (1H, d, *J* 9.0, Naph *H*-8), 7.14 (1H, dd, *J* 7.5, 1.5, Ar *H*), 4.16 (2H, q, *J* 7.0, OC*H*$_2$), 3.69 (3H, s, OC*H*$_3$), 1.07 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 165.7 (s), 162.9 (s), 148.6 (d), 145.4 (s), 144.4 (s), 140.4 (d), 139.9 (s), 138.8 (s), 132.8 (s), 131.7 (s), 129.9 (d), 129.2 (d), 127.1 (d), 126.0 (s), 118.6 (d), 61.9 (O*C*H$_2$), 54.0 (O*C*H$_3$), 13.9 (*C*H$_3$); *m/z* (EI) 378 (M^++2, 0.2%), 376 (M^+, 0.2), 343 [(M^++2)-Cl, 36], 341 (M^+-Cl, 100), 333 (2), 331 (4), 315 (17), 313 (61), 298 (10), 278 (7), 270 (11), 254 (7), 225 (7), 198 (8), 189 (4), 162 (8), 126 (5), 99 (5), 63 (9).

Ethyl 4-(2,4-dichlorophenyl)-6-methoxy-1,5-naphthyridine-3-carboxylate 240

(323 mg, 86%) as colorless cubes, mp 82-83 ºC (pentane), R_f 0.29 (Hexane/*t*-BuOMe, 8:2); (found: C, 57.5; H, 3.7; N, 7.4. $C_{18}H_{14}Cl_2N_2O_3$ requires C, 57.3; H, 3.7; N, 7.4%); λ_{max}(DCM)/nm 232 (log ε 3.66), 261 inf (2.87), 270 inf (2.76), 329 (2.95), 339 (2.93); ν_{max}/cm^{-1} 2986w, 2941w, 1712s (C=O), 1612m, 1595w, 1570w, 1557w, 1501s, 1464m, 1435w, 1404s, 1366m, 1340m, 1321s, 1281s, 1267s, 1248m, 1225m, 1207m, 1180w, 1138s, 1115m, 1099m, 1057m, 1034m, 1016m, 1001w, 932w, 866m, 845s, 833s, 814m, 791m, 775m; δ_H(300 MHz; CD_2Cl_2) 9.30 (1H, s, Naph *H*-2), 8.26 (1H, d, *J* 9.0, Naph *H*-7), 7.55 (1H, d, *J* 2.1, Ar *H*), 7.37 (1H, dd, *J* 8.3, 2.1, Ar *H*), 7.25-7.20 (2H, m, Ar & Naph *H*), 4.19 (2H, q, *J* 7.2, OC*H*$_2$), 3.72 (3H, s, OC*H*$_3$), 1.11 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 165.8 (s), 162.9 (s), 148.4 (d), 144.8 (s), 144.2 (s), 140.3 (d), 139.9 (s), 135.1 (s), 134.3 (s), 134.1 (s), 132.0 (d), 129.0 (d), 126.7 (d), 126.3 (s), 118.6 (d), 62.0 (O*C*H$_2$), 54.1 (O*C*H$_3$), 14.0 (*C*H$_3$); *m/z* (EI) 343 [(M^++2)-

Cl, 33%], 341 (M^+-Cl, 100), 333 (3), 331 (5), 315 (19), 313 (63), 298 (14), 278 (5), 270 (7), 253 (7), 225 (9), 198 (11), 190 (4), 163 (3), 147 (5), 124 (3), 99 (4), 80 (5).

Ethyl 4-[2-chloro-4-(trifluoromethyl)phenyl]-6-methoxy-1,5-naphthyridine-3-carboxylate 241

(377 mg, 92%) as colorless prisms, mp 90-91 ºC (pentane), R_f 0.29 (Hexane/*t*-BuOMe, 8:2); (found: C, 55.6; H, 3.3; N, 6.6. $C_{19}H_{14}ClF_3N_2O_3$ requires C, 55.6; H, 3.4; N, 6.8%); λ_{max}(DCM)/nm 233 (log ε 3.71), 272 (2.83), 325 (2.97), 340 (2.89); ν_{max}/cm^{-1} 2986w, 2945w, 1713m (C=O), 1612m, 1499m, 1472w, 1406w, 1391w, 1368w, 1343w, 1323s, 1288w, 1271m, 1254w, 1227w, 1209w, 1177s, 1138s, 1117w, 1082m, 1063w, 1036w, 1015w, 1003w, 934w, 897w, 868w, 843m, 814w; δ_H(300 MHz; CD_2Cl_2) 9.33 (1H, s, Naph *H*-2), 8.28 (1H, d, *J* 9.0, Naph *H*-7), 7.80 (1H, s, Ar *H*), 7.64 (1H, d, *J* 8.1, Ar *H*), 7.39 (1H, d, *J* 8.1, Ar *H*), 7.20 (1H, d, *J* 9.0, Naph *H*-8), 4.17 (2H, q, *J* 7.1, OC*H*$_2$), 3.68 (3H, s, OC*H*$_3$), 1.06 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 165.6 (s), 163.0 (s), 148.6 (d), 144.5 (s), 144.4 (s), 140.7 (s), 140.4 (d), 139.7 (s), 134.1 (s), 131.6 (d), 131.2 (q, $^2J_{CF}$ 33.2, F_3CC), 125.9 (q, $^3J_{CF}$ 3.8, F_3CC_qCH), 122.3 (q, $^3J_{CF}$ 3.8, F_3CC_qCH), 123.1 (q, $^1J_{CF}$ 269.8, F_3C), 118.8 (d), 62.0 (O*C*H$_2$), 54.1 (O*C*H$_3$), 13.8 (*C*H$_3$); *m/z* (EI) 411 (M^++H, 0.5%), 409 (M^+-H, 1), 376 (MH^+-Cl, 22), 375 (M^+-Cl, 100), 365 (4), 347 (70), 332, (10), 315 (4), 304 (6), 294 (5), 287 (4), 259 (5), 232 (6), 80 (4), 64 (2).

Ethyl 4-(2-chloro-4-methylphenyl)-6-methoxy-1,5-naphthyridine-3-carboxylate 242

(299 mg, 84%) as colorless cubes, mp 69-71 ºC (pentane), R_f 0.35 (Hexane/*t*-BuOMe, 8:2); (found: C, 64.1; H, 4.7; N, 7.7. $C_{19}H_{17}ClN_2O_3$ requires C, 64.0; H, 4.8; N, 7.9%); λ_{max}(DCM)/nm 237 (log ε 4.18), 250 inf (3.90), 258 inf (3.78), 267 inf (3.67), 329 (3.77); ν_{max}/cm^{-1} 2982w, 2943w, 2853w, 1726s (C=O), 1609m, 1574w, 1493s, 1468w, 1433w, 1402m, 1368m, 1341m, 1283m, 1259s, 1223s, 1207m, 1140m, 1138m, 1111m, 1059w, 1038w, 1024m, 993w, 943w, 878w, 851m, 829m, 818w, 772m; δ_H(500 MHz; CD_2Cl_2) 9.25 (1H, s, Naph *H*-2), 8.26 (1H, d, *J* 9.0, Naph *H*-7), 7.33 (1H, s, Ar *H*), 7.17 (1H, d, *J* 9.0, Naph *H*-8), 7.13-7.11 (2H, m, Ar *H*), 4.17 (2H, q, *J* 7.2, OC*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 2.43 (3H, s, C*H*$_3$), 1.09 (3H, t, *J* 7.2, C*H*$_3$); δ_C(125 MHz; CD_2Cl_2) 166.2 (s), 162.7 (s), 148.4 (d), 145.9 (s), 144.2 (s), 140.9 (d), 140.3 (s), 139.8 (s), 133.0 (s), 132.9 (C_q), 130.9 (d), 129.6 (d), 127.1 (d), 126.9 (s), 118.2 (d), 61.8 (O*C*H$_2$), 54.0 (O*C*H$_3$), 21.3 (*C*H$_3$), 14.0 (*C*H$_3$); *m/z* (EI) 322 (MH^+-

Cl, 19%), 321 (M^+-Cl, 100), 311 (4), 293 (53), 278 (11), 261 (4), 250 (6), 240 (4), 233 (6), 205 (6), 178 (3), 151 (3), 138 (3), 127 (2).

Ethyl 4-(2-chloro-4-methoxyphenyl)-6-methoxy-1,5-naphthyridine-3-carboxylate 243

(335 mg, 90%) as colorless cubes, mp 97-99 ºC (pentane), R_f 0.23 (Hexane/*t*-BuOMe, 8:2); (found: C, 61.1; H, 4.6; N, 7.4. $C_{19}H_{17}ClN_2O_4$ requires C, 61.2; H, 4.6; N, 7.5%); λ_{max}(DCM)/nm 234 (log ε 4.11), 248 inf (3.77), 259 inf (3.67), 269 inf (3.55), 288 (3.39), 326 (3.55); ν_{max}/cm^{-1} 2984w, 2943w, 2907w, 2832w, 1726s (C=O), 1609s, 1572w, 1506w, 1491s, 1464w, 1427m, 1402m, 1368w, 1339m, 1310w, 1277m, 1260s, 1236s, 1217s, 1206s, 1182w, 1136m, 1109m, 1043m, 1036m, 1018m, 991w, 943w, 889m, 878w, 851s, 831s, 772m; δ_H(300 MHz; CD_2Cl_2) 9.23 (1H, s, Naph *H*-2), 8.25 (1H, d, *J* 9.0, Naph *H*-7), 7.17 (2H, d, *J* 8.4, Ar *H*), 7.07 (1H, d, *J* 3.9, Ar *H*), 6.92 (1H, dd, *J* 8.4, 3.6, Ar *H*), 4.18 (2H, q, *J* 7.0, OCH_2), 3.87 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 1.11 (3H, t, *J* 7.2, CH_3); δ_C(75 MHz; CD_2Cl_2) 166.2 (s), 162.7 (s), 160.3 (s), 148.2 (d), 145.7 (s), 144.0 (s), 140.4 (s), 140.2 (d), 133.9 (s), 131.9 (d), 128.0 (s), 127.1 (s), 118.3 (d), 114.4 (d), 112.4 (d), 61.8 (OCH_2), 56.0 (OCH_3), 54.0 (OCH_3), 14.0 (CH_3); *m/z* (EI) 338 (MH^+-Cl, 25%), 337 (M^+-Cl, 100), 327 (5), 309 (42), 294 (13), 277 (3), 265 (4), 251 (8), 241 (3), 221 (3), 213 (3), 178 (3), 151 (4), 99 (3).

Ethyl 4-(2-chloro-4-fluorophenyl)-6-methoxy-1,5-naphthyridine-3-carboxylate 244

(320 mg, 89%) as colorless cubes, mp 75-77 ºC (pentane), R_f 0.35 (Hexane/*t*-BuOMe, 8:2); (found: C, 60.1; H, 3.9; N, 7.8. $C_{18}H_{14}ClFN_2O_3$ requires C, 59.9; H, 3.9; N, 7.8%); λ_{max}(DCM)/nm 233 (log ε 3.88), 261 (3.32), 271 (3.29), 325 (3.20), 339 (3.14); ν_{max}/cm^{-1} 3048w, 2986w, 1730s (C=O), 1611m, 1572w, 1495s, 1470w, 1435w, 1402m, 1369w, 1339m, 1273s, 1234m, 1213m, 1200m, 1182w, 1144w, 1113w, 1036w, 1016m, 991w, 945w, 899m, 853s, 820w, 804w, 774m; δ_H(300 MHz; CD_2Cl_2) 9.28 (1H, s, Naph *H*-2), 8.26 (1H, d, *J* 9.0, Naph *H*-7), 7.30-7.11 (4H, m, Ar *H*), 4.18 (2H, q, *J* 7.1, OCH_2), 3.72 (3H, s, OCH_3), 1.10 (3H, t, *J* 9.0, CH_3); δ_C(75 MHz; CD_2Cl_2) 165.9 (s), 164.2 (s), 161.9 (d, $^1J_{CF}$ 249.2, F*C*), 148.5 (d), 144.9 (s), 144.3 (s), 140.4 (d), 140.1 (s), 134.1 (d, $^3J_{CF}$ 10.6, FCCH*C*Cl), 132.1 (d, $^4J_{CF}$ 3.8, FCCHCHC_q), 132.4 (d, $^3J_{CF}$ 9.1, FCCH*C*H), 126.6 (s), 118.5 (d), 116.5 (d, $^2J_{CF}$ 25.7, FC*C*H), 113.7 (d, $^2J_{CF}$ 21.9, FC*C*H), 61.9 (OCH_2), 54.0 (OCH_3), 14.0 (CH_3); *m/z* (EI) 325 (M^+-Cl, 100%), 315 (5), 297 (55), 282 (13), 265 (7), 254 (7), 244 (7), 237 (6), 223 (3), 209 (8), 182 (11), 156 (3), 131 (5), 80 (3).

