UNIVERSITY OF CYPRUS
DEPARTMENT OF CHEMISTRY

Doctorate Thesis

New Chemistry of Isothiazoles and 1,2,3-Dithiazoles

Irene Costa Christoforou

December 2007

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December 2007

EXPERIMENTAL PROCESSES ACCOMPLISHMENT STATEMENT

Except where noted below the work described within this thesis has been carried out exclusively by Irene C. Christoforou at the Organic Chemistry Research Laboratory, in the Department of Chemistry, University of Cyprus under the supervision of Dr. Panayiotis A. Koutentis, (September 2002 – February 2007).

The exceptions include: the single crystal X-ray crystallographic studies (performed by Dr. Anastasios J. Tasiopoulos of the Department of Chemistry, University of Cyprus; the elemental analysis of all compounds (performed by Stephen Boyer of London Metropolitan University); and high resolution mass spectrometry (performed by John Barton of Imperial College London).

Date

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Signature

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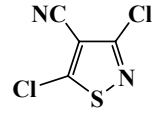
To my family and fiancé



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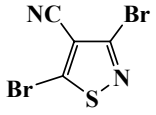

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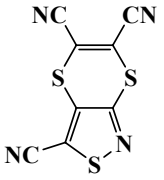

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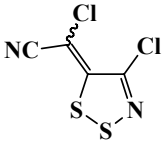

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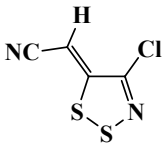

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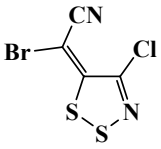

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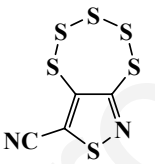

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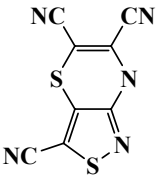

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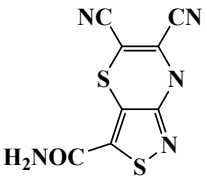

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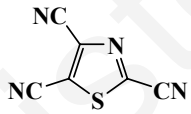

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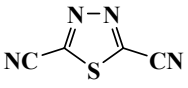

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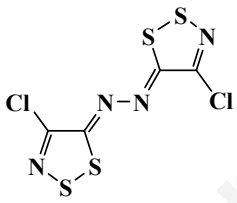

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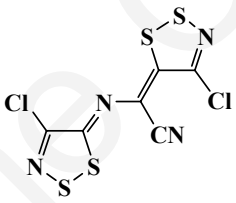

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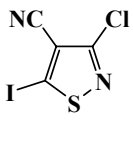

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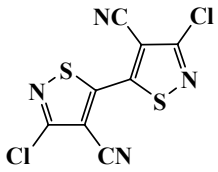

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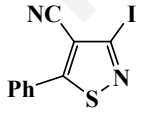

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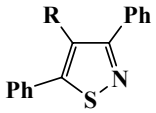


291, **307-321**

R = Ph, 3-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-Tol, 3-Tol, 2-Tol, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-(4-ClC_6H_4)C_6H_4, 3-(3-ClC_6H_4)C_6H_4, 3-Thienyl, 2-Thienyl, 2-Furyl

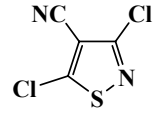
ABSTRACT

After an introduction on isothiazoles and their preparation (Chapter 1), new chemistry of 1,2,3-dithiazoles is discussed in Chapters 2 and 3. Substituted 1,2,3-dithiazolylidene acetonitriles **129**, **139** and **142** are synthesised and treated with anhydrous HBr and tetraalkylammonium halides to give 3-halo-4-(substituted)isothiazole-5-carbonitriles in low yields. The reaction of the (dithiazolylidene)acetonitrile **139** with tetraalkyl-ammonium chloride gives the heterocycles **93**, **95** and **146-148**. A tentative mechanistic rational for their formation proposes the *in situ* formation of dicyanoacetylene and diatomic sulfur *via* degradation of the dithiazole (Chapter 2).

The 1,2,3-dithiazole ring, which is highly electrophilic at C-5, is a source of both electrophilic and nucleophilic sulfur. Careful consideration of these properties allows for the transformation of either bisdithiazole **181** or **182**, on treatment with soft nucleophiles, into the expected percyano-1,3,4-thiadiazole **173** and thiazole **169** respectively in good yields (Chapter 3).

Chapters 4-6 focus on isothiazole C-C coupling chemistry. 3,5-Dichloro- and dibromoisothiazole-4-carbonitriles **5** and **6** give highly regioselective Pd catalysed Suzuki reactions to afford 3-halo-5-(substituted)isothiazole-4-carbonitriles (Chapter 4). 3,5-Dibromoisothiazole **6** is more reactive than the 3,5-dichloroisothiazole **5** and also participates in Stille, Negishi and Sonogashira couplings. 5,5'-Bi(3-chloroisothiazole-4-carbonitrile) **228** is prepared *via* Pd catalysed Ullmann type coupling from 3-chloro-5-iodoisothiazole-4-carbonitrile **204**. A variety of 3-substituted isothiazoles (3-substituents = Cl, Br, OMs, OTs and OTf) are less reactive. The 3-iodo-5-phenylisothiazole-4-carbonitrile **245**, participates in Suzuki, Ullmann type, Stille, Negishi and Sonogashira coupling reactions (Chapter 5).

The synthesis of 3,4,5-triarylisothiazoles, *via* C–C coupling reactions, is achieved *via* the arylation sequences C-5 : C-4 : C-3 and also C-5 : C-3 : C-4, the latter triarylation sequence being more versatile (Chapter 6). Several new triarylisothiazoles **191**, **307-321** are synthesised in high yields. The isothiazole C-4 cyano substituent is converted into either bromo *via* Hunsdiecker reaction or iodo *via* Hoffmann degradation followed by Sandmeyer iodination. The reactivity of haloisothiazoles towards the coupling methods follows the anticipated order I>Br>Cl. All products are fully characterized (Chapter 7).



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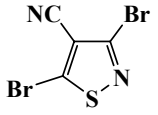

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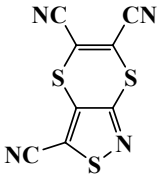

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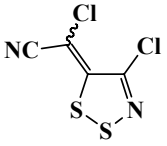

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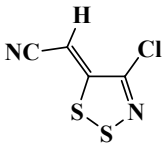

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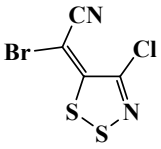

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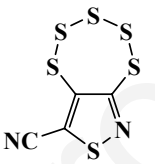

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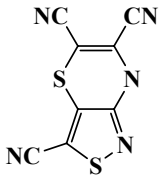

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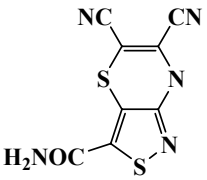

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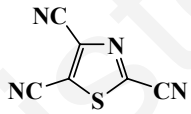

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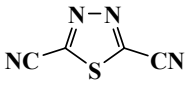

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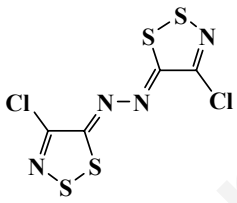

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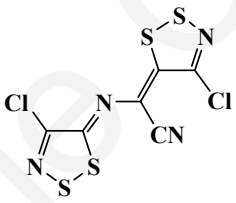

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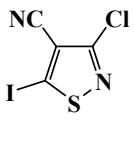

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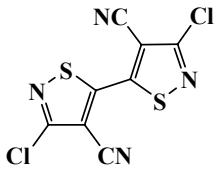

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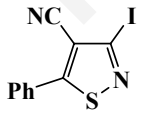

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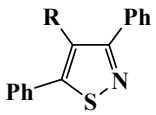

291, **307-321**

R = Ph, 3-$NO_2C_6H_4$, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 4-Tol, 3-Tol, 2-Tol, 4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4, 4-(4-ClC_6H_4)C_6H_4, 3-(3-ClC_6H_4)C_6H_4, 3-Thienyl, 2-Thienyl, 2-Furyl

ΠΕΡΙΛΗΨΗ

Μετά τη σύντομη εισαγωγή (Κεφάλαιο 1) περί ισοθειαζολών, ακολουθεί περιγραφή νέας χημείας των 1,2,3-διθειαζολών στα Κεφάλαια 2 και 3. Συντίθενται τα υποκατεστημένα 1,2,3-διθειαζολυλίδενο ακετονιτρίλια **129**, **139** και **142** και κατεργάζονται με άνυδρο HBr και τριαιθυλαμμωνιακά αλογονίδια αποφέροντας 3-αλογονο-4-(υποκατεστημενα)-ισοθειαζολο-5-καρβονιτρίλια σε χαμηλές αποδόσεις. Η αντίδραση του διθειαζολυλίδενο ακετονιτριλίου **139** με τριαιθυλαμμωνιακό χλωρίδιο επιφέρει το σχηματισμό των ενώσεων **93**, **95**, **146-148**. Προτείνεται ο *in situ* σχηματισμός δικυανοακετυλενίου και διατομικού θείου μέσω αποικοδόμησης του διθειαζολικού δακτυλίου (Κεφάλαιο 2).

Ο 1,2,3-διθειαζολικός δακτύλιος είναι ισχυρά ηλεκτρονιόφιλος στη θέση C-5 και δρα ως πηγή ηλεκτρονιόφιλου αλλά και πυρηνόφιλου θείου. Λαμβάνοντας υπόψη αυτές τις ιδιότητες, επιτυγχάνεται ο μετασχηματισμός των διθειαζολών **181** και **182** στις προβλεπόμενες περκυανο-1,3,4-θειοδιαζόλη **173** και θειαζόλη **169**, σε καλές αποδόσεις, μετά από κατεργασία με μαλακά πυρηνόφιλα (Κεφάλαιο 3).

Τα κεφάλαια 4-6 εστιάζονται σε αντιδράσεις σύζευξης C-C του ισοθειαζολικού δακτυλίου. Τα 3,5-διχλωρο- και 3,5-διβρωμοϊσοθειαζολο-4-καρβονιτρίλια **5** και **6** δίνουν τοποεκλεκτικές αντιδράσεις Suzuki παρέχοντας 3-αλογονο-5-(υποκατεστημενα)ισοθειαζολο-4-καρβονιτρίλια (Κεφάλαιο 4). Η 3,5-διβρωμοϊσοθειαζόλη **6** είναι δραστικότερη της 3,5-διχλωροϊσοθειαζόλης **5** και συμμετέχει στις αντιδράσεις σύζευξης Suzuki, Stille, Negishi και Sonogashira. Η 5,5'-διϊσοθειαζόλη **228** παρασκευάζεται με αντίδραση Ullmann από το 3-χλωρο-5-ιωδοϊσοθειαζολο-4-καρβονιτρίλιο **204**. Μια ποικιλία 3-υποκατεστημένων ισοθειαζολών (3-υποκαταστάτες = Cl, Br, OMs, OTs και OTf) αποδεικνύονται λιγότερο δραστικές. Το 3-ιωδο-5-φαινυλοϊσοθειαζολο-4-καρβονιτρίλιο **245**, συμμετέχει σε αντιδράσεις Suzuki, Ullmann, Stille, Negishi και Sonogashira (Κεφάλαιο 5).

Επιτυγχάνεται η σύνθεση των νέων 3,4,5-τριαρυλοϊσοθειαζολών **191**, **307-321**, σε ψηλές αποδόσεις, με αντιδράσεις σύζευξης C-C ακολουθώντας τις αλληλουχίες C-5 : C-4 : C-3 και C-5 : C-3 : C-4 με την τελευταία να είναι πιο ευέλικτη (Κεφάλαιο 6). Ο κύανο-υποκαταστάτης της C-4 θέσης μετατρέπεται σε βρώμο μέσω αντίδρασης Hunsdiecker ή σε ιώδο μέσω αποικοδόμησης Hoffmann ακολουθούμενη από ιωδίωση Sandmeyer. Η δραστικότητα των αλογονομένων ισοθειαζολών στις μεθόδους σύζευξης ακολουθεί την αναμενόμενη σειρά I>Br>Cl. Όλα τα προϊόντα χαρακτηρίζονται πλήρως (Κεφάλαιο 7).

ACKNOWLEDGEMENTS

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Furthermore I would like to thank my family for their love, support and encouragement. Finally many thanks to my fiancé for being such a special part of my life and for all the strength that I drew from him during the last three years of my PhD.

CONTENTS

Brief Contents

Detailed Contents

ABBREVIATIONS

Å	Ångström unit
Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
Adogen 464®	methyltrialkyl(C_8-C_{10})ammonium chloride
Alk	alkyl
AM1	Austin Method 1
amyl	pentyl
app.	apparent
aq.	aqueous
Ar	aryl
Bn	benzyl
br	broad
Bz	benzoyl
ca.	approximately (latin: *circa*)
CD_2Cl_2	deuterated dichloromethane
$CDCl_3$	deuterated chloroform
c*f*.	compare (latin: *confer*)
cm^{-1}	wavelength unit
cp	cyclopentadienyl
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
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	double doublet
ddd	doublet of double doublets
DDQ	2,3-dichloro-5,6-dicyano-4-benzoquinone
decomp.	decomposition

DEPT	distortionless enhancement by polarization transfer
DMAD	dimethyl acetylenedicarboxylate
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMSO-d_6	deuterated dimethylsulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
E	electrophile
e.g.	for example, (Latin: *exempli gratia*)
EI	electron ionization
equiv.	equivalent
Et	ethyl
Et_2O	diethyl ether
EtOH	ethanol
eV	electron volt unit
FTIR	Fourier transform infrared
g	gas
GCMS	gas chromatography mass spectrometry
gem	geminal
h	hour
Hal	halogen
HOMO	highest occupied molecular orbital
HSA	hydroxylamine-*O*-sulfonic acid
Hünig's base	diisopropylethylamine
hv	photolysis
Hz	Hertz unit
I_A	Birds aromaticity index
inf.	inflection
in vacuo	under reduced pressure
^{i}Pr	isopropyl
IR	infrared
J	coupling constant
LDA	lithium diisopropylamide

LG	leaving group
liq.	liquid
lit.	literature
LRMS	low resolution mass spectrometry
LUMO	lowest unoccupied molecular orbital
m	multiplet (NMR) or medium (IR)
m/z	mass to charge ratio
M^+	molecular ion
Me	methyl
MeOH	methanol
MHz	megahertz unit
min	minutes
mmHg	millimeters of mercury (760 mmHg equals to 101325 Pa)
mp	melting point
Ms	methanesulfonyl
MW	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
nd	no data
NIR	near infrared
NIS	*N*-iodosuccinimide
nm	nanometer unit
NMR	nuclear magnetic resonance
^{n}Pr	n-propyl
Nu	nucleophile
^{o}C	Celsius degrees
ox	oxidation
Ph	phenyl
pH	potential of hydrogen
PhCl	chlorobenzene
PhH	benzene
PhMe	toluene
ppm	parts per million

psi	pounds per square inch (1 psi equals to 6894.76 Pa)
PTC	phase transfer catalyst
Py	pyridine
q	quartet
rt	room temperature (*ca.* 20 ^{o}C)
rxn	reaction
s	singlet (NMR) or strong (IR)
sat.	saturated
t	triplet
TCNEO	tetracyanoethyleneoxide
Tf	trifluoromethanesulfonyl
THF	tetrahydronfuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Torr	Torricelli (unit of pressure equal to 1/760 atmosphere)
Ts	4-toluenesulfonyl
TsOH	4-toluenesulfonic acid
TTF	tetrathiafulvalene
UV	ultra-violet
VdW	Van der Waals
Vis	visible
W	Watt unit
w	weak (IR)
δ	chemical shift relative to a standard
Δ	heat (Thermolysis)
λ_{max}	maximum wavelength
μl	microliter unit

CHAPTER 1

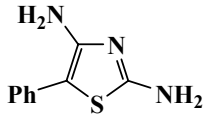
Introduction

Sections

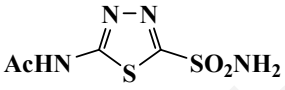
1.1 Introduction

1.1.1 Heteroaromaticity

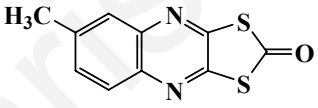
The term heteroatom refers to any atom other than carbon, usually nitrogen, oxygen or sulfur. Any ring system which contains at least one heteroatom can be described as heterocyclic and such ring systems are well known in organic synthesis. Many of them present important properties in various drugs, toxicants, agrochemicals and find applications in material science. The majority of heterocycles contain nitrogen or oxygen but an increasing number of important compounds are appearing which contain sulfur. Some sulfur rich examples include: the banned bodybuilding drug amiphenazole,[1] which is a thiazole effective against respiratory depression caused by morphine-like analgesics; the 1,3,4-thiadiazole acetazolamide[2, 3] which was first launched as a diuretic and later on as an antiepileptic agent; the quinomethionate[4-6] which is used to control spider mites and has also fungicidal properties; and the tetrathiafulvalene (TTF)[7] which has been used for the preparation of electrical conductive materials.



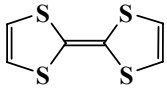
Amiphenazole



Acetazolamide

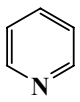


Quinomethionate

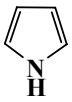


Tetrathiafulvalene

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



Pyridine



Pyrrole

Furan

Thiophene

The pyridine ring nitrogen is sp^2 hybridized, planar and trigonal with one lone pair in the plane of the ring occupying the space of the C-H bond in benzene (Figure 1). The pyrrole ring nitrogen is also sp^2 hybridized but here the lone pair of electrons is

orthogonal to the plane of the ring and participates in electron delocalization. The heteroatoms of furan and thiophene have two lone pairs of electrons, one in the plane of the ring and one orthogonal to the plane of the ring.

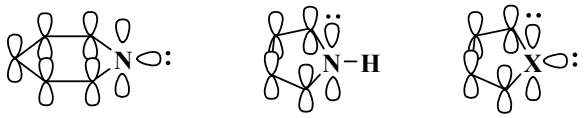
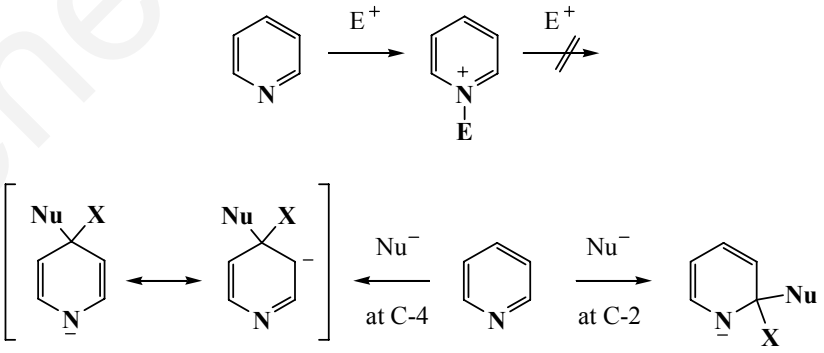


Figure 1 Selected orbital representations of pyridine, pyrrole, furan and thiophene.

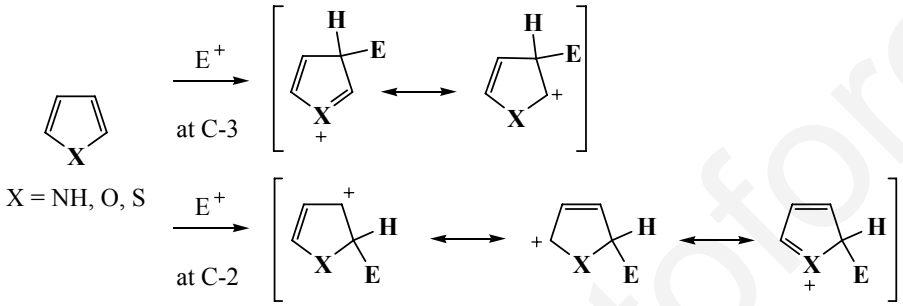
The replacement of a benzene CH group by a heteroatom results in significant changes of both the physical and chemical properties. For example pyridine is a weak base (pK_a = 5.5) and since the lone pair of electrons on nitrogen cannot be delocalised around the ring, pyridine is nucleophilic *via* the nitrogen atom. The electronegative nitrogen atom makes pyridine less reactive than benzene towards electrophilic aromatic substitution and the nitrogen preferentially attacks the incoming electrophile making the ring even less reactive. Nucleophilic substitution however, which is difficult for benzene, occurs easily on pyridine. The nitrogen atom makes pyridine more reactive towards nucleophilic substitution, particularly at the C-2 and C-4 positions (Scheme 1). Attack at the C-3 position is not favoured because the negative charge on the intermediate cannot be delocalized onto the electronegative nitrogen atom.



Scheme 1

The lone pair of electrons on the 5-membered heterocycles pyrrole, furan and thiophene is not readily available for protonation and consequently these heterocycles are not basic. The extent of delocalization depends on the electronegativity of the

heteroatom. Increased electronegativity reduces the contribution of the lone pair to the delocalization and hence the aromaticity follows the order thiophene > pyrrole > furan. The C-2 position is more reactive than the C-3 position towards electrophiles because reaction at the C-2 position results in better delocalization of the positive charge (Scheme 2). Nucleophilic substitution is a relatively rare reaction with pyrrole, thiophene and furan, since these systems are electron rich, and requires an activating group just as it does with benzene.

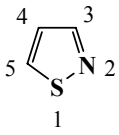


Scheme 2

Multiple replacements of CH groups are also possible and 5- or 6-membered heterocycles with up to four heteroatoms are common. Therefore the structural possibilities that arise from the displacement of CH groups by heteroatoms are many and the physical, chemical and biological applications of heterocyclic aromatic systems are numerous. As such it is not surprising that a large number of heterocycles find important applications in life. A relatively new aromatic heterocycle, which is the main focus of this thesis, is isothiazole. A brief introduction on isothiazoles is presented below.

1.2 Isothiazoles

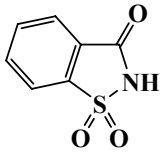
Isothiazoles (1,2-thiazoles) are 5-membered ring systems which contain three carbons and two adjacent heteroatoms, one sulfur and one nitrogen. Although benzoisothiazoles have been known for many years, monocyclic isothiazoles are relatively new. The parent isothiazole **1**, the first discovered isothiazole, was prepared *via* a multistep synthesis by Arthur Adams and Ronald Slack in 1956.[8] The reduced forms, the tetrahydroisothiazoles as well as the 1-oxides and 1,1-dioxides are also known.



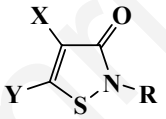
1

1.2.1 Applications

The most important synthetic isothiazole derivative is saccharin which was discovered by Constantine Fahlberg in 1879 and was the first non-carbohydrate sweetening agent.[9] Fahlberg spilled a chemical on his hand and later while eating dinner, he noticed more sweetness in the bread he was eating. He later realised that the sweet taste came from one of his chemicals. The reason why saccharin tastes sweet is still unclear, but its shape must be correct to fit into specific receptors in the taste buds. Evidence for this comes from the fact that when the shape of saccharin was modified slightly, the new molecule no longer tasted sweet. Other important commercial isothiazoles include the Kathon® preservatives[10-14] and the antibacterial sulfa drug, sulfasomizole.[15]



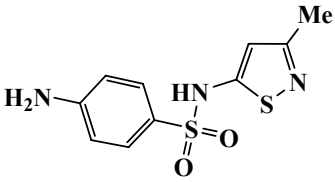
Saccharin



X, Y = H, Cl

R = Me, *n*-octyl

Kathon®

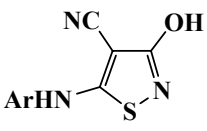


Sulfasomizole

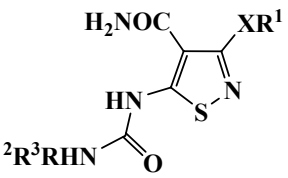
Recently, isothiazoles have been reported as potential anticancer agents which inhibit the MEK-1 and MEK-2 kinases,[16, 17] as useful prodrugs for the treatment of hyper-proliferative disorders,[18] and as novel active site inhibitors for the hepatitis C virus NS5B polymerase.[19] The biological and other uses of isothiazoles have been reviewed extensively.[20-24]

R = alkyl, Ar = aryl

MEK-1 & MEK-2 active

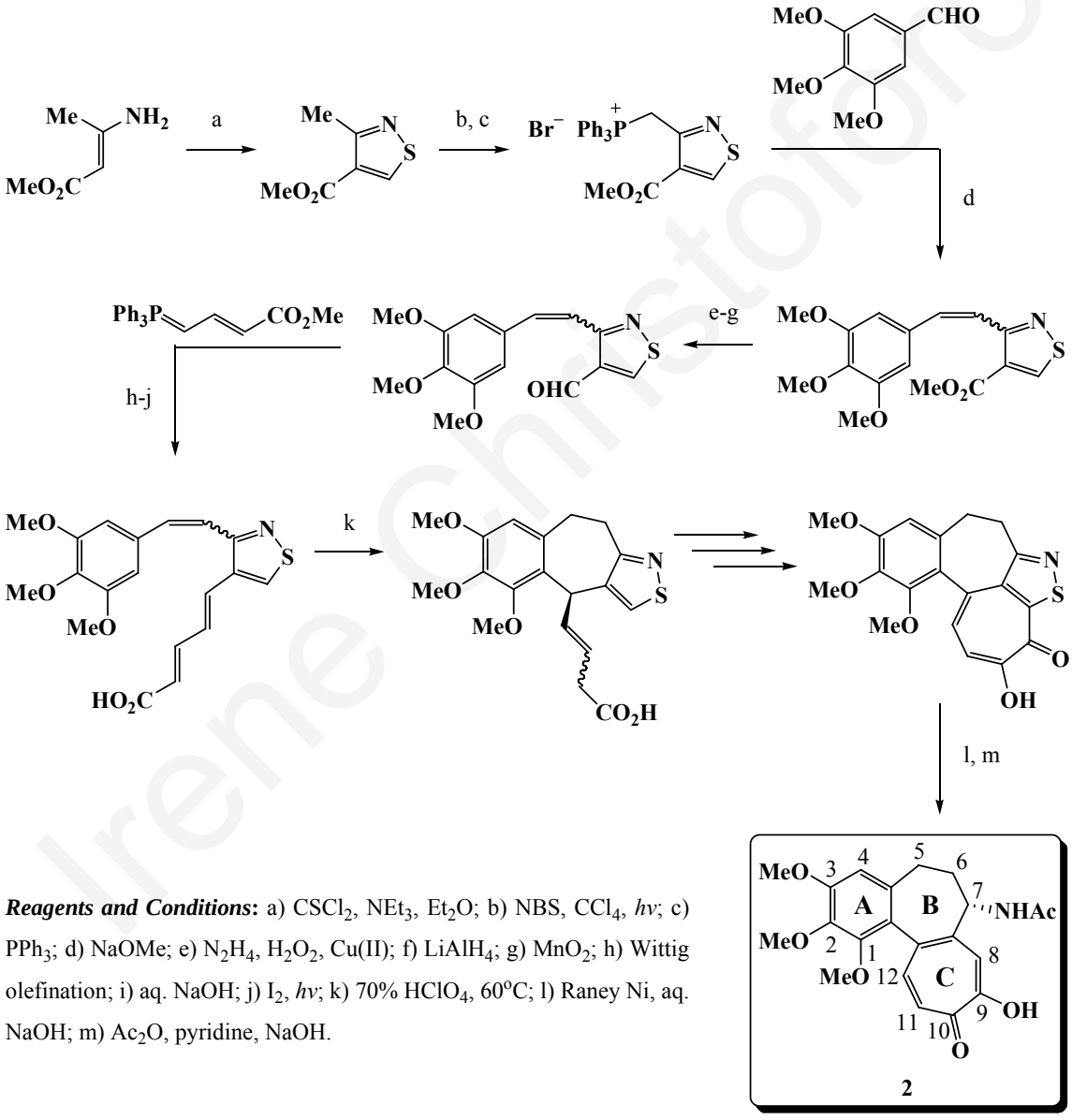


HCV NS5B polymerase active



Active against hyperproliferative disorders

In addition to isothiazoles' interesting biological and pharmacological properties, isothiazoles also find many uses as synthetic precursors and the use of isothiazoles in the search for alternative synthetic strategies in the development of novel molecular structures has grown steadily. An illustrative early example is the Woodward's total synthesis of alkaloid colchicine **2** (Scheme 3). The synthesis was presented by Woodward in 1963 during a Harvey Lecture.[25] A remarkable feature of Woodward's synthesis was the implementation of the nitrogen functionality at the C-7 position as an integral part of the synthesis. The isothiazole ring served as a masked amino function and acted as a platform for the cyclization of rings B and C.



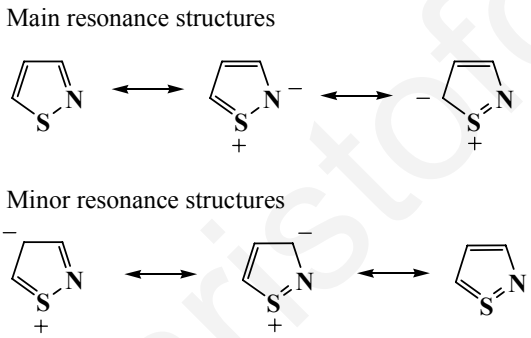
***Reagents and Conditions*:** a) $CSCl_2$, NEt_3, Et_2O; b) NBS, CCl_4, *hv*; c) PPh_3; d) NaOMe; e) N_2H_4, H_2O_2, Cu(II); f) $LiAlH_4$; g) MnO_2; h) Wittig olefination; i) aq. NaOH; j) I_2, *hv*; k) 70% $HClO_4$, 60°C; l) Raney Ni, aq. NaOH; m) Ac_2O, pyridine, NaOH.

Scheme 3

1.2.2 Physical Properties

Isothiazole **1** is liquid at room temperature and atmospheric pressure with a boiling point of 113 ^{o}C.[26] Substituents that can introduce hydrogen bonding stabilize the crystalline state and increase the melting point. Isothiazole **1** has a low solubility in water and is miscible with most organic solvents as are the majority of isothiazoles. The pK_a value of isothiazole **1** is –0.51 and strong acids can protonate the ring nitrogen.[27] The acidity of the ring protons is reported to be H-5 > H-4 > H-3.[28]

Isothiazole behaves as a typical aromatic molecule and can be represented by three main resonance structures that are accompanied by three less charge extended resonance structures (Scheme 4).



Scheme 4

Bird's aromaticity index (I_A) (*cf.* benzene I_A = 100), which is based on the statistical degree of uniformity of the bond orders of the ring periphery for heteroaromatic compounds, shows that isothiazole has comparable aromaticity to pyrazole (Figure 2).[29]

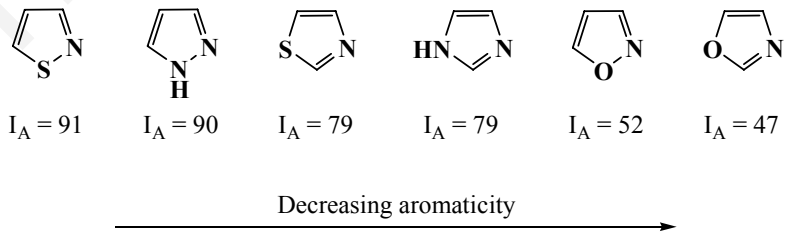


Figure 2 Bird's aromaticity index (I_A).

The molecular orbital energies of isothiazole **1** have been calculated by the semi-empirical AM1 method and gave the HOMO and LUMO energies at –9.93 and –0.21 eV respectively.[30] The calculations suggest that there is a net negative charge density on the

nitrogen, a net positive charge on sulfur and greater electron density at C-5 than at C-4 (Figure 3).[31]

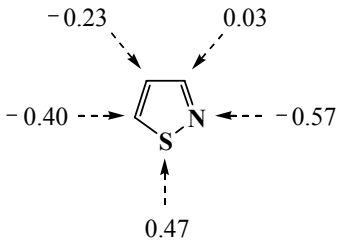


Figure 3 Charge distributions on isothiazole ring studied by 6-31G*//STO-3G* calculation.[31]

1.2.3 Experimental Structural Methods

Electron diffraction studies on isothiazole show a significant degree of bond delocalization which supports the aromatic character of the compound (Figure 4).[32] For comparison the standard related single and double bond lengths are as follows: [1.54 (C-C), 1.74 (S-N), 1.41 (C-N), 1.81 (C-S), 1.34 (C=C), 1.53 (S=N), 1.29 (C=N) and 1.55 Å (C=S)]. The UV/vis spectrum of isothiazole shows a major band at λ_{max} = 244 nm (log ε = 3.72). Isothiazoles display common peaks in IR spectra at 1310 (C-C), 1400 (C=N), 1510 cm^{-1} (C=C) and intense bands also occur near 750 and 840 cm^{-1}. ^{1}H (CCl_4)[33] and ^{13}C NMR ($CDCl_3$)[34] data have also been recorded (Figure 4).

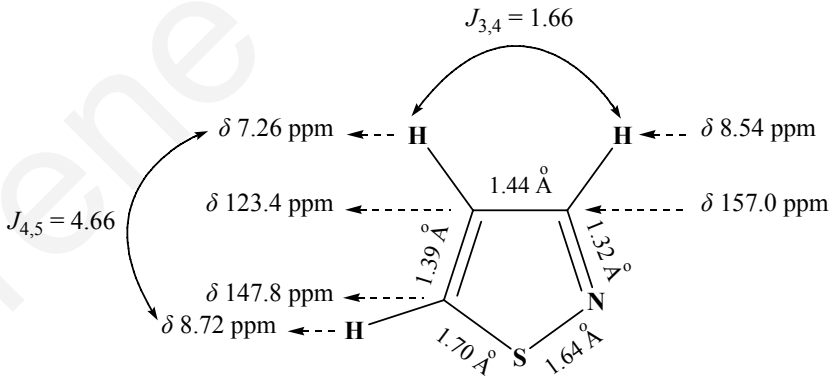
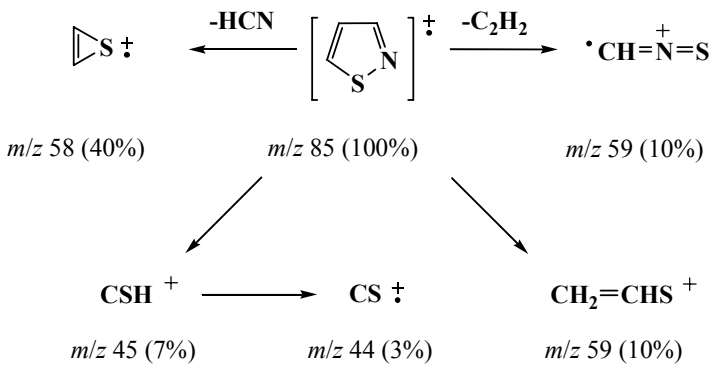


Figure 4 Isothiazole bond lengths and NMR data.