Ethyl 4-(2,5-dichlorophenyl)-6-methoxy-1,5-naphthyridine-3-carboxylate 245

(345 mg, 92%) as colorless cubes, mp 85-86 ºC (pentane), R_f 0.35 (Hexane/*t*-BuOMe, 8:2); (found: C, 57.3; H, 3.7; N, 7.5. $C_{18}H_{14}Cl_2N_2O_3$ requires C, 57.3; H, 3.7; N, 7.4%); λ_{max}(DCM)/nm 232 (log ε 3.74), 261 inf (2.93), 268 inf (2.84), 328 inf (3.01), 340 inf (2.99); ν_{max}/cm^{-1} 2990w, 2957w, 2905w, 1711s (C=O), 1612m, 1558w, 1497s, 1456m, 1431w, 1402s, 1379w, 1368m, 1339m, 1317s, 1275m, 1263m, 1252m, 1225m, 1207m, 1177w, 1140m, 1128m, 1113m, 1094m, 1055m, 1032m, 1011w, 988w, 883w, 870w, 849s, 824m, 814m; δ_H(500 MHz; CD_2Cl_2) 9.31 (1H, s, Naph *H*-2), 8.27 (1H, d, *J* 9.0, Naph *H*-7), 7.45 (1H, d, *J* 8.7, Ar *H*), 7.38 (1H, d, *J* 8.4, Ar *H*), 7.27 (1H, s, Ar *H*), 7.19 (1H, d, *J* 9.0, Naph *H*-8), 4.20 (2H, q, *J* 6.7, OC*H*$_2$), 3.73 (3H, s, OC*H*$_3$), 1.11 (3H, t, *J* 7.1, C*H*$_3$); δ_C(125 MHz; CD_2Cl_2) 165.7 (s), 162.9 (s), 148.5 (d), 144.5 (s), 144.4 (s), 140.4 (d), 139.8 (s), 138.0 (s), 132.1 (s), 131.9 (s), 130.9 (d), 130.3 (d), 129.3 (d), 126.1 (s), 118.7 (d), 62.0 (O*C*H$_2$), 54.1 (O*C*H$_3$), 14.0 (*C*H$_3$); *m/z* (EI) 343 [(M$^+$+2)-Cl, 40%], 341 (M$^+$-Cl, 100), 333 (2), 331 (4), 315 (24), 313 (60), 298 (17), 278 (5), 270 (12), 253 (6), 225 (8), 198 (9), 147 (4), 99 (3), 80 (4).

Ethyl 4-[2-chloro-5-(trifluoromethyl)phenyl]-6-methoxy-1,5-naphthyridine-3-carboxylate 246

(377 mg, 92%) as colorless cubes, mp 89-90 ºC (pentane), R_f 0.47 (Hexane/*t*-BuOMe, 8:2); (found: C, 55.6; H, 3.1; N, 6.8. $C_{19}H_{14}ClF_3N_2O_3$ requires C, 55.6; H, 3.4; N, 6.8%); λ_{max}(DCM)/nm 232 (log ε 3.70), 262 (3.02), 271 (2.98), 329 (3.00), 341 (2.99); ν_{max}/cm^{-1} 2990w, 2947w, 1724m (C=O), 1611m, 1574w, 1495m, 1437w, 1400m, 1371w, 1344m, 1325m, 1300w, 1287m, 1263s, 1219m, 1206w, 1167m, 1148m, 1125s, 1113m, 1080s, 1040w, 1018m, 989w, 928w, 876w, 845m, 833m, 816w, 793w; δ_H(300 MHz; CD_2Cl_2) 9.34 (1H, s, Naph *H*-2), 8.29 (1H, d, *J* 9.0, Naph *H*-7), 7.66 (2H, s, Ar *H*), 7.56 (1H, s, Ar *H*), 7.20 (1H, d, *J* 9.0, Naph *H*-8), 4.17 (2H, q, *J* 7.5, OC*H*$_2$), 3.68 (3H, s, OC*H*$_3$), 1.06 (3H, t, *J* 7.4, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 165.6 (s), 163.0 (s), 148.6 (d), 144.5 (s), 144.1 (s), 140.4 (d), 139.8 (s), 137.4 (s), 129.8 (d), 127.9 (q, $^2J_{CF}$ 33.0, F_3C*C*), 128.9 (s), 128.4 (q, $^3J_{CF}$ 3.7, F_3CC*C*H), 126.3 (q, $^3J_{CF}$ 3.7, F_3CCC*H*), 126.0 (q, $^1J_{CF}$ 246.0, F_3*C*), 122.7 (s), 118.7 (d), 62.0 (O*C*H$_2$), 54.0 (O*C*H$_3$), 13.9 (*C*H$_3$); *m/z* (EI) 376 (MH$^+$-Cl, 22%), 375 (M$^+$-Cl, 100), 365 (4), 347 (70), 332 (11), 315 (4), 304 (6), 294 (5), 287 (4), 259 (5), 232 (6), 80 (4).

Ethyl 3-(2-chloropyrid-3-yl)-6-methoxy-1,5-naphthyridine-3-carboxylate 247

(220 mg, 64%) as colorless cubes, mp 120-122 ºC (pentane), R_f 0.77 (*t*-BuOMe); (found: C, 59.4; H, 4.1; N, 12.3. $C_{17}H_{14}ClN_3O_3$ requires C, 59.4; H, 4.1; N, 12.2%); λ_{max}(DCM)/nm 232 (log ε 3.69), 263 (3.07), 328 (3.01), 338 (3.00); ν_{max}/cm^{-1} 3044w, 2986w, 2945w, 2907w, 1722s (C=O), 1611m, 1572w, 1557w, 1495s, 1479w, 1449w, 1429w, 1395s, 1371w, 1341m, 1281m, 1261m, 1234s, 1215m, 1179w, 1146w, 1115m, 1074w, 1015m, 974w, 851m, 810m, 773m; δ_H(500 MHz; CD_2Cl_2) 9.38 (1H, s, Naph *H*-2), 8.50 (1H, br s, Ar *H*), 8.32 (1H, d, *J* 9.0, Naph *H*-7), 7.66 (1H, d, *J* 7.4 Ar *H*), 7.43-7.41 (1H, m, Ar *H*), 7.24 (1H, d, *J* 9.2, Naph *H*-8), 4.24-4.22 (3H, m, OCH_2), 3.74 (3H, s, OCH_3), 1.13 (3H, t, *J* 7.0, CH_3); δ_C(125 MHz; CD_2Cl_2); 165.6 (s), 162.9 (s), 149.8 (s), 149.0 (d), 148.6 (d), 144.5 (s), 143.9 (s), 140.4 (d), 139.8 (s), 139.7 (d), 133.1 (s), 125.9 (s), 122.0 (d), 118.8 (d), 62.0 (O*C*H$_2$), 54.1 (O*C*H$_3$), 14.0 (*C*H$_3$); *m/z* (EI) 309 (MH$^+$-Cl, 19%), 308 (M$^+$-Cl, 100), 298 (3), 280 (69), 252 (7), 237 (4), 227 (4), 220 (3), 206 (4), 192 (5), 165 (6), 138 (3), 126 (2), 114 (2), 100 (2), 87 (2).

Ethyl 4-(3-chloropyrid-4-yl)-6-methoxy-1,5-naphthyridine-3-carboxylate 248

(220 mg, 64%) as colorless needles, mp 95-97 ºC (pentane), R_f 0.77 (*t*-BuOMe); (found: C, 59.5; H, 4.3; N, 12.2. $C_{17}H_{14}ClN_3O_3$ requires C, 59.4; H, 4.1; N, 12.2%); λ_{max}(DCM)/nm 229 (log ε 3.31), 249 (2.82), 261 inf (2.85), 267 (2.87), 318 (2.97), 327 (2.97); ν_{max}/cm^{-1} 2982w, 2922w, 1726m (C=O), 1612w, 1587w, 1566w, 1499m, 1464w, 1433w, 1402m, 1371w, 1339m, 1288m, 1263m, 1225m, 1207w, 1180w, 1138w, 1121m, 1096s, 1024m, 980w, 932s, 901s, 854m, 818w, 770w; δ_H(500 MHz; CD_2Cl_2) 9.35 (1H, s, Naph *H*-2), 8.70 (1H, s, Ar *H*), 8.56 (1H, s, Ar *H*), 8.28 (1H, d, *J* 9.0, Naph *H*-7), 7.21-7.19 (2H, m, Ar *H*), 4.19 (3H, q, *J* 6.6, OCH_2), 3.69 (3H, s, OCH_3), 1.09 (3H, t, *J* 7.0, CH_3); δ_C(125 MHz; CD_2Cl_2); 165.3 (s), 163.0 (s), 149.2 (d), 148.6 (d), 147.3 (d), 144.8 (s), 144.5 (s), 143.0 (s), 140.4 (d), 139.3 (s), 131.3 (s), 125.5 (s), 125.3 (d), 118.9 (d), 62.1 (O*C*H$_2$), 54.1 (O*C*H$_3$), 13.8 (CH$_3$); *m/z* (EI) 309 (MH$^+$-Cl, 19%), 308 (M$^+$-Cl, 100), 298 (3), 280 (65), 252 (7), 237 (4), 227 (4), 206 (4), 192 (5), 165 (5), 138 (2), 114 (2).

Ethyl 4-(2-bromophenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 249; Typical procedure (Table 24)

To a stirred solution of ethyl 4-(2-bromophenyl)-6-methoxy-1,5-naphthyridine-3-carboxylate **237** (187 mg, 0.5 mmol) and NaI (255 mg, 1.5 mmol) in MeCN (1 mL) was added dropwise TMSCl (314 μL, 2.5 mmol). An orange suspension formed in the reaction mixture which was

then refluxed for 1-2 h until the reaction was finished (TLC). The reaction was diluted with H_2O (10 mL) and $Na_2S_2O_2$ (25 mg) was added. The mixture was extracted (DCM, 15 mL), dried (Na_2SO_4), filtered and adsorbed onto silica gel. Dry flash chromatography (*t*-BuOMe) gave the *title compound* **249** (130 mg, 70%) as colorless plates, mp 201-203 ºC (*t*-BuOMe), R_f 0.36 (*t*-BuOMe, 8:2); (found: C, 54.5; H, 3.9; N, 7.3. $C_{17}H_{13}BrN_2O_3$ requires C, 54.7; H, 3.5; N, 7.5%); λ_{max}(DCM)/nm 233 (log ε 3.10), 349 (2.68); ν_{max}/cm^{-1} 1718m (C=O), 1666s (NHC=O), 1317m, 1213m, 1141m, 1028w, 900w, 852m, 758m; δ_H(500 MHz; CD_2Cl_2) 9.08 (1H, s, Naph *H*-2), 8.33 (1H, br s, N*H*), 8.01 (1H, d, *J* 9.8, Naph *H*-7), 7.77 (1H, dd, *J* 7.9, 1.1, Ar *H*), 7.50 (1H, ddd, *J* 7.5, 7.6, 1.1, Ar *H*), 7.43 (1H, ddd, *J* 8.0, 7.6, 1.7, Ar *H*), 7.23 (1H, dd, *J* 7.6, 1.6, Ar *H*), 6.84 (1H, d, *J* 9.8, Naph *H*-8), 4.11 (2H, q, *J* 7.1, OC*H*$_2$), 1.03 (3H, t, *J* 7.1, C*H*$_3$); δ_C(125 MHz; CD_2Cl_2) 165.0 (s), 161.6 (s), 146.4 (d), 142.0 (d), 140.4 (s), 135.5 (s), 133.9 (d), 133.8 (s), 132.7 (s), 131.5 (d), 130.8 (d), 128.8 (d), 128.1 (d), 126.3 (s), 123.5 (s), 62.0 (*C*H$_2$), 13.9 (*C*H$_3$); *m/z* (EI) 373 (M$^+$+1, 1%), 372 (M$^+$, 2), 293 (M$^+$-Br, 35), 266 (11), 220 (5), 192 (9).

Ethyl 4-(2-chlorophenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 250

(150 mg, 81%) as colorless needles, mp 130-132 ^{o}C (*t*-BuOMe), R_f 0.35 (*t*-BuOMe); (found: C, 62.2; H, 4.0; N, 8.6. $C_{17}H_{13}ClN_2O_3$ requires C, 62.1; H, 4.0; N, 8.5%); λ_{max}(DCM)/nm 235 (log ε 3.89), 262 (3.51), 271 (3.50), 338 inf (3.37), 348 (3.48), 363 (3.36); ν_{max}/cm^{-1} 3036w, 2990w, 2953w, 2926w, 1715m (C=O), 1661s (NHC=O), 1605m, 1580w, 1487w, 1450w, 1431w, 1366m, 1325m, 1314m, 1250w, 1234w, 1207m, 1138m, 1109m, 1059w, 1022w, 930w, 856w, 826w, 768m; δ_H(500 MHz; CD_2Cl_2) 9.07 (1H, s, Naph *H*-2), 8.45 (1H, br s, N*H*), 8.01 (1H, d, *J* 9.8, Naph *H*-7), 7.59 (1H, dd, *J* 8.1, 1.0, Ar *H*), 7.51 (1H, ddd, *J* 7.6, 7.9, 1.8, Ar *H*), 7.46 (1H, ddd, *J* 7.5, 7.6, 1.2, Ar *H*), 7.24 (1H, dd, *J* 7.6, 1.6, Ar *H*), 6.84 (1H, d, *J* 9.8, Naph *H*-7), 4.80 (2H, dq, *J* 7.2, 1.6, OC*H*$_2$), 1.03 (3H, t, *J* 7.2, C*H*$_3$); δ_C(125 MHz; CD_2Cl_2) 165.1 (s), 161.6 (s), 146.3 (d), 142.0 (d), 140.3 (s), 134.0 (s), 133.8 (s), 132.9 (s), 131.7 (s), 131.5 (d), 130.7 (d), 130.6 (d), 128.2 (d), 128.1 (d), 126.6 (s), 62.0 (O*C*H$_2$), 13.9 (*C*H$_3$); *m/z* (EI) 330 (M$^+$+2, 3%), 328 (M$^+$, 6), 293 (M$^+$-Cl, 69), 265 (100), 247 (7), 219 (8), 192 (11), 164 (6), 139 (3), 113 (6), 63 (3).