The mass spectrum of the parent isothiazole gives an intense peak for the molecular ion which expels hydrogen cyanide, ethyne and other less important fragmentations (Scheme 5).[35]



Scheme 5

1.2.4 Chemistry

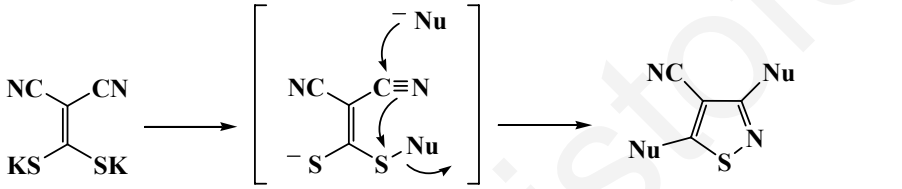
Recently a series of reviews have been published in the literature regarding the chemistry of isothiazoles.[20-24] Very briefly, isothiazoles are electron-rich heteroaromatic systems (formally 6π electrons distributed over 5 atoms) and thus undergo electrophilic substitution reactions. The most reactive position for electrophilic substitution is C-4 while the C-3 position is relatively inert to attack. Nitration occurs at C-4 in good yield but halogenation is less controllable giving polyhalogenated products. Unexpectedly, isothiazoles bearing electron donating groups at either C-3 or C-5 are less prone to over reactions and bromination gives the corresponding 4-bromo derivatives in 63-98% yield.[36-43] Despite isothiazoles being aromatic compounds, they can suffer nucleophilic attack quite easily. Nucleophiles will react with isothiazole at the sulfur atom effecting ring opening, however, attack is switched to C-5 if a suitable leaving group (LG) is present, *e.g.*, LG = Hal, OMs, SO_2R. The C-5 position of isothiazole is more susceptible to nucleophilic attack than C-3 because the nearby sulfur polarises to stabilize the neighbouring build up of charge. Interestingly, the experimental data concerning the electrophilic substitution and nucleophilic attack on isothiazole ring differ from the expectations based on the calculated charges[31] (Figure 3). Recently C-C palladium catalysed coupling reactions have been reported for several chloro, bromo and iodo halogenated isothiazoles to give aryl, heteroaryl, alkenyl and alkynyl substituted isothiazoles.[44-48] The modification of existing ring substituents has also been well reviewed.[20-24]

1.2.5 Synthesis of Isothiazole

1.2.5.1 Synthesis by Ring Forming Reaction

1.2.5.1.1 By Formation of One S-N Bond

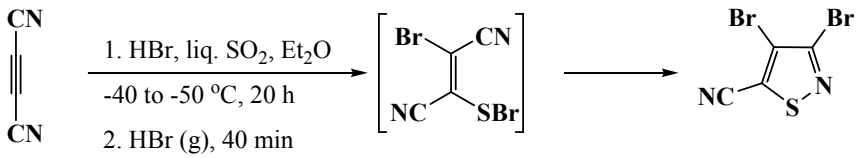
The most common route to isothiazoles is *via* the formation of the N-S bond. Substituted isothiazoles were synthesized by ring closure reactions of 2-cyano-1-mercaptoethylene derivatives **3**.[49-53] The reaction mechanism possibly involves the intermediate **4**. Treatment of dithiolate **3** with excess Cl_2 gave the 3,5-dichloroisothiazole-4-carbonitrile **5** in 57% (Scheme 6). The analogous 3,5-dibromoisothiazole-4-carbonitrile **6** was prepared in low yield.[54] Reaction of the dithiolate **3** with sulfur in boiling MeOH gave the 3,5-dimercaptoisothiazole-4-carbonitrile salts **7** which are readily alkylated to afford the bis(alkylthio) isothiazole-4-carbonitrile derivatives.[51]



3 **4** **5**, Nu = Cl, 57%; **6**, Nu = Br; **7**, Nu = S^-, 88%

Scheme 6

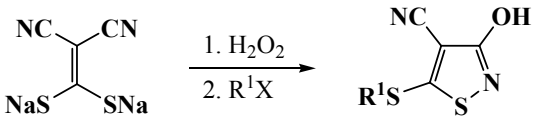
The synthesis of 3,4-dibromoisothiazole-4-carbonitrile **10** was achieved by the treatment of dicyanoacetylene **8** with HBr in liquid sulfur dioxide / diethyl ether at low temperature (Scheme 7).[55, 56] The sulfenyl bromide **9**, which is similar to the above intermediate **4**, was proposed as a key intermediate. A similar reaction with acetylenedicarboxamide gave 4-bromo-3-hydroxyisothiazole-5-carboxamide in 44% yield.[56, 57]



8 **9** **10**, 35%

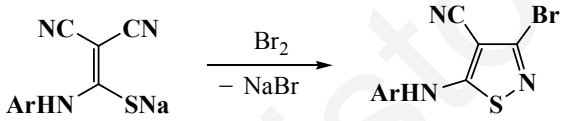
Scheme 7

Disodium 2,2-dicyanoethene-1,1-dithiolate **11** was oxididatively cyclized with hydrogen peroxide and subsequently alkylated to afford the corresponding isothiazoles **12-14** in good yield (Equation 1).[50, 52, 58] Direct oxidation of the analogous 2,2-dicyano-1-arylaminoethylenethiolate salt **15**, prepared from malononitrile and arylisothiocyanates, gave the 5-(*N*-arylamino)-3-bromoisothiazole-4-carbonitriles **16** in modest yields (Equation 2).[59] Several other isothiazole derivatives have also been prepared by oxidation of 2-cyanoethenethiolates.[60-68]



11 **12-14**

12, R^1 = Me, 71%
13, R^1 = $CH_2CH{=}CH_2$, 70%
14, R^1 = 3,4-$Cl_2C_6H_3CH_2$, 70% (1)

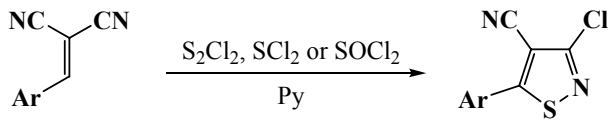


(2)

15, Ar = 4-Tol
4-BrC_6H_4
4-$EtOC_6H_4$

16, 61-68%

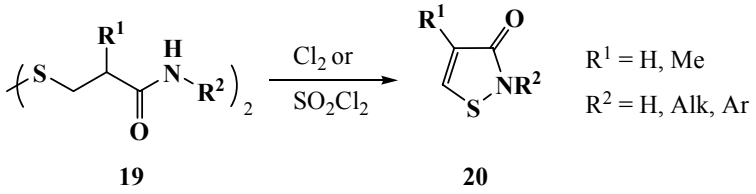
A simple method for isothiazole formation involves reaction of arylylidene-malononitriles **17** with sulfur chlorides or thionyl chloride in the presence of Py to afford 5-aryl-3-chloroisothiazole-4-carbonitriles **18** in 38-80% yields (Equation 3).[69] This reaction also tolerated 1-aminopropene-2-ones and 1-aminopropene-2-nitriles as starting materials.[70, 71]



17 (3)

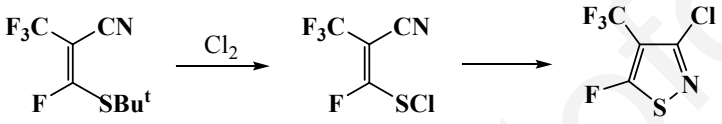
18, 38-80%

Cyclization of the readily available 3,3'-dithiodipropionamides **19**, induced by Cl_2 or sulfuryl chloride, gave a series of substituted isothiazol-3-ones **20** (Equation 4).[10, 11, 72]



19 **20**

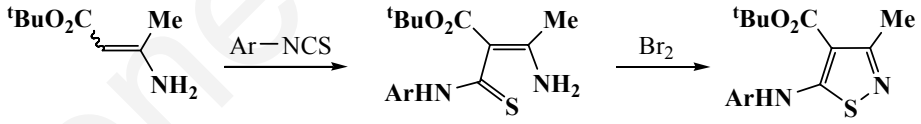
Chlorolysis of *tert*-butyl 2-cyano-1,3,3,3-tetrafluoropropenyl sulfide **21** using excess Cl_2 in a sealed tube at 20 °C gave the sulfenyl chloride **22** which, after removal of the volatiles *in vacuo*, was partially characterized by ^{19}F NMR. The resulting sulfenyl chloride **22** was thermally labile and cyclized to form the 4-trifluoromethylisothiazole **23** (Scheme 8).[73]



21 **22** **23**

Scheme 8

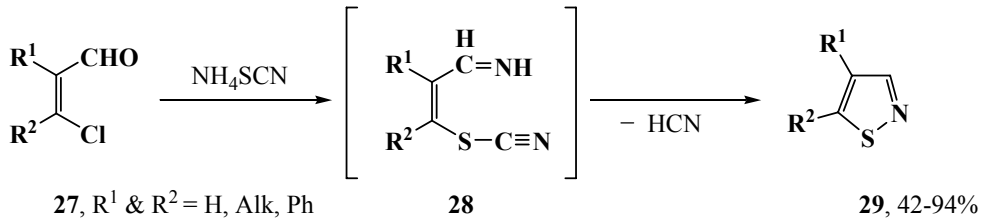
One of the first routes to polyfunctionalized isothiazoles was the reaction of substituted enamine **24** with an isothiocyanate. Ring closure of the resulting intermediate **25** by an oxidative S-N bond formation gave the fully substituted isothiazoles **26** (Scheme 9).[74]



24 **25** **26**

Scheme 9

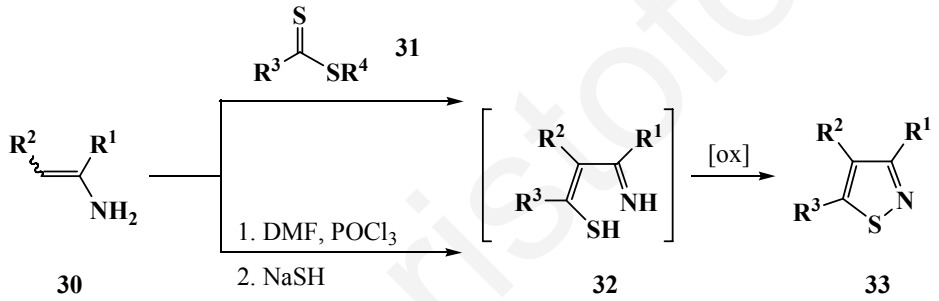
4,5-Substituted isothiazoles **29** can be prepared by direct reaction of 3-chloroprop-2-enals **27** with ammonium thiocyanate in boiling acetone (Scheme 10).[75-81] Alkyl-, cycloalkyl- or aryl-substituted isothiazoles were synthesized in modest yields. Some imino/hydrazino-thiocyanates, analogous to intermediate **28**, were also synthesized and converted into isothiazoles in acidic medium.[41, 75-87]



27, R^1 & R^2 = H, Alk, Ph **28** **29**, 42-94%

Scheme 10

Treatment of substituted enamines **30** with dithioesters **31** afforded the intermediates **32**, which could be oxidized with I_2 to the 3,4,5-substituted isothiazoles **33** (Scheme 11).[88] The intermediates **32** could also be synthesized by condensation of a Vilsmeier salt, with the substituted enamines **30**.[89]



30 **32** **33**

R^1 = Me, Ar

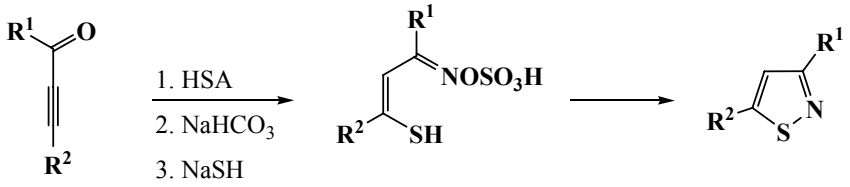
R^2 = CN, CO_2Et

R^3 = H, Me, Ph

R^4 = Et, CH_2CO_2H, CH_2CO_2Me

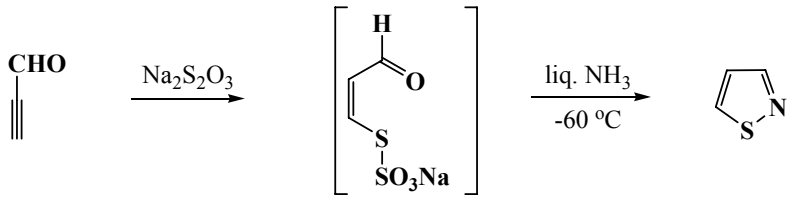
Scheme 11

4-Unsubstituted isothiazoles **35** can be prepared by treating *α*-acetylenic ketones or aldehydes **34** with hydroxylamine-*O*-sulfonic acid (HSA) and then with sodium hydrosulfide in buffered aqueous solution between 0 °C and rt, in an open vessel (Scheme 12).[90, 91] A similar method provided an alternative route to the parent isothiazole **1**.[92, 93] Propiolaldehyde **36** treated with sodium thiosulfate gave the intermediate **37** which cyclized to isothiazole **1** in liquid ammonia at –60 °C. The overall yield of this reaction is 61% and this is the best method for preparation of the parent isothiazole **1**.



34, R^1 = H, Alk
R^2 = H, Me, Ph, CH_2OH, $CHOHCH_3$

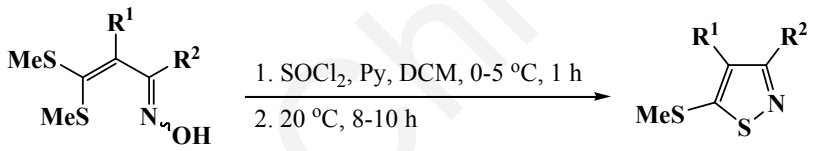
35, 27-62%



36 **37** **1**

Scheme 12

Hydroxylamine reacts with *α*-oxo ketene dithioacetals in refluxing EtOH to afford the corresponding oximes **38** which can be converted into isothiazoles **39** with thionyl chloride in Py (Equation 5).[94]

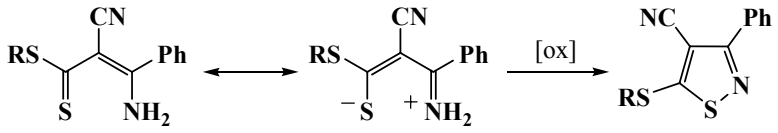


(5)

38, R^1 = H, Me, $-(CH_2)_3-$, $-(CH_2)_4-$
R^2 = H, Et, $-(CH_2)_3-$, $-(CH_2)_4-$

39, 60-85%

3-Amino-2-cyano-3-phenylpropenedithioates **40**, obtained by alkylation of the condensation product of 3-amino-3-phenylacrylonitrile and carbon disulfide, can be oxidized with I_2 to give near quantitative yields of 5-alkylthio-3-phenylisothiazole-4-carbonitriles **41** (Scheme 13).[95] The synthesis of isothiazoles *via* other substituted 3-aminoprop-2-enethiones has been widely achieved and common oxidizing agents include air, hydrogen peroxide, ammonium persulfate, Br_2 and I_2.[74, 85, 88, 89, 96-125]

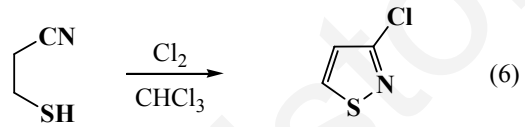


40 "inner salt" **41**

R = Me, Bn, CH_2COMe, CH_2CO_2Me, CH_2CO_2Et

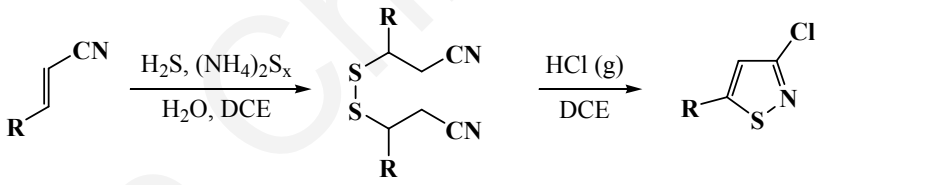
Scheme 13

3-Mercaptopropanenitrile **42** cyclizes to 3-chloroisothiazole **43** on treatment with Cl_2 (Equation 6).[126] The intermediate of this reaction was suggested to be the disulfide **45** (R = H) which can be prepared directly by the addition of ammonium polysulfide to acrylonitrile **44** (R = H) and can be oxidized to the same isothiazoles **43** and **46** (Scheme 14).[126, 127] Similar reactions with other disulfides have also been successful.[94, 128-131]



(6)

42 **43**, 55%



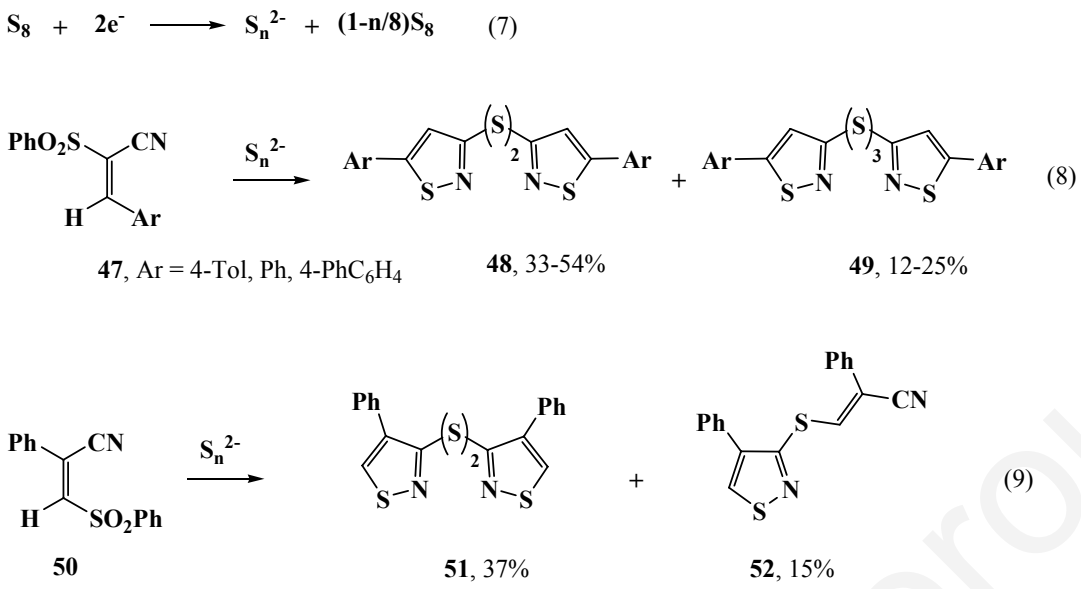
44 **45**

43, R = H, 82%

46, R = Me, 38%

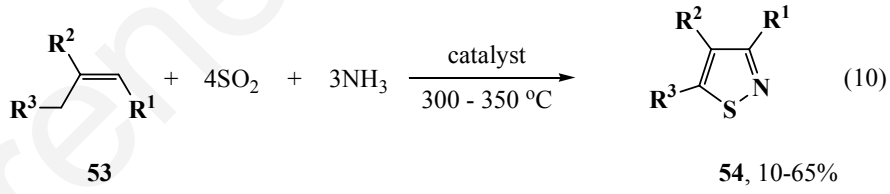
Scheme 14

Electrosynthesis of isothiazoles from vinyl sulfones having a cyano group was studied using a reactive sulfur-graphite electrode.[132] Electroreduction of vinyl sulfones **47** having geminal cyano and phenylsulfonyl groups, subjected to desulfurization gave the 5-arylisothiazole disulfides **48** as the major products (33-54% yields) accompanied with minor amounts of the 5-arylisothiazoles trisulfides **49** (12-25% yields) (Equations 7 & 8). With a vinyl sulfone **50** having vicinal cyano and phenylsulfonyl groups, 4-phenylisothiazole disulfide **51** was obtained together with 3-[(*Z*)-2-cyano-2-phenylethenylthio]-5-phenylisothiazole **52** (Equation 9).



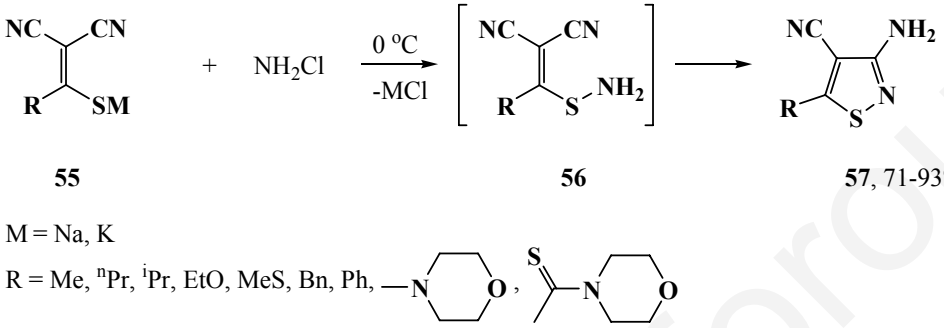
1.2.5.1.2 By Formation of One N-C Bond

A second method to form the isothiazole ring requires the formation of one N-C bond. Substituted isothiazoles **54** were formed by interaction of olefins with sulfur dioxide and ammonia at high temperature in the presence of catalyst (Equation 10).[133-135] Suitable catalysts included activated alumina or silica gel containing oxides of aluminium, titanium, zirconium or other multivalent metals. The versatility of this method relies on the simplicity of the starting materials and the low large-scale production costs, however, mixtures of substituted isothiazole can be obtained; *e.g.*, with *n*-butenes. 3-Amino, 3-hydroxy or 3-alkoxyisothiazole derivatives cannot be synthesized *via* this method.

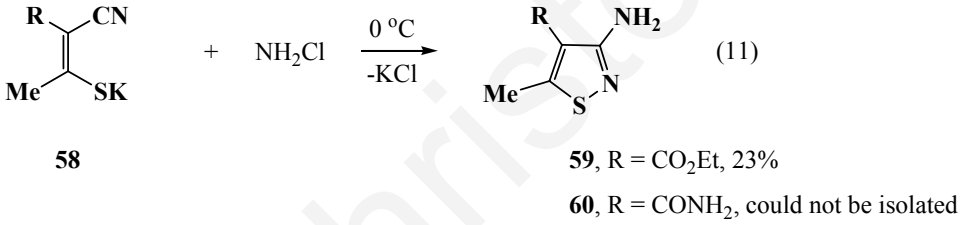


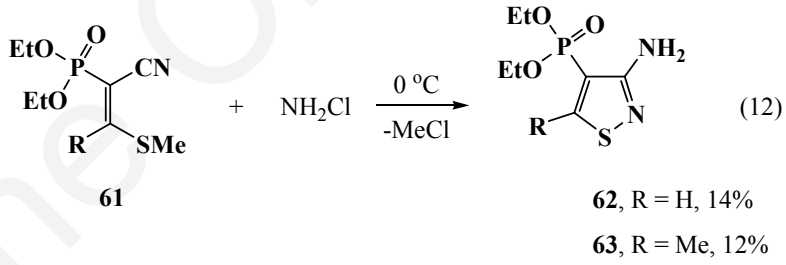
Alkali salts of 1-substituted 2,2-dicyanoethenethiolates **55** react with chloramine to afford 3-aminoisothiazole-4-carbonitriles **57** in good yields (Scheme 15).[136-138] The yields of isothiazoles **57** were lower using HSA instead of chloramine. The analogous reaction with 2-substituted thiolates **58** (R = CO_2Et & $CONH_2$) failed to give good yields of the expected products **59** and **60** respectively (Equation 11).[136] Similarly reactions with diethyl 2-substituted-1-cyano-2-(methylthio)vinylphosphonates **61** (R = H & Me)

gave only low yields of the expected isothiazoles **62** and **63** respectively (Equation 12).[139] While the reaction mechanism was unclear, it was assumed that salts **55** reacted with chloramine to form the intermediate **56** which then cyclized to the corresponding isothiazole.

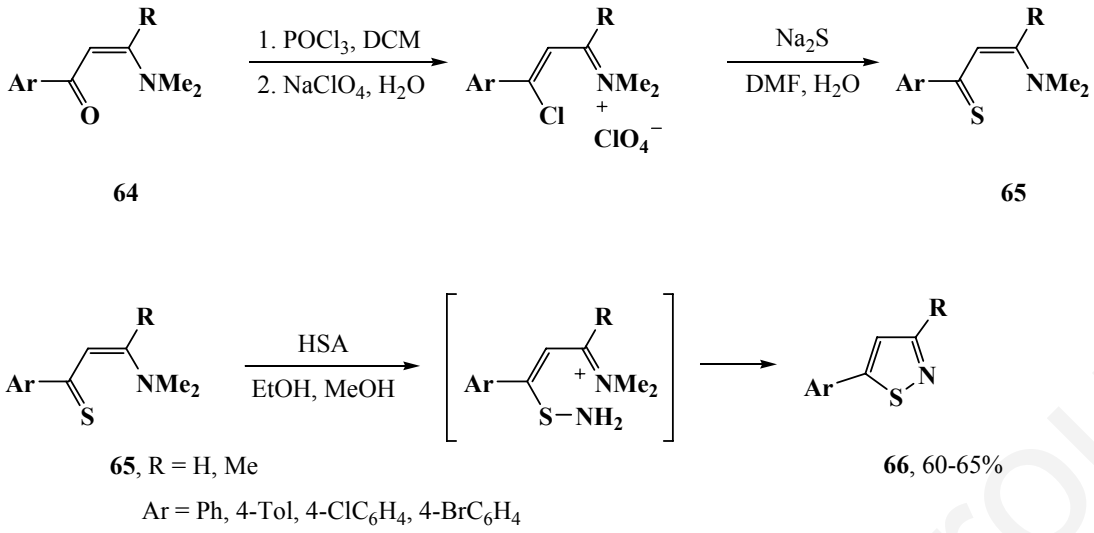


Scheme 15





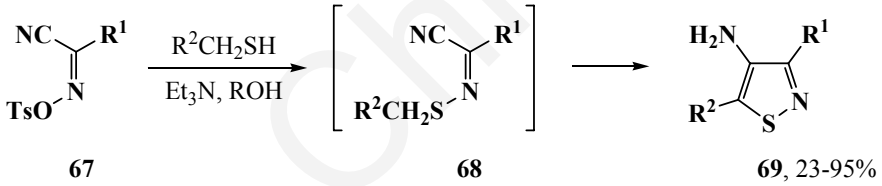
The reaction of analogous enaminones **64** with phosphorus oxychloride in DCM followed by treatment with sodium perchlorate in water and reaction with sodium sulfide in aqueous DMF gave the thioenamines **65** in 40-73% yields. The reaction of thioenaminones with HSA gave isothiazoles **66** in 60-65% yields (Scheme 16).



Scheme 16

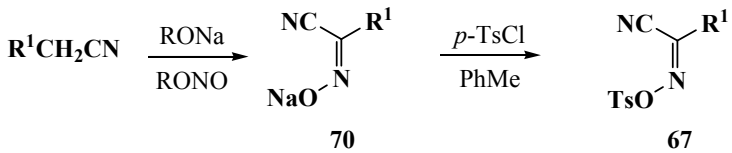
1.2.5.1.3 By Formation of One C-C Bond

A common method to form isothiazoles *via* the formation of a C-C bond requires the generation of intermediate **68** which under basic conditions cyclizes to 4-aminoisothiazoles **69** (Scheme 17).[140-145]



Scheme 17

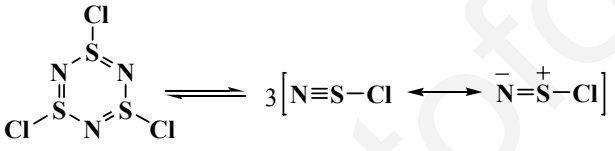
The intermediate **68** can be synthesized in three steps. Substituted acetonitriles react with alkyl nitrite in the present of a sodium alkoxide to afford salts **70** which are then treated with 4-tosyl chloride to give 2-(tosyloxyimino)acetonitriles **67** (Scheme 18). Compounds **67** react with alkanethiols to form *in situ* the intermediate **68**.



Scheme 18

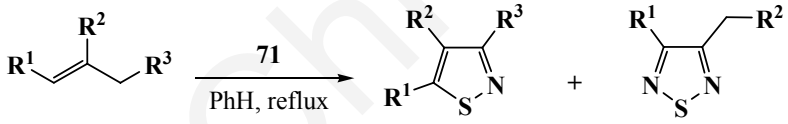
1.2.5.1.4 By Formation of One S-C and One N-C Bond

The cyclic species trithiazyl trichloride "trimer" **71** is in thermal equilibrium with the monomer thiazyl chloride **72** (Scheme 19) and reacts with allylic compounds to give poor yields of isothiazoles.[146-148] Treatment of compound **73a** with trithiazyl trichloride **71** gave isothiazole **74a** while the major product was the 1,2,5-thiadiazole **75a** (Equation 13). The formation of the latter was prevented with the introduction of an allylic 2-substituent. Allylic compounds with terminal electron withdrawing groups showed increased reactivity and unsymmetric allylic compounds, reacted regiospecifically to afford isothiazoles with the more electron withdrawing group adjacent to the ring sulfur.[149]



71 **72**

Scheme 19

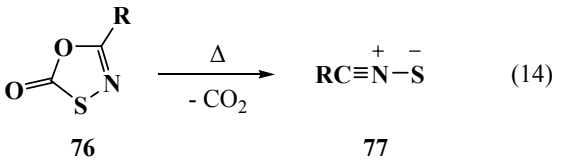


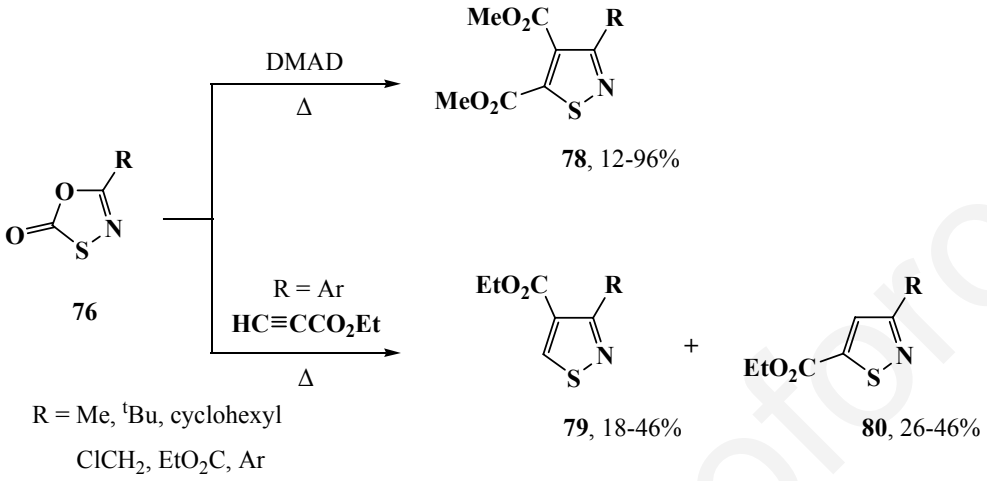
73a-d	**74a-d**	**75a-d**
a: R^1 = Ph, R^2 = H, R^3 = Cl	not isolated	56%
b: R^1 = R^3 = Ph, R^2 = H	29%	not isolated
c: R^1 = Ph, R^2 = Me, R^3 = Bn	19%	not isolated
d: R^1 = CO_2Et, R^2 = R^3 = Bn	32%	not isolated

(13)

1.2.5.1.5 By Formation of One S-C and One C-C Bond

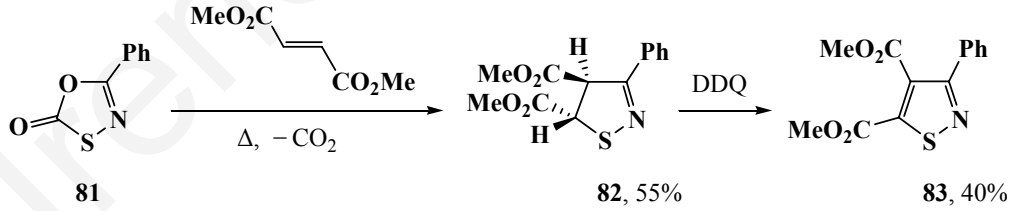
A route to isothiazoles bearing ester groups at C-3 and/or C-4 involves the 1,3-dipolar addition of nitrile sulfides **77** to electron-poor alkynes.[150-152] Nitrile sulfides **77** can be produced *in situ* by thermolysis of 1,3,4-oxathiazol-2-ones **76** (Equation 14). 5-Substituted-1,3,4-oxathiazol-2-ones **76** were heated in boiling PhCl with dimethyl acetylenedicarboxylate (DMAD) to afford good yields of isothiazoles **78** (Scheme 20). When the reactions were repeated with ethyl propiolate, isothiazoles **79** and **80** were obtained in nearly equivalent amounts.[153, 154]





Scheme 20

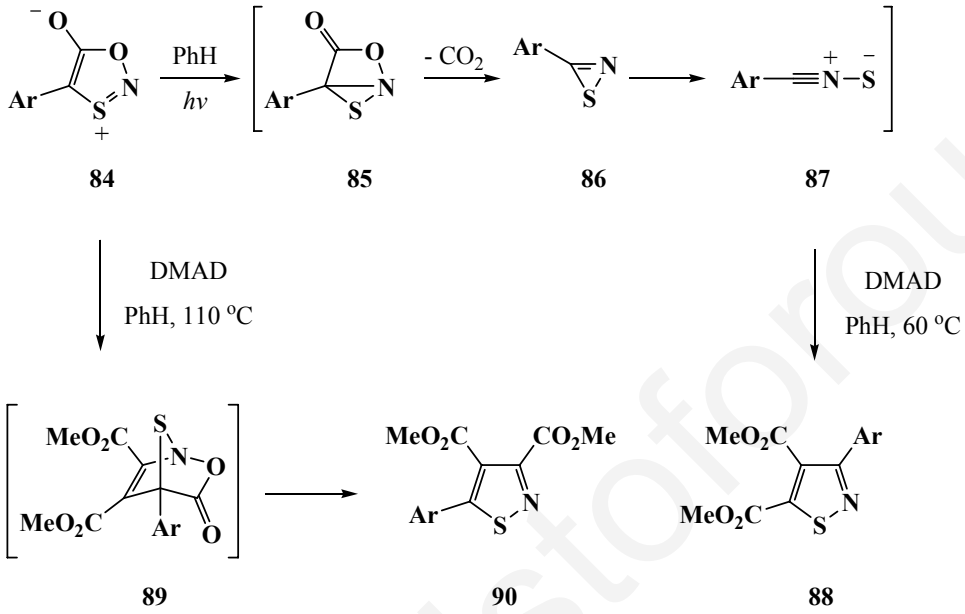
Arenecarbonitrile sulfides, produced by thermolysis of 5-aryl-1,3,4-oxathiazol-2-ones, have been treated with various olefins.[155, 156] Thermolysis of 5-phenyl-1,3,4-oxathiazol-2-one **81** at 190 °C in dimethyl fumarate (4 equiv.), under nitrogen gave dimethyl 3-phenyl-2-isothiazoline-*trans*-4,5-dicarboxylate **82**. Dehydrogenation of **82** with 2,3-dichloro-5,6-dicyano-4-benzoquinone (DDQ) gave dimethyl 3-phenyl-4,5-isothiazoledicarboxylate **83** (Scheme 21).