Ethyl 4-(2,3-dichlorophenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 251

(166 mg, 92%) as colorless plates, mp 171.5-172.5 ºC (*t*-BuOMe), R_f 0.38 (*t*-BuOMe); (found: C, 56.4; H, 3.3; N, 7.6. $C_{17}H_{12}Cl_2N_2O_3$ requires C, 56.2; H, 3.3; N, 7.7%); λ_{max}(DCM)/nm 232 (log ε 3.59), 250 inf (3.01), 259 inf (2.88), 268 inf (2.75), 337 inf (3.03), 349 (3.15), 362 (3.04); ν_{max}/cm^{-1} 2978w, 2932w, 1724m (C=O), 1665s (NHC=O), 1607w, 1578w, 1487w, 1450w, 1418w, 1395w, 1379w, 1325w, 1304m, 1281w, 1217m, 1144m, 1117m, 1098w, 1047w, 1026w, 972w, 928w, 851m, 783m; δ_H(500 MHz; CD_2Cl_2) 9.10 (1H, s, Naph *H*-2), 8.59 (1H, br s, N*H*), 8.02 (1H, d, *J* 9.8, Naph *H*-7), 7.67 (1H, d, *J* 8.0, Ar *H*), 7.41 (1H, dd, *J* 7.8, 7.8, Ar *H*), 7.15 (1H, d, *J* 7.6, Ar *H*), 6.84 (1H, d, *J* 9.8, Naph *H*-8), 4.13 (2H, m, OCH_2), 1.05 (3H, t, *J* 7.1, CH_3); δ_C(125 MHz; CD_2Cl_2) 164.8 (s), 161.7 (s), 146.5 (d), 142.0 (d), 140.6 (s), 134.7 (s), 134.1 (s), 133.6 (s), 132.7 (s), 132.5 (s), 132.0 (d), 129.0 (d), 128.9 (d), 128.2 (d), 126.1 (s), 62.1 (O*C*H$_2$), 13.9 (*C*H$_3$); *m/z* (EI) 364 (M$^+$+2, 3%), 362 (M$^+$, 5), 329 (20), 327 (M$^+$-Cl, 63), 317 (5), 301 (36), 299 (100), 281 (6), 264 (20), 253 (7), 226 (13), 207 (7), 198 (4), 191 (6), 173 (5), 164 (8), 147 (8), 138 (6), 127 (4), 113 (7), 99 (6), 64 (5), 57 (7).

Ethyl 4-(2,4-dichlorophenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 252

(150 mg, 83%) as colorless plates, mp 155-156.5 ºC (*t*-BuOMe), R_f 0.38 (*t*-BuOMe); (found: C, 56.4; H, 3.3; N, 7.8. $C_{17}H_{12}Cl_2N_2O_3$ requires C, 56.2; H, 3.3; N, 7.7%); λ_{max}(DCM)/nm 233 (log ε 3.61), 259 inf (2.99), 268 inf (2.90), 338 inf (3.04), 349 (3.15), 362 (3.04); ν_{max}/cm^{-1} 3090w, 3032w, 2941w, 1732m (C=O), 1707m, 1659s (NHC=O), 1603w, 1557w, 1481w, 1447w, 1379w, 1368w, 1327m, 1310w, 1296m, 1206w, 1144m, 1130m, 1115w, 1099w, 1059w, 1030w, 1016w, 997w, 856m, 835w, 822w, 773w, 760w; δ_H(500 MHz; CD_2Cl_2) 9.09 (1H, s, Naph *H*-2), 8.82 (1H, br s, N*H*), 8.02 (1H, d, *J* 9.9, Naph *H*-7), 7.62 (1H, s, Ar *H'*-3), 7.45 (1H, d, *J* 8.2, Ar *H'*-5), 7.19 (1H, d, *J* 8.1, Ar *H'*-6), 6.83 (1H, d, *J* 9.8, Naph *H*-8), 4.15 (2H, q, *J* 7.0, OCH_2), 1.10 (3H, t, *J* 7.1, CH_3); δ_C(125 MHz; CD_2Cl_2) 164.9 (s), 161.9 (s), 146.4 (d), 142.1 (d), 140.5 (s), 136.7 (s), 134.8 (s), 133.0 (s), 132.9 (s), 131.7 (d), 130.6 (d), 130.5 (s), 128.6 (d), 128.2 (d), 126.4 (s), 62.2 (O*C*H$_2$), 14.0 (*C*H$_3$); *m/z* (EI) 364 (M$^+$+2, 8%), 362 (M$^+$, 12), 329 (29), 327 (M$^+$-Cl, 82), 319 (5), 317 (7), 301 (40), 299 (100), 283 (3), 281 (8), 264 (18), 253 (10), 236 (4), 225 (18), 207 (5), 200 (4), 191 (8), 179 (3), 164 (10), 147 (11), 138 (7), 113 (8), 99 (5), 87 (4), 63 (6).

Ethyl 4-[2-chloro-4-(trifluoromethyl)phenyl]-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carb-oxylate 253

(158 mg, 80%) as colorless cubes, mp 189-191 ºC (*t*-BuOMe), R_f 0.51 (*t*-BuOMe); (found: C, 54.5; H, 3.0; N, 7.0. $C_{18}H_{12}ClF_3N_2O_3$ requires C, 54.5; H, 3.1; N, 7.1%); λ_{max}(DCM)/nm 234 (log ε 4.06), 263 (3.57), 269 (3.53), 339 inf (3.56), 349 (3.66), 362 (3.54); ν_{max}/cm^{-1} 3019w, 2986w, 2941w, 2851w, 1724m (C=O), 1665s (NHC=O), 1605m, 1487w, 1450w, 1395m, 1368w, 1321s, 1287w, 1204m, 1171m, 1134s, 1080m, 1065m, 1020w, 883m, 864m, 839m, 800w, 775w; δ_H(300 MHz; CD_2Cl_2) 9.13 (1H, s, Naph *H*-2), 8.61 (1H, br s, N*H*), 8.04 (1H, d, *J* 9.8, Naph *H*-7), 7.88 (1H, br s, Ar *H'*-3), 7.73 (1H, d, *J* 7.9, Ar *H'*-5), 7.41 (1H, d, *J* 7.9, Ar *H'*-6), 6.84 (1H, d, *J* 9.8, Naph *H*-8), 4.12 (2H, q, *J* 7.1, OC*H*$_2$), 1.05 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 164.7 (s), 162.1 (s), 146.4 (d), 142.0 (d), 140.6 (s), 136.1 (s), 134.9 (s), 133.4 (q, $^2J_{CF}$ 33.5, F_3C*C*), 133.0 (s), 132.7 (s), 131.6 (d), 128.2 (d), 127.6 (q, $^3J_{CF}$ 3.8, F_3CCC*C*H), 126.1 (s), 123.7 (q, $^1J_{CF}$ 272.8, F_3*C*), 124.9 (q, $^3J_{CF}$ 3.5, F_3CC*C*H), 62.3 (O*C*H$_2$), 13.8 (*C*H$_3$); *m/z* (EI) 398 (M^++2, 3%), 396 (M^+, 8), 361 (M^+-Cl, 50), 351 (5), 333 (100), 315 (7), 287 (7), 260 (9), 241 (4), 232 (4), 207 (4), 192 (3), 181 (3).

Ethyl 4-(2-chloro-4-methylphenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 254

(127 mg, 74%) as colorless cubes, mp 164-166 ºC (*t*-BuOMe), R_f 0.40 (*t*-BuOMe); (found: C, 63.3; H, 4.4; N, 8.1. $C_{18}H_{15}ClN_2O_3$ requires C, 63.1; H, 4.4; N, 8.2%); λ_{max}(DCM)/nm 234 (log ε 3.83), 261 (3.30), 268 (3.25), 339 inf (3.27), 349 (3.37), 360 (3.25); ν_{max}/cm^{-1} 2941w, 2870w, 1732m (C=O), 1717m, 1665s (NHC=O), 1605w, 1558w, 1541w, 1506w, 1485w, 1447w, 1395w, 1381w, 1366w, 1327w, 1310w, 1204m, 1113m, 1061w, 1028w, 982w, 966w, 934w, 883w, 849m, 818m, 802w; δ_H(300 MHz; CD_2Cl_2) 9.06 (1H, s, Naph *H*-2), 8.18 (1H, br s, N*H*), 8.01 (1H, d, *J* 9.9, Naph *H*-7), 7.42 (1H, s, Ar *H'*-2), 7.27 (1H, dd, *J* 7.8, 0.6, Ar *H'*-5), 7.12 (1H, d, *J* 7.8, Ar *H'*-6), 6.86 (1H, d, *J* 9.9, Naph *H*-8), 4.12 (2H, q, *J* 7.1, OC*H*$_2$), 2.45 (3H, s, C*H*$_3$), 1.06 (3H, t, *J* 7.1, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 165.1 (s), 161.6 (s), 146.3 (d), 142.3 (s), 142.1 (d), 140.3 (s), 134.2 (s), 133.4 (s), 133.0 (s), 131.2 (d), 130.4 (d), 129.0 (d), 128.4 (s), 128.0 (d), 126.8 (s), 62.1 (O*C*H$_2$), 21.3 (*C*H$_3$), 13.9 (*C*H$_3$); *m/z* (EI) 344 (M^++2, 4%), 342 (M^+, 7), 307 (M^+-Cl, 79), 297 (6), 279 (100), 261 (7), 251 (3), 233 (9), 205 (12), 192 (3), 179 (3), 152 (4), 139 (3), 126 (9), 103 (4), 89 (3), 77 (3), 63 (3).

Ethyl 4-(2-chloro-4-methoxyphenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 255

(159 mg, 89%) as colorless plates, mp 169-171 ºC (*t*-BuOMe), R_f 0.23 (*t*-BuOMe); (found: C, 60.1; H, 4.1; N, 7.8. $C_{18}H_{15}ClN_2O_4$ requires C, 60.3; H, 4.2; N, 7.8%); λ_{max}(DCM)/nm 240 (log ε 4.22), 259 inf (3.95), 268 inf (3.80), 286 (3.60), 341 inf (3.99), 348 (4.05), 358 inf (3.97); ν_{max}/cm^{-1} 2970w, 1736m (C=O), 1713m (C=O), 1662s (NHC=O), 1605m, 1560w, 1497w, 1485w, 1450w, 1367m, 1329m, 1310w, 1290m, 1227s, 1204m, 1142m, 1119w, 1051m, 1038m, 1018w, 862m, 853m, 812w, 775w, 764w; δ_H(300 MHz; CD_2Cl_2) 9.05 (1H, s, Naph *H*-2), 8.32 (1H, br s, N*H*), 8.01 (1H, d, *J* 9.9, Naph *H*-7), 7.15-7.12 (2H, m, Ar *H*), 7.01 (1H, dd, *J* 8.4, 2.4, Ar *H*), 6.84 (1H, d, *J* 9.9, Naph *H*-8), 4.14 (2H, q, *J* 7.1, OC*H*$_2$), 3.89 (3H, s, OC*H*$_3$), 1.08 (3H, t, *J* 7.2, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 165.2 (s), 161.8 (s), 161.6 (s), 146.3 (d), 142.0 (d), 140.2 (s), 134.5 (s), 133.9 (s), 133.3 (s), 131.4 (d), 128.0 (d), 127.1 (s), 123.2 (s), 116.1 (d), 114.3 (d), 62.0 (O*C*H$_2$), 56.3 (O*C*H$_3$), 14.0 (*C*H$_3$); *m/z* (EI) 360 (M$^+$+2, 3%), 358 (M$^+$, 8), 323 (M$^+$-Cl, 80), 315 (2), 313 (6), 295 (100), 280 (6), 252 (9), 242 (6), 236 (6), 224 (4), 207 (6), 179 (9), 152 (4), 125 (5), 99 (5), 75 (4), 63 (3).