Scheme 21

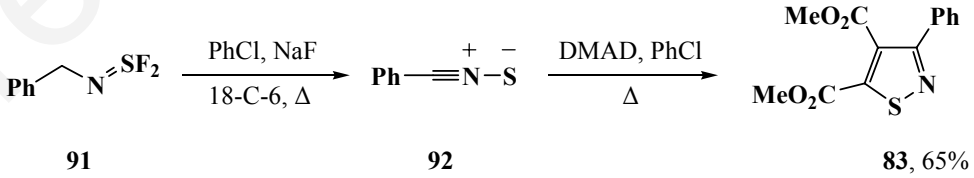
An alternative way of generating nitrile sulfides required the irradiation of 4-aryl-1,3,2-oxathiazolium-5-olates **84** with ultraviolet light.[140, 157-159] The proposed reaction mechanism involved formation of the intermediate **85**, followed by expulsion of carbon dioxide, to afford the 3-aryl-1,2-thiazirene intermediate **86**. The thiazirene finally opens

to the desired nitrile sulfide **87** which reacted with DMAD to give isothiazoles **88** (Scheme 22). In the absence of ultraviolet light isothiazole **90** was isolated suggesting that this time the intermediate was compound **89**.[140, 155, 158, 160-162]



Scheme 22

Other routes to nitrile sulfides also exist which avoid the use of a preformed oxathiazole derivative. Benzonitrile sulfide **92** can be prepared by the treatment of *N*-(benzylimino)sulfur difluoride **91** with sodium fluoride and a catalytic amount of 18-crown-6, eliminating two molecules of hydrogen fluoride. When the reaction was carried out in the presence of an alkyne like DMAD, the corresponding isothiazole **83** was isolated (Scheme 23).[163, 164]

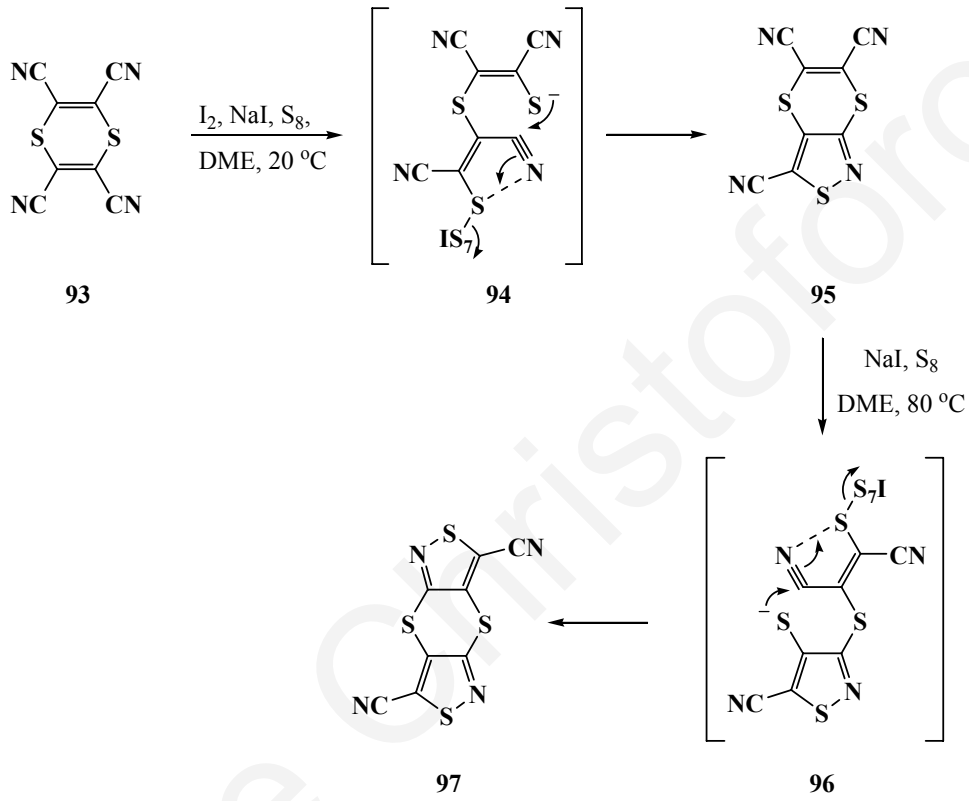


Scheme 23

1.2.5.2 Synthesis by Ring Transformation

1.2.5.2.1 From 1,4-Dithiines

1,4-Dithiine-2,3,5,6-tetracarbonitrile **93** reacts with elemental sulfur in the presence of I_2/NaI to form [1,4]dithiino[2,3-*c*]isothiazole-3,5,6-tricarbonitrile **95** (59%). Further treatment of the latter dithiine with sulfur and NaI at 80 °C gave [1,4]dithiino[2,3-*c*:5,6-*c*']diisothiazole-3,7-dicarbonitrile **97** in almost quantitative yield (Scheme 24).[165-169]



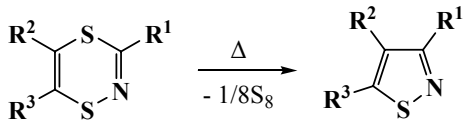
93 **94** **95** **96** **97**

Scheme 24

In both cases the *in situ* formed anion IS_7-S^-, promoted ring cleavage of the 1,4-dithiine to afford the intermediates **94** and **96**. Subsequent addition of the mercaptide anion to the *α*-nitrile gave the 5- and 6-membered rings as shown.

1.2.5.2.2 From 1,4,2-Dithiazines

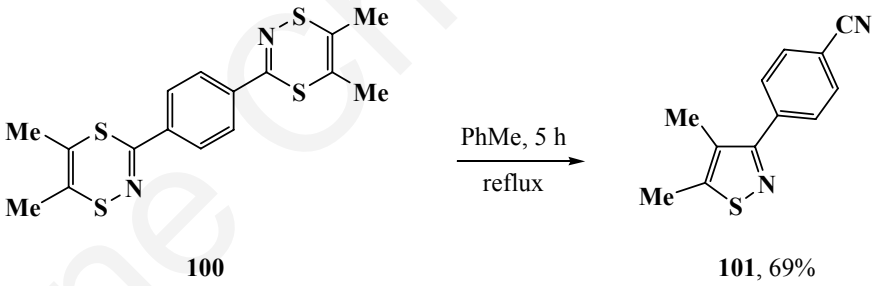
Thermal ring contraction of 1,4,2-dithiazines **98** (neat or in refluxing PhMe) gives isothiazoles.[170-172] The mechanism proceeds *via* the selective extrusion of the sulfur atom at the 4-position to yield the substituted isothiazoles **99** (Equation 15).



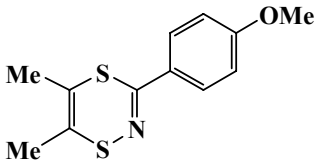
98 **99**, 37-100% (15)

R^1 = H, Me, Ph, SMe
R^2 = H, Me, Ph, 4-Tol, 4-$MeOC_6H_4$
R^3 = H, Ph, 4-Tol, 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$NO_2C_6H_4$

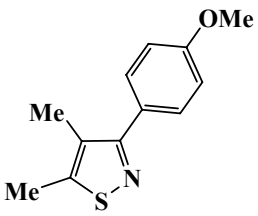
Thermolysis of 1,4-bis(5,6-dimethyl-1,4,2-dithiazin-3-yl)benzene **100** was anomalous, leading not to the corresponding 1,4-di(isothiazol-3-yl)benzene derivative, but to isothiazole derivative **101**, which resulted from contraction of only one 1,4,2-dithiazine ring to form the isothazole ring and fragmentation of the other 1,4,2-dithiazine ring to form the nitrile group (Equation 16).[172] At higher temperatures the 1,4,2-dithiazine derivative **102** behaved similarly, yielding 4-methoxybenzonitrile along with a trace of the isothiazole **103**.



100 **101**, 69% (16)



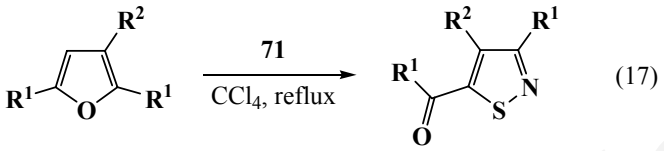
102



103

1.2.5.2.3 From Furan

Trithiazyl trichloride **71** reacts with di- and trisubstituted furans **104** in boiling tetrachloromethane (CCl_4) to give stable di- or trisubstituted isothiazoles **105** in good yields (Equation 17).[173, 174] Fully substituted furans did not react with the trimer **71** suggesting that a ring hydrogen, for subsequent loss as HCl, was required. Trithiazyl trichloride **71** in CCl_4 has also been used to synthesise isothiazoles from thiophenes and pyrroles.[175]

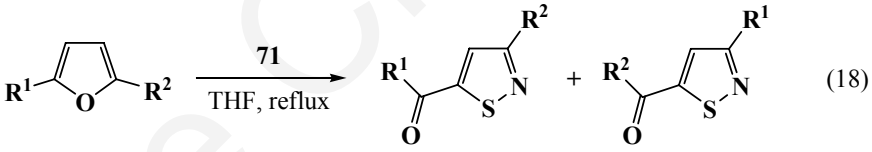


(17)

104, R^1 = Alk, Ph
R^2 = H, Cl, Br, Ph

105, 50-85%

This work was extended to show that if unsymmetrical 2,5-diarylfurans **106a-c** react with trithiazyl trichloride **71** the more electron releasing aryl group becomes incorporated into the 5-aroyl group of the isothiazole as the exclusive or major product (*cf.* isothiazoles **107a-c** and **108a-c**) (Equation 18).



(18)

106a-c **107a-c** **108a-c**

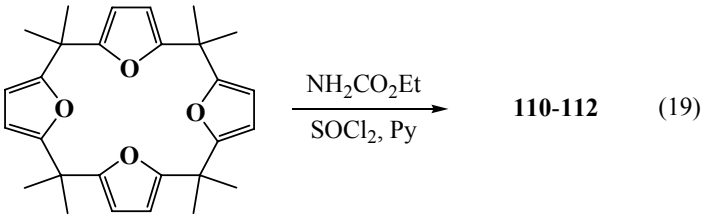
a: R^1 = 4-$MeOC_6H_4$, R^2 = 4-$NO_2C_6H_4$ — 85% (**108a** was not detected)

b: R^1 = 4-Tol, R^2 = Ph — 56% total yield [3.3 (**107b**) : 1 (**108b**)]

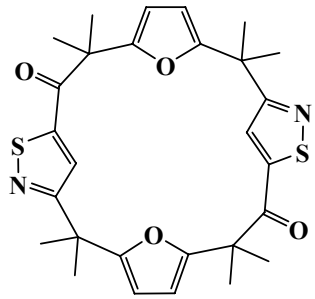
c: R^1 = 4-$MeOC_6H_4$, R^2 = 4-Tol — 65% total yield [3.9 (**107c**) : 1 (**108c**)]

The trimer **71** is not commercially available, is moisture sensitive and is made by heating ammonium chloride with sulfur and disulfur dichloride, followed by chlorination of the resulting salt $S_3N_2Cl_2$. The reactive thiazyl chloride NSCl could also be generated *in situ* by using a mixture of ethyl carbamate, thionyl chloride and Py, known as Katz reagent. Katz reagent has proved to be a good substitute for the preformed trimer and some of the above isothiazoles were produced very cleanly and conveniently in even higher yields.[176,177] Katz reagent was applied to calixhetarenes **109** to synthesise the first

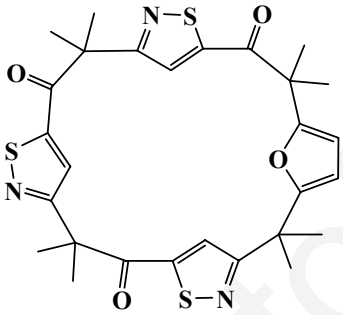
calixhetarenes with more than one heteroatom in the constituent ring (Equation 19). The products **110–112** were characterized by single crystal X-ray crystallography.[178]



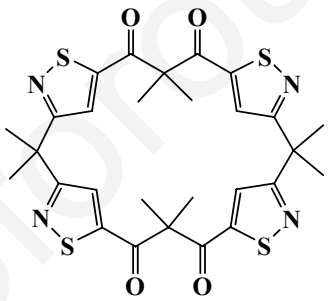
109 **110-112** (19)



110



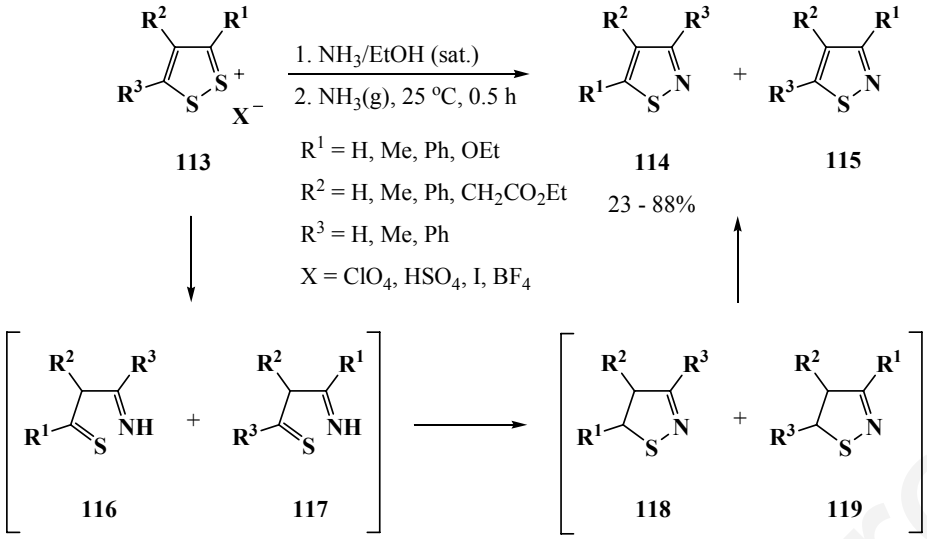
111



112

1.2.5.2.4 From 1,2-Dithiolium Salts

Treatment of substituted 1,2-dithiolium salts **113** [63, 83, 179-195] with ammonia or ammonium acetate gave isothiazoles in moderate to good yields (Scheme 25).[83, 179, 180, 182-184, 186-191] Non-symmetrical 1,2-dithiolium salts, however, afforded a mixture of isomeric isothiazoles **114** and **115**.[181, 185] The proposed mechanism involved the formation of the intermediate 3-iminopropane-1-thiones **116** that cyclize to partially saturated isothiazoles **118** and **119** which, after spontaneous oxidation, give the respective aromatic isothiazoles.

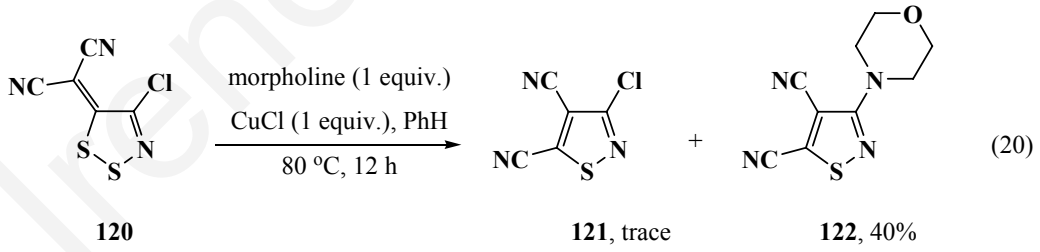


Scheme 25

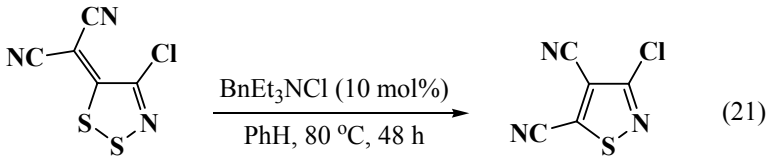
When ammonia was replaced by primary alkyl or arylamines, and I_2 or I_2 and perchloric acid were added as oxidants, substituted isothiazolium salts were obtained.[192] Only a few transformations of neutral 1,2-dithioles into isothiazoles have been reported.[63, 120, 195]

1.2.5.2.5 From 1,2,3-Dithiazoles

Treating the (1,2,3-dithiazolylidene)acetonitrile **120** with morpholine in refluxing PhH gave 3-(*N*-morpholino)isothiazole-4,5-dicarbonitrile **122** and traces of 3-chloro-isothiazole-4,5-dicarbonitrile **121** (Equation 20).[196]



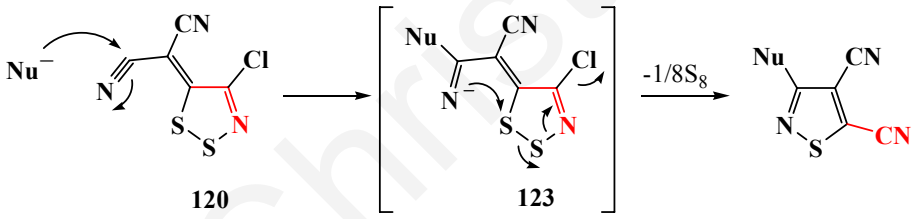
The isolation of the 3-chloroisothiazole **121** suggested that chloride could compete with morpholine under the reaction conditions. Treatment of the (dithiazolylidene)-acetonitrile **120** with anhydrous benzyltriethylammonium chloride (10 mol%) in refluxing PhH or PhMe gave the 3-chloroisothiazole **121** and sulfur in almost quantitative yields (Equation 21).[196]



(21)

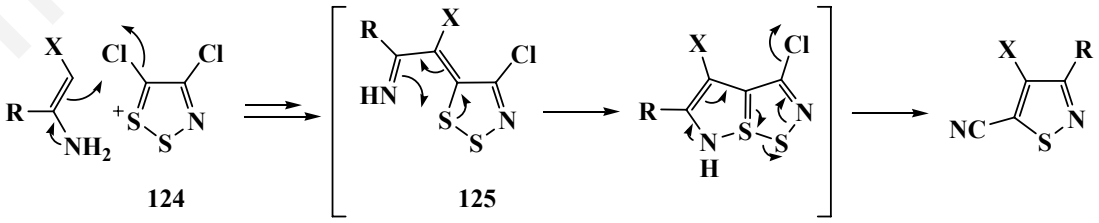
120 **121**, 100%

An early proposed mechanism for the formation of isothiazoles **121** and **122** involved nucleophilic attack by either morpholine or chloride on the nitrile group leading to the formation of the intermediate **123** 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 monocyclic 5-membered heterocycle.[197] Intramolecular cyclization of the proposed iminide intermediate **123** onto the dithiazole ring sulfur atom (S-1) afforded the aromatic isothiazole; concomitant cleavage of the dithiazole released the new nitrile group (Scheme 26).



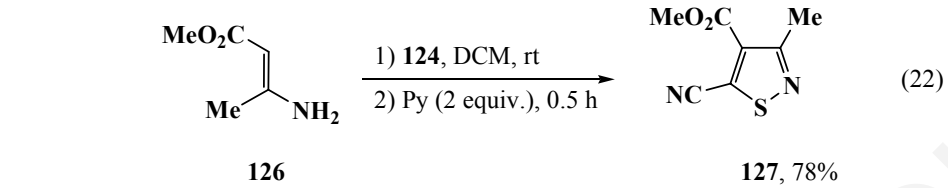
Scheme 26

The dithiazole intermediate **123** suggested a new route to isothiazoles and led to the reaction of enamines with 4,5-dichloro-1,2,3-dithiazolium salt **124** (Appel's salt). This was expected to involve the intermediate dithiazolylidene adduct **125**, which was very similar to the proposed intermediate **123** (Scheme 27).



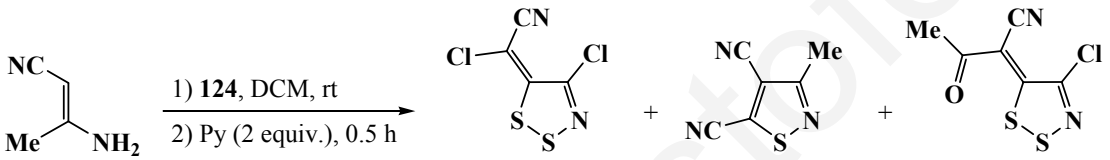
Scheme 27

As such, treatment of methyl 3-aminocrotonate **126** with Appel's salt **124** and Py gave methyl 5-cyano-3-methylisothiazole-4-carboxylate **127** (78%) (Equation 22) while similar treatment of 3-aminocrotononitrile **128** gave a markedly more complex reaction mixture affording the expected 3-methylisothiazole-4,5-dicarbonitrile **130** (40%) together with 2-chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **129** and three other additional products (Equation 23).[198]

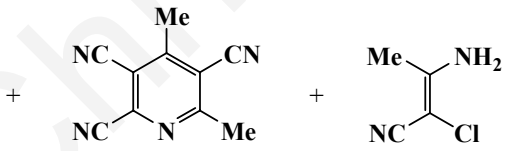


(22)

126 **127**, 78%



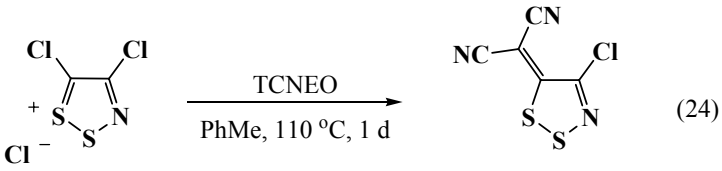
128 (2 equiv.) **129**, 8% **130**, 40% 5%



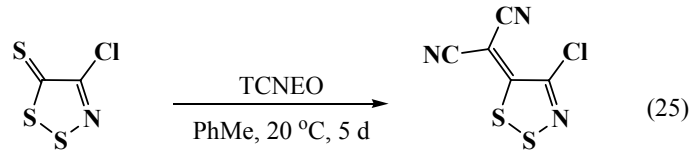
(23)

20% 5%

Despite the high yielding conversion of dithiazolylidene **120** into 3-chloroisothiazole-4,5-dicarbonitrile **121** the usefulness of the transformation was hampered by the low yielding (40%) preparation of the dithiazolylidene **120**.[196] Attempts to improve the yield of the ylidene **120** involved the use of expensive tetracyanoethyleneoxide (TCNEO) which reacts with either the dithiazolium salt **124** or the dithiazolethione **131** to afford the desired ylidene **120** in significantly higher yields (Equations 24 & 25).[196, 199]

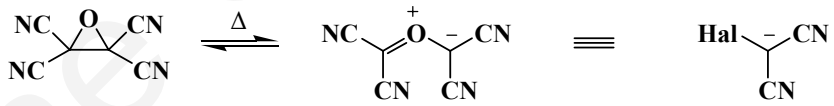


124 **120**, 61% (24)

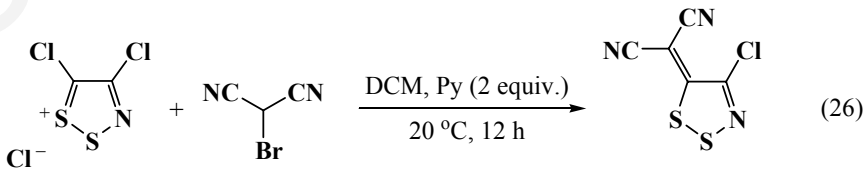


131 **120**, 53% (25)

TCNEO appeared to react through its ring opened stabilized ylide form, $(CN)_2C{=}\overset{+}{O}{-}\overset{-}{C}(CN)_2$ (Scheme 28).[196, 199, 200] Based on the proposed mechanism for the TCNEO reaction an effort to develop a low cost procedure for synthesizing the dithiazole **120** using halogenated malononitriles was successfully achieved.[201] In the ylide form of TCNEO the leaving group, $-\overset{+}{O}{=}C(CN)_2$, was replaced by halogen. Monobromo-, dibromo- and dichloromalononitrile, all readily prepared from malononitrile in one step,[202-204] were therefore investigated as TCNEO substitutes.[201] This investigation was successfully completed affording the desired dithiazolylidene **120** in high yield using convenient reaction conditions (Equation 26).[201]



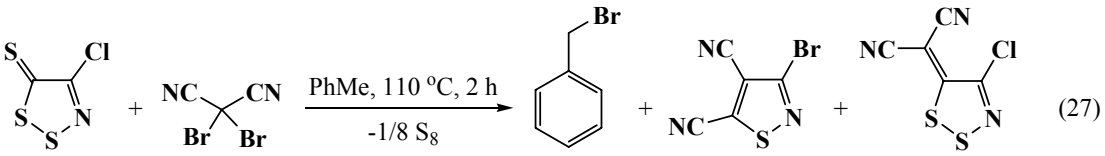
Scheme 28



124 (2 equiv.) **120**, 73% (26)

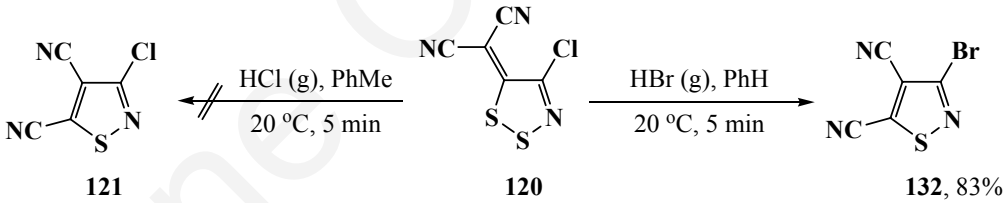
Interestingly, treatment of dithiazolethione **131** with dibromomalononitrile in refluxing PhMe gave benzyl bromide, the previously unknown 3-bromoisothiazole-4,5-

dicarbonitrile **132** as the main product and only traces of the desired (dithiazolylidene)-malononitrile **120** (Equation 27).[201]



131 (3 equiv.) 85% **132**, 59% **120**, trace (27)

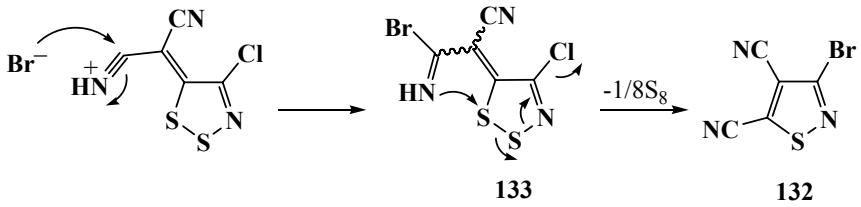
3-Bromoisothiazole-4,5-dicarbonitrile **132** was not observed in refluxing PhH, and in refluxing PhCl it was isolated only in low yield. The formation of benzyl bromide was possibly caused by bromination of the toluene benzylic position by Br_2 which was generated from some decomposition of the dibromomalononitrile. The formation of benzyl bromide was also assumed to be accompanied by the release of HBr which reacted with the desired (dithiazolylidene)malononitrile **120** to give the unexpected 3-bromoisothiazole-4,5-dicarbonitrile **132**. This assumption was supported by independent synthesis of the 3-bromoisothiazole **132** from (dithiazolylidene)-malononitrile **120** with anhydrous HBr in 83% (Scheme 29).[201] The analogous reaction with anhydrous HCl failed to give the expected 3-chloroisothiazole **121**.



121 **120** **132**, 83%

Scheme 29

The proposed reaction mechanism for the transformation involves activation of either nitrile group of the (dithiazolylidene)malononitrile **120** to generate the imidoyl bromide **133** which then cyclizes onto the dithiazole ring sulfur S-1 (Scheme 30). Anhydrous HCl being a weaker acid (pK_a = -7) than HBr (pK_a = -9) was unable to activate the nitrile group and therefore drive this transformation.[205]



Scheme 30

1.2.5.3 Comparison of the Available Synthetic Methods

Generally, the synthesis of isothiazoles *via* ring forming reactions is more common than the synthesis *via* ring transformation. This is because a wide variety of acyclic starting materials is commercially available or can be produced easily. Among the acyclic methods, the synthesis of the isothiazole ring by formation of one S-N bond can be considered as the most convenient since the starting materials (mercaptoethylene derivatives **3**, **11**, **15**, **21**, 3-chloroprop-2-enals **27**) are readily prepared and the procedures are high yielding. In contrast, the synthesis of isothiazoles by ring transformation requires the preparation of often commercially unavailable precursor heterocycles, such as in the case of 1,4,2-dithiazines and 1,2-dithiolium salts, making this route inconvenient and expensive. The acyclic methods however, often require oxidizing conditions which involve hazardous (Cl_2, Br_2, HBr, SO_2Cl_2, $POCl_3$, H_2S), tricky, and nasty [SCl_2, S_2Cl_2, $(NSCl)_3$] reagents. This drawback is often avoided with ring transformation methods since they are frequently driven by the thermodynamic force to form the more aromatic isothiazole ring and therefore simple triggers such as mild nucleophiles or moderate temperatures are sufficient to start the transformation.

Furthermore, in some cases the substitution pattern of the isothiazole will determine the synthetic strategy that will be chosen for the compound's preparation. One such example is the synthesis of 4,5-isothiazoledicarbonitriles since no successful acyclic route has been devised and the ring transformation of 1,2,3-dithiazolylidenes is to date the only known method to build this heterocycle. An additional limitation to isothiazole preparations is the often product specific nature of the synthesis. This could be overcome by developing more methods for functional group modification at all positions around the isothiazole ring.

In light of the recent discovery of the biological importance of the 3-haloisothiazole-4,5-dicarbonitriles and their derivatives,[200] the ring transformation of 1,2,3-dithiazol-ylidenes into isothiazoles and related transformations will be investigated further.

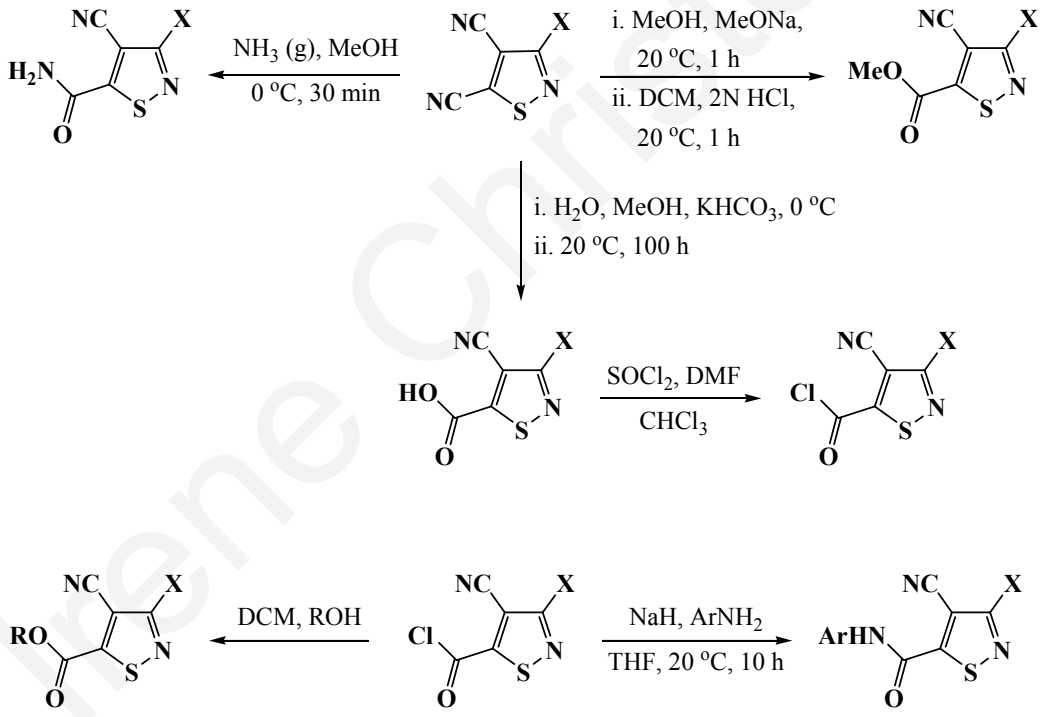
CHAPTER 2

New 1,2,3-Dithiazole Chemistry

Sections

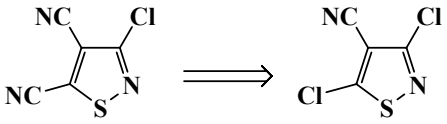
2.1 Introduction

Our interest in 1,2,3-dithiazole chemistry revolves around the construction of dithiazoles that can be converted into new heterocycles *via* ring transformation.[175, 196, 199, 201, 206-212] One such ring transformation is the conversion of dithiazoles into isothiazoles although only a few methods have been reported (Chapter 1, Section 1.2.5.2.5). This relatively new ring transformation has already proved its worth since 3-chloroisothiazole-4,5-dicarbonitrile **121** was shown by Bayer Cropsciences to be an important building block for the synthesis of new isothiazole biocides.[200] The isothiazole-5-carboxylic acid derivatives (Scheme 31) are outstandingly active as biocides in agriculture and horticulture, particularly as microbiocides for the direct control of plant diseases or for causing resistance against plant pathogens. The isothiazole compounds have a much better biocidal activity than many of the existing compounds, which are structurally similar and have the same type of action.