Ethyl 4-(2-chloro-4-fluorophenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 256

(170 mg, 98%) as colorless cubes, mp 169-170 ºC (*t*-BuOMe), R_f 0.38 (*t*-BuOMe); (found: C, 59.0; H, 3.4; N, 8.0. $C_{17}H_{12}ClFN_2O_3$ requires C, 58.9; H, 3.5; N, 8.1%); λ_{max}(DCM)/nm 234 (log ε 3.55), 251 inf (2.99), 259 inf (2.88), 267 inf (2.76), 339 inf (3.03), 348 (3.13), 362 (3.01); ν_{max}/cm^{-1} 3173w, 3103w, 3032w (Ar CH), 2990w, 2941w, 1715m (C=O), 1667s (NHC=O), 1605m, 1555w, 1493m, 1452w, 1391m, 1369m, 1328m, 1312m, 1263w, 1217m, 1198m, 1134m, 1105w, 1049w, 1024m, 899m, 851m, 824w, 760m; δ_H(500 MHz; CD_2Cl_2) 9.08 (1H, s, Naph *H*-2), 8.67 (1H, br s, N*H*), 8.02 (1H, d, *J* 9.8, Naph *H*-7), 7.36 (1H, d, *J* 8.5, Ar *H*), 7.23-7.20 (2H, m, Ar *H*), 6.82 (1H, d, *J* 9.9, Naph *H*-8), 4.14 (2H, q, *J* 6.9, OC*H*$_2$), 1.09 (3H, t, *J* 7.1, C*H*$_3$); δ_C(125 MHz; CD_2Cl_2) 165.0 (s), 163.8 (d, $^1J_{CF}$ 251.0, F*C*), 161.8 (s), 146.4 (d), 142.1 (d), 140.5 (s), 135.1 (d, $^3J_{CF}$ 10.8, FCCH*C*Cl), 133.1 (d, $^4J_{CF}$ 5.4, FCCHCH*C*$_q$), 132.1 (d, $^3J_{CF}$ 9.0, FCCH*C*H), 128.1 (d), 128.0 (s), 126.7 (s), 118.2 (d, $^2J_{CF}$ 25.3, FC*C*H), 115.7 (d, $^2J_{CF}$ 21.7, FC*C*H), 62.2 (O*C*H$_2$), 14.0 (*C*H$_3$); *m/z* (EI) 348 (M$^+$+2, 4%), 346 (M$^+$, 11), 311 (M$^+$-Cl, 71), 301 (6), 283 (100), 265 (14), 237 (14), 210 (21), 191 (5), 182 (10), 157 (5), 131 (10), 105 (3), 81 (3).

Ethyl 4-(2,5-dichlorophenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 257

(176 mg, 97%) as colorless cubes, mp 160-161.5 ºC (*t*-BuOMe), R_f 0.57 (*t*-BuOMe); (found: C, 56.1; H, 3.3; N, 7.8. $C_{17}H_{12}Cl_2N_2O_3$ requires C, 56.2; H, 3.3; N, 7.7%); λ_{max}(DCM)/nm 232 (log ε 3.70), 259 inf (2.95), 268 inf (2.82), 339 inf (3.10), 348 (3.20), 362 (3.08); ν_{max}/cm^{-1} 2959w, 2924w, 2851w, 1726m (C=O), 1667s (NHC=O), 1607w, 1578w, 1557w, 1489w, 1470w, 1454w, 1406w, 1381m, 1325m, 1292w, 1207m, 1136m, 1103m, 1057w, 1034w, 972w, 872w, 947m, 818m; δ_H(500 MHz; CD_2Cl_2) 9.11 (1H, s, Naph *H*-2), 8.51 (1H, br s, N*H*), 8.02 (1H, d, *J* 9.8, Naph *H*-7), 7.55-7.49 (2H, m, Ar *H*), 7.26 (1H, s, Ar *H*), 6.86 (1H, d, *J* 9.9, Naph *H*-8), 4.16 (2H, q, *J* 7.0, OC*H*$_2$), 1.09 (3H, t, *J* 7.1, C*H*$_3$); δ_C(125 MHz; CD_2Cl_2) 164.7 (s), 161.7 (s), 146.5 (d), 142.0 (d), 140.6 (s), 134.0 (s), 133.5 (s), 132.7 (s), 132.6 (s), 132.4 (s), 131.9 (d), 131.5 (d), 130.7 (d), 128.3 (d), 126.1 (s), 62.2 (O*C*H$_2$), 13.9 (*C*H$_3$); *m/z* (EI) 364 (M^++2, 6%), 362 (M^+, 10%), 329 (42), 327 (M^+-Cl, 87), 319 (5), 317 (9), 301 (54), 299 (100), 283 (3), 281 (7), 264 (26), 255 (9), 226 (17), 207 (4), 198 (3), 191 (6), 164 (4), 147 (4), 138 (2), 113 (2).

Ethyl 4-[2-chloro-5-(trifluoromethyl)phenyl]-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 258

(182 mg, 92%) as colorless plates, mp 201-203.5 ºC (*t*-BuOMe), R_f 0.57 (*t*-BuOMe); (found: C, 54.5; H, 3.0; N, 6.9. $C_{18}H_{12}ClF_3N_2O_3$ requires C, 54.5; H, 3.1; N, 7.1%); λ_{max}(DCM)/nm 232 (log ε 3.56), 263 (3.22), 270 (3.21), 283 inf (3.09), 338 inf (3.03), 348 (3.13), 362 (3.01); ν_{max}/cm^{-1} 3036w, 2967w, 1724m (C=O), 1668s (NHC=O), 1609m, 1578w, 1487w, 1381m, 1327s, 1296s, 1209m, 1169s, 1123s, 1084s, 1057w, 1034m, 972w, 934w, 872w, 845m, 837m; δ_H(300 MHz; CD_2Cl_2) 9.13 (1H, s, Naph *H*-2), 8.70 (1H, br s, N*H*), 8.02 (1H, d, *J* 9.9, Naph *H*-7), 7.80-7.75 (2H, m, Ar *H*), 7.53 (1H, d, *J* 0.6, Ar *H*), 6.82 (1H, d, *J* 9.6, Naph *H*-8), 4.12 (2H, dq, *J* 7.2, 1.5, OC*H*$_2$), 1.03 (3H, t, *J* 7.2, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 164.7 (s), 162.0 (s), 146.6 (d), 142.1 (d), 140.7 (s), 138.1 (s), 133.1 (s), 132.8 (s), 132.6 (s), 131.4 (d), 130.7 (q, $^2J_{CF}$ 32.9, F_3CC), 128.2 (m, *C*H), 128.1 (q, $^3J_{CF}$ 3.8, F_3CCCH), 126.1 (q, $^1J_{CF}$ 272.8, F_3C), 62.2 (O*C*H$_2$), 13.8 (*C*H$_3$); *m/z* (EI) 398 (M^++2, 8%), 396 (M^+, 22), 361 (M^+-Cl, 84), 353 (3), 351 (9), 333 (100), 315 (9), 313 (8), 287 (10), 264 (3), 260 (12), 241 (7), 232 (4), 226 (3), 207 (4), 192 (4), 181 (3).

Ethyl 4-(2-chloropyrid-3-yl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 259

(137 mg, 83%) as colorless cubes, mp 194-196 ºC (*t*-BuOMe), R_f 0.09 (*t*-BuOMe); (found: C, 58.4; H, 3.7; N, 12.7. $C_{16}H_{12}ClN_3O_3$ requires C, 58.3; H, 3.7; N, 12.7%); λ_{max}(DCM)/nm 217 (log ε 4.15), 348 (3.30); ν_{max}/cm^{-1} 1724m (C=O), 1697s (NHC=O), 1602m, 1556w, 1402w, 1384m, 1305w, 1220m, 1141m, 1076m, 1026m, 856w; δ_H(500 MHz; CD_2Cl_2) 9.96 (1H, br s, N*H*), 9.14 (1H, s, Naph *H*-2), 8.62 (1H, d, 2.0, Ar *H*), 8.06 (1H, d, *J* 9.8, Naph *H*-7), 7.62 (1H, d, *J* 7.4, Ar *H*), 7.47 (1H, d, *J* 6.2, Ar *H*), 6.79 (1H, d, *J* 9.8, Naph *H*-8), 4.17 (2H, q, *J* 6.8, OC*H*$_2$), 1.11 (3H, t, *J* 7.2, C*H*$_3$); δ_C(125 MHz; CD_2Cl_2) 164.8 (s), 162.6 (s), 150.8 (d), 150.5 (s), 146.6 (d), 142.1 (d), 140.7 (s), 139.8 (d), 133.0 (s), 132.5 (s), 129.1 (s), 128.1 (d), 126.1 (s), 123.4 (d), 62.2 (O*C*H$_2$), 14.0 (*C*H$_3$); *m/z* (EI) 329 (M$^+$, 11%), 294 (M$^+$-Cl, 95), 284 (7), 266 (100), 256 (4), 248 (6), 238 (9), 221 (10), 193 (15), 167 (11), 140 (7), 114 (8), 100 (3), 96 (4), 87 (7), 62 (6).

Ethyl 4-(3-chloropyrid-4-yl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate 260

(110 mg, 67%) as colorless needles, mp 161-163 ºC (*t*-BuOMe); R_f 0.09 (*t*-BuOMe); (found: C, 58.2; H, 3.6; N, 12.7, $C_{13}H_8ClN_3O$ requires C, 58.3; H, 3.7; N, 12.7%); λ_{max}(DCM)/nm 216 (log ε 4.16), 336 (3.47); ν_{max}/cm^{-1} 1714m (C=O), 1660s (NHC=O), 1602w, 1557w, 1371w, 1327m, 1215m, 1141m, 1091w, 1018m, 854m; δ_H(500 MHz; CD_2Cl_2) 9.56 (1H, br s, N*H*), 9.12 (1H, s, Naph *H*-2), 8.77 (1H, s, Ar *H*), 8.63 (1H, br s, Ar *H*), 8.02 (1H, d, *J* 9.8, Naph *H*-7), 7.19 (1H, d, *J* 2.1, Ar *H*), 6.77 (1H, d, *J* 9.9, Naph *H*-8), 4.14 (2H, q, *J* 6.8, OC*H*$_2$), 1.07 (3H, t, *J* 7.1, C*H*$_3$); δ_C(125 MHz; CD_2Cl_2) 164.6 (s), 162.4 (s), 150.6 (d), 148.8 (d), 146.5 (d), 142.1 (d), 140.8 (s), 140.4 (s), 132.3 (s), 131.7 (s), 131.5 (s), 128.3 (d), 125.6 (s), 125.1 (d), 62.4 (O*C*H$_2$), 13.8 (*C*H$_3$); *m/z* (EI) 329 (M$^+$, 13%), 294 (M$^+$-Cl, 77), 266 (100), 233 (9), 220 (3), 193 (9), 114 (10), 100 (5).

Ethyl 6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-1-carboxylate 261 (Table 25, entry 1)

To a stirred solution of ethyl 4-(2-bromophenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate **249** (48 mg, 0.13 mmol), Cs_2CO_3 (85 mg, 0.26 mmol), CuI (2.5 mg, 0.013 mmol) in dioxane (1 mL) was added DMEDA (2.9 μL, 0.026 mmol) and H_2O (4.5 μL, 0.26 mmol). The stirred reaction mixture was refluxed (preheated oil bath) until the reaction was complete (TLC, 1 h) and then allowed to cool to *ca.* 20 ^{o}C. The mixture was diluted (DCM), dried (Na_2SO_4), filtered and adsorbed onto silica gel. Dry flash chromatography (*t*-BuOMe) gave the *title compound* **261** (32 mg, 85%) as light yellow needles mp 158-160 ºC (EtOH), R_f 0.35

(*t*-BuOMe); (found: C, 70.0; H, 4.1; N, 9.5. $C_{17}H_{12}N_2O_3$ requires C, 69.9; H, 4.1; N, 9.6%); λ_{max}(DCM)/nm 232 inf (log ε 3.25), 244 (3.29), 250 inf (3.28), 263 inf (3.13), 269 inf (2.99), 305 (3.07), 314 (3.06), 363 inf (2.94), 378 (3.10), 398 (3.05); ν_{max}/cm^{-1} 2957w, 2922 br m, 2853w, 1722m (C=O), 1692s (C=O), 1665m, 1622w, 1601w, 1582w, 1555w, 1483w, 1468w, 1441w, 1416m, 1391m, 1366w, 1342w, 1329w, 1294s, 1250m, 1217m, 1136s, 1109m, 1094m, 1055m, 1016w, 930w, 910w, 893w, 874w, 854w, 839m, 804w; δ_H(500 MHz; CD_2Cl_2) 9.32 (1H, s, *H*-2), 8.95 (1H, d, *J* 7.9, *H*-8 or 11), 8.64 (1H, d, *J* 8.2, *H*-8 or 11), 7.98 (1H, d, *J* 9.8, *H*-4), 7.70-7.74 (1H, m, *H*-9 or 10), 7.51-7.54 (1H, m, *H*-9 or 10), 6.98 (1H, d, *J* 9.8, *H*-5), 4.58 (2H, q, *J* 7.2, OCH_2), 1.53 (3H, t, *J* 7.2, CH_3); δ_C(75 MHz; $CDCl_3$) 165.3 (*C*O_2Et), 159.3 (N*C*=O), 147.8 (d), 140.2 (s), 139.2 (d), 138.5 (s), 132.2 (s), 132.0 (d), 130.6 (d), 130.4 (s), 128.3 (d), 126.0 (d), 123.5 (s), 121.2 (s), 116.7 (d), 62.1 (O*C*H_2), 14.5 (*C*H_3); *m/z* (EI) 293 (M^++1, 20%), 292 (M^+, 100), 277 (7), 264 (36), 247 (60), 236 (21), 219 (26), 191 (25), 164 (22), 138 (7), 113 (4), 110 (7), 96 (8), 86 (5), 63 (4). The *title compound* could also be obtained microanytically pure without the use of chromatography, by filtering the dried solution through a short pad of silica, evaporation and recrystallisation.