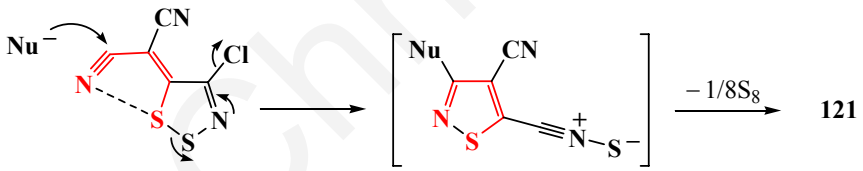
Scheme 31

Interestingly all attempts to prepare 3-chloroisothiazole-4,5-dicarbonitrile **121** from readily available 3,5-dichloroisothiazole-4-carbonitrile **5** with various sources of cyanide failed (Chapter 4, Section 4.1).[213]



121 **5**

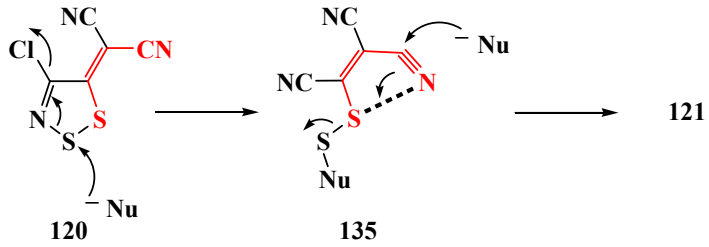
As such the mechanistically attractive 1,2,3-dithiazole chemistry and the lack of a convenient procedure for synthesising isothiazole-5-carbonitriles encouraged us to investigate further the transformation of (dithiazolylidene)malononitrile **120** into 3-chloroisothiazole-4,5-dicarbonitrile **121**. The proposed Boulton-Katritzky type mechanism had several weaknesses. All attempts to trap the anticipated nitrile-sulfide intermediate **134** (Scheme 32) using norbornene, anthracene, several dienes and acetylenes had failed and secondly when the reaction was repeated with stoichiometric amount of benzyltriethylammonium bromide the 3-chloroisothiazole-4,5-dicarbonitrile **121** was still formed in significant yield.[214] Since bromide is more nucleophilic than chloride, this latter result was not in good agreement with the proposed mechanism which failed to explain the formation of the 3-chloroisothiazole **121** in good yield.



120 **134**

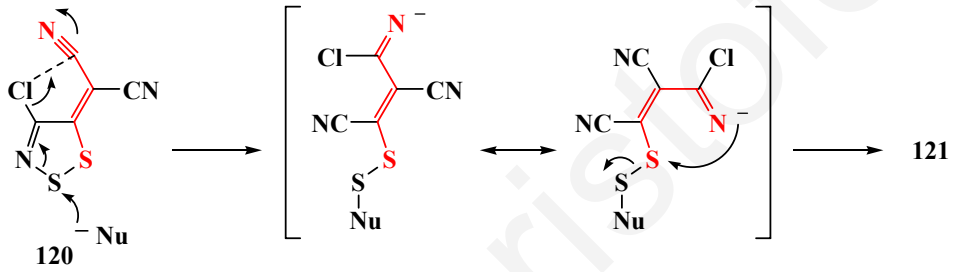
Scheme 32

In order to offer a more satisfying explanation an alternative mechanism was proposed. Nuclephilic attack at the S-2 ring sulfur atom gave the ring opened intermediate **135** which, after a second nucleophilic attack at the nitrile group, cyclized to the isothiazole ring system (Scheme 33). This proposed mechanism, however, also failed to explain the formation of the 3-chloroisothiazole **121** in good yield when stoichiometric amount of tetraalkylammonium bromide was used. A minor modification can offer some hope of understanding the observed products.



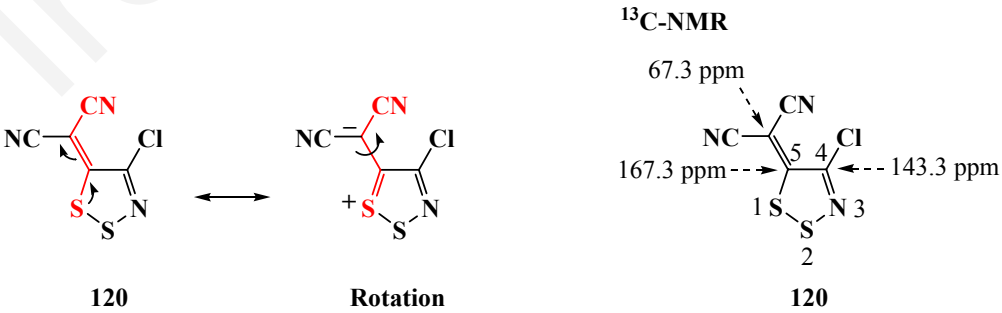
Scheme 33

After nucleophilic attack at the dithiazole S-2 ring sulfur, chloride could be transferred directly to the nitrile group which then cyclized onto the dithiazole ring sulfur S-1 (Scheme 34). This proposal tentatively explained the formation of the 3-chloro-isothiazole **121** in good yield in the reaction with stoichiometric amount of bromide.



Scheme 34

This latter mechanism, however, required rotation around the exocyclic double bond. ^{13}C NMR data suggested the exocyclic C=C double bond may have considerable single bond character [*C*-5 167.3 and *C*(CN)$_2$ 67.3 ppm] and this was not unexpected owing to a strong contribution of the *push-pull* resonance structures, where the ring sulfur atoms S-1 and S-2 push electron density to the electron deficient dicyanomethylene unit (Scheme 35).

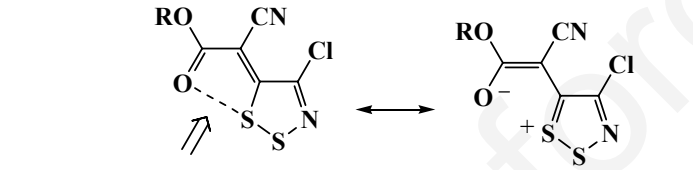


Scheme 35

2.2 1.2.3-Dithiazole Chemistry

2.2.1 Synthesis of (Dithiazolylidene)acetonitriles

To investigate the above mechanistic possibility a series of substituted (dithiazolylidene)acetonitriles were synthesized starting from dithiazole esters of type **136** (Scheme 36). According to the literature a strong interaction between the carbonyl oxygen and the electron deficient ring sulfur atom S-1 exists which forces the stereochemistry of the molecule to be *E* and does not permit the facile rotation of the exocyclic double bond.[215]

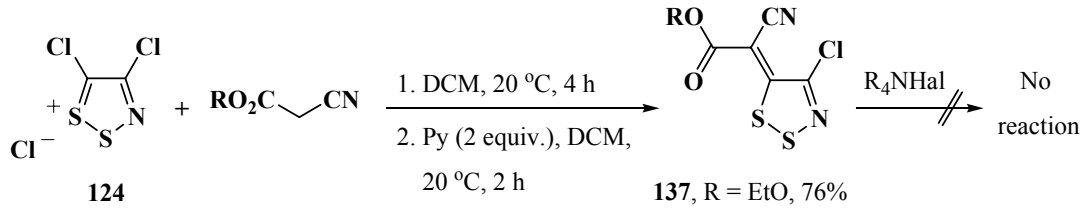


Strong non-bonding interaction

136

Scheme 36

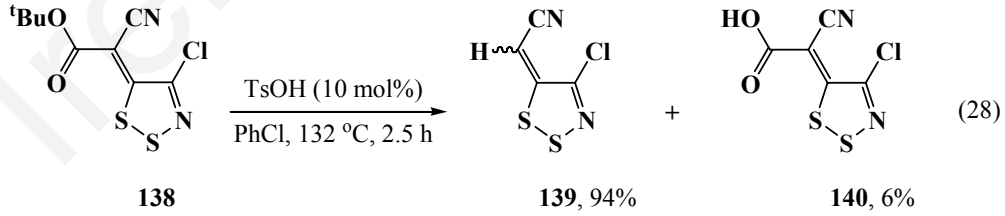
Two 1,2,3-dithiazole esters of type **136** were synthesized following standard procedures, the known ethyl ester **137**[216] and the novel *tert*-butyl ester **138** (Scheme 37). The stereochemistry of the dithiazole *tert*-butyl ester **138** was supported by IR and ^{13}C NMR spectroscopic data which were similar to that of the ethyl ester. The carbonyl peak was observed at 1648 cm^{-1} and 166.6 ppm with IR and ^{13}C NMR spectroscopy respectively. Both data are very characteristic for 1,2,3-dithiazole esters that have the carbonyl group *syn* to ring sulfur atom S-1.[215] 1,2,3-Dithiazole esters that have the carbonyl group *anti* to ring sulfur atom S-1 give the carbonyl peak at about 1700 cm^{-1} and 180.0 ppm with IR and ^{13}C NMR spectroscopy respectively.[215] Treatment of the two dithiazole esters **137** and **138** with benzyltriethylammonium chloride, however, gave only unreacted starting dithiazole esters.

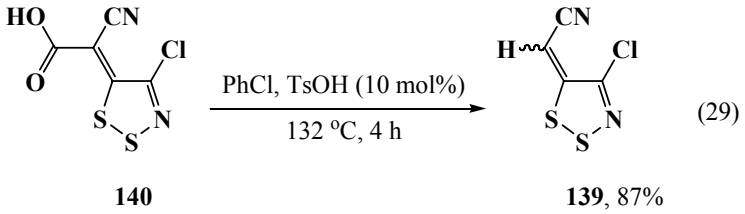


	IR	^{13}C-NMR
	ν(C=O)/cm^{-1}	*C*=O/ppm
137	1655	167.1
138	1648	166.6

Scheme 37

Since no reaction was observed with benzyltriethylammonium chloride probably owing to the strong interaction of the carboxylate functionality with the ring sulfur, it was decided to remove the carboxyl group to eliminate the interaction. As such attempted hydrolysis of the esters to afford the carboxylic acid which could then be decarboxylated was made. Under basic conditions decomposition of both starting dithiazole esters **137** and **138** was observed, which was accompanied with strong H_2S odour. However, while the dithiazole ethyl ester **137** was stable under acidic hydrolytic conditions, the *tert*-butyl ester **138** could be hydrolysed in refluxing PhCl, using catalytic amount of TsOH, to afford the dithiazolylidene acetonitrile **139** in 94% yield together with a minor amount of the corresponding carboxylic acid **140** (Equation 28). Decarboxylation of the carboxylic acid **140**, under the same reaction conditions, was also achieved affording the (dithiazolylidene)acetonitrile **139** in 87% yield (Equation 29).

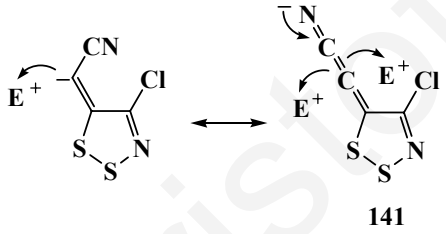




(29)

140 **139**, 87%

At this point the stereochemistry of the (dithiazolylidene)acetonitrile **139** could not be predicted, not only because of a possible rotation around the exocyclic double bond but also because the decarboxylation process could pass *via* the intermediate **141** that could possibly trap the electrophile from opposite sides leading to the formation of either *syn* or *anti* isomers (Scheme 38).



141

Scheme 38

^{1}H NMR spectroscopy gave a strong, singlet at 5.81 ppm and ^{13}C NMR spectroscopy gave four carbon signals in the range of 158.2-83.2 ppm indicating the existence of a single isomer on the NMR time scale. The stereochemistry of (dithiazolylidene)-acetonitrile **139** was eventually determined by single crystal X-ray crystallography.

The molecular structure of the (dithiazolylidene)acetonitrile **139** showed the nitrile group to be *syn* to the ring sulfur S-1 (Figure 5). The compound is not perfectly planar with the nitrile nitrogen and dithiazole sulfur S(1) deviating the greatest from the plane of the molecule by 0.044 and 0.050 Å respectively. The C(2)-C(3) and C(1)-N(1) bonds [1.344(5) and 1.277(5) Å respectively] have pronounced double bond character (typical C=C and C=N bond lengths are 1.34 Å and 1.29 Å respectively) while the C(1)-C(2) bond [1.456(5) Å] is shorter than a typical single C-C bond (1.54 Å) and closer to the bond length associated with butadiene sp^2C-sp^2C single bond (1.45 Å). C(3)-C(4) bond [1.456(5) Å] is shorter than C(1)-C(2) bond presumably because it is an spC-sp^2C single bond. The C(2)-S(1) bond [1.730(4) Å] is midway between a typical C-S single (1.82 Å) and C=S double (1.60 Å) bond. In conjunction with ^{13}C NMR data, which shows the

exocyclic double bond at 158.2 [*C*CHC≡N or C(2)] and 83.2 ppm [*C*C≡N or C(3)], the bond lengths derived from the X-ray structure show only a small degree of delocalization extending between the dithiazole ring and the nitrile group. The small degree of delocalization of the exocyclic double bond and the decreased ^{13}C NMR value (83.2 ppm) of the [*C*C≡N or C(3)] carbon in comparison with the ^{13}C NMR data of dithiazole *tert*-butyl ester **138** [92.8 ppm (*C*C≡N)] suggest that as the *C*CN ^{13}C NMR value increases less rotation of the exocyclic double bond is expected. (Dithiazolylidene)malononitrile **120** gives an even lower ^{13}C NMR value [67.3 ppm (*C*C≡N)] due to the more efficient stabilization of the increased electron density (caused by the extending delocalization of the dithiazole ring to the exocyclic double bond) of the *C*(CN)$_2$ carbon by the two electron withdrawing nitrile substituents.

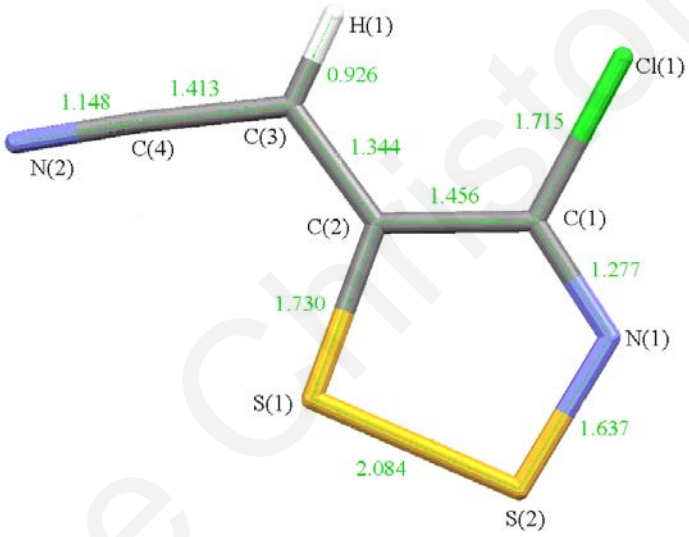


Figure 5 X-ray structure of (1,2,3-dithiazolylidene)acetonitrile **139** showing bond lengths (Å) in green.

The crystal packing of the (dithiazolylidene)acetonitrile **139** showed an orientation of parallel sheets separated by alternating distances of 3.151 and 3.163 Å (Figure 6). Between the sheets there were no significant interactions (less than the sum of the van der Waals radii). The shortest Cl···Cl interactions, 4.088 and 4.090 Å, were significantly longer than the sum of their van der Waals radii (Cl···Cl 3.50 Å),[217] however, there was a possible electrostatic Cl···arene ring intersheet interaction measuring 3.348 Å. No significant S···S or S···N intersheet interactions were visible. The molecules are stacked

in columns in a manner that the chlorine atoms of alternating molecules within the columns form an angle of 43.38° (Figure 7). This arrangement is probably adopted in order to avoid steric interactions between the chlorine atoms.

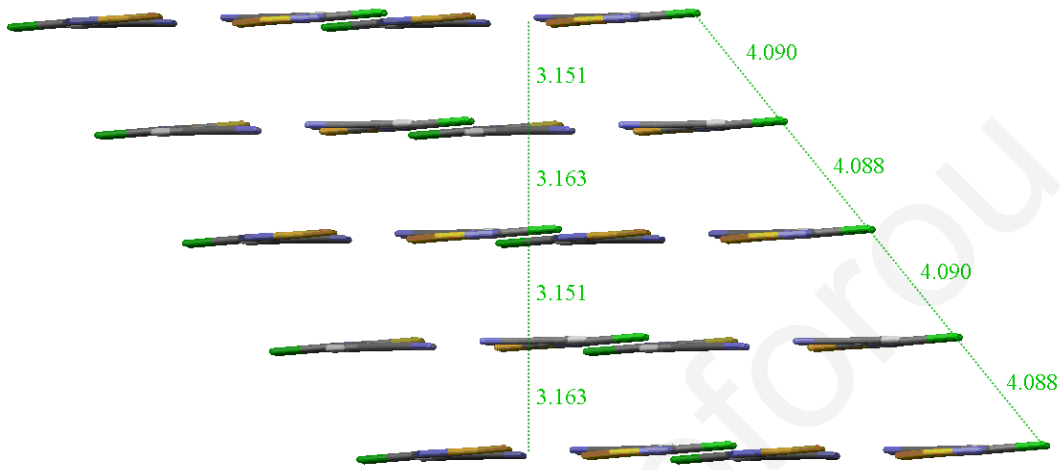


Figure 6 View along *b* axis showing alternating intersheet distances (Å) and weak Cl···Cl contacts of 4.09 Å.

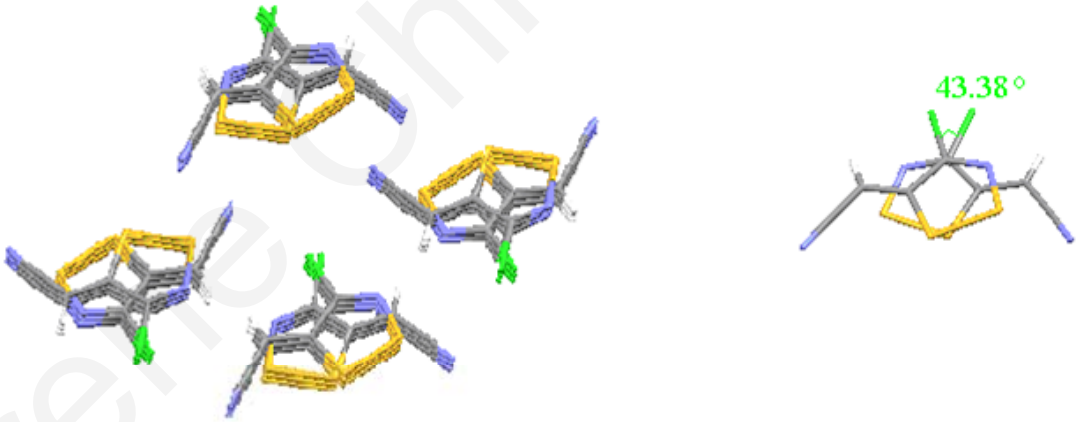


Figure 7 View along *c* axis showing overlap of sheets of (1,2,3-dithiazolylidene)-acetonitrile **139**.

Intrasheet contacts involved almost equidistant triangular S-S···N contacts, 2.898 and 2.871 Å, between the nitrile nitrogen and both the dithiazole sulfur atoms (Figure 8). These S···N contacts were significantly shorter than the sum of the van der Waals radii

(N···S 3.26 Å).[217] A possible C(3)-H(1)···N(1) (3.394 Å, 157.61°) hydrogen bond interaction may also be present.

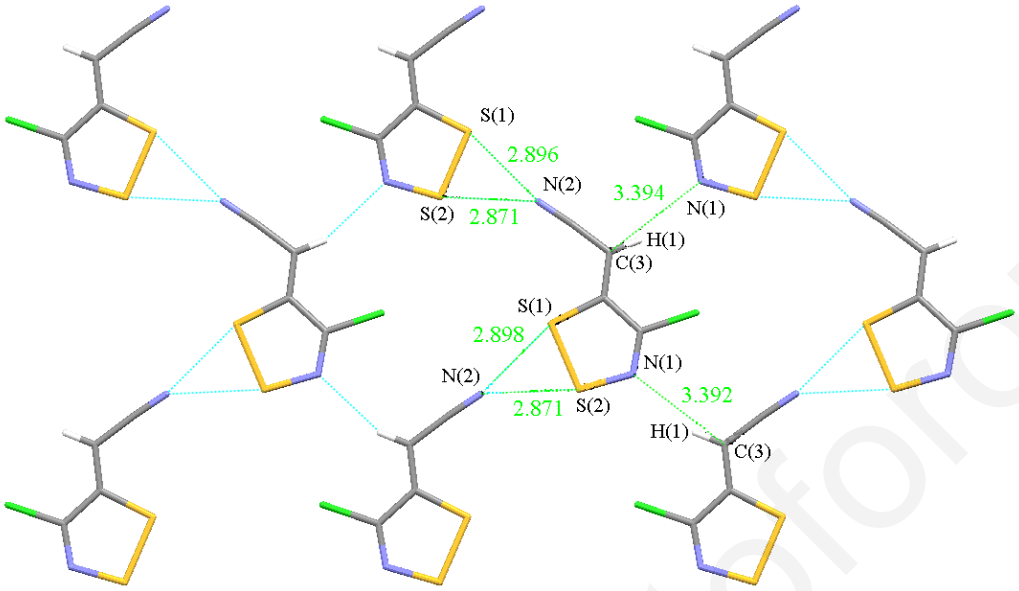
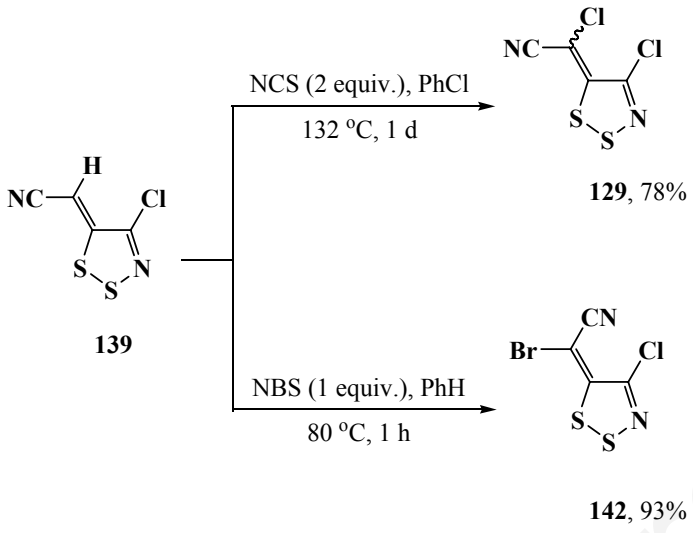


Figure 8 Intrasheet intermolecular interactions viewed along *a* axis for 2-chloro-(1,2,3-dithiazolylidene)acetonitrile **139**. Contact distances (Å): S(1)···N(2) 2.896, S(2)···N(2) 2.871, C(3)-H(1)···N(1) 3.394.

Having successfully prepared the (dithiazolylidene)acetonitrile **139** the synthesis of the halogenated derivatives was pursued. The 2-chloro-(1,2,3-dithiazolylidene)-acetonitrile **129** was synthesized in 78% yield using *N*-chlorosuccinimide (NCS) (2 equiv.) in refluxing PhCl (Scheme 39). The use of only one equivalent of NCS in refluxing PhCl gave an incomplete reaction even when catalytic amount of benzoyl peroxide (10 mol%) was added to the reaction mixture as initiator. Lower reaction temperatures (refluxing PhH, PhMe) with or without catalytic amount (10 mol%) of initiator (benzoyl peroxide, AIBN), using NCS (1 equiv.) resulted in the formation of only traces of the 2-chloro-(dithiazolylidene)acetonitrile **129**. The 2-bromo-(1,2,3-dithiazolylidene)acetonitrile **142** was synthesized in 93% yield under milder conditions using *N*-bromosuccinimide (NBS) (1 equiv.) in refluxing PhH.



Scheme 39

The analogous synthesis of the 2-iodo-(dithiazolylidene)acetonitrile failed since the starting dithiazolylidene **139** was stable in the presence of NIS in refluxing PhH or PhMe. Reactions with Cl_2 or Br_2 were more complex giving the desired compounds **129** and **142** respectively in low yields (TLC). In particular at 5-10 °C in PhH the addition of Br_2 to a solution of the (dithiazolylidene)acetonitrile **139** led to the immediate formation of an unidentified red precipitate together with a low yield of the desired product **142** (24%), sulfur and 4 other products (3 colourless and 1 yellow). One of the colourless products was determined to be the known 3,4-dibromoisothiazole-5-carbonitrile **6**[57] (by TLC), and its presence in the reaction mixture indicated the formation of HBr or bromide could have led to the transformation of the dithiazole into isothiazole. The addition of Py (1 equiv.) failed to give a cleaner reaction. In refluxing PhH the red precipitate dissolved but the yield of 2-bromo-(dithiazolylidene)acetonitrile **142** (27%) was not significantly affected.

The stereochemistry of the chloro-(dithiazolylidene)acetonitrile **129** could not be verified since single crystals could not be grown for structure determination, however, single crystals of the bromo-(dithiazolylidene)acetonitrile **142** were suitable for X-ray crystallography studies.

The structure of the bromo-(dithiazolylidene)acetonitrile **142** showed the nitrile group interactions to be *anti* to the ring sulfur S-1 (Figure 9). This orientation presumably avoids steric interactions between the bromo and the C-4 chlorine. The molecule is planar. The C(2)-C(3) and C(1)-N(1) bonds [1.376(6) and 1.284(6) Å

respectively] have pronounced double bond character (typical C=C and C=N bond lengths are 1.34 Å and 1.29 Å respectively) while the C(1)-C(2) and C(3)-C(4) bonds [1.454(6) and 1.426(7) Å respectively] are shorter than a typical single C-C bond (1.54 Å) and closer to the bond length associated with an aromatic C-C bond (1.40 Å). The C(2)-S(1) [1.738(5) Å] is midway between a typical C-S single (1.82 Å) and C=S double (1.60 Å) bond. In conjunction with ^{13}C NMR data, which shows the exocyclic double bonds at 157.6 [*C*CBrC≡N or C(2)] and 74.6 ppm [*C*C≡N or C(3)], the bond lengths derived from the X-ray structure show only a small degree of delocalization extending between the dithiazole ring and the nitrile group.

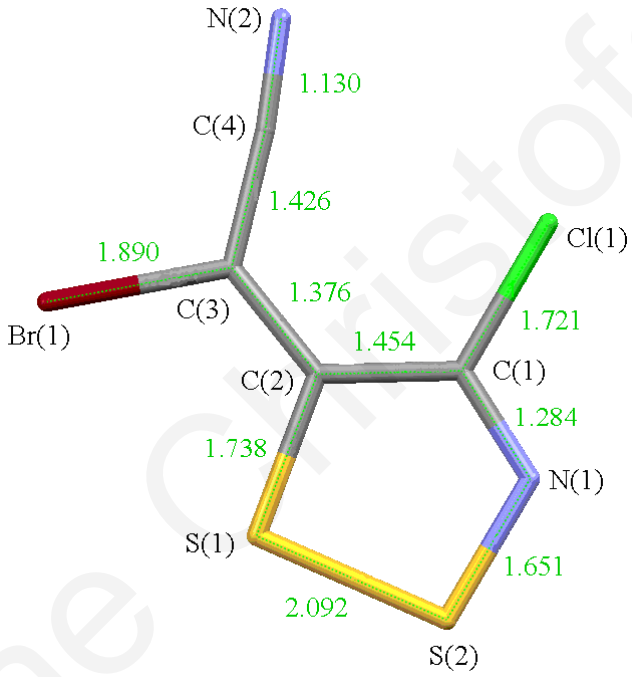


Figure 9 X-ray structure of 2-bromo-(1,2,3-dithiazolylidene)acetonitrile **142**.

The crystal packing of bromo-(dithiazolylidene)acetonitrile **142** indicated that the molecules are orientated in centrosymmetrically orientated sheets separated by 3.366 Å. The only observable intersheet contacts are S-S interactions of 3.553 and 3.555 Å between overlaying dithiazolylidenes which are marginally shorter than the sum of van der Waals radii (3.60 Å)[217] (Figure 10). The molecules of (bromoacetonitrile)-dithiazoles **142** are stacked in columns in a manner that molecules within the columns have overlapping sulfur atoms area (Figure 11).

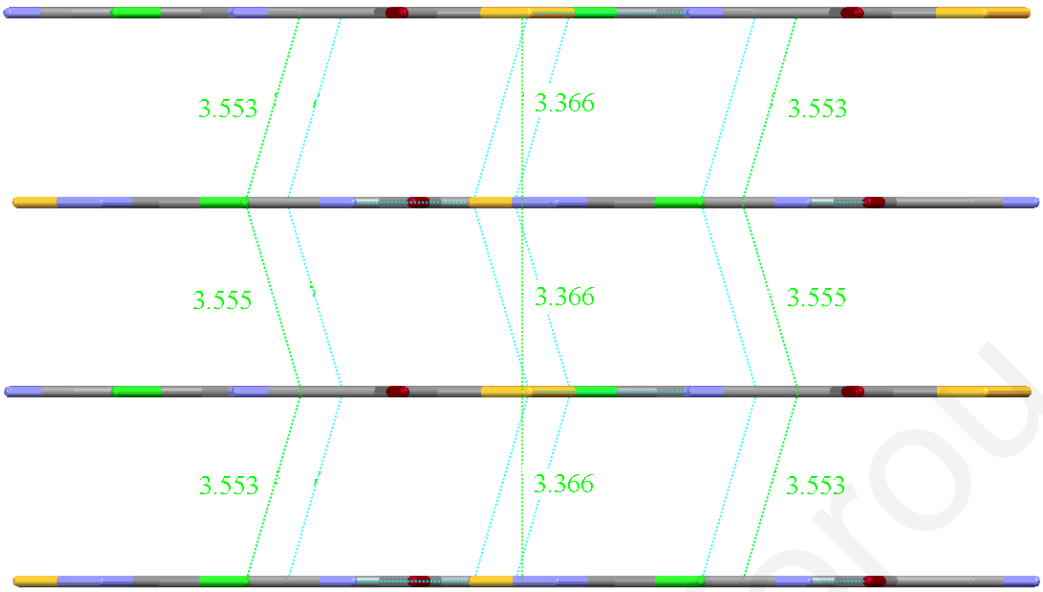


Figure 10 View along *c* axis showing intersheet distances (Å) and S···S contacts for 2-bromo-(1,2,3-dithiazolylidene)acetonitrile **142**.

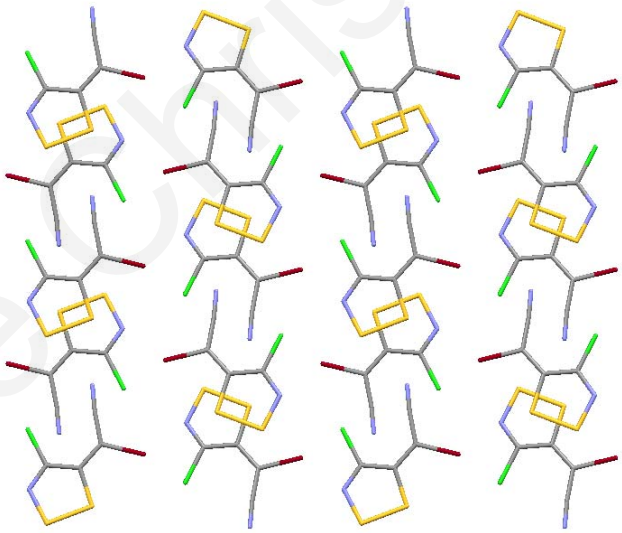


Figure 11 View along *b* axis showing overlap of sheets of 2-bromo-(1,2,3-dithiazolylidene)acetonitrile **142**.

Within each sheet there are strong in plane triangular S-N···Cl (3.088 Å), N-S···Cl (3.471 Å) and S-S···N (2.915 and 2.939 Å) interactions which are significantly shorter than the sum of the van der Waals radii (N···Cl 3.21 Å, S···Cl 3.55 Å, S···N 3.26 Å)[217] (Figure 12). These interactions align the molecules together in ribbons that have the

bromo substitutents at their periphery (Figure 11). Despite bromine atoms having enhanced electropositive character in comparison with chlorine atoms, the N···Br short contacts, 3.332 Å, are very close to the corresponding sum of their van der Waals radii (N···Br 3.33 Å)[217] and probably not of great importance.

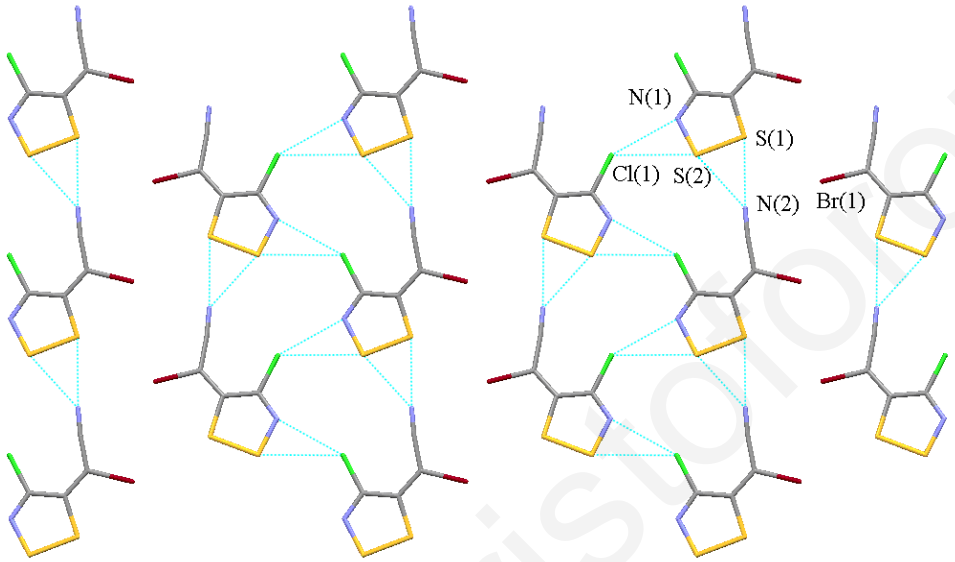
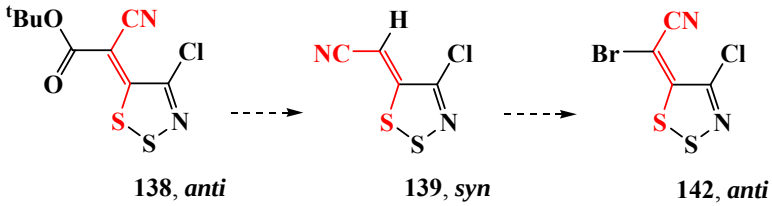


Figure 12 Intrasheet intermolecular interactions viewed along *b* axis for 2-bromo-(1,2,3-dithiazolylidene)acetonitrile **142**. Contact distances (Å): S(1)···N(2) 2.915; S(2)···N(2) 2.939; S(2)···Cl(1) 3.471; N(1)···Cl(1) 3.088; Br(1)···N(2) 3.332.