Ethyl 9-chloro-6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-1-carboxylate 262; Typical procedure for entries 4-20 (see Table 25)

To a stirred solution of ethyl 4-(2,4-dichlorophenyl)-6-oxo-5,6-dihydro-1,5-naphthyridine-3-carboxylate **252**) (43 mg, 0.13 mmol), Cs_2CO_3 (85 mg, 0.26 mmol) in dioxane (1 mL)/ H_2O (2.4 μL, 0.13 mmol) a deep blue solution of CuI (2.5 mg, 0.013 mmol) and DMCDA (4 μL, 0.026 mmol) in dioxane (1 mL)/ H_2O (2.4 μL, 0.13 mmol) was added. The stirred reaction mixture was refluxed (preheated oil bath) until the reaction was complete (TLC, 1 h) and then allowed to cool to *ca.* 20 ^oC. The mixture was diluted (DCM), dried (Na_2SO_4), filtered and adsorbed onto silica gel. Dry flash chromatography (*t*-BuOMe*) g*ave the *title compound* **262** (28 mg, 74%) as bright yellow needles, mp 217.5-218.5 ^oC (EtOH), R_f 0.70 (*t*-BuOMe); (found: C, 62.5; H, 3.5; N, 8.5. $C_{17}H_{11}ClN_2O_3$ requires C, 62.5; H, 3.4; N, 8.6%); λ_{max}(DCM)/nm 231 (log ε 2.30), 243 inf (3.28), 252 inf (3.30), 256 (3.32), 266 (3.27), 274 (3.18), 307 inf (3.14), 315 (3.16), 348 inf (2.96), 361 (3.09), 378 (3.26), 398 (3.21); ν_{max}/cm^{-1} 3117w, 3069w, 3042w, 2992w, 1722m (C=O), 1692s (NC=O), 1624w, 1599w, 1555w, 1474w, 1429m, 1414m, 1395m, 1366w, 1323w, 1308m, 1288s, 1271m, 1250w, 1217w, 1196w, 1159m, 1105m, 1069w, 1053m, 1016w, 937w, 910w, 868m, 853m, 837s, 797m,

766m; δ_H(300 MHz; CD_2Cl_2) 9.39 (1H, s, *H*-2), 8.98 (1H, d, *J* 8.4, *H*-11), 8.73 (1H, d, *J* 1.8, *H*-8), 8.05 (1H, d, *J* 9.9, *H*-4), 7.55 (1H, dd, *J* 8.7, 2.1, *H*-10), 7.04 (1H, d, *J* 9.9, *H*-5), 4.61 (2H, q, *J* 7.1, OCH_2), 1.56 (3H, t, *J* 7.2, CH_3); δ_C(125 MHz; CD_2Cl_2) 165.5 (*C*O_2Et), 159.4 (N*C*=O), 148.2 (d), 140.9 (s), 139.9 (d), 139.1 (s), 137.9 (s), 132.9 (s), 130.6 (d), 129.5 (s), 129.4 (d), 126.5 (d), 122.6 (s), 121.4 (s), 117.0 (d), 62.5 (O*C*H_2), 14.5 (*C*H_3); *m/z* (EI) 328 (M^++2, 33%), 326 (M^+, 100), 313 (3), 311 (8), 300 (11), 298 (32), 283 (20), 281 (55), 272 (5), 270 (14), 253 (32), 247 (4), 225 (24), 198 (13), 189 (10), 174 (5), 163 (9), 138 (10), 112 (6), 99 (7), 86 (5), 63 (5).

Ethyl 6-oxo-9-(trifluoromethyl)-6H-indolo[3,2,1-de][1,5]naphthyridine-1-carboxylate 263 (42 mg, 90%) as colorless needles, mp 187.5-189 ºC (EtOH), R_f 0.68 (*t*-BuOMe); (found: C, 59.9; H, 3.0; N, 7.6. $C_{18}H_{11}F_3N_2O_3$ requires C, 60.0; H, 3.1; N, 7.8%); λ_{max}(DCM)/nm 230 (log ε 3.43), 243 (3.41), 251 (3.39), 265 (3.13), 274 (3.03), 298 (3.22), 307 (3.21), 365 inf (3.07), 378 (3.33), 398 (3.33); ν_{max}/cm^{-1} 2988w, 2924w, 2860w, 1717m (C=O), 1686m (C=O), 1608w, 1587w, 1558w, 1472w, 1420m, 1393w, 1368w, 1337s, 1290s, 1269s, 1246w, 1221w, 1213w, 1175s, 1150s, 1126s, 1109s, 1053s, 1007w, 989w, 935w, 914w, 897m, 878w, 837s, 814w, 807w; δ_H(500 MHz; CD_2Cl_2) 9.38 (1H, s, *H*-2), 9.13 (1H, d, *J* 8.4, *H*-10 or 11), 8.94 (1H, s, *H*-8), 8.03 (1H, d, *J* 9.8, *H*-4), 7.78 (1H, d, *J* 8.4, *H*-10 or 11), 7.03 (1H, d, *J* 9.8, *H*-5), 4.59 (2H, q, *J* 7.1, OCH_2), 1.53 (3H, t, *J* 7.1, CH_3); δ_C(125 MHz; CD_2Cl_2) 165.4 (*C*O_2Et), 159.5 (N*C*=O), 148.4 (d), 140.0 (s), 139.9 (d), 139.6 (s), 138.8 (s), 133.2 (q, $^2J_{CF}$ 32.5, F_3CC), 131.0 (d), 129.2 (d), 129.0 (s), 126.9 (s), 124.4 (q, $^1J_{CF}$ 271.3, F_3C), 122.9 (q, $^3J_{CF}$ 3.6, F_3CCCH), 122.1 (s), 114.1 (q, $^3J_{CF}$ 3.9, F_3CCCH), 62.7 (O*C*H_2), 14.6 (*C*H_3); *m/z* (EI) 361 (M^++1, 21%), 360 (M^+, 100), 345 (10), 332 (48), 315 (65), 304 (14), 287 (38), 259 (32), 247 (5), 232 (19), 209 (5), 180 (5), 157 (5), 144 (9), 130 (6), 87 (5), 57 (7).

Ethyl 9-methyl-6-oxo-6H-indolo[3,2,1-de][1,5]naphthyridine-1-carboxylate 264 (32 mg, 80%) as beige needles, mp 173.5-174.5 ºC (EtOH), R_f 0.50 (*t*-BuOMe); (found: C, 70.6; H, 4.5; N, 9.1. $C_{18}H_{13}N_2O_3$ requires C, 70.6; H, 4.6; N, 9.2%); λ_{max}(DCM)/nm 232 (log ε 3.31), 246 inf (3.37), 256 (3.41), 263 inf (3.39), 273 (3.24), 309 (3.21), 318 (3.22), 350 inf (3.01), 365 inf (3.15), 380 (3.29), 400 (3.21); ν_{max}/cm^{-1} 3078w, 2980w, 2932w, 1707s (O-C=O), 1670s (N-C=O), 1665s (C=O), 1626m, 1605w, 1585w, 1557w, 1468w, 1429m, 1416m, 1395w, 1362w, 1335m, 1287s, 1250m, 1231m, 1150s, 1109s, 1099m, 1053m, 1022w, 955w, 881w, 849m, 837s, 802m; δ_H(500 MHz; CD_2Cl_2) 9.28 (1H, s, *H*-2), 8.77 (1H, d, *J* 8.2, *H*-10 or

11), 8.45 (1H, s, *H*-8), 7.96 (1H, d, *J* 9.8, *H*-4), 7.31 (1H, d, *J* 8.2, *H*-10 or 11), 6.95 (1H, d, *J* 9.6, *H*-5), 4.56 (2H, q, *J* 7.1, OCH_2), 2.58 (3H, s, CH_3), 1.52 (3H, t, *J* 7.1, CH_3); δ_C(125 MHz; CD_2Cl_2) 165.8 (*C*O_2Et), 159.7 (N*C*=O), 148.1 (d), 143.7 (s), 141.0 (s), 139.6 (d), 138.8 (s), 132.8 (s), 130.7 (d), 130.6 (s), 128.1 (d), 127.4 (d), 121.6 (s), 121.1 (s), 117.2 (d), 62.4 (O*C*H_2), 22.5 (*C*H_3), 14.6 (*C*H_3); *m/z* (EI) 308 (M^++1, 14%), 307 (M^+, 62), 297 (5), 279 (100), 261 (6), 233 (9), 205 (13), 192 (4), 179 (4), 152 (6), 127 (9), 77 (6), 57 (6).

Ethyl 9-methoxy-6-oxo-6H-indolo[3,2,1-de][1,5]naphthyridine-1-carboxylate 265

(30.5 mg, 73%) as bright colored yellow needles, mp 187-188 ºC (EtOH), R_f 0.45 (*t*-BuOMe); (found: C, 67.2; H, 4.5; N, 8.6. $C_{18}H_{14}N_2O_4$ requires C, 67.1; H, 4.4; N, 8.7%); λ_{max}(DCM)/nm 231 (log ε 3.36), 261 inf (3.34), 268 (3.43), 278 (3.50), 308 (3.10), 318 (3.12), 376 (3.29); ν_{max}/cm^{-1} 2976w, 2945w, 1721s (C=O), 1694m (NC=O), 1624m, 1608m, 1557w, 1495m, 1470w, 1439m, 1418m, 1393m, 1369w, 1335w, 1292s, 1243s, 1186w, 1167w, 1150s, 1115m, 1099m, 1057m, 1032m, 1015w, 930w, 875w, 854w, 837s, 800w; δ_H(300 MHz; CD_2Cl_2) 9.27 (1H, s, *H*-2), 8.82 (1H, d, *J* 8.7, *H*-11), 8.18 (1H, d, *J* 2.4, *H*-8), 7.96 (1H, d, *J* 9.9, *H*-4), 7.04 (1H, dd, *J* 9.0, 2.4, *H*-10), 6.95 (1H, d, *J* 9.9, *H*-5), 4.56 (2H, q, *J* 7.1, OCH_2), 3.99 (3H, s, OCH_3), 1.52 (3H, t, *J* 7.1, CH_3); δ_C(125 MHz; CD_2Cl_2) 165.9 (s), 163.6 (s), 159.7 (s), 148.2 (d), 142.6 (s), 139.9 (d), 138.2 (s), 133.0 (s), 130.6 (s), 130.3 (d), 129.5 (d), 120.4 (s), 116.9 (s), 114.1 (d), 101.0 (d), 62.3 (O*C*H_2), 56.4 (O*C*H_3), 14.6 (*C*H_3); *m/z* (EI) 324 (M^++1, 11%), 323 (M^+, 80), 295 (100), 277 (5), 263 (2), 252 (8), 249 (6), 207 (7), 179 (10), 125 (5), 99 (5), 75 (5), 57 (4).

Ethyl 9-fluoro-6-oxo-6H-indolo[3,2,1-de][1,5]naphthyridine-1-carboxylate 266

(28 mg, 70%) as colorless needles, mp 203-204.5 ºC (EtOH), R_f 0.75 (*t*-BuOMe); (found: C, 65.9; H, 3.5; N, 8.9. $C_{17}H_{11}FN_2O_3$ requires C, 65.8; H, 3.6; N, 9.0%); λ_{max}(DCM)/nm 254 (log ε 3.60), 263 (3.58), 271 (3.52), 292 inf (3.37), 299 (3.40), 307 inf (3.34), 345 inf (306), 356 (3.22); ν_{max}/cm^{-1} 3042w, 2988w, 2918w, 1724m (C=O), 1694s, 1628w, 1607w, 1557w, 1541w, 1522w, 1472w, 1456w, 1435w, 1422m, 1396m, 1331w, 1314w, 1267w, 1233m, 1161w, 1150m, 1117w, 1105w, 1059w, 1015w, 934w, 878w, 856m, 843s, 831m, 802w, 768m; δ_H(300 MHz; CD_2Cl_2) 9.34 (1H, s, *H*-2), 9.00 (1H, dd, $^3J_{HH}$ 8.9, $^4J_{HF}$ 5.6, *H*-11), 8.38 (1H, dd, $^3J_{HF}$ 9.1, $^4J_{HH}$ 2.5, *H*-8), 8.01 (1H, d, *J* 10.0, *H*-4), 7.26 (1H, ddd, $^3J_{HF}$ 9.0, $^3J_{HH}$ 9.0, $^4J_{HH}$ 2.5, *H*-10), 6.99 (1H, d, *J* 9.8, *H*-5), 4.57 (2H, q, *J* 7.1, OCH_2), 1.52 (3H, t, *J* 7.2, CH_3);

δ_C(75 MHz; CD_2Cl_2) 165.6 (*C*O_2Et), 165.2 (d, $^1J_{CF}$ 250.9, F*C*), 159.5 (N*C*=O), 148.3 (d), 141.5 (d, $^3J_{CF}$ 13.7, FCCH*C*$_q$, *C*-7a), 140.0 (d), 138.8 (s), 132.7 (s), 130.5 (d), 130.2 (d, $^3J_{CF}$ 10.4, FCCH*C*H, *C*-11), 129.8 (s), 121.3 (s), 120.4 (s), 113.9 (d, $^2J_{CF}$ 23.6, FC*C*H, *C*-8 or 10), 104.5 (d, $^2J_{CF}$ 28.6, FC*C*H, *C*-8 or 10), 62.5 (O*C*H_2), 14.6 (*C*H_3); *m/z* (EI) 311 (M^++1, 20%) 310 (M^+, 75), 295 (9), 282 (42), 265 (73), 254 (18), 237 (42), 209 (37), 182 (36), 158 (10), 156 (13), 131 (11), 119 (9), 106 (8), 81 (7), 57 (9).

Ethyl 10-chloro-6-oxo-6H-indolo[3,2,1-de][1,5]naphthyridine-1-carboxylate 267

(38 mg, 89%) as light yellow needles, mp 191-193 ºC (EtOH), R_f 0.70 (*t*-BuOMe); (found: C, 62.4; H, 3.3; N, 8.5. $C_{17}H_{11}ClN_2O_3$ requires C, 62.5; H, 3.4; N, 8.6%); λ_{max}(DCM)/nm 399 (log ε 2.35), 381 (3.40), 306 (2.18), 228 (3.16); ν_{max}/cm^{-1} 3115w, 3051w (Ar CH), 2983w, 2947w, 2859w, 1719m (C=O), 1679s (NC=O), 1624w, 1587w, 1557w, 1458w, 1439m, 1402m, 1387m, 1366w, 1329s, 1296s, 1254s, 1225w, 1198w, 1150s, 1121m, 1105w, 1074m, 1049w, 1016w, 991w, 941w, 897w, 856m, 847m, 829m, 806w, 766m; δ_H(300 MHz; CD_2Cl_2) 9.33 (1H, s, *H*-2), 8.95 (1H, d, *J* 2.1, *H*-11), 8.55 (1H, d, *J* 8.7, *H*-8), 7.99 (1H, d, *J* 9.9, *H*-4), 7.66 (1H, dd, *J* 8.7, 2.1, *H*-10), 6.98 (1H, d, *J* 9.9, *H*-5), 4.58 (2H, q, *J* 7.1, OC*H*$_2$), 1.54 (3H, t, *J* 7.2, C*H*$_3$); δ_C(75 MHz; CD_2Cl_2) 165.4 (*C*O_2Et), 159.2 (N*C*=O), 148.2 (d), 139.7 (d), 139.2 (s), 138.6 (s), 132.6 (s), 131.9 (d), 131.6 (s), 130.8 (d), 129.0 (s), 128.2 (d), 125.2 (s), 121.5 (s), 117.6 (d), 62.7 (O*C*H_2), 14.5 (*C*H_3); *m/z* (EI) 328 (M^++2, 42%), 326 (M^+, 100), 300 (15), 298 (41), 283 (16), 281 (46), 272 (8), 270 (26), 253 (31), 247 (10), 225 (22), 198 (15), 190 (12), 163 (10), 149 (10), 138 (11), 126 (7), 112 (8), 99 (7), 88 (6), 63 (5).

Ethyl 6-oxo-10-(trifluoromethyl)-6H-indolo[3,2,1-de][1,5]naphthyridine-1-carboxylate 268

(44.5 mg, 95%) as beige needles, mp 188.5-190 ºC (EtOH), R_f 0.70 (*t*-BuOMe); (found: C, 60.0; H, 3.0; N, 7.8. $C_{18}H_{11}F_3N_2O_3$ requires C, 60.0; H, 3.1; N, 7.8%); λ_{max}(DCM)/nm 231 (log ε 3.26), 234 inf (3.24), 241 inf (3.19), 250 inf (3.14), 260 inf (3.00), 270 inf (2.86), 299 (3.03), 307 (3.03), 344 inf (2.61), 359 (2.88), 376 (3.14), 394 (3.13); ν_{max}/cm^{-1} 3119w, 3057w, 2999w, 1713m (C=O), 1682m (NC=O), 1628w, 1612w, 1589w, 1560w, 1474w, 1449w, 1406m, 1393m, 1342m, 1323s, 1298s, 1260m, 1219w, 1200w, 1163s, 1144s, 1123s, 1101m, 1063m, 1049w, 1013w, 995w, 922w, 897w, 880w, 845s, 837m, 806w, 768m; δ_H(500 MHz; CD_2Cl_2) 9.38 (1H, s, *H*-2 or 11), 9.32 (1H, s, *H*-2 or 11), 8.77 (1H, d, *J* 8.6, *H*-8 or 9), 8.03 (1H, d, *J* 9.8, *H*-4), 7.98 (1H, d, *J* 8.5, *H*-8 or 9), 7.01 (1H, d, *J* 9.8, *H*-5), 4.61 (2H, q, *J* 7.1,

OCH_2), 1.55 (3H, t, *J* 7.1, CH_3); δ_C(125 MHz; CD_2Cl_2) 165.5 (*C*O_2Et), 159.5 (N*C*=O), 148.6 (d), 142.1 (s), 140.1 (d), 139.6 (s), 133.1 (s), 130.9 (d), 129.3 (s), 128.9 (q, $^3J_{CF}$ 3.3, F_3CC*C*H, *C*-9 or 11), 128.1 (q, $^2J_{CF}$ 32.5, F_3C*C*, *C*-10), 126.0 (q, $^3J_{CF}$ 4.2, F_3CC*C*H, *C*-9 or 11), 124.8 (q, $^1J_{CF}$ 272.6, F_3*C*), 124.3 (s), 121.8 (s), 117.3 (d), 62.9 (O*C*H_2), 14.5 (*C*H_3); *m/z* (EI) 361 (M^++1, 21%), 360 (M^+, 100), 345 (11), 332 (54), 315 (70), 304 (13), 287 (34), 259 (32), 239 (4), 232 (17), 209 (7), 180 (4), 157 (5), 143 (8), 130 (5), 111 (3).

Ethyl 6-oxo-6H-pyrido[3',2':4,5]pyrrolo[3,2,1-de][1,5]naphthyridine-1-carboxylate 269 (26 mg, 69%) as a fine brown powder, mp (DSC) 263.6 ºC (onset), peak 268.7 ºC (EtOH), R_f 0.38 (MeOH/*t*-BuOMe, 1:9); (found: C, 65.6; H, 3.7; N, 14.2. $C_{16}H_{11}N_3O_3$ requires C, 65.5; H, 3.8; N, 14.3%); λ_{max}(DCM)/nm 238 (log ε 4.02), 254 inf (3.95), 257 (3.98), 284 (3.79), 294 (3.82), 328 inf (3.54), 340 (3.76), 354 (3.94), 365 (3.73), 372 (3.92); ν_{max}/cm^{-1} 3078w, 2924w, 2853w, 1690s (C=O), 1672s (C=O), 1632s, 1587w, 1483w, 1462w, 1435m, 1400m, 1337m, 1321w, 1298m, 1231m, 1190m, 1152w, 1115m, 1057m, 970w, 893w, 862m, 847m, 824m, 804m; δ_H(500 MHz; CD_2Cl_2) 9.40 (1H, s, *H*-2), 9.37 (1H, dd, *J* 8.1, 1.8, *H*-11), 8.82 (1H, dd, *J* 4.8, 1.7, *H*-9), 8.02 (1H, d, *J* 9.8, *H*-4), 7.54 (1H, dd, *J* 8.1, 4.8, *H*-10), 7.03 (1H, d, *J* 10.0, *H*-5), 4.58 (2H, q, *J* 7.2, OCH_2), 1.52 (3H, t, *J* 7.2, CH_3); δ_C(125 MHz; CD_2Cl_2) 165.6 (*C*O_2Et), 158.2 (N*C*=O), 153.3 (s), 151.7 (d), 148.2 (d), 139.8 (d), 139.6 (C_q), 137.5 (d), 131.9 (C_q), 131.8 (*C*H), 127.5 (C_q), 121.5 (d), 121.6 (s), 117.8 (s), 62.6 (O*C*H_2), 14.6 (*C*H_3); *m/z* (EI) 294 (M^++1, 21%), 293 (M^+, 100), 265 (40), 248 (76), 237 (20), 220 (37), 192 (22), 165 (17), 138 (7), 114 (6), 96 (6), 87 (7), 63 (5).

Ethyl 6-oxo-6H-pyrido[4',3':4,5]pyrrolo[3,2,1-de][1,5]naphthyridine-1-carboxylate 270 (21 mg, 56%) as a fine bright yellow powder, mp (DSC) 206.5 ºC (onset), peak 213.6 ºC (EtOH), R_f 0.34 (MeOH/*t*-BuOMe, 1:9); (found: C, 65.7; H, 3.7; N, 14.2. $C_{16}H_{11}N_3O_3$ requires C, 65.5; H, 3.8; N, 14.3%); λ_{max}(DCM)/nm 245 (log ε 2.98), 272 inf (2.98), 276 (2.99), 284 inf (2.97), 296 inf (2.88), 369 inf (2.52), 382 (2.76), 402 (2.77); ν_{max}/cm^{-1} 3034w, 2976w, 2918w, 1718s (C=O), 1688s (NC=O), 1624w, 1589w, 1553w, 1466w, 1427s, 1398w, 1368w, 1325m, 1308s, 1292m, 1265m, 1233w, 1204w, 1179w, 1134m, 1109w, 1059m, 1013w, 989m, 934w, 922w, 864m, 851s, 806w; δ_H(500 MHz; CD_2Cl_2) 9.94 (1H, br s, *H*-8), 9.41 (1H, s, *H*-2), 8.82 (2H, br s, *H*-10 & 11), 8.05 (1H, d, *J* 10.0, *H*-4), 7.11 (1H, d, *J* 9.8, *H*-5), 4.60 (2H, q, *J* 7.2, OCH_2), 1.54 (3H, t, *J* 7.2, CH_3); δ_C(75 MHz; CD_2Cl_2) 165.3 (*C*O_2Et), 159.0 (N*C*=O), 148.3

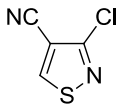
(d), 146.8 (d), 140.5 (s), 139.9 (d), 139.4 (d), 136.0 (s), 132.7 (s), 131.2 (d), 130.4 (s), 128.7 (s), 122.8 (s), 121.7 (d), 62.8 (O*C*H_2), 14.6 (*C*H_3); *m/z* (EI) 294 (M^++1, 20%), 293 (M^+, 100), 265 (45), 248 (50), 237 (23), 220 (29), 192 (15), 165 (21), 138 (10), 110 (5), 87 (8), 63 (4).

6-Oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-1-carboxylic acid 271

To a stirred suspension of ethyl canthin-6-one-1-carboxylate **261** (50 mg, 0.17 mmol) in DCM/methanol (9:1, 2 mL) at *ca.* 20 ^oC was added NaOH (27.2 mg, 0.68 mmol). After 24 h a yellow precipitate was formed. The solvent was then removed *in vacuo* to leave a residue which was dissolved in H_2O (5 mL), acidified using 5% HCl to give a precipitate that was collected by filtration, washed (H_2O) and air dried to give the *title compound* **271** as yellow plates (44 mg, 99%), mp >300 ºC (EtOH), R_f 0.20 (MeOH/*t*-BuOMe, 1:9); (found: C, 68.1; H, 3.0; N, 10.5. $C_{15}H_8N_2O_3$ requires C, 68.2; H, 3.1; N, 10.6%); λ_{max}(DCM)/nm 231 inf (log ε 3.60), 247 inf (3.70), 250 (3.70), 263 (3.65), 270 (3.60), 300 (3.47), 310 inf (3.43), 361 inf (3.29), 376 (3.44), 394 (3.37); ν_{max}/cm^{-1} 3042w, 2907w, 2776w, 1730m (C=O), 1713m, 1688s (NC=O), 1643m, 1632m, 1620m, 1591m, 1557m, 1470w, 1445w, 1418s, 1344w, 1329m, 1304s, 1250s, 1217s, 1143s, 1111w, 1101w, 1047w, 1022w, 989w, 937w, 895w, 835s, 808w, 770s; δ_H(500 MHz; DMSO-d_6) OH missing 9.08 (1H, s, *H*-2), 8.60 (1H, d, *J* 8.1, Ar *H*), 8.36 (1H, d, *J* 8.1, Ar *H*), 8.00 (1H, d, *J* 9.8, Ar *H*), 7.65 (1H, t, *J* 7.9, *H*-9 or 10), 7.45 (1H, t, *J* 7.6, *H*-9 or 10), 6.95 (1H, d, *J* 9.8, Ar *H*); δ_C(125 MHz; DMSO-d_6) 166.3 (*C*O_2H), 158.6 (N*C*=O), 147.2 (d), 139.2 (s), 139.1 (d), 138.0 (s), 131.7 (s), 131.5 (d), 130.1 (d), 128.7 (d), 127.7 (d), 125.5 (s), 122.9 (s), 121.3 (s), 115.7 (d); *m/z* (EI) 264 (M^+, 100%), 247 (7), 236 (38), 219 (12), 191 (14), 164 (15), 139 (5), 132 (6), 113 (5), 104 (5), 95 (4), 88 (4), 63 (7).