The structural identification of the substituted (dithiazolylidene)acetonitriles **139** and **142** by X-ray crystallography showed that the stereochemistry of the exocyclic C=C bond had changed (Figure 13). The dithiazole ester **138** has an *anti* orientation with respect to the nitrile group and the ring sulfur atom S-1 which switched to *syn* in the case of the dithiazole **139** (Scheme 40). An analogous switch of the orientation was also observed with the synthesis of the bromo(dithiazolylidene) **142** (*anti*) from the (dithiazolylidene)acetonitrile **139** (*syn*). The recurrent change of the orientation of the substituted dithiazolylidenes **138**, **139** and **142** supported that under the reaction conditions an intermediate was involved that allows the exocyclic double bond to adopt the preferred conformation.



138, ***anti*** **139**, ***syn*** **142**, ***anti***

Scheme 40

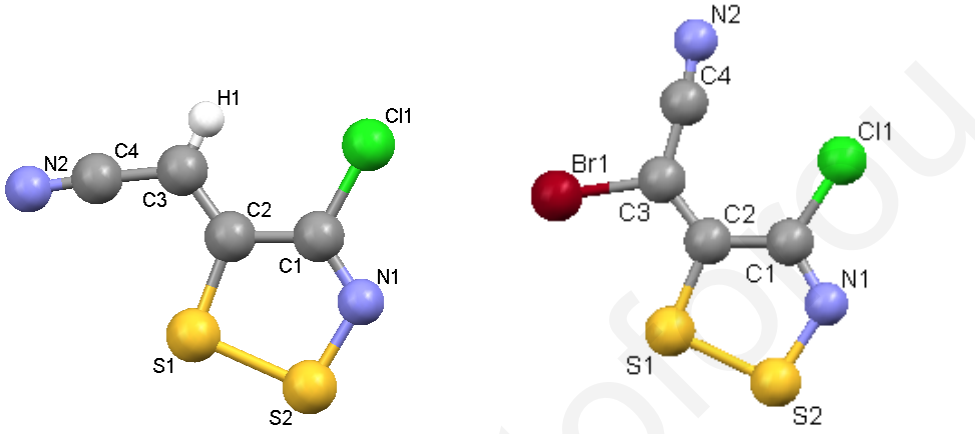
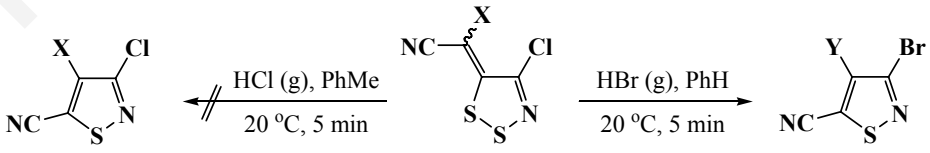


Figure 13 X-ray structures of the dithiazolylidenes **139** and **142**.

2.2.2 Reactions with Anhydrous HBr and HCl

The dithiazolylidenes **139** (X=H), **129** (X=Cl) and **142** (X=Br), having been prepared in good yields, were subsequently reacted with anhydrous HBr. Unlike the (dithiazolylidene)malononitrile **120**, which gave the desired 3-bromoisothiazole-4,5-dicarbonitrile **132** in 83% yield,[201] the dithiazolylidenes **139** and **142** gave only low to moderate yields of the expected isothiazoles **143** and **10** respectively (Scheme 41). Furthermore, the chloro substituted dithiazolylidene **129** gave an inseparable mixture of 4-chloro- and 5-bromoisothiazoles **144** and **10** respectively. As expected, the analogous reactions with anhydrous HCl failed to give any products and the starting dithiazoles **139**, **129** and **142** were recovered unchanged.



139, X = H
129, X = Cl
142, X = Br

143, Y = H, 24%
144, Y = Cl & **10**, Y = Br
10, Y = Br, 42%

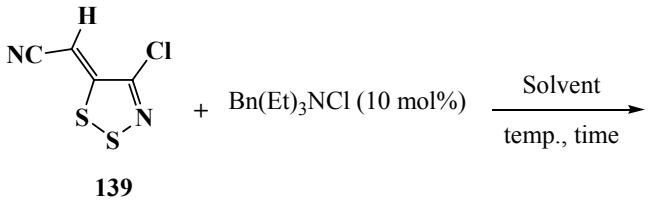
Scheme 41

In general HBr gave complex reaction mixtures and the expected isothiazoles were isolated in low yields. Since the anhydrous HBr method proved to be unsatisfactory for the synthesis of cyanosubstituted isothiazoles the reactions with tetraalkylammonium halides were then investigated.

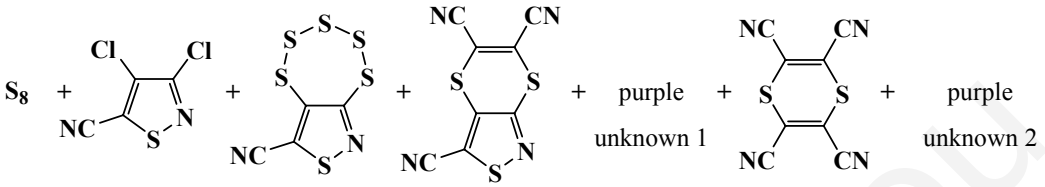
2.2.3 Reactions with Tetraalkyammonium Halides

Surprisingly, treatment of the dithiazolylidenes **129**, **139** and **142** with catalytic amount of benzyltriethylammonium chloride in refluxing DCM gave many unexpected products (at least seven). The reaction mixtures consisted of both colourless and coloured (yellow, purple) products. Owing to the complexity of these reaction mixtures a careful study was performed on the simplest analogue the dithiazolylidene **139** (X=H). Reaction of the dithiazolylidene **139** with benzyltriethylammonium chloride (10 mol%) in refluxing DCM gave, according to the TLC, sulfur followed by two colourless products, one yellow product, one purple product, a pale yellow product and a second purple coloured product. These products were isolated and fully characterized where possible. Two of the colourless products, 3,4-dichloroisothiazole-5-carbonitrile **145**[27] [mp 88-90 ^{o}C (from cyclohexane), lit.,[27] mp 84-85 ^{o}C (from cyclohexane)] and 1,2,3,4,5-pentathiepino[6,7-*c*]isothiazole-8-carbonitrile **146**,[165, 218, 219] [mp 141-142 ^{o}C (from pentane), lit.,[164] mp 143-144 ^{o}C (from CCl_4)] which were formed in 3 and 7% yields respectively, and two of the yellow products 1,4-dithiino[2,3-*c*]isothiazole-3,5,6-tricarbonitrile **95**[166] (11%) [mp 176-177 ^{o}C (from cyclohexane), lit.,[166] mp 181-182 ^{o}C (from PhH)] and 1,4-dithiine-2,3,5,6-tetracarbonitrile **93** (54%)[166] [mp 205-206 ^{o}C (from DCM), lit.,[166] mp 207-208 ^{o}C (from PhMe)] were previously reported in the literature (Table 1). Interestingly 1,4-dithiino[2,3-*c*]isothiazole-3,5,6-tricarbonitrile **95** has been previously prepared from 1,4-dithiine-2,3,5,6-tetracarbonitrile **93** and elemental sulfur.[166] The only new compounds were the two purple couloured products **147** [mp 172-173 ^{o}C (from cyclohexane), λ_{max}(DCM) 544nm (log ε 2.82)] and **148** [mp >300 ^{o}C (from DCE), λ_{max}(EtOH) 553nm (log ε 2.75)]. At higher temperatures (refluxing PhH, PhMe, PhCl) the reaction times were reduced significantly, the yield of 1,4-dithiino[2,3-*c*]isothiazole-3,5,6-tricarbonitrile **95** was increased but the yield of 1,4-dithiine-2,3,5,6-tetracarbonitrile **93** was reduced (Table 1). Furthermore the reaction mixtures became more complex especially in refluxing PhCl where one brown, one light blue and at least 4 additional colourless and polar compounds where observed by TLC.

Table 1. Reaction of (dithiazolylidene)acetonitrile **139** (0.570 mmol) in solvent (3 ml) with $Bn(Et)_3Cl$.



139



145 **146** **95** **147** **93** **148**

Solvent	Temp.	Time	Yields (%)						
	(^{o}C)	(min)	**S_8**	**145**	**146**	**95**	**147**	**93**	**148**
DCM[a]	40	90	15	3	7	11	7	54	3
PhH[a]	82	30	28	trace	nd	12	2	12	5
PhMe[a]	110	8	21	3	nd	17	-	8	7
PhCl[a]	135	5	32	trace	nd	16	3	-	9
PhCl[a,b]	135	5	25	6	11	7	9	7	1

[a]Preheated oil; [b]1g scale reaction.

A 2D TLC study and spectroscopic analysis confirmed that the first purple product hydrated on silica to afford the second purple product. ^{1}H NMR spectroscopy gave no protons for compound **147**, however, one broad singlet peak at 8.21 ppm was observed for compound **148**. Both compounds gave 8 signals in ^{13}C NMR spectra (in the range of 129.4-100.4 for **147** and 180.5-103.9 ppm for **148**). IR spectroscopy on compound **147** supported the absence of carbonyl and amino functionalities and strongly supported the presence of conjugated nitriles $\nu(C\equiv N)_s$ at 2232, 2219 and 2212 cm^{-1} while for compound **148** IR spectroscopy indicated the presence of an amino group $\nu(NH_2)$ at 3390 cm^{-1}, conjugated nitriles $\nu(C\equiv N)_s$ at 2237 and 2203 cm^{-1} and a carbonyl $\nu(C=O)$ at 1669 cm^{-1}. Mass spectrometry gave strong peaks for each molecular ion at 248 (100%) and 266 Da (100%) for compounds **147** and **148** respectively; the difference of 18 Da corresponds to one O and two H atoms (H_2O) and suggested a possible hydration had occurred. According to the spectroscopic data and the 2D TLC technique one of the nitriles of the first purple coloured unknown **147** had hydrated into carboxamide to afford the second purple coloured unknown **148**.

Although the spectroscopic data were not sufficient to determine the structure of the compounds **147** and **148**, several possible structures could be proposed (Figure 14). The structures proposed below can support the intense colour of the compounds since they can stabilize charge transfer between the two fused rings.

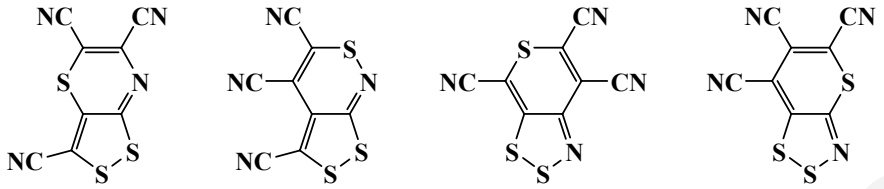
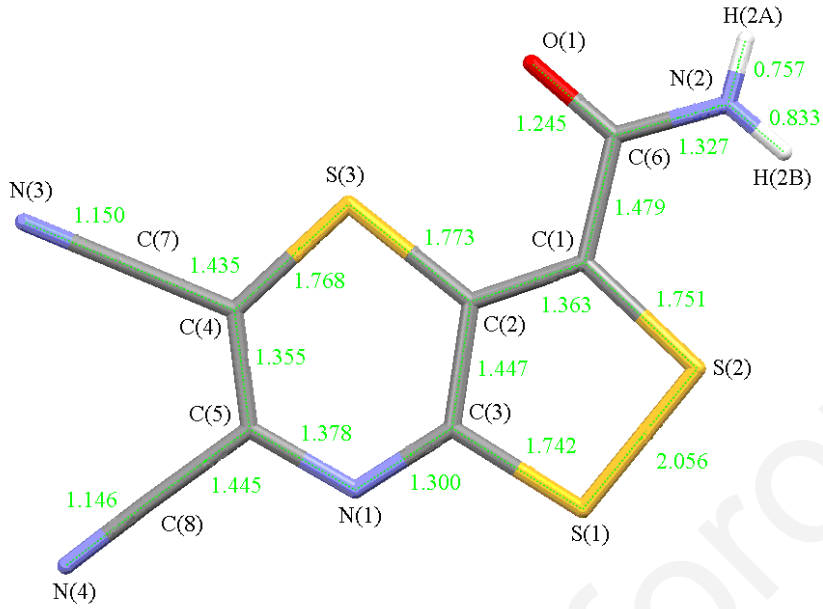
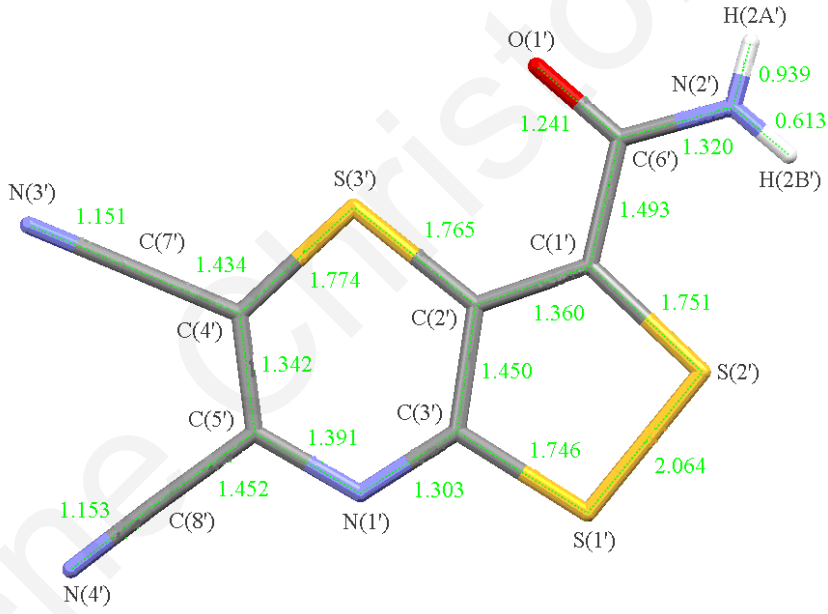


Figure 14 Possible structures of compound **147**.

The structure determination was eventually achieved with single crystal X-ray crystallographic analysis of the second purple compound which supported the previously unreported fused dithiolo[4,3-*b*][1,4]thiazine ring system (Figure 15). The X-ray structure also showed that the sensitive nitrile of the 1,2-dithiolo[4,3-*b*][1,4]thiazine-3,5,6-tricarbonitrile **147** was that at the C-3 position of the 1,2-dithiole ring. The X-ray diffraction analysis of crystals of 5,6-dicyano[1,2]dithiolo[4,3-b][1,4]thiazine-3-carboxamide **148** showed the structure to contain two crystallographically independent molecules (A and B) in the asymmetric unit. These two molecules are linked to each other *via* the N–H···O hydrogen bonds to the three included DMSO solvent molecules to form a five moiety unit (Figure 16). The heterocyclic molecules are almost planar with the greatest deviation for heterocycle A being seen from the nitrile nitrogens N(4) and N(3), and the dithiole sulfur S(1) which are 0.112, -0.124 and 0.107 Å respectively from the plane and for heterocycle B the nitrile nitrogen N(7), the dithiole sulfur S(5) and the carboxamide oxygen O(2) which are 0.118, 0.770 and -0.142 Å respectively. The carboxamide of heterocycle A O(1)-C(6)-N(2) shows a small torsional angle of 3^{o} with respect to the dithiazole S(2)-C(1)-C(2) fragment, while that of heterocycle B shows only 2.56^{o} [between fragments O(1')-C(6')-N(2') and S(2')-C(1')-C(2')]. These bond length variations and deviations from planarity appear to be owed to interactions with the co-crystallised DMSO molecules.



Heterocycle A



Heterocycle B

Figure 15 X-ray structure of the two independent molecules of 5,6-dicyano[1,2]dithiolo-[4,3-*b*][1,4]thiazine-3-carboxamide **148** found in crystal structure; top structure labeled heterocycle A and bottom labeled heterocycle B.

Molecules A and B are further linked by O···S contacts from O(1') to S(1) and S(2) (2.91 and 2.87 Å respectively) and by N···S contacts from N(3) to S(1') and S(2') (3.00 and 3.16 Å respectively) (Figure 16), forming a continuous chain of molecules (Figure 17).

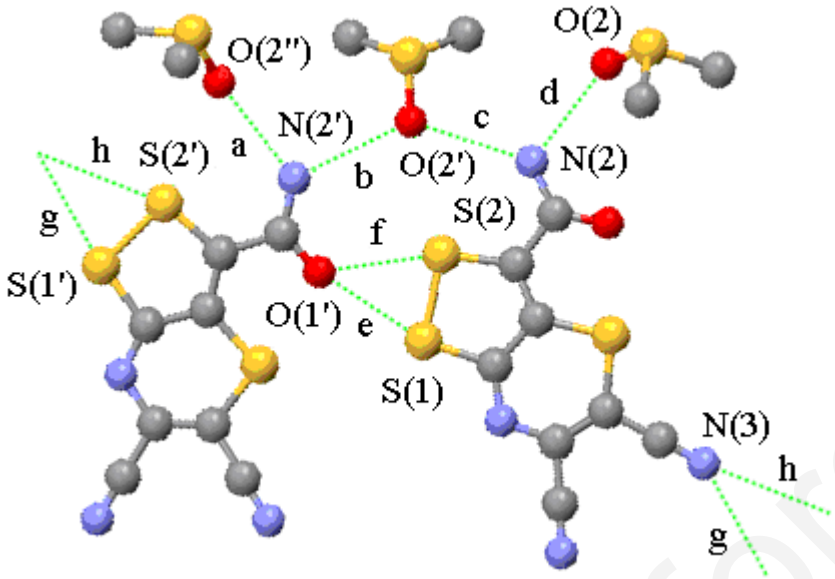


Figure 16 The molecular structure of 5,6-dicyano[1,2]dithiolo[4,3-*b*][1,4]thiazine-3-carboxamide **148** showing the two independent molecules of **148**, the three independent DMSO solvent molecules, and the intermolecular interactions between them. The N-H···O hydrogen bonds have N···O separations of *ca.* **a**) 2.85, **b**) 3.02, **c**) 2.98 and **d**) 2.89 Å respectively. The O···S contacts **e** and **f** have S···O separations of *ca.* 2.91 and 2.87 Å respectively, whilst the N···S contacts **g** and **h** have N···O separations of *ca.* 3.00 and 3.16 Å respectively.

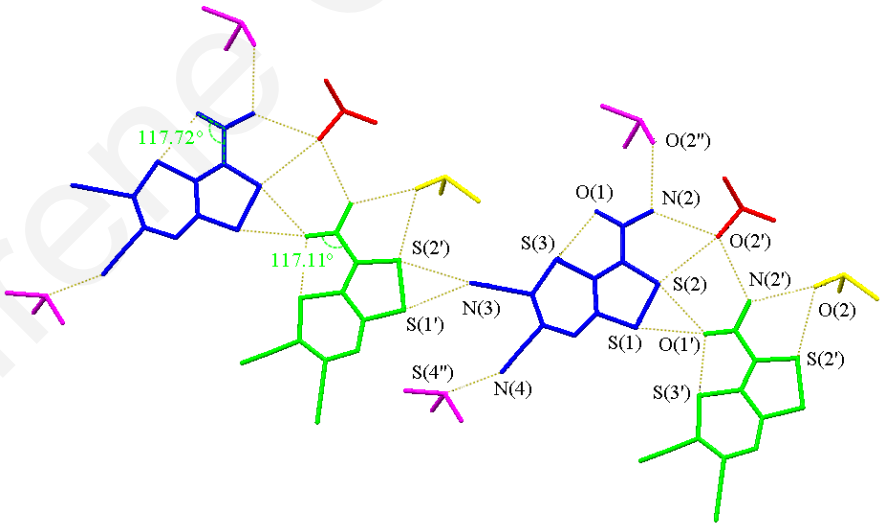


Figure 17 Packing motif showing intersheet distances and co-crystallised DMSO molecules.

These “ribbons” are repeated in the vertical plane, antiparralel with respect to each other and with some horizontal displacement (Figure 18). The distance between the planes alternates between 3.269 and 3.369 Å. The heterocycles within the ribbons show no significant interactions with heterocycles in adjacent ribbons to account for the alternating intersheet distances. However on close inspection the shorter distance between two ribbons (3.269 Å) might be attributed to weak S···N and O···C electrostatic interactions between DMSO (red) and the 1,2-dinitrile functionality of one of the thiazine molecules (green). There is approximately equidistant alignment of the DMSO S-O bond above the two cyano groups with O(2') centered between the nitrile carbons C(8') and C(7'), 3.348 and 3.220 Å respectively, and S(4') centered between the nitrile nitrogens N(4') and N(3'), 3.686 and 3.453 Å respectively.

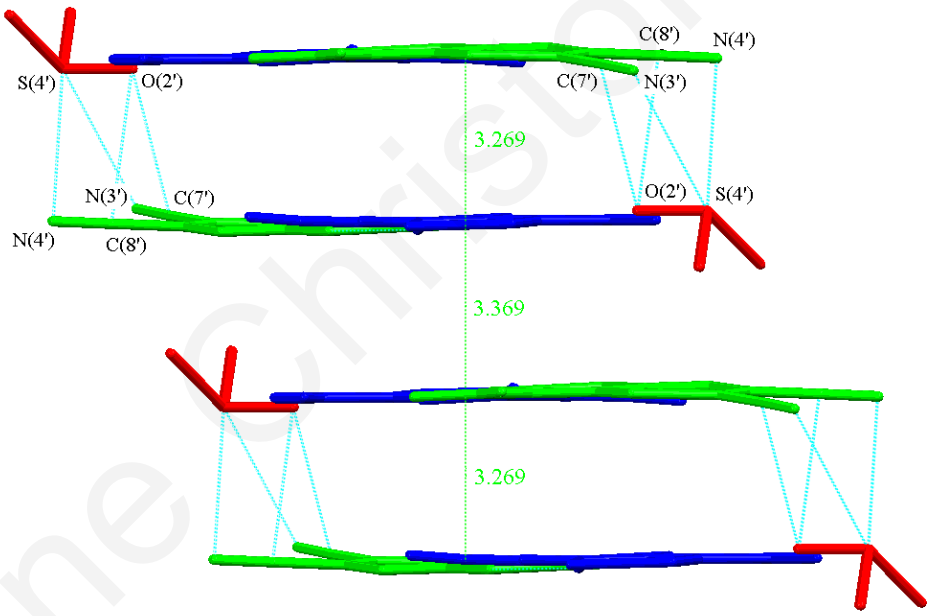


Figure 18 Packing motif featuring DMSO – dinitrile interactions.

This coordination of DMSO to the nitriles may also be responsible for the heterocycles deviation from planarity and notably the thiazine nitriles deviate from the plane of the heterocycle towards the DMSO molecule. This alignment of heterocycles is repeated in an almost perpendicular (76.8º) herringbone motif to these ribbons (Figure 19), and these near perpendicular ribbons are interlinked by DMSO molecules *via* weak C-H···O bonded interactions.

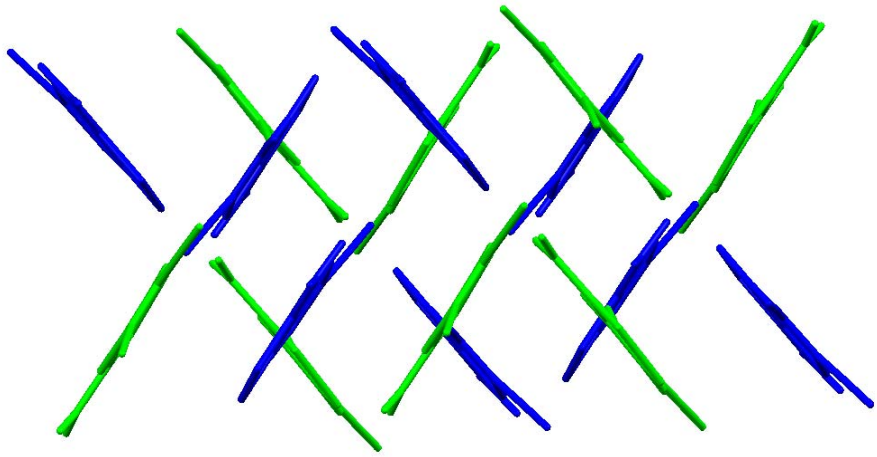
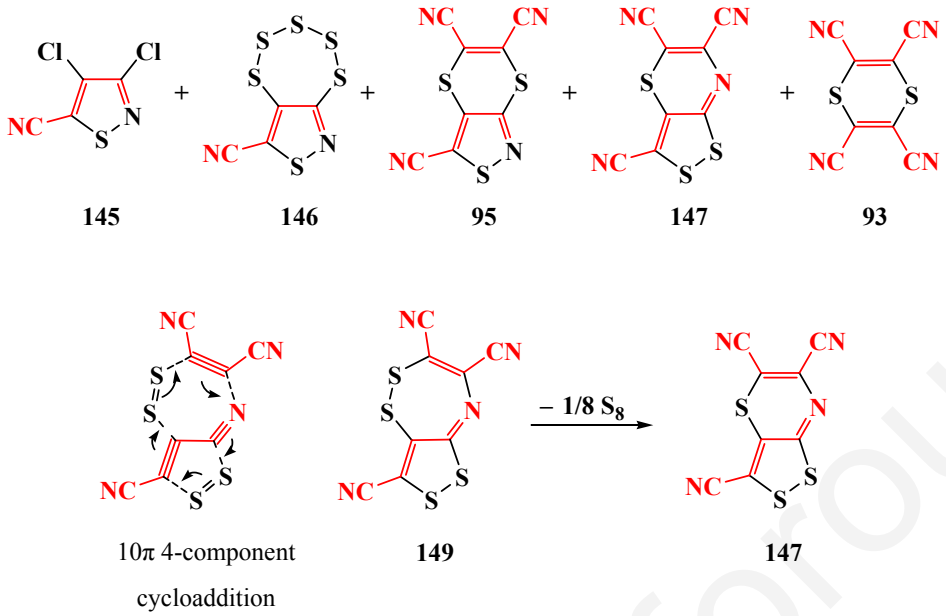


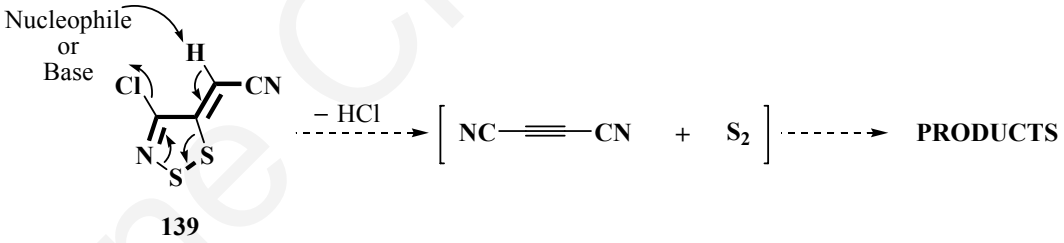
Figure 19 Herringbone packing conformation with DMSO molecules removed for clarity.

A careful look at the unexpected products **93**, **95**, and **145-148** showed that all the products comprised of at least one dicyanoacetylene unit and sulfur. Tentatively all the compounds could therefore be formally derived from multicomponent cycloadditions between dicyanoacetylene and diatomic sulfur followed by the appropriate ring contractions where necessary. For example, the new 1,2-dithiolo[4,3-*b*][1,4]thiazine-3,5,6-tricarbonitrile **147** could result from a 10π four-component cycloaddition between two units of dicyanoacetylene and two units of diatomic sulfur to afford the intermediate **149** which after loss of sulfur gives the observed compound **147** (Scheme 42). If this were true, it would necessitate the formation of both dicyanoacetylene and diatomic sulfur during the reaction.



Scheme 42

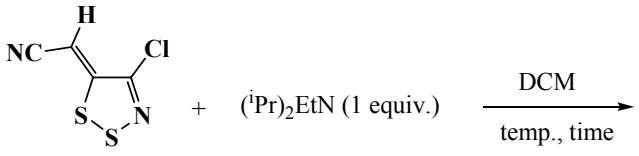
A tentative mechanism which involved elimination of HCl, dicyanoacetylene and diatomic sulfur could readily be proposed (Scheme 43). Accordingly the products should be observed if the benzyltriethylammonium chloride was replaced by a non nucleophilic base like *N*,*N*-diisopropylethylamine (Hünig's base).



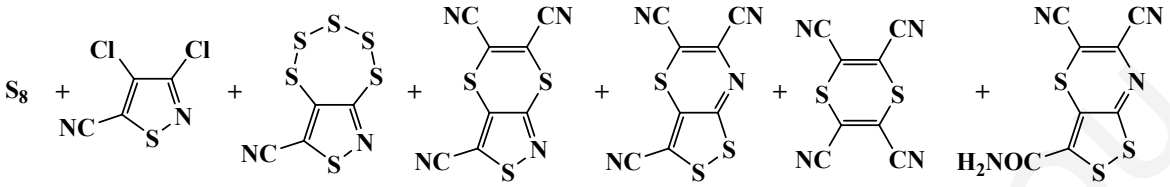
Scheme 43

The possibility that the (dithiazolylidene)acetonitrile **139** could be *unzipped* by deprotonation with Hünig's base to afford HCl, dicyanoacetylene and diatomic sulfur was investigated. Treatment of the dithiazolylidene **139** with Hünig's base (1 equiv.) indeed resulted in the formation of the same products (Table 2). The reaction time was considerable faster at 40 °C (refluxing DCM) compared with the same reaction at rt, however, in both cases the main products were 1,4-dithiino[2,3-*c*]isothiazole-3,5,6-tricarbonitrile **95** and 1,4-dithiine-2,3,5,6-tetracarbonitrile **93**.

Table 2. Reaction of (dithiazolylidene)acetonitrile **139** (0.285 mmol) with $(^{i}Pr)_2EtN$ (1 equiv.) in DCM (3 ml).



139



145 **146** **95** **147** **93** **148**

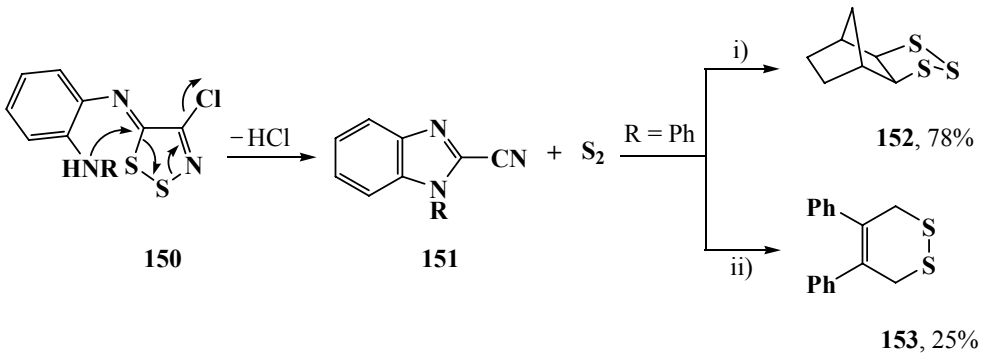
Temp.	Time	Yields (%)						
(^{o}C)	(h)	**S_8**	**145**	**146**	**95**	**147**	**93**	**148**
20	7	26	4	5	39	trace	19	-
40[a]	1.5	28	3	7	54	6	30	-

[a]Preheated oil.

The formation and ratio of products **93**, **95**, **145-148** in reactions of (dithiazolylidene)acetonitrile) **139** with benzyltriethylammonium chloride or with Hünig's base tentatively supported the production of dicyanoacetylene and diatomic sulfur in the reaction mixture. Additional support for the presence of diatomic sulfur and dicyanoacetylene was gathered by conducting the reactions in the presence of various trapping agents.

2.2.4 Reactions with 2,3-Diphenyl-1,3-butadiene

1,2,3-Dithiazoles are known to eliminate diatomic sulfur on thermolysis.[209, 220] The loss of diatomic sulfur was claimed when *N*-arylimino-1,2,3-dithiazoles **150** were converted to 2-cyanobenzimidazoles **151** under thermolysis reactions (140-150 ^{o}C). Both norbornene and 2,3-diphenylbutadiene were used to trap the S_2 to afford the 1,2,3-trithiole **152** and the Diels-Alder adduct 4,5-diphenyl-3,6-dihydro-1,2-dithiine **153** in 78 and 25% yields respectively (Scheme 44). This is however, the first time that the loss of dicyanoacetylene is proposed in 1,2,3-dithiazole chemistry.

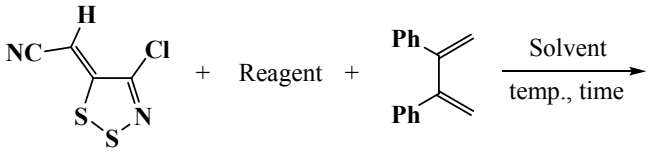


***Reagents and Conditions*:** i) norbornylene (6.7 equiv.), 140-150 ^{o}C, 4 h, sealed tube; ii) 2,3-diphenyl-1,3-butadiene (6.7 equiv.), 140-150 ^{o}C, 3 h, sealed tube.

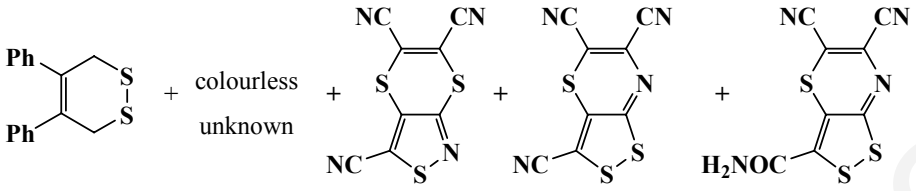
Scheme 44

In order to support the formation of dicyanoacetylene and diatomic sulfur the reactions of (dithiazolylidene)acetonitrile **139** with benzyltriethylammonium chloride / Hünig's base were repeated in the presence of 2,3-diphenylbutadiene (2 equiv.). In refluxing DCM only a low consumption of 2,3-diphenylbutadiene was observed and the expected diphenyl-1,2-dithiine **153** was formed in traces. The main product was 1,4-dithiino[2,3-*c*]isothiazole-3,5,6-tricarbonitrile **95** which was formed in 41% yield in the reaction with benzyltriethylammonium chloride (10 mol%) and in 54% yield in the reaction with Hünig's base (1 equiv.). One new colourless product, compound **154**, was also isolated but its structure has not yet been elucidated. A less complex reaction mixture was observed with benzyltriethylammonium chloride in refluxing PhCl; under these conditions the desired diphenyl-1,2-dithiine **153** was formed in 16%, the unknown colourless compound **154** in 22% and the purple compound **148** in 12% yield. With Hünig's base (1 equiv.), in refluxing PhCl, the reaction was complex. The most intense products, according to the TLC, were the compounds **153** and **95** which were isolated in 14 and 19% yields respectively (Table 3).

Table 3. Reaction of (dithiazolylidene)acetonitrile **139** (0.285 mmol) with 2,3-diphenylbutadiene.



139 (2 equiv.)



153 **154** **95** **147** **148**

Reagent (equiv.)	Solvent	Temp. (°C)	Time (h)	Yields (%) **153**	**154**	**95**	**147**	**148**
$BnEt_3NCl$ (10%)	DCM (3ml)	40	1.75	trace	23	41	trace	3
$BnEt_3NCl$ (10%)	PhCl (3ml)	132[a]	1	16	22	-	-	12
$(^iPr)_2EtN$ (1)	DCM (3ml)	40	1.25	trace	2	54	trace	-
$(^iPr)_2EtN$ (1)	PhCl (3ml)	132[a]	1	14	4	19	-	-

[a]In a sealed tube.

The unknown compound **154** was partially characterized but its structure cannot yet be solved without the help of the single crystal X-ray crystallography. IR spectroscopy supported the presence of conjugated nitriles, with $\nu(C{\equiv}N)_s$ at 2235 and 2194 cm^{-1}, which indicated that the new colourless compound **154** consisted of at least one dicyano-acetylene unit. ^1H NMR spectroscopy gave two multiplets in the aromatic region at 7.22-7.13 and 7.08-7.04 ppm with total integration of 10H and also a complex spectrum at the upfield area (4.08-3.29 ppm) with total integration of 4H which indicated the existence of at least one 2,3-diphenylbutadiene unit. Mass spectrometry (EI) gave a weak peak for a possible molecular ion at 552 (22%) and a base peak at 227 Da (100%). The tentative molecular weight of compound **154** corresponds to two 2,3-diphenylbutadiene units, one dicyanoacetylene unit and one unit of diatomic sulfur. This conclusion was also supported by elemental analysis data (C, 76.6; H, 4.7; N, 5.6) which was close to the theoretical microanalysis (C, 78.2; H, 5.1; N, 5.1%) of a possible compound that consisted of two 2,3-diphenylbutadiene units, one dicyanoacetylene unit and one unit of diatomic sulfur. Two control experiments showed that the unknown colourless

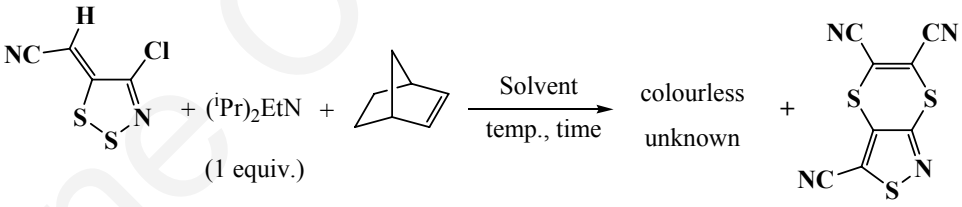
compound **154** was thermally stable in refluxing PhCl and also did not decompose when treated with triphenylphosphine in DCM at reflux.

Although the diphenyl-1,2-dithiine **153** was isolated in only 16 and 14% yields, these results were comparable with the previous study (25% yield).[209] Furthermore the formation of the diphenyl-1,2-dithiine **153** in combination with the unknown colourless product **154**, which tentatively consisted of two 2,3-diphenylbutadiene units, one dicyanoacetylene unit and one S_2 unit, supported the formation of dicyanoacetylene and S_2 during the reaction.

2.2.5 Reactions with Norbornene

The above results encouraged the analogous trapping experiments to be performed with norbornene. Treatment of the (dithiazolylidene)acetonitrile **139** with Hünig's base (1 equiv.) in the presence of norbornene (large excess) in refluxing DCM gave two products; one colourless compound **155** and the known [1,4]dithiino[2,3-*c*]isothiazole-3,5,6-tricarbonitrile **95**[166] in 27 and 28% yields respectively. The reaction was also performed in the absence of solvent at 100 °C in a sealed tube and gave the colourless compound **155** as the only product in 30% yield (Table 4).

Table 4. Reaction of (dithiazolylidene)acetonitrile **139** (0.285 mmol) with norbornene.



139 **155** **95**

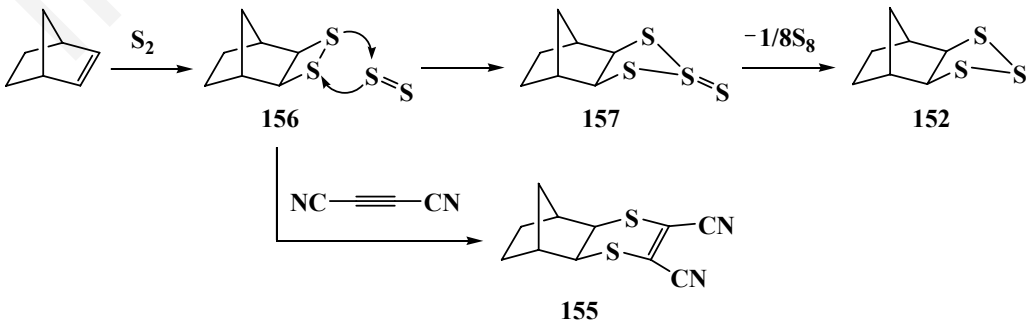
Norbornylene (equiv.)	Solvent	Temp. (°C)	Time (h)	Yields (%) **155**	**95**
2	DCM (3 ml)	40	1.5	27	28
excess	no solvent[a]	100	2	30	-

[a]In a sealed tube.

The structure of the colourless compound **155** was determined by spectroscopic analysis. IR spectroscopy gave two peaks for conjugated nitrile groups at 2226 and 2212 cm^{-1} which indicated the presence of at least one dicyanoacetylene unit. ^1H NMR

spectroscopy gave six different peaks in the range 3.55-1.33 ppm with total integration of 10H which correspond to a norbornene unit. ^{13}C NMR spectroscopy gave one tertiary carbon at 127.4, one carbon signal at 113.6 which corresponds to a nitrile group and 4 carbon signals in the range of 60.2-29.0 ppm, two of which were assigned to be C*H*s (60.2 and 44.7 ppm) by DEPT-90 NMR and the other two were assigned to be CH_2 peaks (35.0 and 29.0 ppm) by DEPT-135 NMR. The ^{13}C NMR data indicated the molecule has a plane of symmetry and in combination with mass spectrometry, which gave a strong peak for the molecular ion at 234 Da (100%), and elemental analysis (C, 56.4; H, 4.2; N, 11.9) the molecular formula $C_{11}H_{10}N_2S_2$ was proposed. The colourless compound was determined to be bicyclo[2.2.1]heptane[3,4-*e*][1,4]dithiine-2,3-dicarbonitrile **155**. The exo-selectivity of **155** was determined by ^{1}H NMR analysis. The doublet peak at 3.55 ppm which corresponds to the proton at C-2 (carbon bearing the sulfur atom) has a W-coupling of ^4J = 1.8 Hz between the endo proton at C-2 and the anti proton at the bridge carbon. This supported the exo-isomer since an endo proton coupled with the *anti* methylene bridge proton has a typical coupling constant of *ca.* 2.0 Hz while an exo proton coupled with the bridgehead proton has a typical coupling constant of *ca.* 4.0 Hz, the W-coupling in this latter case being absent.[221-223]

The formation of compound **155** was an unexpected result since the expected trithiole **152** was not observed. According to the literature the trithiole **152** is formed as a consequence of sulfur deposition from an insertion of a second molecule of S_2 to the highly strained S-S bond of the corresponding dithietane intermediate **156** forming the subsequent intermediate **157** (Scheme 45).[224] Sulfur insertion into strained sulfur-sulfur bonds[223, 225] and sulfur deposition[226, 227] are well known. In this reaction it was possible that instead of an insertion of a second molecule of S_2, there was a competitive insertion of one dicyanoacetylene molecule to afford the isolated compound **155**.



Scheme 45

Tentatively the formation of compound **155** supported the proposed mechanism (Scheme 45) involving the formation of dicyanoacetylene and diatomic sulfur during the ring transformation.

2.3 Summary

Dithiazolylidenacetonitriles **129**, **139** and **142** react with anhydrous HBr and trialkylammonium chloride to afford 3-halo-4-substituted-isothiazole-5-carbonitriles in low yields. The reaction of (dithiazolylidene)acetonitrile **139** with tetraalkylammonium chloride was complicated owing to the formation of isothiazolopentathiepin-8-carbonitrile **146**, isothiazolodithiine-4,5,7-tricarbonitrile **95**, 1,4-dithiine-2,3,5,6-tetracarbonitrile **93** and the novel dithiolo[4,3-*b*][1,4]thiazines **147** and **148**.[228] Mechanistic rationale for the formation of the identified products was proposed which involved the elimination of dicyanoacetylene and diatomic sulfur that were trapped with 2,3-diphenyl-1,3-butadiene and norbornene giving the cycloaddition products 4,5-diphenyl-1,2-dithiine **153** and bicyclo[2.2.1]heptane[3,4-*e*][1,4]dithiine-2,3-dicarbonitrile **155** respectively. This chemistry looks promising as a possible new route to both novel heterocyclic compounds and to new methods for the *in situ* generation of cyanoacetylene derivatives, however, it does not serve our purpose for developing high yield routes to cyanosubstituted isothiazoles since the reactions were proved to be complex giving many and unexpected products.

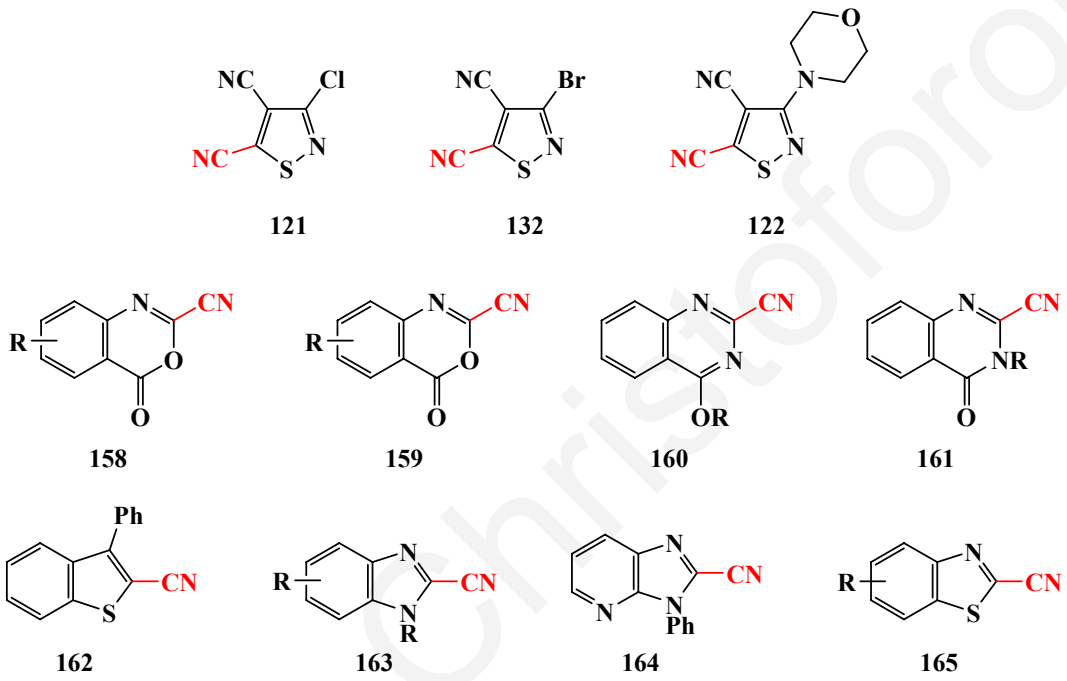
CHAPTER 3

Synthesis of Percyano Heterocycles *via* 1,2,3-Dithiazole Chemistry

Sections

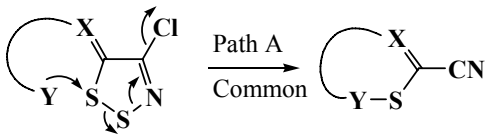
3.1 Introduction

The investigation of (1,2,3-dithiazolylidene)acetonitriles (Chapter 2) afforded unexpected results, however, one feature remained consistent. Cleavage of the 1,2,3-dithiazole ring led to a new cyano substituted heterocycle. The following cyano substituted heterocycles **121**,[196] **122**,[196] **132**[201] and **158-165**[175, 206-209, 212] have been prepared *via* ring transformation of 1,2,3-dithiazoles. The nitrile group that is formed by the cleavage of the dithiazole ring is coloured red.

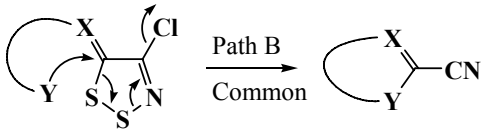


The majority of the 1,2,3-dithiazole ring transformations involve the initial preparation of a neutral dithiazole which supports a potentially nucleophilic side chain or substituent capable of attacking the electrophilic dithiazole at either S-1 (Path A) or at C-5 (Path B) with subsequent ring opening (Scheme 46).[198, 206, 207, 209-211, 229, 230] Dithiazoles, however, can also be ring opened with the use of soft thiophilic nucleophiles to afford the disulfide intermediate **166** (Path C) (Scheme 46).[228] This disulfide intermediate can be a source of both electrophilic and nucleophilic sulfur. The generation of a nucleophilic sulfur combined with a side chain bearing an electrophilic trap can lead to alternative type of ring closure.

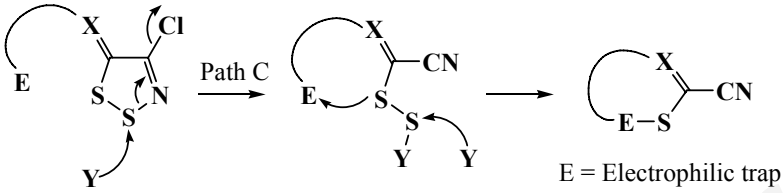
Ring Opening *via* attack on S-1.



Ring Opening *via* attack on C-5.



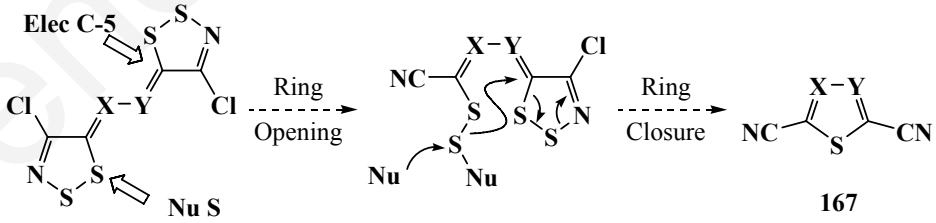
Ring Opening - Ring Closure *via* attack at S-2 with generation and entrapment of nucleophilic S-1.



166

Scheme 46

After a careful consideration of the mechanisms involving ring transformations of 1,2,3-dithiazoles it was realized that exciting new routes to a special class of percyano heterocycles were possible. If the electrophilic trap outlined in the third mechanism (Path C) could be replaced by the C-5 electrophilic carbon of a second dithiazole unit, percyano-heterocycles could be formed (Scheme 47). The double nucleophilic attack at S-2 ring sulfur of the first 1,2,3-dithiazole unit infuses nucleophilic character to the S-1 ring sulfur which can be trapped by the electrophilic C-5 ring carbon atom of the second 1,2,3-dithiazole unit affording the synthesis of percyano-heterocyclic systems of type **167**.

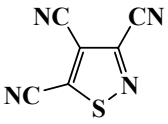


167

Scheme 47

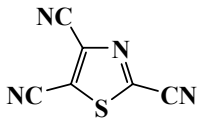
3.2 Percyanothioazoles

Percyano thio-azoles are unusual compounds. They are 6π, planar and therefore aromatic molecules which contain both S and N heteroatoms that can participate in intermolecular interactions. The nitrile groups enhance the electrophilic character of the molecule and therefore percyano thio-azoles are sensitive to nucleophilic attack. As such their synthesis is somewhat complicated by their highly elecrophilic nature which makes them susceptible to hydration and to ring opening reactions. Percyano thio–azoles **168**-**173** are a sub domain of the empirical formula $C_xN_yS_z$. Several have been previously reported and some have been shown to display important biological activities.

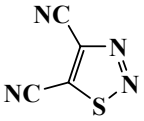


168

UNKNOWN

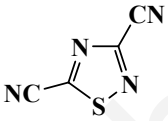


169



170

UNKNOWN



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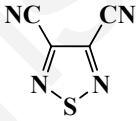
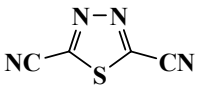


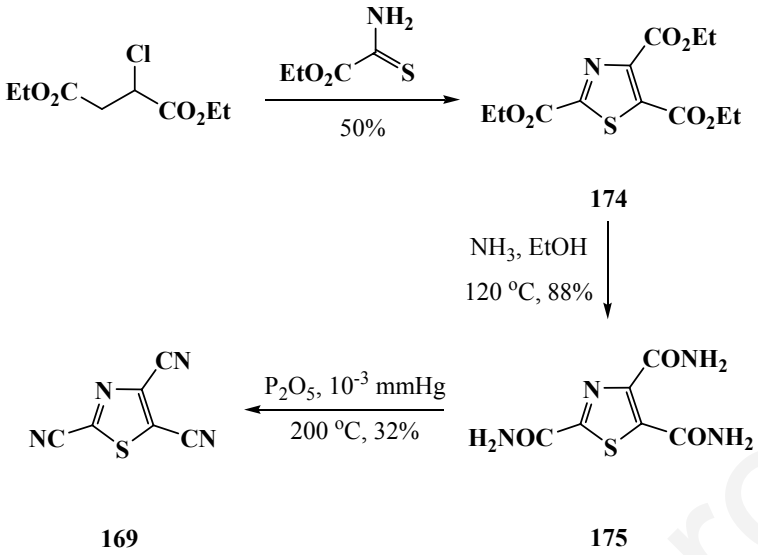
172



173

3.2.1 Isothiazoles and Thiazoles

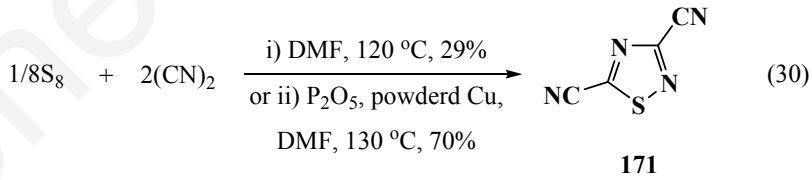
Percyanoisothiazole **168** was not reported in the literature and efforts to prepare this compound are discussed below (Chapter 4), however thiazole-2,3,4-tricarbonitrile **169** was prepared by a 3-step process. The first step was the formation of the thiazole ring from the acyclic compounds diethyl 2-chloro-3-oxosuccinate and ethyl thiooxamate which gave triethyl thiazole-2,4,5-tricarboxylate **174** in moderate yield (50%). Treatment of triethyl thiazole-2,4,5-tricarboxylate **174** with ammonia afforded thiazole-2,4,5-tricarboxamide **175** in 88% and dehydration with P_2O_5 at 200 ^oC and 10^{-3} mmHg gave percyanothiazole **169** in only 32% and an overall yield of 14% (Scheme 48).[231]



Scheme 48

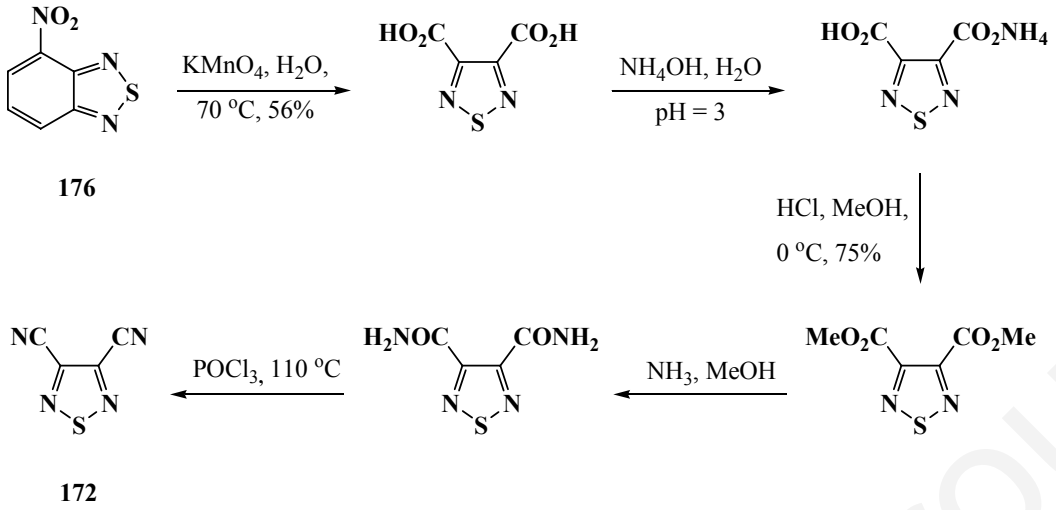
3.2.2 Thiadiazoles

1,2,3-Thiadiazole-4,5-dicarbonitrile **170** was not known. 1,2,4-Thiadiazole-3,5-dicarbonitrile **171** however was known and first synthesized in low yield (29%) from sulfur and cyanogen.[232] A year later, the same authors published an improved synthesis for 1,2,4-thiadiazole-3,5-dicarbonitrile **171**. Reaction of cyanogen, sulfur, P_2O_5 and powdered Cu in dried DMF gave the percyano-1,2,4-thiadiazole **171** in 70% yield (Equation 30).[233] Both procedures suffer from the low availability of the starting cyanogen which was not readily commercially available.



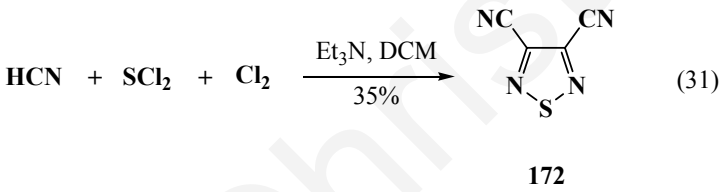
(30)

1,2,5-Thiadiazole-3,4-dicarbonitrile **172** has interesting applications as fungicide, bactericide and also as intermediate for organic syntheses; *e.g.*, of polyamides, pigments and adhesives.[234] Several methods of preparing 1,2,5-thiadiazole-3,4-dicarbonitrile **172** are available. The very first method was based on the oxidative-destruction of 4-nitro-2,1,3-benzothiadiazole **176** with $KMnO_4$ followed by conversion of the carboxylic groups to nitrile groups in a 4-step process (Scheme 49).[235]



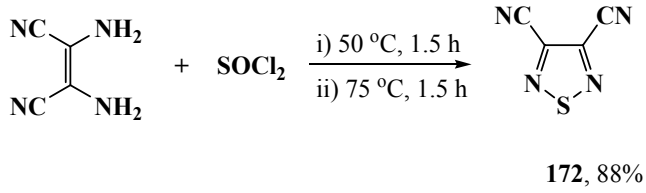
Scheme 49

A later procedure required reaction of hydrocyanic acid, Cl_2 and sulfur dichloride or sulfur (Equation 31).[236] Both procedures afford low yields and complicated separation and purification processes are required.



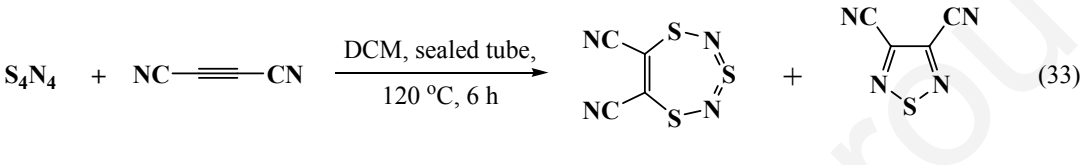
(31)

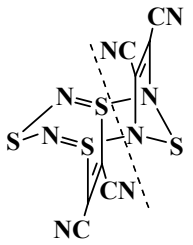
A simpler and much more efficient process was later published which involved reaction of diaminomaleonitrile with neat thionyl chloride (3 equiv.) at 50-75 °C and gave the percyano-1,2,5-thiadiazole **172** in 88% yield (Equation 32). This procedure was adopted on a commercial scale, 10.8 g of diaminomaleonitrile afforded about 12 g of percyano-1,2,5-thiadiazole **172** (88%).[234] A year later an effort to produce 1,2,5-thiadiazole-3,4-dicarbonitrile **172** on a larger scale using a slightly modified procedure led to a reduced yield. Treatment of diaminomaleonitrile (250 g) with thionyl chloride (1.1 equiv.) in MeCN using catalytic amount of Py at 0-2 °C afforded the desired percyano-1,2,5-thiadiazole **172** in only 44% yield (138.6 g).[237]



(32)

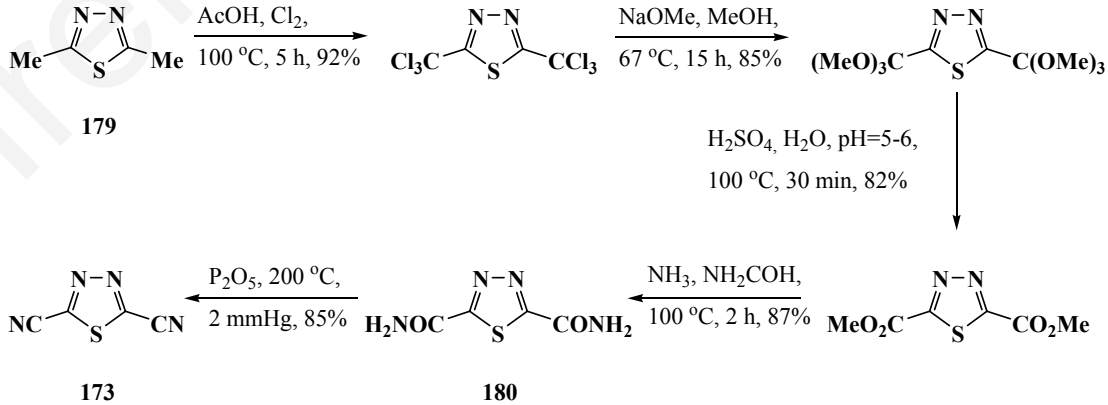
1,2,5-Thiadiazole-3,4-dicarbonitrile **172** was also isolated as a by-product in 60% yield from the reaction of dicyanoacetylene with tetrasulfur tetranitride (S_4N_4).[238, 239] The main product was the 1,3,5-trithia-2,4-diazepine-6,7-dicarbonitrile **177** which was formed in 81% yield (Equation 33). The proposed mechanism involves the formation of the 1,3-cycloadduct **178** which could be formed by cycloaddition of alkyne across the nitrogens and 1,5-cycloaddition across the sulfurs and could dissociate directly into the aromatic products **177** and **172**.





178

The last isomer, 1,3,4-thiadiazole-2,5-dicarbonitrile **173**, is an excellent fungicide for *aspergillus* and has been proposed as plant protection agent.[240] Its synthesis was achieved with a 5-step process which began with the commercially available 2,5-dimethyl-1,3,4-thiadiazole **179** (Scheme 50). The desired percyano-1,3,4-thiadiazole **173** was finally obtained in 85% yield after dehydration of 1,3,4-thiadiazole-2,5-dicarboxamide **180** with P_2O_5 at 200 °C at 2 mmHg. This well established procedure, however, was time-consuming and had a moderate overall yield (38%).

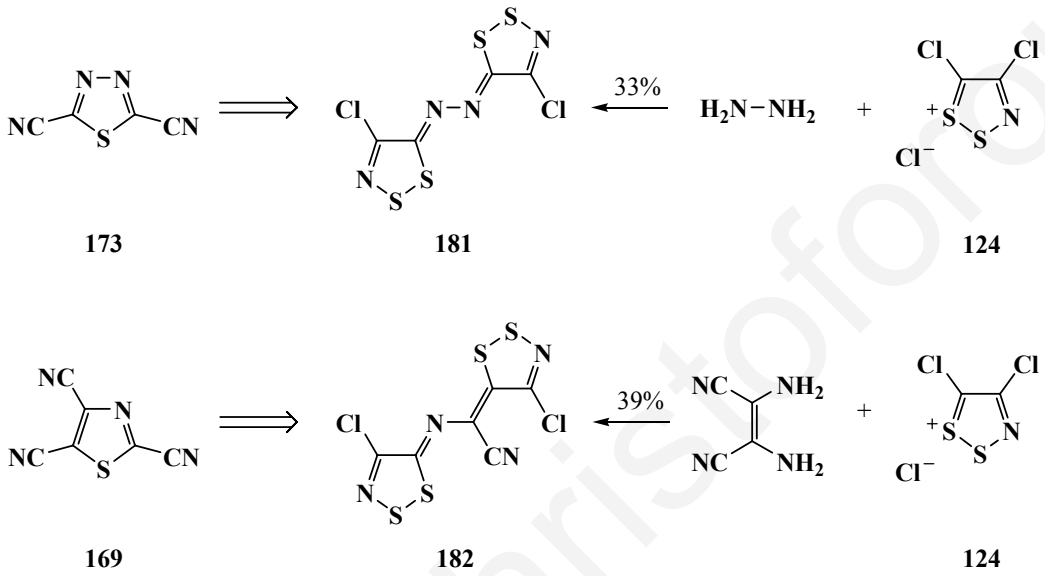


179 **173** **180**

Scheme 50

3.3 Synthesis of Percyano Heterocycles

Having in mind the ring opening-ring closing reaction mechanism (Path C) (Scheme 47) we searched the literature and found two examples of bisdithiazoles suitable for conversion into percyano-heterocyclic systems of type **167**. Bisdithiazoles **181**[241] and **182**[198] served as possible precursors for the synthesis of percyano-1,3,4-thiadiazole **173** and percyanothiazole **169** respectively (Scheme 51).



173 **181** **124**

169 **182** **124**

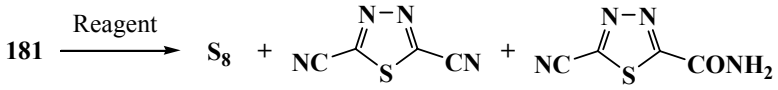
Scheme 51

3.3.1 Synthesis of Percyano-1,3,4-thiadiazole **173**

The bisdithiazole **181** was synthesized according to the literature procedure[241] and reacted with tetraalkylammonium halides. The highest obtained yield of 1,3,4-thiadiazole-2,5-dicarbonitrile **173** (79%) was from the reaction of benzyltriethyl-ammonium iodide (1 equiv.) in refluxing PhCl, under argon atmosphere (Table 5). Partial hydration of the thiadiazole **173** during chromatography led to the isolation of some 5-cyano-1,3,4-thiadiazole-2-carboxamide **183** (21%). This was confirmed by a 2D TLC study. Under an air atmosphere the percyanothiadiazole **173** was isolated after chromatography in only a moderate yield (53-55%). The use of microwave conditions gave good yields of the percyanothiadiazole **173** and reduced reaction time as expected. Good yields were also obtained with reduced amount of benzyltriethylammonium iodide (0.5-0.25 equiv.) although the reaction time increased. Lower amounts of benzyltriethylammonium iodide (0.05 equiv.) failed to drive the reaction to completion.

The use of less powerful halides, like benzyltriethylammonium chloride and bromide led to a significant increase in the reaction times (Table 5).

Table 5. Transformation of bisdithiazole **181** into 1,3,4-thiadiazoles **173** and **183**.



173 **183**

Reagent (equiv.)	Conditions	Yields (%) **173**	**183**
$BnEt_3NCl$ (1 equiv.)	Ar, PhCl, 132 °C, 14 h	67	33
$BnEt_3NBr$ (1 equiv.)	PhCl, 132 °C, 51 h	53	40
$BnEt_3NI$ (1 equiv.)	PhCl, 132 °C, 1 h	55	27
$BnEt_3NI$ (1 equiv.)	Ar, PhCl, 132 °C, 40 min	79	21
$BnEt_3NI$ (1 equiv.)	MW, PhCl, 160 °C, 250 W, 5 min[b]	72	23
$BnEt_3NI$ (0.5 equiv.)	Ar, PhCl, 132 °C, 2 h	78	19
$BnEt_3NI$ (0.25 equiv.)	Ar, PhCl, 132 °C, 6 h	76	18
$BnEt_3NI$ (0.05 equiv.)	Ar, PhCl, 132 °C, 72 h	[c]	
PPh_3-polymer bound[a] (4 equiv.)	DCM, 20 °C, 24 h	[c]	
PPh_3-polymer bound[a] (5 equiv.)	DCM, 20 °C, 24 h	[c]	
PPh_3-polymer bound[a] (6 equiv.)	DCM, 20 °C, 10 min	69	-

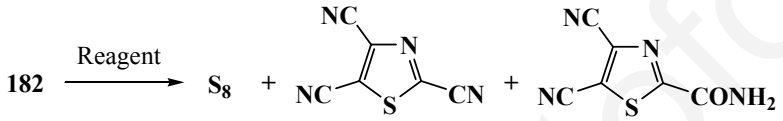
[a]PPh_3-polymer bound (3.2 mmol/g); [b]Sealed tube; [c]Incomplete reaction.

In order to avoid chromatography and consequently the hydration of percyano-thiadiazole **173** polymer bound triphenylphosphine was used as an alternative thiophilic agent. The polymer bound triphenylphosphine (6 equiv.) permitted trapping of the sulfur as polymer bound triphenylphosphine sulfide and a clean solution of the desired product **173** was obtained by a simple filtration. Evaporation of the solvent afforded the percyanothiadiazole **173** in 69% yield. Less than 6 equivalents of polymer bound triphenylphosphine failed to drive the reaction to completion (Table 5). Surprisingly, free triphenylphosphine gave incomplete reaction and only traces of the percyanothiadiazole (by TLC).

3.3.2 Synthesis of Percyanothiazole **169**

Similar reactions were conducted with the bisdithiazole **182**. With benzyltriethyl-ammonium chloride (1 equiv.) in refluxing PhCl the percyanothiazole **169** and the hydrated thiazole **184** were isolated in 70 and 15% yields respectively. Good to moderate yields of the percyanothiazole **169** were also achieved with benzyltriethylammonium bromide (0.1 to 1 equiv.) and benzyltriethylammonium iodide (1 equiv.). The use of polymer bound triphenylphosphine (5 equiv.) allowed the chromatography free isolation of the percyanothiazole **169** in 76% yield. Again free triphenylphosphine gave only traces of the percyanothiazole **169** (Table 6).

Table 6. Transformation of bisdithiazole **182** into thiazoles **169** and **184**.