LIST OF COMPOUNDS PREPARED

Compound number in bold followed by page number where compound appears in Chapter 9 (Experimental).



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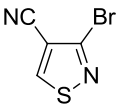

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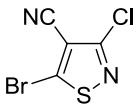

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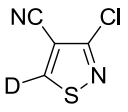

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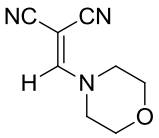

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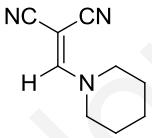

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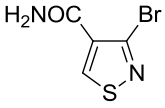

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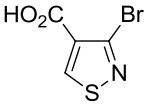

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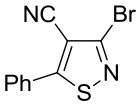

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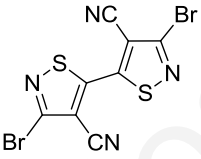

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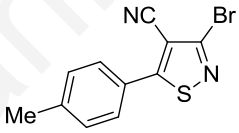

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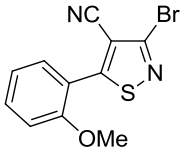

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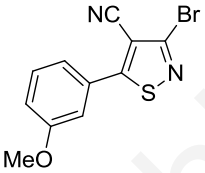

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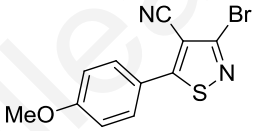

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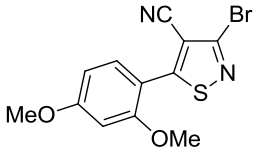

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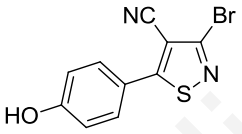

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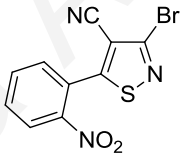

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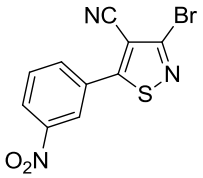

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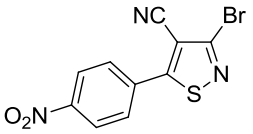

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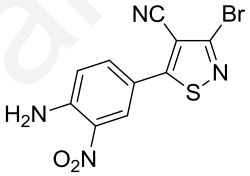

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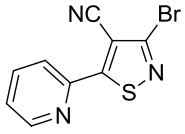

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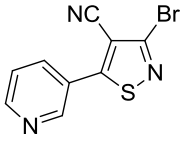

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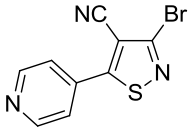

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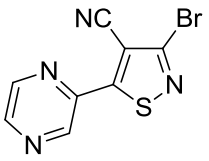

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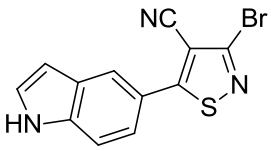

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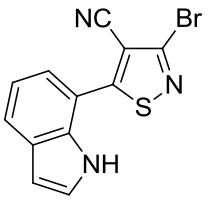

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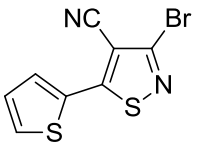

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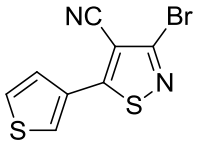

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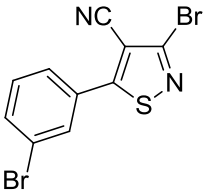

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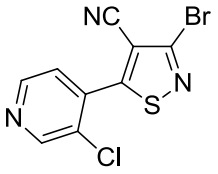

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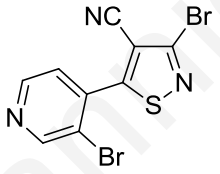

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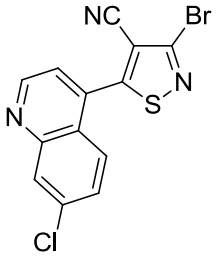

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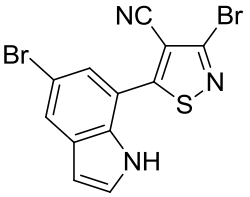

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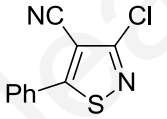

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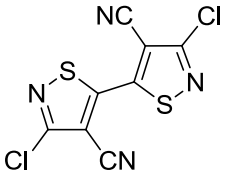

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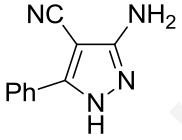

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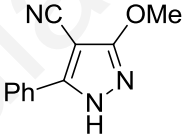

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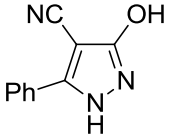

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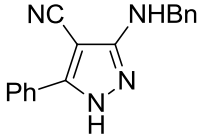

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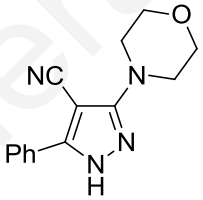

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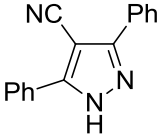

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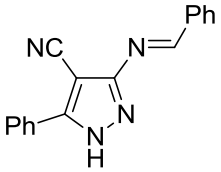

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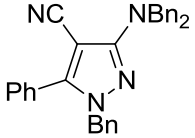

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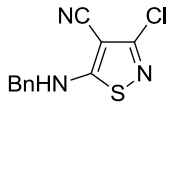

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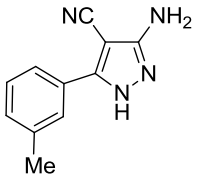

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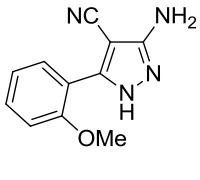

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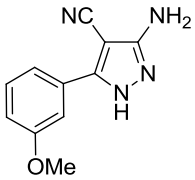

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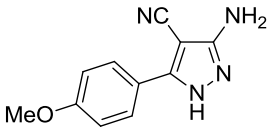

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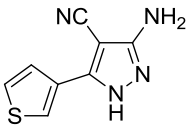

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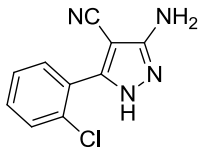

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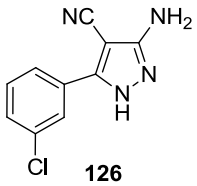

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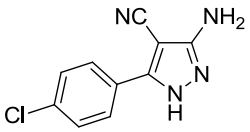

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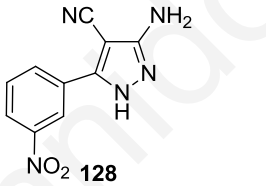

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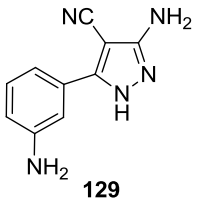

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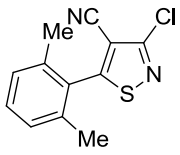

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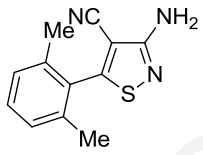

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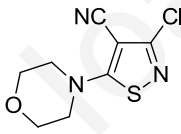

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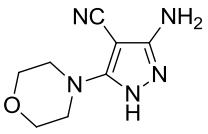

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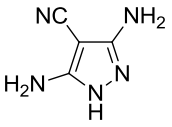

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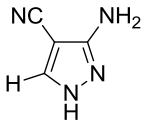

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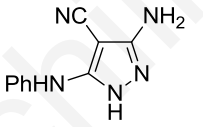

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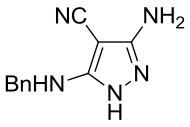

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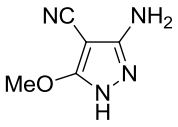

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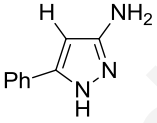

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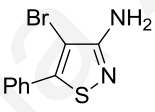

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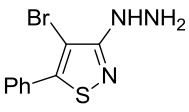

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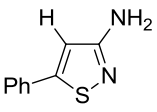

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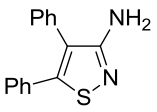

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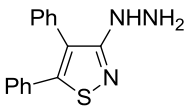

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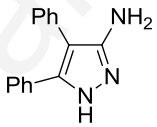

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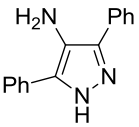

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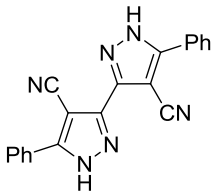

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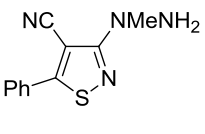

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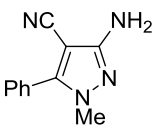

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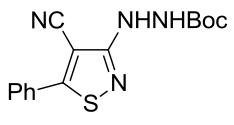

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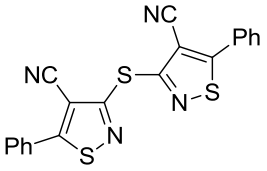

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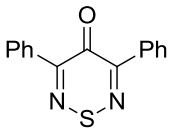

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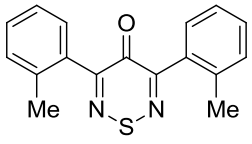

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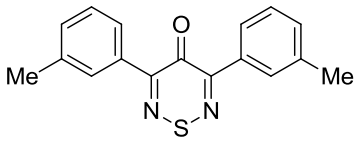

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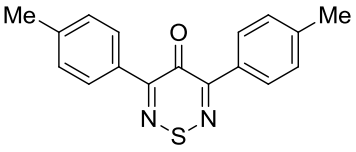

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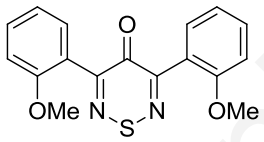

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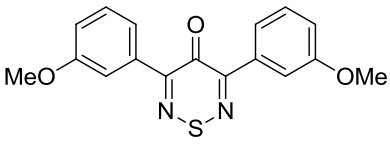

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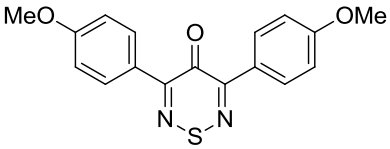

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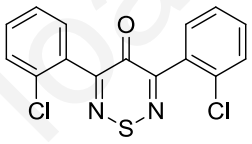

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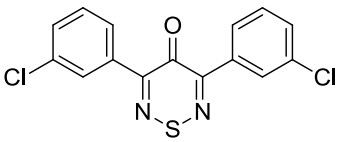

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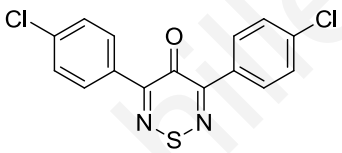

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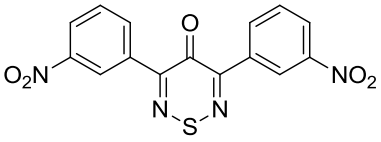

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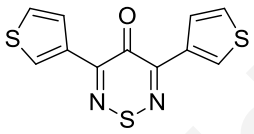

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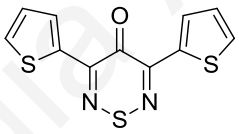

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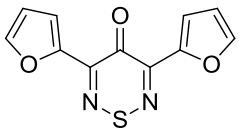

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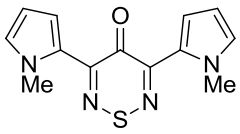

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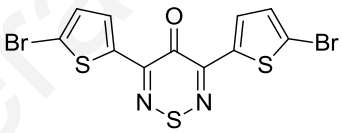

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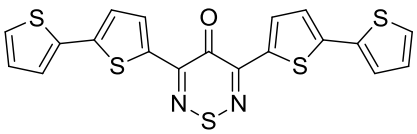

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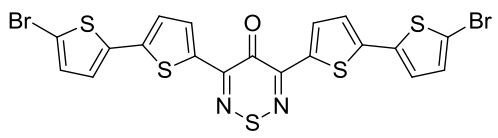

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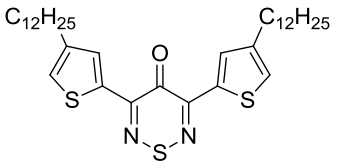

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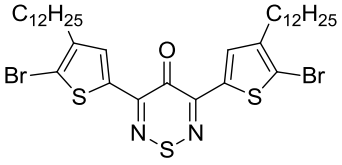

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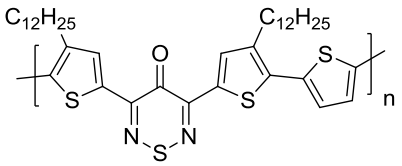

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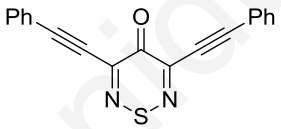

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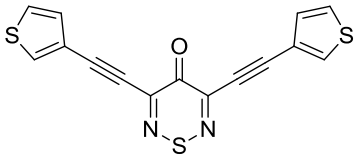

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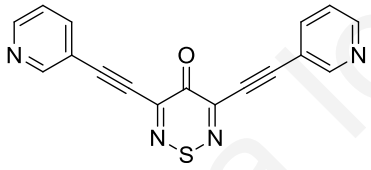

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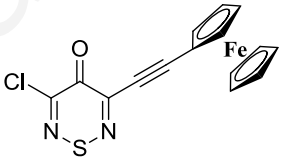