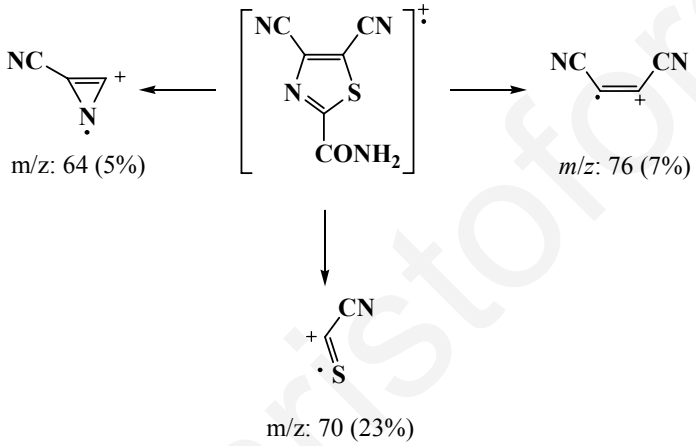
169 **184**

Reagent (equiv.)	Conditions	Yields (%) **169**	**184**
$BnEt_3NCl$ (1 equiv.)	Ar, PhCl, 132 °C, 1 h	70	15
$BnEt_3NCl$ (0.1 equiv.)	Ar, PhCl, 132 °C, 48 h	[b]	
$BnEt_3NBr$ (1 equiv.)	Ar, PhCl, 132 °C, 5 min	63	11
$BnEt_3NBr$ (0.5 equiv.)	Ar, PhCl, 132 °C, 15 min	68	20
$BnEt_3NBr$ (0.1 equiv.)	Ar, PhCl, 132 °C, 4 h 50 min	63	17
$BnEt_3NI$ (1 equiv.)	Ar, PhCl, 132 °C, 35 min	56	14
$BnEt_3NI$ (0.1 equiv.)	Ar, PhCl, 132 °C, 48 h	[b]	
PPh_3-polymer bound[a] (4 equiv.)	DCM, 20 °C, 24 h	[b]	
PPh_3-polymer bound[a] (5 equiv.)	DCM, 20 °C, 4 h	76	-

[a]PPh_3-polymer bound (3.2 mmol/g); [b]Incomplete reaction.

4,5-Dicyanothiazole-2-carboxamide **184** has not been previously reported in the literature. The position of the carboxamide substituent was tentatively determined by mass spectroscopy (Scheme 52). The LRMS-EI spectrum gave two characteristic peaks which correspond to the loss of the SCC≡N (108 Da, 27%) and N=CCN fragments (126, 4%), and also five peaks which correspond to the fragments NCC=CCN (76, 7%), $N{=}CCONH_2$ or SCC≡N (70, 23%), NC=CCN (64, 5%) and C=CC≡N (50, 4%). The fragments NCC=CCN (76, 7%) and NC=CCN (64, 5%) supported the formation of

4,5-dicyanothiazole-2-carboxamide **184**. This tentative conclusion was also supported by the electron distribution around the thiazole ring. An analysis, based on the donor-acceptor concept concerning the general reactivity of the thiazole ring, shows that the C-2 position is relatively electron-deficient while the C-5 position is electron-rich and the C-4 position is neutral.[242, 243] As such, the reactivity of the substituents linked to carbon atoms of the thiazole ring depends on their position on the heterocyclic nucleus. The nitrile group that is linked to the C-2 carbon atom, the most electron deficient carbon, was therefore expected to hydrate preferentially.



Scheme 52

3.4 Summary

Our methods for synthesizing 1,3,4-thiadiazole-2,5-dicarbonitrile **173** and thiazole-2,4,5-tricarbonitrile **169** using polymer bound triphenylphosphine was superior compared with the existing procedures.[228, 231, 240] Both literature syntheses were multi-step processes (3 to 5 steps) with low overall yields. Furthermore both procedures required low pressures and high temperatures (200 ^{o}C) at the last synthetic step which made the processes inconvenient. The syntheses described above are very practical and simple, affording the desired products in high yields while avoiding chromatography. Proper optimizations on the syntheses of starting bisdithiazoles **181** and **182** could make the bisdithiazole routes very attractive.

CHAPTER 4

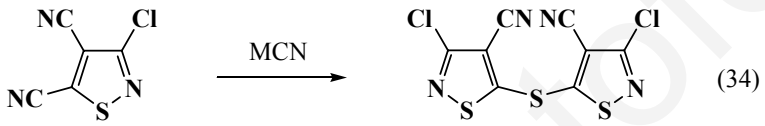
New Regiospecific Isothiazole C-C Cross Coupling Chemistry at the C-5 Position

Sections

4.1 Introduction

The successful synthesis of percyano-1,3,4-thiadiazole **173** and thiazole **169** from carefully selected 1,2,3-dithiazoles (Chapter 3, Sections 3.3.1 and 3.3.2) combined with the availability of 3-haloisothiazole-4,5-dicarbonitriles **121** (halo = Cl) and **132** (halo = Br)[196, 201] (Chapter 1, Section 1.2.5.2.5) initiated an investigation into the preparation of the unreported percyanoisothiazole.

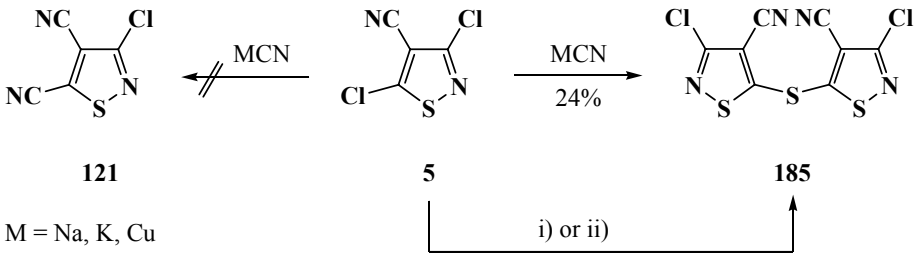
Since the displacement of halides by cyanide are well reported,[244] this appeared to be a good synthetic strategy, however, efforts to introduce a nitrile group at the C-3 position of 3-chloroisothiazole-4,5-dicarbonitrile **121** led only to the isolation of 5,5'-thiobis(3-chloroisothiazole-4-carbonitrile) **185** which indicated cleavage of the isothiazole ring (Equation 34).



(34)

121 **185**

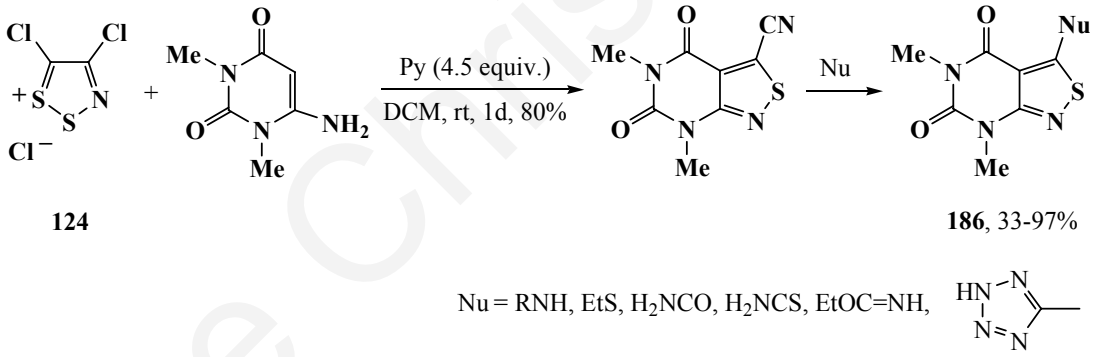
Interestingly an early attempt to prepare 3-chloroisothiazole-4,5-dicarbonitrile **121** from 3,5-dichloroisothiazole-4-carbonitrile **5** using CuCN at 160-250 ^{o}C also gave 5,5'-thiobis(3-chloroisothiazole-4-carbonitrile) **185** in 24% yield together with unreacted 3,5-dichloroisothiazole-4-carbonitrile **5** (48%) (Scheme 53).[213] Presumably cyanide, which is a known thiophile,[245-248] 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 **185**. An independent synthesis of 5,5'-thiobis(3-chloroisothiazole-4-carbonitrile) **185** was subsequently carried out *via* the reaction of 3,5-dichloroisothiazole-4-carbonitrile **5** with MSCN (M = Na, K, Cu) or with Na_2S.[60, 213]



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 53

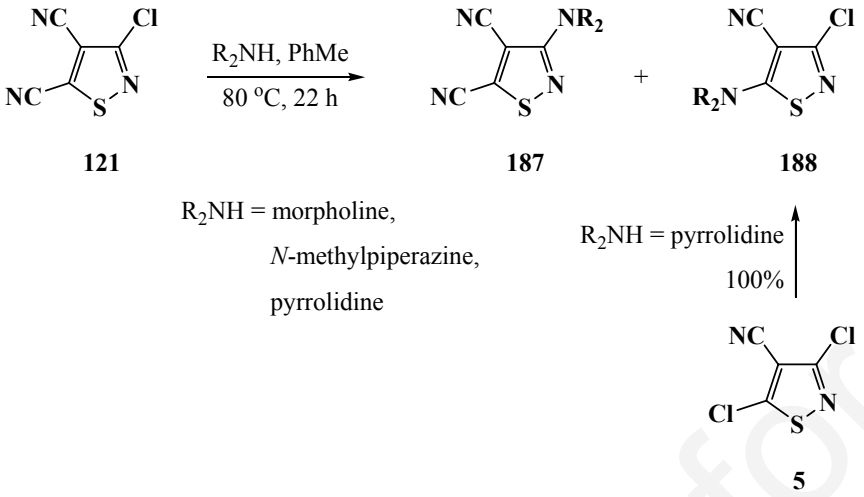
The competitive displacement of the 5-cyano *vs* the 3-chloro substituent was at first surprising, however, nucleophilic displacement of cyanide was not unknown.[249-265] In particular the synthesis of new 3-substituted isothiazolo[3,4-*d*]pyrimidine-1,3-dialkyl-uracils **186** by nucleophilic displacement of cyanide (Scheme 54) showed that the C-5 cyano substituent of isothiazoles was indeed quite labile.[266]



Scheme 54

In order to shed light on this, 3-chloroisothiazole-4,5-dicarbonitrile **121** was treated with a series of cyclic secondary amines. Nucleophilic reactions on the dicyano 3-chloroisothiazole **121** with the secondary amines morpholine and *N*-methylpiperazine resulted in the formation of 3-alkylaminoisothiazole-4,5-dicarbonitriles **187** and 5-alkyl-amino-3-chloroisothiazole-4-carbonitriles **188**. In contrast, the reaction with pyrrolidine gave only traces of the dicyano 3-alkylaminoisothiazole **187** (R_2N = pyrrolidinyl) and the 5-alkylamino-3-chloroisothiazole-4-carbonitrile **188** (R_2N = pyrrolidinyl) was the main product (Scheme 55).[267] 5-Alkylamino-3-chloroisothiazole-4-carbonitrile **188** (R_2N =

pyrrolidinyl) could be synthesized alternatively in quantitative yield by regioselective displacement of the C-5 chloro substituent using pyrrolidine.[267]



Scheme 55

The surprizing nucleophilic displacement of the C-5 nitrile group can be partially explained since it is activated by the ring nitrogen and by the C-4 nitrile group. The difference in the reactivity of the three alkylamines could be explained by considering the pK_a values and the bond angles. The relative basicity followed the order pyrrolidine > *N*-methylpiperazine > morpholine which suggested that there was a significant inductive effect due to the presence of the second heteroatom in *N*-methylpiperazine and morpholine. The second heteroatom reduced the availability of the nitrogen lone pairs and thereby lowered the nucleophilicity of the alkylamines. The C-N-C bond angles are smallest in pyrrolidine, compared to that of 6-membered ring alkylamines, which results in pyrrolidine being the stronger nucleophile and hence the most reactive of the three nucleophiles, with morpholine being the least reactive. Pyrrolidine as the strongest nucleophile can displace the nitrile group at C-5 more effectively which led to the formation of 5-alkylamino-3-chloroisothiazole-4-carbonitrile **188** (R_2N = pyrrolidinyl) as the main product. This result was also in agreement with the reactivity of isothiazole carbon positions towards nucleophilic addition (see below).

In general the reactivity of isothiazoles towards nucleophilic attack follows the order C-5 ~ S > C-4 > C-3 and this was tentatively supported by the resonance structures of the intermediates (Scheme 56).

Nucleophilic addition at C-3 Nucleophilic addition at C-4 Nucleophilic addition at C-5

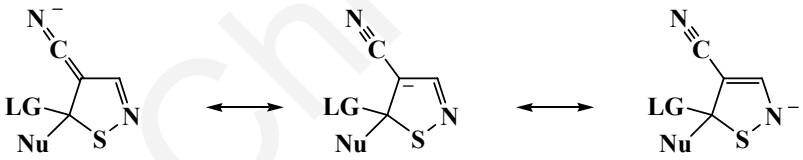
LG = Leaving Group

Nu = Nucleophile

Scheme 56

In the absence of strongly thiophilic reagents, nucleophilic addition at C-5 is stabilized by two resonance structures. The C-4 position is more susceptible to nucleophilic attack than the C-3 since any build up of negative charge at C-5 is strongly stabilized by the polarisable sulfur atom. In the case of the 4-carbonitriles an enhanced reactivity at C-5 was observed possibly because of the additional stabilization provided by a third resonance structure involving the nitrile (Scheme 57).

Nucleophilic addition at C-5

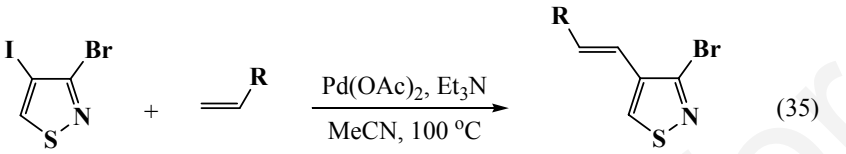


Scheme 57

Taking the above into consideration it was no longer a surprize to find that high regioselective nucleophilic displacement could be achieved on treating 3,5-dichloro-isothiazole-4-carbonitrile **5** with a variety of nucleophiles.[54] The high regioselectivity displayed with 3,5-dichloroisothiazole-4-carbonitrile **5** towards nucleophilic displacement and the body of evidence supporting a correlation between nucleophilic aromatic displacement and Pd catalysed C-C coupling reactions[268] suggested the 3,5-dichloro-isothiazole **5** was potentially a useful building block for other isothiazole systems.

4.2 Isothiazole C-C Cross Coupling Reactions

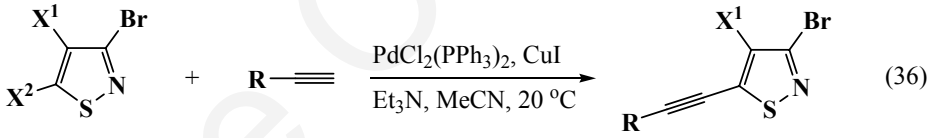
Although there are many examples of C-C coupling reactions on the thiazole ring[269, 270] only few publications referred to coupling reactions on the isothiazole ring. Tribromo-isothiazole **190** failed to give a regioselective Heck coupling reaction at C-5 due to protodebromination of the starting isothiazole to 3,4-dibromoisothiazole. A successful Heck reaction was eventually achieved at the C-4 position of 3-bromo-4-iodoisothiazole **189** in low to moderate yields using $Pd(OAc)_2$-Et_3N in refluxing MeCN (Equation 35).[44]



189 (35)

R = CO_2Me, 29%; R = Ph, 60%
R = CN, 33%; R = CH_2OH, 13%

Protodehalogenation was also observed when Sonogashira reactions were performed on tribromoisothiazole **190**, 3,4-dibromo-5-iodoisothiazole **191** and 3-bromo-4,5-diiodo-isothiazole **192** which afforded the analogous 5-alkynylisothiazoles in low to moderate yields (Equation 36).



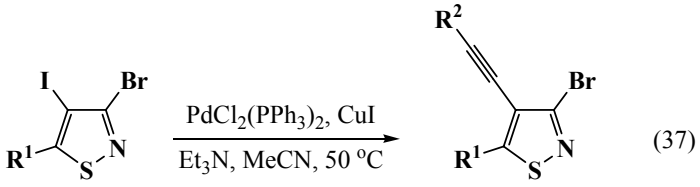
(36)

190, $X^1 = X^2 = Br$

191, $X^1 = Br$, $X^2 = I$
192, $X^1 = X^2 = I$

X^1 = Br, R = Ph, *n*-Hexyl, CH_2OH, CH_2OCH_3, 20-56%
X^1 = Br, R = Ph, 45%
X^1 = I, R = Ph, CH_2OCH_3, 35-58%

Displacement of halogen at the C-4 position with acetylenic components was possible only with the 4-iodo-substituted starting isothiazoles **193** and **194**.[45] Both Heck and Sonogashira couplings suffered not only from protodehalogenation of the starting isothiazole but also from their low availability (Equation 37).

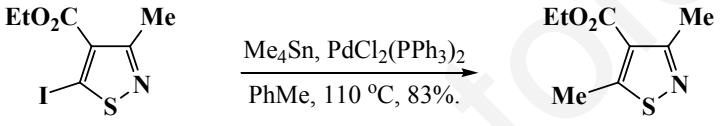


(37)

193, R^1 = C≡CPh — R^1 = C≡CPh, R^2 = CH_2OCH_3, 42%

194, R^1 = H — R^1 = H, R^2 = Ph, 49%

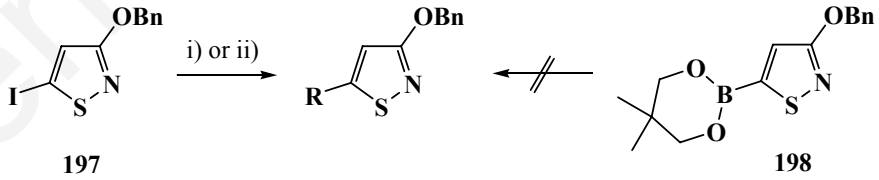
One example of the Stille reaction was also reported. Introduction of a methyl group at C-5 position of isothiazole **195** was achieved in 83% yield with Me_4Sn in the presence of $PdCl_2(PPh_3)_2$ (Equation 38). The dimethylisothiazole **196** was used for the synthesis of a highly active HIV protease inhibitor.[46]



(38)

195 **196**

Phenyl and several heteroaryl rings where introduced at the C-5 position of the 5-iodoisothiazole **197** using standard Suzuki or Negishi cross-coupling reaction conditions (Scheme 58).[47] The isothiazole substituted boronic ester **198** was also synthesized in 89% yield, however, no successful coupling reactions were obtained due to the instability of the boronate **198** in certain solvents.

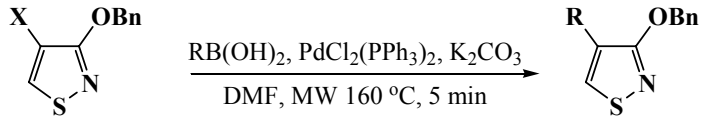


197 **198**

Reagents and conditions: i) $RB(OH)_2$ (R = Ph, 2-thienyl, 3-thienyl, 2-furyl, 2-pyridyl, 3-pyridyl, 4-pyridyl), $PdCl_2(PPh_3)_2$, DME, H_2O, rt, 71-94%; ii) RZnCl (R = Ph, 2-thienyl, 2-pyridyl), $PdCl_2(PPh_3)_2$, THF, DMF, 48-95%.

Scheme 58

The related Suzuki couplings at the C-4 position of 4-halo-3-benzyloxyisothiazoles **199** (X = Br) and **200** (X = I) have also been reported (Equation 39).[48] Both isothiazoles **201** and **202** were used for the synthesis of glutamate receptor ligands.



(39)

199, X = Br
200, X = I

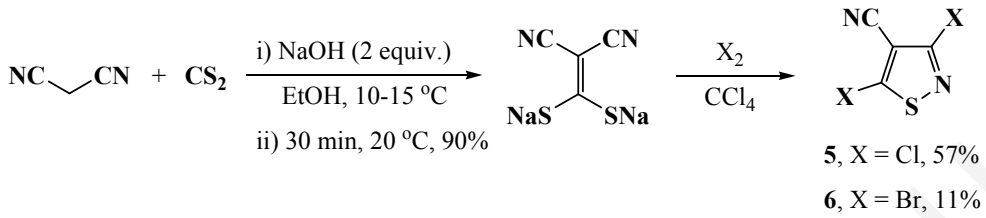
201, R = Me, 32% from **199**
202, R = Ph, 94% from **200**

This rather limited literature encouraged us to attempt regiospecific coupling reactions on the isothiazole ring. Interestingly at the time we began our study on the coupling reactions of isothiazoles only the work of Zlotin (Equations 35-37)[44, 45] had been reported. Furthermore most of the above isothiazole coupling chemistry required isothiazoles that were either not readily available or were target specific molecules. A general (non-product specific) procedure for isothiazole C-C coupling chemistry had yet to be reported. Furthermore the three electronically different isothiazole positions offered the possibility for regiospecific/regiocontrolled coupling reactions. Finally, since Pd catalysed C-C coupling methods for cyanations are well known,[271-275] the development of successful regioselective C-C coupling reactions on isothiazole ring could also help in the synthesis of the desired but as yet unknown percyanoisothiazole **168**.

4.2.1 Synthesis of 3,5-Dihaloisothiazole-4-carbonitriles

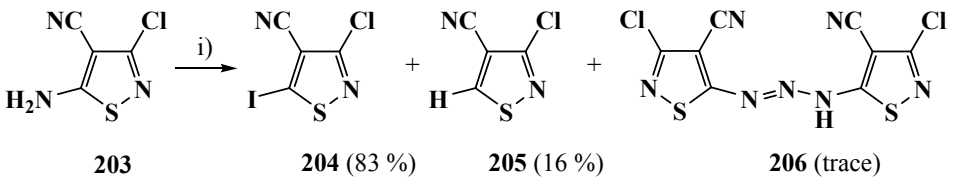
A recent series of articles have described the broad antiviral activity of 5-aryl-3-methylthioisothiazole-4-carbonitrile derivatives.[276-279] These isothiazoles were prepared by cyclization of arylmethylene-malononitriles with disulfur dichloride and Py to afford the 5-aryl-3-chloroisothiazole-4-carbonitriles.[69, 276] These were then converted into the 3-methylthio derivatives by treatment with sodium sulfide followed by iodomethane or alternatively by treating aryl thioesters with malononitrile followed by heating with elemental sulfur and treatment with iodomethane.[276] Both routes required the preparation of product specific intermediates. This could be overcome by starting from an appropriate halogenated isothiazole combined with modern aryl–aryl C–C bond forming techniques.[280] 3,5-Dihaloisothiazole-4-carbonitriles are possible alternative synthetic precursors to 5-aryl-3-haloisothiazole-4-carbonitriles. 3,5-Dichloroisothiazole-4-carbo-

nitrile **5** and 3,5-dibromoisothiazole-4-carbonitrile **6** were readily available by condensation of malononitrile and carbon disulfide, followed by halogenation (Scheme 59, see also Scheme 6).[54]



Scheme 59

Several 5-iodoisothiazoles were known and have been prepared from isothiazoles not substituted at C-5 using both butyllithium and I_2[24] or periodic acid and I_2,[25] or by nucleophilic displacement of 5-bromoisothiazoles[26] or 5-hydrazinoisothiazoles[27] using NaI. Sandmeyer iodination of the readily available 5-amino-3-chloroisothiazole-4-carbonitrile **203**[7] was not, however, reported. Diazotization[28] of 3-, 4- and 5-amino-isothiazoles has been reported using nitrosyl tetrafluoroborate in a 1:1 mixture of acetic and propionic acids or by treating the amine with sodium nitrite and concentrated acids.[29] Sandmeyer iodination has also been achieved for 4-aminoisothiazoles using standard diazotization conditions.[30] The successful Sandmeyer iodination of 3-amino-5-phenyl-isothiazole-4-carbonitrile **251** using isoamylnitrite in I_2 saturated MeCN (Chapter 5, Section 5.2) was modified to achieve Sandmeyer iodination at C-5. Treatment of an I_2 saturated MeCN solution of the 5-aminoisothiazole **203** with isoamylnitrite at *ca.* 20 °C gave the 3-chloro-5-iodoisothiazole-4-carbonitrile **204** (55%) together with a trace of 3-chloroisothiazole-4-carbonitrile **205** and the triazene **206** (42%). The yield of the 5-iodoisothiazole **204** was significantly improved when the reaction was conducted at higher temperatures in either refluxing MeCN (*ca.* 80 °C, 79% yield) or in refluxing nitromethane (*ca.* 100 °C, 83% yield) (Equation 40).



(40)

Reagents and conditions: i) I_2 (3 equiv.), $MeNO_2$, isoamylONO (4 equiv.), 120 °C, 1 h.

Activation of the 5-halogen by the 4-cyano substituent and the ring nitrogen results in their enhanced activity. Thus a regioselective C-C coupling strategy was considered as an alternative route to the 5-arylisothiazoles.

4.2.2 Suzuki Coupling Reactions at C-5

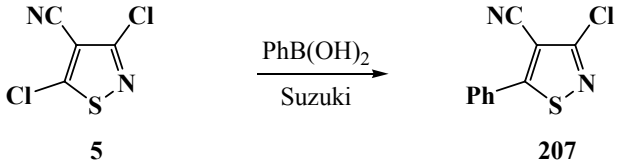
Initial attempts at Suzuki coupling of phenylboronic acid and 3,5-dichloroisothiazole-4-carbonitrile **5** in biphasic mixtures of water and hydrocarbon solvents could not readily be driven to completion without significant reduction in the product yields to 60–70%. A variety of bases and several solvent systems were screened without overcoming this problem; nevertheless the reaction was qualitatively shown to proceed faster as the base strength and cation size increased for $NaHCO_3$, M_2CO_3 (M = Na or K), and MOH, (M = Li, Na and K). Similar observations have appeared elsewhere and the effect has been attributed to faster transmetallation rates.[281-283] It is possible that reaction pathways such as protodeboronation, hydrolytic deboronation and homocoupling of the boronic acid to give biphenyl (observed by TLC) were competing with the desired coupling. Fluoride ion has been used to replace traditional bases in such situations and can enhance the nucleophilicity of the boronic acid by increasing the valence of the boron atom,[282, 284-286] making the rate of Suzuki coupling more competitive. The use of KF in a biphasic system gave only marginally better reaction rates and yields.

A report of anhydrous conditions in a case of a difficult cross-coupling[287] prompted the use of non-aqueous conditions. The use of $Pd(OAc)_2$, 18-crown-6, and vacuum oven-dried KF in dry PhMe gave near quantitative conversions of the dichloroisothiazole **5** into 3-chloro-5-phenylisothiazole-4-carbonitrile **207**. Replacing KF by anhydrous K_2CO_3 (3.5 equiv.) resulted in a longer reaction time (16 h) and lower yield (81%), and combinations of KF and K_2CO_3 were also less effective than neat KF.

The reaction was initially optimized with respect to phenylboronic acid, KF and temperature (Table 7). The reactions, which were performed in air (protected by calcium chloride drying tubes), progressed faster at higher temperatures and required at least 1.5 equivalents of phenylboronic acid. The reaction times improved significantly with three or more equivalents of dry KF, although no significant advantage was gained by use of more than three equivalents. Interestingly the progress of the reaction was sensitive to the timing of the applied heating. Placing the reaction mixture into a preheated oil bath at 140 ^{o}C resulted in increased biphenyl production (TLC) and when only 1.5 equivalents of

phenylboronic acid were present this led to incomplete consumption of isothiazole **5**. Presumably the rate of phenylboronic acid homocoupling increases with temperature and becomes competitive.

Table 7. Reaction of 3,5-dichloroisothiazole-4-carbonitrile **5** (0.3 mmol) with $PhB(OH)_2$, KF, 18-crown-6 (0.5 equiv.) and $Pd(OAc)_2$ (5 mol%).



5 **207**

$PhB(OH)_2$ (equiv.)	KF (equiv.)	Solvent	Temp.[a] (^oC)	Time (h)	Yield **207** (%)
1.5	2	PhMe	20-140	12	[c]
1.5	3	PhMe	20-140	3	93
1.5	4	PhMe	20-140	3	95
2	3.5	PhH	20-110	26	91
2	3.5	PhMe	20-140	3	97
2	3.5	PhMe	140[b]	3	95
1.5	3.5	PhMe	20-140	3	96
1.5	3.5	PhMe	140[b]	12	[c]
1.3	3.5	PhMe	20-140	3	79
1.1	3.5	PhMe	20-140	24	72

[a]Oil bath temperature; [b]Preheated to 140 ^{o}C; [c]Incomplete reaction.

Next the choice of phase transfer catalyst was examined (Table 8). 18-Crown-6 was preferred since various tetraalkylammonium salts gave either lower yields or required longer reaction times. Reducing the amount of 18-crown-6 gave slower reactions but had little effect on the product yield. The use of crown ethers in Suzuki reactions was not common,[283] but palladium-catalysed aminations of aryl halides[288-291] and Ullmann type couplings[291] have been performed in good yields with crown ethers.

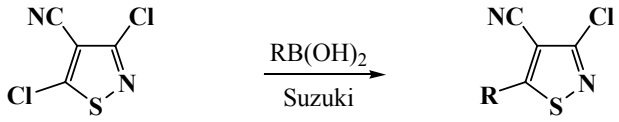
Table 8. Reaction of 3,5-dichloroisothiazole-4-carbonitrile **5** (0.3 mmol) with $PhB(OH)_2$ (1.5 equiv.), KF (3.5 equiv.), $Pd(OAc)_2$ (5 mol%) and various PTC in PhMe reflux.

PTC	PTC (equiv.)	Time (h)	Yield **207** (%)
$Bn(Et)_3NCl$	0.5	33	69
Et_4NBr	0.5	24	60
$CH_3(CH_2)_{15}N(CH_3)_3Br$	0.5	48	70
$Bn(Et)_3NI$	0.5	8	75
Adogen 464®	1.0	24	[a]
Adogen 464®	0.5	14	86
Adogen 464®	0.25	30	97
Adogen 464®	0.15	27	96
18-Crown-6	0.5	3	96
18-Crown-6	0.25	4.5	90
18-Crown-6	0.15	7	96
18-Crown-6	0.1	9	95
18-Crown-6	0.05	24	[a]

[a]Incomplete reaction.

Finally a series of commercially available palladium catalysts were compared against $Pd(OAc)_2$. $Pd(PPh_3)_4$ and $(Ph_3P)_2PdCl_2$ gave significantly slower rates of reaction (by TLC) whilst $(PhCN)_2PdCl_2$, $(CH_3CN)_2PdCl_2$, $(dba)_3Pd_2$, and $(dppf)PdCl_2.CH_2Cl_2$ gave significantly better initial activity than $Pd(OAc)_2$, however, with the latter, traces of unreacted isothiazole **5** remained even after prolonged reaction times. For these catalysts the following conditions were investigated; increasing the catalyst loading from 5 to 10 mol%, degassing the reactions and performing them under argon atmosphere, varying the reaction temperatures and rate of applied heating; increasing the quantity of phenylboronic acid from 1.5 to 2 equivalents, however, these efforts did not give complete consumption of the starting isothiazole. Having optimized the reaction conditions for the phenylboronic acid coupling a variety of boronic acids were investigated (Table 9).

Table 9. Reaction of 3,5-dichloroisothiazole-4-carbonitrile **5** (0.3 mmol) with $PhB(OH)_2$ (2 equiv.), KF (3.5 equiv.), 18-crown-6 (0.5 equiv.) and $Pd(OAc)_2$ (5 mol%).



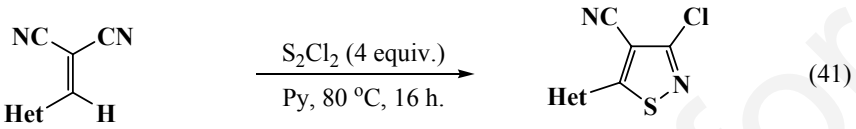
5 **207 - 220**

R	Solvent	Temp. (°C)	Time (h)	Yields (%)
Ph	PhH	80	26	**207** (91)
Ph	PhMe	110	3	**207** (97)
2-MeC_6H_4	PhMe	110	1	**208** (95)
3-MeC_6H_4	PhMe	110	1.5	**209** (99)
2-$MeOC_6H_4$	PhMe	110	1.5	**210** (89)
3-$MeOC_6H_4$	PhMe	110	1.5	**211** (96)
4-$MeOC_6H_4$	PhMe	110	1	**212** (80)
4-$MeOC_6H_4$	PhH	80	2	**212** (95)
2-ClC_6H_4	PhMe	110	77[a]	**213** (89)
3-ClC_6H_4	PhMe	110	74[b]	**214** (91)
4-ClC_6H_4	PhMe	110	4	**215** (97)
3-$NO_2C_6H_4$	PhMe	110	30[c]	**216** (43)
4-Vinylphenyl	PhMe	110	24	**217** (30[d])
2-Thienyl	PhMe	110	24	**218** ([e])
3-Thienyl	PhMe	110	3	**219** (93)
3-Thienyl	PhH	80	24	**219** (93)
Me	PhMe	110	21.5	**220** (67)

[a]Extra 2-$ClC_6H_4B(OH)_2$ (0.7 equiv.) and $Pd(OAc)_2$ (3 mol%); [b]Extra 3-$ClC_6H_4B(OH)_2$ (0.7 equiv.) and $Pd(OAc)_2$ (3 mol%); [c]Extra KF (2 equiv.), 3-$NO_2C_6H_4B(OH)_2$ (0.7 equiv.) and $Pd(OAc)_2$ (5 mol%); [d]Low yield due to unidentified co-running by-product which required repeated fractional recrystallization to separate; [e]Compound **5** was not consumed.

Generally electron rich boronic acids led to faster reactions and substituents in the *ortho* positions had little steric influence on the reaction. Electron poor boronic acids gave lower yields or required further addition of reagents to drive the reaction to completion. While 3-thienylboronic acid reacted in high yield the 2-thienylboronic acid reaction showed no consumption of the starting isothiazole **5**. The poor reactivity of

2-thienylboronic acid compared to that of 3-thienylboronic acid could arise from a more ready protodeboronation of 2-thienylboronic acid.[292-294] Similar problems have been solved by the use of anhydrous conditions.[282, 287] Rigorous drying of the reagents and employing anhydrous reaction conditions under an argon atmosphere failed to give the desired Suzuki coupling with 2-thienylboronic acid, however. The 2- and 3-thienyl derivatives **218** and **219** were prepared independently from the corresponding thienyl-methylenemalononitriles **221** and **222** on treatment with disulfur dichloride and Py in *ca.* 30% yields (Equation 41).