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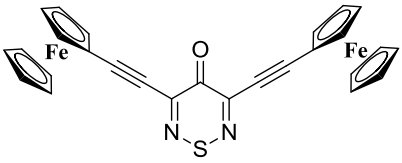

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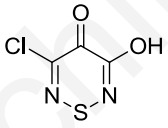

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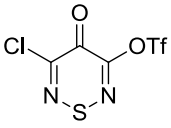

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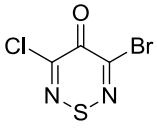

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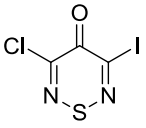

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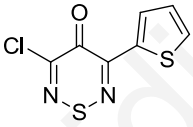

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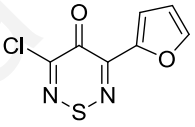

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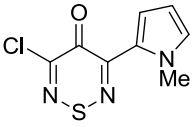

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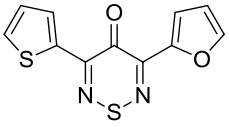

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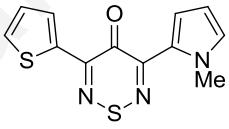

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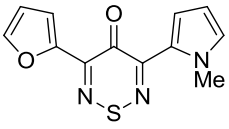

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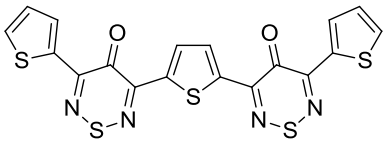

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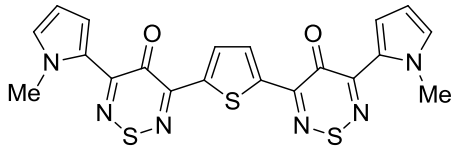

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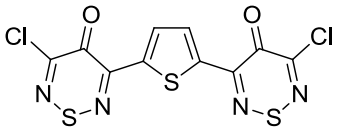

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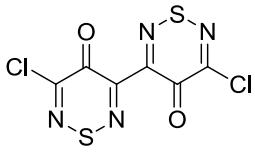

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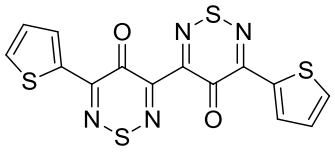

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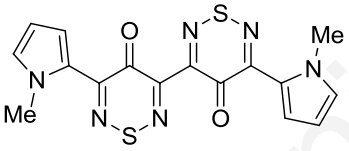

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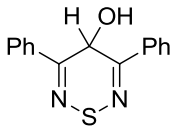

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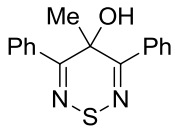

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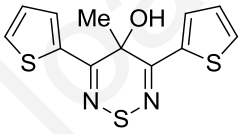

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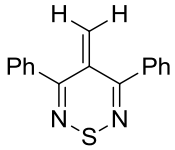

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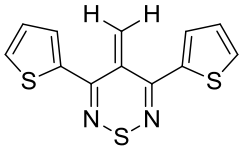

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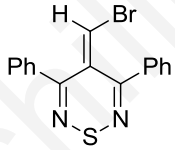

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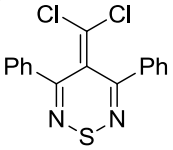

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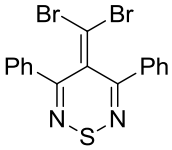

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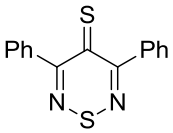

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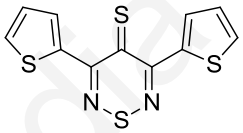

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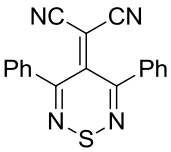

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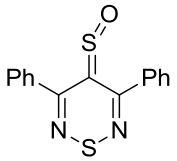

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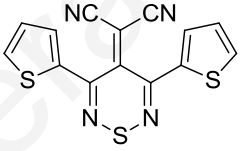

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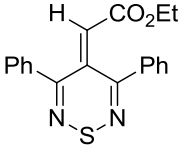

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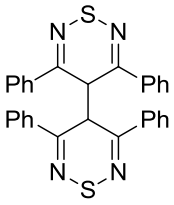

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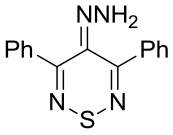

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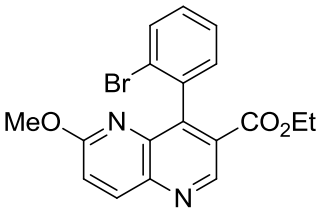

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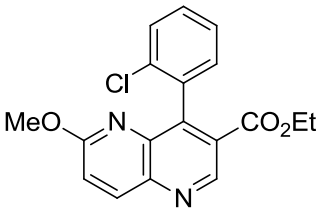

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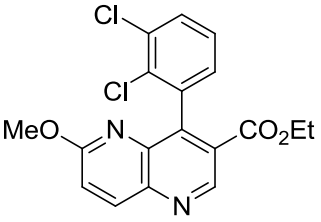

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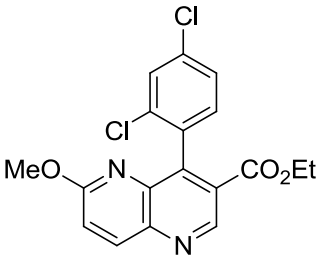

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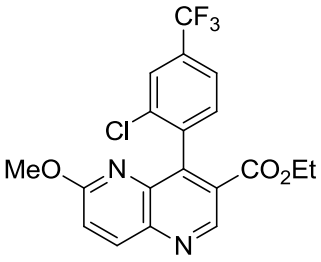

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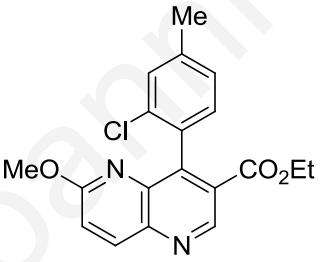

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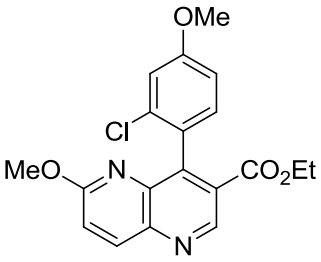

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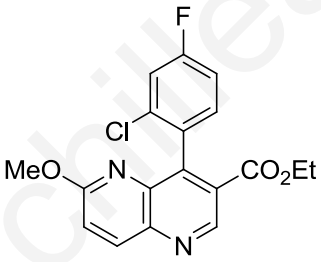

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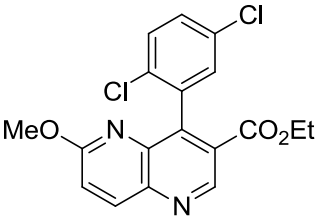

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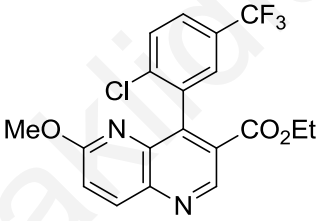

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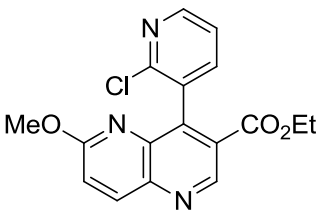

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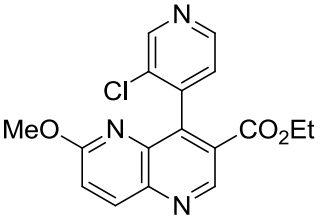

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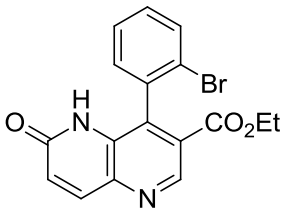

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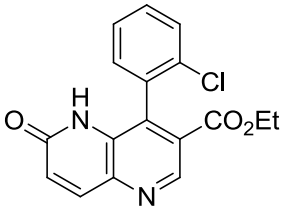

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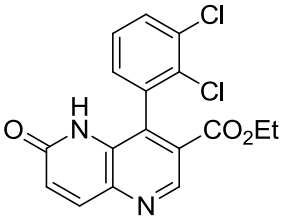

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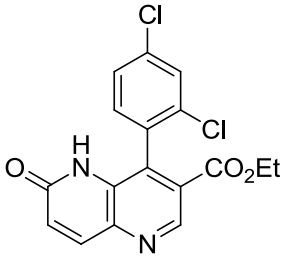

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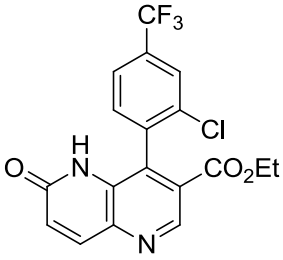

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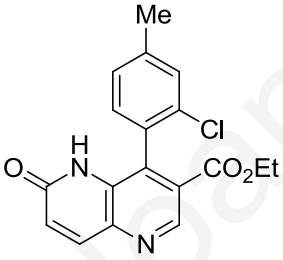

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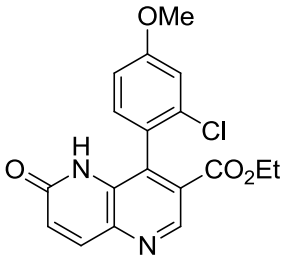

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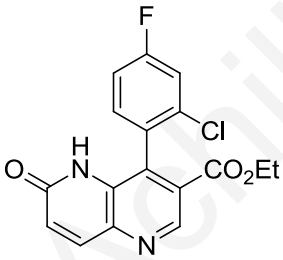

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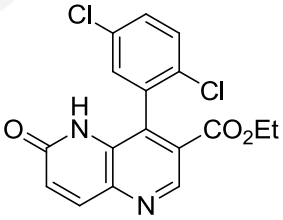

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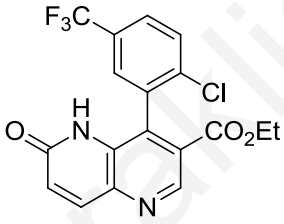

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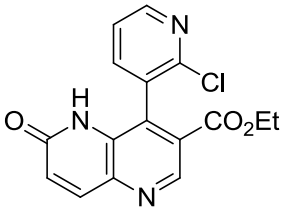

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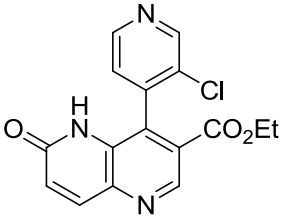

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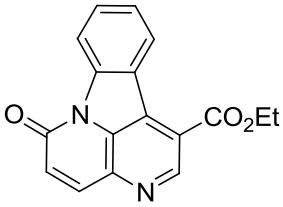

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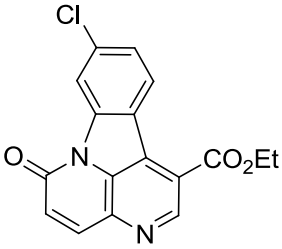

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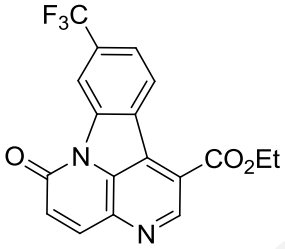

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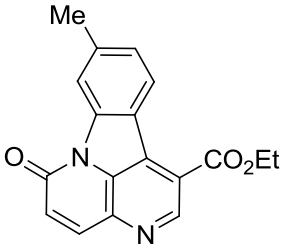

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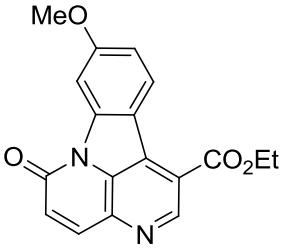

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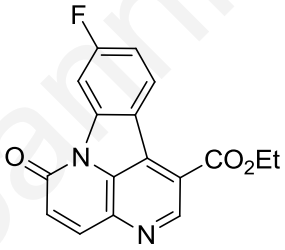

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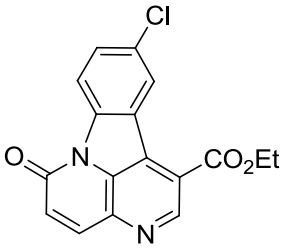

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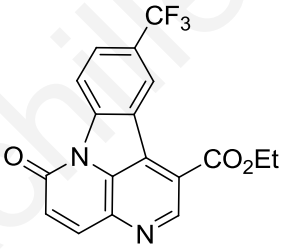

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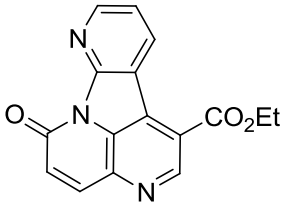

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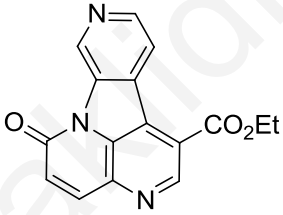

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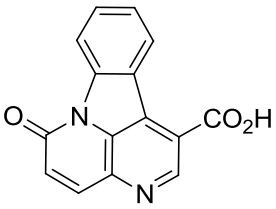

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