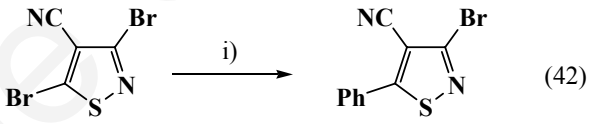


(41)

221, Het = 2-Thienyl
222, Het = 3-Thienyl

218, 29%
219, 30%

Successful Suzuki coupling was also achieved regiospecifically at C-5 with 3,5-dibromoisothiazole-4-carbonitrile **6** to afford 3-bromo-5-phenylisothiazole-4-carbo-nitrile **223** in almost quantitative yield (Equation 42). Aryl bromides are more reactive than aryl chlorides in Suzuki couplings and the reaction of phenylboronic acid with dibromoisothiazole **6** reached completion slightly faster than with dichloroisothiazole **5**.



(42)

6

223, 97%

Reagents and conditions: i) $PhB(OH)_2$ (2 equiv.), KF (3.5 equiv.) 18-crown-6 (0.5 equiv.), $Pd(OAc)_2$ (5 mol%), PhMe, 110 °C, 2 h.

4.2.3 Reactions with Organotrifluoroborates

For comparison, the above Suzuki couplings were reinvestigated using the readily available and air stable organotrifluoroborates[295] which have recently found use in several such couplings.[296-302] The reaction of 3,5-dichloroisothiazole-4-carbonitrile **5** with organotrifluoroborate was optimized in the open atmosphere with respect to potassium phenyltrifluoroborate (1.5 equiv.), 18-crown-6 (0.5 equiv.), $Pd(OAc)_2$ (5 mol%) in refluxing solvents in the presence of various bases (1 equiv.) such as K_3PO_4, $KHCO_3$, K_2CO_3, KOH and KF. The reaction proceeded to completion rapidly and in high yield with K_2CO_3 (2 h) and somewhat less rapidly with $KHCO_3$. The use of KF or K_3PO_4 failed to drive the reaction to completion after 12 h and no consumption of isothiazole **5** was observed with KOH. Increasing the quantity of base to 1.5 equivalents gave no additional benefit, but with less than 1 equivalent of base over 24 h was required for the reaction to reach completion (Table 10). The reaction required at least 1.5 equivalents of phenyltrifluoroborate and traces of biphenyl were observed by TLC. Interestingly the coupling with trifluoroborates was reported to require water as co-solvent,[297, 298] however under the above conditions the reaction between 3,5-dichloroisothiazole-4-carbonitrile **5** and phenyltrifluoroborate proceeded to completion in high yield as rapidly in anhydrous PhMe as in undried PhMe. The presence of additional water (PhMe : H_2O = 4 : 1 or 20 : 1) significantly delayed the reaction from reaching completion. Higher temperatures (refluxing xylene) marginally improved reaction times but gave considerably reduced yields. Silver(I) oxide is known to be a beneficial additive, in particular for alkylboronic acid Suzuki couplings;[303, 304] however, in our reactions added Ag_2O led to an increase in the biphenyl production (TLC) and was not investigated further.

Table 10. Reaction of 3,5-dichloroisothiazole-4-carbonitrile **5** (0.3 mmol) with $PhBF_3K$ (1.5 equiv.), K_2CO_3, 18-crown-6 (0.5 equiv.) and $Pd(OAc)_2$ (5 mol%).

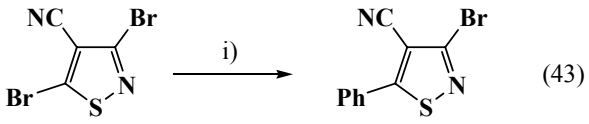
Solvent[a]	K_2CO_3 (equiv.)	Temp. (^oC)	Time (h)	Yield **207** (%)
PhH	1.5	80	12	[c]
PhMe	0	110	12	[c]
PhMe	1	110	2	99
PhMe[b]	1	110	2	93
PhMe	1.5	110	2	96
PhMe-H_2O (4 :1)	1.5	110	12	[c]
PhMe-H_2O (20 :1)	1.5	110	12	[c]
Xylene	1.5	140	2	57

[a]Reactions performed in open air atmosphere with undried solvents; [b]Anhydrous toluene and argon atmosphere; [c]Incomplete reactions.

Phenylboronic acid and KF are proposed to yield phenyltrifluoroborate[284, 305] but had the borate been the only active species in the transmetallation step then the reaction with phenyltrifluoroborate should have proceeded rapidly even in the absence of base, which was not the case. It has been proposed[297, 298, 300, 302, 306] that the intermediate boronates $PhBF(OH)_2^-$ and $PhBF_2(OH)^-$, which are formed in the presence of trace amounts of water and base, could be involved in the transmetallation step.

The above studies with anhydrous PhMe show the reactions proceed to completion in comparable times and the participation of trifluoroborate is possible, although the presence and effect of trace amounts of water cannot be excluded.

Potassium phenyltrifluoroborate coupling proceeded successfully with 3,5-di-bromoisothiazole-4-carbonitrile **6** to afford 3-bromo-5-phenylisothiazole-4-carbonitrile **223** in almost quantitative yield (Equation 43). Contrary to expectations, the potassium phenyltrifluoroborate reaction proceeded significantly slower with dibromoisothiazole **6** than with the dichloroisothiazole **5**. The possibility that bromide anions were interfering was considered and a series of experiments were conducted with both isothiazoles in the presence of 1 equivalent of oven dried KCl or KBr. The dichloroisothiazole reaction times were not significantly affected by the addition of either KCl or KBr and reactions were complete in approximately 3.5 h. However, the dibromoisothiazole reactions were affected; addition of KBr inhibited the reaction from reaching completion within 12 h, whilst addition of KCl resulted in a shortened reaction time of 6 h.



(43)

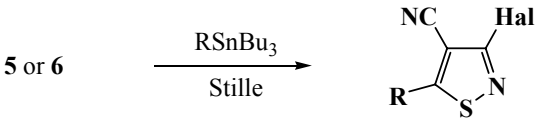
6 **223**, 99%

Reagents and conditions: i) $PhBF_3K$ (1.5 equiv.), K_2CO_3 (1-1.5 equiv.) 18-crown-6 (0.5 equiv.), $Pd(OAc)_2$ (5 mol%), PhMe, 110 ^oC, 18 h.

4.2.4 Stille Coupling Reactions at C-5

The successful results on the Suzuki reactions encouraged us to attempt other types of coupling reactions. Initial attempts at Stille coupling of 3,5-dichloroisothiazole-4-carbonitrile **5** and tributylphenyltin (following similar reaction conditions to the above optimised Suzuki reaction) in PhMe could not be driven to completion and most of the starting isothiazole was recovered. The use of more polar solvent such as THF or MeCN at reflux improved the product ratio (by TLC) but even with excess organotin reagent complete consumption of the starting isothiazole was not achieved. Complete consumption of the starting isothiazole however, was possible with the use of tributylphenyltin (1 equiv.) in DMF at 100 ^oC for 72 h and gave 3-chloro-5-phenyl-isothiazole-4-carbonitrile **207** in moderate yield (68%). The use of excess tributyl-phenyltin (2 equiv.) under the same conditions gave a shorter reaction time (23 h) and an improved yield (84%). 3,5-Dibromoisothiazole-4-carbonitrile **6**, however, was more reactive and complete consumption of starting isothiazole was observed in both MeCN and DMF. The reaction time and the product yield were also improved. Using MeCN as solvent, $Pd(OAc)_2$ as catalyst and a variety of commercially available organotin reagents aryl, heteroaryl, vinyl and propynyl, C-5 substituted isothiazoles **207** and **223-227** were prepared (Table 11). No trace of the 3,5-disubstituted isothiazoles was observed by TLC.

Table 11. Stille coupling reaction of 3,5-dihaloisothiazole-4-carbonitriles **5** and **6** with $Pd(OAc)_2$ (5 mol %) at 20 °C heated to 100 °C.



207, **223 - 227**

Hal	R	$RSnBu_3$ (equiv.)	Solvent	Time (min)	Yields (%)
Cl	Ph	1	DMF	72 h	**207** (68)
Cl	Ph	2	DMF	23 h	**207** (84)
Br	Ph	1.2	MeCN	20	**223** (93)
Br	Ph	1.2	DMF	20	**223** (90)
Br	2-Furyl	1	MeCN	6 h	**224** (86)
Br	2-Furyl	1.2	MeCN	20	**224** (100)
Br	2-Thienyl	1	MeCN	10	**225** (93)
Br	Vinyl	1.2	MeCN	45	**226** (94)
Br	Propynyl	1.2	MeCN	30	**227** (86)
Br	Bu_3Sn	1	MeCN	24 h	[a]

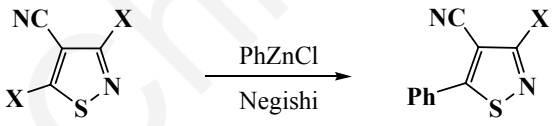
[a] No reaction after 24 h.

It is worthy of note that the 5-(thien-2-yl)isothiazole **225** was synthesized in high yield while, according to our previous work (Section 4.2.2),[307] Suzuki methods using 2-thienylboronic acid failed to introduce the 2-thienyl substituent at C-5 position. These results demonstrated that the Stille reaction can be used for regioselective synthesis of C-5-substituted isothiazoles but there are drawbacks; organotin reagents and their residues are highly toxic[308, 309] and these residues could not be removed easily by chromatography. Attempts to extract the organotin side products with pentane or hexane[310] failed because the isothiazole products were also soluble. The organotin residues were finally removed after recrystallization of the isothiazole products from cyclohexane. Another disadvantage of the Stille coupling reaction was the failure to synthesis the 5,5'-biisothiazole **228** using the bis(tributyltin) reagent. This 5,5'-biisothiazole **228** was prepared using palladium catalysed Ullmann type homocoupling coupling (see Section 4.2.6).

4.2.5 Negishi Coupling Reactions at C-5

The organozinc reagent used in Negishi couplings is non-toxic and product contamination does not occur readily, and therefore the Negishi coupling reaction was potentially a cleaner alternative to the Stille coupling. Negishi couplings have been conducted with 5-iodoisothiazoles[47] but there are to date no reports of coupling reactions with the less reactive chloro- or bromoisothiazoles. Treatment of 3,5-dichloro- and 3,5-dibromoisothiazole-4-carbonitriles **5** and **6** with phenylzinc chloride (1.5 equiv.) and $(Ph_3P)_2PdCl_2$ (5 mol%) in refluxing THF (25 min) gave the desired products **207** and **223** in 84 and 90% yields respectively (Table 12).[311] The use of less phenylzinc chloride (1 equiv.) led to incomplete consumption of the starting isothiazole, the use of 2 equiv. however, did not affect the product yields or reaction times. As with the Stille and Suzuki reactions no trace of the 3,5-diphenylisothiazole-4-carbonitrile **237** was observed. The synthesis of derivatives was not attempted since arylzinc halides have limited commercial availability and their preparation was less attractive.

Table 12. Negishi coupling reaction of 3,5-dihaloisothiazole-4-carbonitriles **5** and **6** with PhZnCl and $(PPh_3)PdCl_2$ (5mol%) in THF at 20 ^oC heated to 60 ^oC, under Ar.



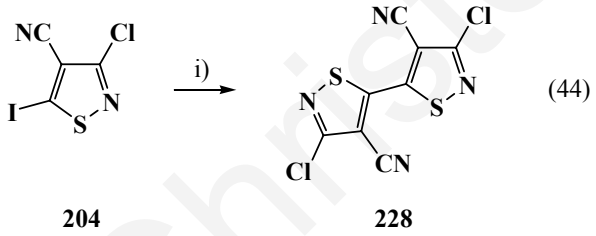
5, X = Cl
6, X = Br

207, X = Cl
223, X = Br

X	PhZnCl (equiv.)	Time (min)	Yields (%)
Cl	1.5	25	**207** (84)
Br	1.5	25	**223** (90)
Br	2	30	**223** (89)

4.2.6 Ullmann Type Coupling Reactions at C-5

Only one example of the 4,4'-biisothiazole,[44] and one of the 5,5'-biisothiazole[44] system have been reported as by-products of Heck cross coupling reactions. Attempts to prepare the 5,5'-biisothiazole starting from either 3,5-dichloro- or 3,5-dibromoisothiazoles **5** and **6** using palladium acetate gave predominantly unreacted starting material. Since aryl iodides were known to be more reactive towards homocoupling reactions[280] an Ullmann type coupling reaction was also attempted with 3-chloro-5-iodoisothiazole-4-carbonitrile **204**. With catalytic $Pd(OAc)_2$ (5 mol%) in DMF at 140 °C the 5-iodoisothiazole **204** was converted into 5,5'-bi(3-chloroisothiazole-4-carbonitrile) **228** in 86% yield although the reaction required heating for over 27 h. The addition of catalytic amount of tri-2-tolylphospine as ligand significantly reduced the reaction time (9 h) but gave a slightly lower yield (72%). A faster reaction time (2.5 h) was observed when 1 equivalent of $Pd(OAc)_2$ was used and this had no adverse effect on the product yield (Equation 44).



(44)

204 **228**

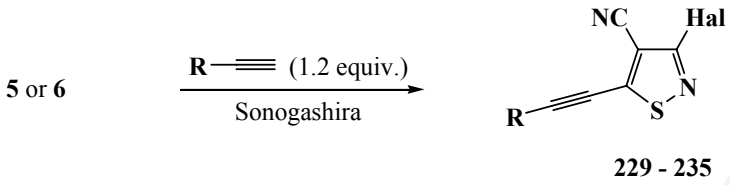
Reagents and conditions: i) $Pd(OAc)_2$ (5 mol%), DMF, 140 °C, 27.5 h, 86%; or $Pd(OAc)_2$ (5 mol%), (*o*-Tolyl)$_3$P (5 mol%), DMF, 140 °C, 9 h, 72%; or $Pd(OAc)_2$ (1 equiv.), DMF, 140 °C, 2.5 h, 85%.

4.2.7 Sonogashira Coupling Reactions at C-5

The reaction of 3,5-dichloroisothiazole **5** with phenylacetylene, triethylamine (2 equiv.), $(Ph_3P)_2PdCl_2$ (5 mol%) and copper iodide (10 mol%) was investigated in several solvents. MeCN and DMF were suitable with the former giving slightly improved reaction times and yields. In PhMe at least 2 equivalents of phenylacetylene were required to drive the reaction with the 3,5-dichloroisothiazole **5** to completion. The more reactive 3,5-dibromoisothiazole **6**, however, could be converted completely to the 5-(phenylethynyl)isothiazole **230** even in PhMe with only 1.2 equivalents of phenyl-acetylene. Starting with 3,5-dibromoisothiazole **6**, the 3-thienyl, ferrocenyl and trimethylsilyl derivatives **231**, **233** and **234** of 5-ethynylisothiazoles were synthesized in

good yields although the trimethylsilyl derivative **234** suffered some desilylation during the work up to afford 3-bromo-5-ethynylisothiazole-4-carbonitrile **235** (Table 13).

Table 13. Sonogashira coupling reaction of 3,5-dihaloisothiazole-4-carbonitriles **5** and **6** with $(PPh_3)_2PdCl_2$ (5 mol%), Et_3N (2 equiv.) and CuI (10 mol%), at 20 °C heated to 100 °C.



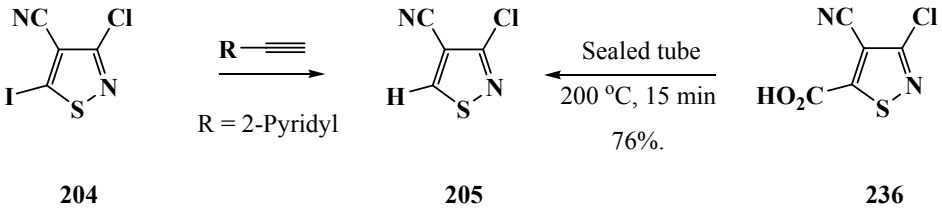
229 - 235

Hal	R	R (equiv.)	Solvent	Time (h)	Yields (%)
Cl	Ph	1.2	PhMe	24	**229** ([a])
Cl	Ph	2.0	PhMe	5.25	**229** (76)
Cl	Ph	1.2	MeCN	1	**229** (91)
Cl	Ph	1.2	DMF	1.5	**229** (80)
Br	Ph	1.2	PhMe	1	**230** (86)
Br	Ph	1.2	MeCN	1	**230** (90)
Br	Ph	1.2	DMF	1	**230** (86)
Br	3-Thienyl	1.2	MeCN	0.5	**231** (77)
Br	2-Pyridyl	1.2	PhMe	24	**232** ([a])
Br	2-Pyridyl	1.2	MeCN	24	**232** ([a])
Br	2-Pyridyl	1.2	DMF	24	**232** ([a])
Br	Ferrocenyl	1.2	MeCN	1.5	**233** (88)
Br	TMS	1.2	PhMe	24	**234** ([a])
Br	TMS	1.5	PhMe	0.25	**234** (69)[b]
Br	TMS	1.2	MeCN	24	**234** ([a])
Br	TMS	1.2	DMF	24	**234** ([a])

[a] Incomplete reaction; [b] 3-Bromo-5-ethynylisothiazole-4-carbonitrile **235** (Hal = Br, R = H) was also isolated in 14% yield.

The reaction involving the 3,5-dibromoisothiazole **6** with 2-pyridinylacetylene (1.2 equiv.) failed to reach completion even with additional equivalents of 2-pyridinyl-acetylene (up to 3 equiv.) after 24 h. The reaction was therefore repeated with 3-chloro-5-iodoisothiazole-4-carbonitrile **204** but when run in either DMF or MeCN the starting isothiazole was consumed rapidly (1 h) and gave only 3-chloroisothiazole-4-carbonitrile

205 as major product (38%). The structure of 3-chloroisothiazole-4-carbonitrile **205** was confirmed by thermal decarboxylation of the known 3-chloro-4-cyanoisothiazole-5-carboxylic acid **236**[200] at 200 °C (Scheme 60).

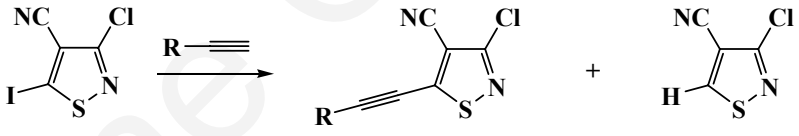


204 **205** **236**

Scheme 60

When the reaction of 3-chloro-5-iodoisothiazole-4-carbonitrile **204** and 2-pyridyl-acetylene (2 equiv.) was performed in PhMe the desired product was obtained in moderate yield together with 3-chloroisothiazole-4-carbonitrile **205**. A similar result was obtained when phenylacetylene (2 equiv.) was used. Increasing the equivalents of 2-pyridylacetylene reduced the reaction time but did not significantly change the product yields (Table 14).

Table 14. Reaction of 3-chloro-5-iodoisothiazole-4-carbonitrile **204** (0.113 mmol) with either 2-pyridylacetylene or phenylacetylene in PhMe (2 ml), Et_3N (2 equiv.), $(PPh_3)_2PdCl_2$ (5 mol%), CuI (10 mol%) at 20 °C heated to 100 °C.



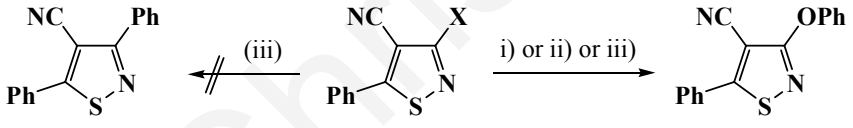
204 **232** (R = 2-Pyridyl) **205**
229 (R = Ph)

R (equiv.)	Time (min)	Yields (%)	
2-Pyridyl (1.2)	[a]		
2-Pyridyl (2)	30	**232** (54)	**205** (40)
2-Pyridyl (3)	15	**232** (49)	**205** (43)
Ph (2)	35	**229** (50)	**205** (36)

[a] Incomplete reaction after 24 h.

4.2.8 Attempted Suzuki Couplings at C-3

An attempt to perform a Suzuki coupling at C-3 with 3-chloro-5-phenylisothiazole-4-carbonitrile **207** or 3-bromo-5-phenylisothiazole-4-carbonitrile **223** was unsuccessful, but gave an interesting product. The reaction with $PhB(OH)_2$–KF showed a long delay (24 h) before a product spot appeared (TLC) and the starting material was only then gradually consumed following further addition of reagents. The isothiazole **207** was consumed fully after 7 d, but the product isolated by chromatography contained an oxygen atom. The stability of the parent ion (*m*/*z* 278, 92%) in the MS did not support the presence of an *S*-oxide or an *N*-oxide and two alternative structures were considered. The first 4-cyano-*N*,5-diphenylisothiazol-3-one was known[312] and could be eliminated by its melting point and the absence of a *ν*(C=O) in the IR, while the second possibility, 3-phenoxy-5-phenylisothiazole-4-carbonitrile **238**, was unknown. This ether was prepared independently in high yield by treating 3-chloro-5-phenylisothiazole-4-carbonitrile **207** with potassium phenoxide in refluxing PhMe in the presence of 18-crown-6 (Scheme 61); the spectral data of the two specimens were identical.



237 **207**, X = Cl **238**

223, X = Br

Reagents and conditions: i) X = Cl, PhOK (1.5 equiv.), 18-crown-6 (0.5 equiv.), PhMe, 20-140 °C, 3 h, 91%; ii) X = Br, PhOK (2 equiv.), 18-crown-6 (0.5 equiv.), PhMe, 20-140 °C, 3.5 h, 66%; iii) X = Cl, $PhB(OH)_2$, $Pd(OAc)_2$, KF, 18-crown-6, 95% (see Experimental section).

Scheme 61

Phenylboronic acid can afford phenol and this conversion was often effected by hydrogen peroxide.[313, 314] The mechanisms proposed suggest the phenol oxygen arises from the phenylboronic acid itself. In the above reaction the conversion could be aided by air oxidation. Furthermore possible mediation at any stage of the mechanism by complexation with the adjacent ring nitrogen atom cannot be discounted. Treatment of 3-bromo-5-phenylisothiazole-4-carbonitrile **223** with potassium phenoxide (2 equiv.) gave the ether in 66% yield. Interestingly the reaction could not be driven to completion

with 1.5 equivalents of potassium phenoxide and TLC analysis indicated a more complex reaction mixture with at least two minor by-products that were not isolated. This complexity could arise from additional nucleophilic attack by phenoxide directly onto the bromine at C-3 and/or the ring sulfur atom.

4.3 Summary

To summarize, optimal conditions for high yielding regioselective Suzuki couplings at C-5 of the readily available 3,5-dichloroisothiazole-4-carbonitrile **5** have been achieved using ligandless palladium catalysis and 18-crown-6 as PTC in refluxing PhMe with either organoboronic acid–KF or organotrifluoroborate–K_2CO_3.[307] The regioselectivity and high yields are maintained with 3,5-dibromoisothiazole-4-carbonitrile **6**. The use of 18-crown-6 and this relatively high temperature significantly shorten the reaction times. Regioselective Stille, Negishi, Sonogashira, and Ullmann type C-C coupling reactions were also demonstrated with 3,5-dihaloisothiazole-4-carbonitriles **5** and **6** in good to high yields at C-5 position of the isothiazole ring.[311] Regiospecific displacement of the 5-Cl over the 3-Cl is presumably because the 5-Cl is activated by both the cyano group and the ring nitrogen atom. Attempted phenylation at C-3 was unsuccessful and under forcing conditions gave only the 3-phenoxy derivative **238** that was prepared independently from 3-chloro-5-phenylisothiazole-4-carbonitrile **207** and potassium phenoxide.

CHAPTER 5

Isothiazole C-C Cross Coupling Chemistry at the Less Reactive C-3 Position

Sections

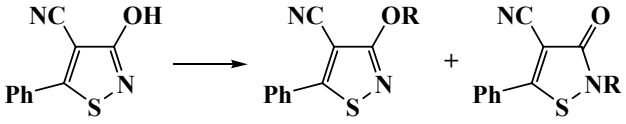
5.1 Introduction

According to our previous work (Chapter 4)[307] 3,5-dichloro- and 3,5-dibromoisothiazole-4-carbonitriles **5** and **6**[54] react regiospecifically with either phenylboronic acid or phenyltrifluoroborate to give in high yields 3-halo-5-phenylisothiazole-4-carbonitriles **207** and **223** respectively. Under the analogous reaction conditions both the 3-chloro- and the 3-bromo-5-phenylisothiazole-4-carbonitrile **207** and **223** failed to give the desired 3,5-diphenylisothiazole-4-carbonitrile **237**.[89, 307] As a logical extension of our earlier work we now present successful regioselective Stille,[315] Negishi,[316] Sonogashira[317] and Ullmann type[318] C-C coupling reactions for 3,5-dihaloisothiazoles and furthermore the work is extended to show for the first time in the literature Suzuki,[319] Stille, Negishi, Ullmann and Songashira couplings at the C-3 position of 3-halo-5-phenylisothiazole-4-carbonitriles.

5.2 Coupling at the Less Reactive Isothiazole C-3 Position

An earlier attempt to achieve the Suzuki coupling reaction at the C-3 position of 3-chloro- and 3-bromo-5-phenylisothiazole-4-carbonitrile **207** and **223** resulted in the unexpected synthesis of 3-phenoxy-5-phenylisothiazole-4-carbonitrile **238** and gave no isolable trace of the desired 3,5-diphenylisothiazole-4-carbonitrile **237** (Chapter 4, Section 4.2.8).[307] The result indicated the need for more reactive 3-substituted isothiazoles. For this purpose the 3-mesylate, tosylate, and triflate isothiazoles **240**-**242** were synthesized (Table 15) starting from the readily available 3-hydroxy-5-phenylisothiazole-4-carbonitrile **239**.[320] In addition the 2-mesyl and 2-tosylisothiazol-3-ones **243** and **244** were isolated as minor by-products. Early studies on the acylation and sulfonylation of 3-hydroxyisothiazoles show a kinetic preference for the formation of the acyloxy and sulfonyloxyisothiazole due to steric reasons. On standing, however, the acyl but not the sulfonyl group migrates to the thermodynamically more stable *N*-acylisothiazolone.[321]

Table 15. Reaction of 3-hydroxy-5-phenylisothiazole-4-carbonitrile **239** with Reagent (2 equiv.) in DCM at 0-10 ^{o}C.

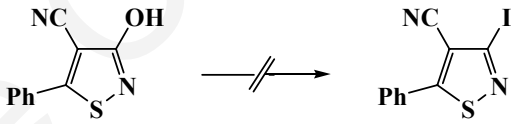


239 **240-242** **243-244**

Reagent (2 equiv.)	Et_3N (equiv.)	Time (h)	R	Yields (%) **240-242**	**243-244**
Ms_2O	1	0.3	Ms	**240** (78)	**243** (16)
TsCl	2	1	Ts	**241** (84)	**244** (12)
Tf_2O	1	0.5	Tf	**242** (86)[a]	-

[a]Based on recovered 3-hydroxyisothiazole **239** (8%).

The synthesis of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** was also targeted. 3-Iodoisothiazoles have to our knowledge not been reported in the literature. Attempts to convert the 3-hydroxyisothiazole **239** into the 3-iodoisothiazole **245** using neat HI, excess of KI / I_2 in refluxing THF, or Ph_3P / I_2 in DMF at 50 ^{o}C, all failed and gave only unreacted 3-hydroxyisothiazole **239** (Equation 45).

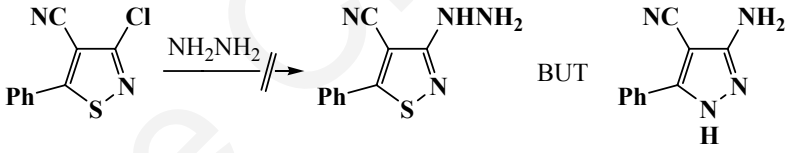


239 **245** (45)

The Sandmeyer iodination route was then investigated but this required the synthesis of 3-amino-5-phenylisothiazole-4-carbonitrile **251** which has been previously prepared from the reaction of potassium 2,2-dicyano-1-phenylethene-thiolate with chloramine (*cf* Compound **57** R=Ph, Scheme 15, Section 1.2.5.1.2).[136] Repetition of the literature method in our hands resulted in a complex and low yielding reaction. Furthermore, our strategy which attempts to avoid product specific synthetic routes required the use of the available 3-halo-5-phenylisothiazoles **207** or **223**. Unlike the halogen at C-5 which can be displaced readily by anhydrous ammonia in refluxing THF,[54] nucleophilic displacement of the halogen at C-3 required vigorous conditions. Treatment of 3-chloro-

5-phenylisothiazole-4-carbonitrile **207** therefore with aqueous ammonia, anhydrous ammonia, potassium phthalimide or sodamide with various solvents and temperatures failed to react or gave very complex mixtures. An attempt to displace the 3-chloro substituent with hydrazine hydrate or anhydrous hydrazine, in order to prepare the 3-hydrazino-5-phenylisothiazole-4-carbonitrile **246** gave instead 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **247**. With stoichiometric addition of hydrazine hydrate only a trace of the 3-amino-5-phenylpyrazole **247** was observed (TLC). The reaction, however, readily came to completion with a large excess or neat anhydrous hydrazine affording the 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile **247** in quantitative yield (Table 16). The same results were observed with hydrate hydrazine. No sulfur was observed on TLC but the odour of H_2S indicated a reduction of sulfur, that was released from the isothiazole ring, to H_2S presumably by the excess hydrazine. The pyrazole **247** has previously been prepared by treating phenylmethylenemalononitrile with hydrazine.[322] Whilst the analogous transformation of isoxazoles into pyrazoles was well documented[323, 324] only one similar report has appeared on the transformation of isothiazoles into pyrazoles using arylhydrazines.[325]

Table 16. Reaction of 3-chloro-5-phenylisothiazole-4-carbonitrile **207** (0.454 mmol) with hydrazine.



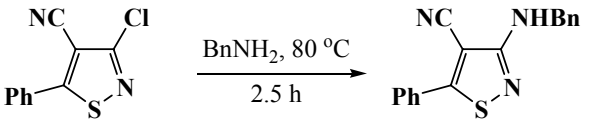
207 **246** **247**

Hydrazine (equiv.)	Solvent	Temp. (^oC)	Time (h)	Yield (%) **247**
NH_2NH_2 (2 ml)	neat	20	5 min	100
$NH_2NH_2.H_2O$ (2 ml)	neat	80	5 min	100
$NH_2NH_2.H_2O$ (1 ml)	EtOH	80	48	100
NH_2NH_2 (2)	CH_2Cl_2	20-40	1	trace
$PhNHNH_2$ (2 ml)	neat	100	48	nr[a]

[a] nr = no reaction

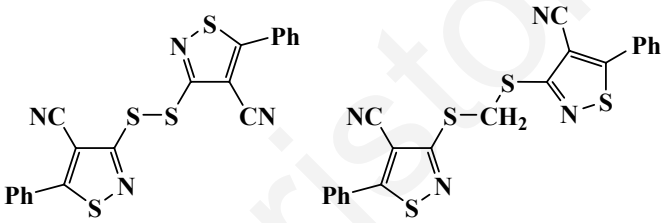
Halogens at the isothiazole C-3 position are known to be labile to alkylamines.[277] Treatment of 3-chloroisothiazole **207** with stoichiometric or excess amount of

benzylamine in a variety of solvents (PhMe, PhCl, DCM, THF, DMF, EtOH) gave only a trace of the 3-(*N*-benzylamino)-5-phenylisothiazole-4-carbonitrile **248** but when the reaction was repeated in neat benzylamine at 80 ^{o}C the desired product was isolated in 90% yield (Equation 46). At higher temperatures (150 ^{o}C) the yield of **248** was reduced and a second product 3,3'-bis(5-phenylisothiazole-4-carbonitrile)-disulfide **249** was observed indicating partial ring cleavage of the isothiazole possibly initiated by nucleophilic attack of benzylamine on the ring sulfur atom.



(46)

207 **248**, 90%

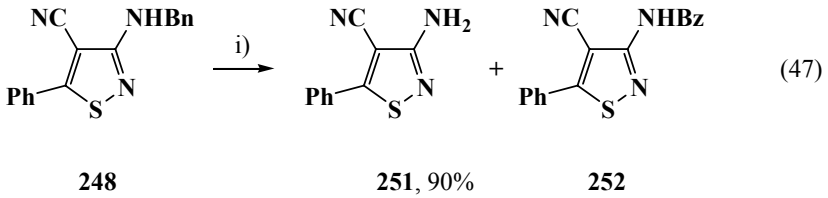


249 **250**

Dimeric isothiazoledisulfides have been previously observed as major products during electrosynthesis of isothiazoles starting from 3-aryl-2-phenylsulfonyl-propenonitriles (Chapter 1, Section 1.2.5.1.1, Equations 8 and 9).[132] Disulfide formation was proposed to arise from the oxidative dimerization of the analogous isothiazole-3-thiolate and it is possible that this also occurred here. Extraction of the benzylamine reaction mixture with hot DCM afforded a trace of a new compound, the bis(isothiazol-3-ylthio)methane **250**, and this could have arisen from reaction of the proposed isothiazole-3-thiolate with the DCM.

Cleavage of the benzyl group of the 3-(*N*-benzylamino)isothiazole **248** was not possible using mild reductive conditions (H_2, Pd/C) or with strong mineral acids possibly due to the amidine nature of the 3-benzylamino nitrogen. A recent publication on the debenzylation of amides using NBS and catalytic AIBN offered an alternative method.[326] With the 3-benzylaminoisothiazole **248**, however, a complex reaction was observed. Replacing the NBS with Br_2 gave a much cleaner reaction and the desired

3-aminoisothiazole **251** was isolated in high yield together with traces of 3-(*N*-benzamido)-5-phenylisothiazole-4-carbonitrile **252** and benzaldehyde (Equation 47).

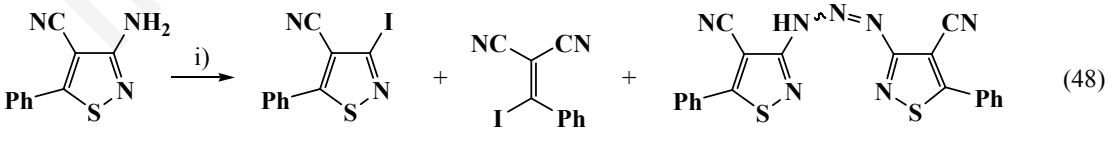


(47)

248 **251**, 90% **252**

***Reagents and conditions*:** i) Br_2 (1.5 equiv.), AIBN (0.2 equiv.), PhH/H_2O (2:1), 0.5 h, 80 ^oC.

Diazotization of the 3-aminoisothiazole **251** could not be achieved using sodium nitrite with a variety of acids (H_2SO_4, AcOH, HI, HIO_4, $HClO_4$) and similarly nitrous acid (HNO_3 / $Na_2S_2O_5$) also failed to effect diazotization. In nearly all cases the 3-aminoisothiazole **251** decomposed or was converted into mainly polar products; *e.g.*, 3-hydroxy-5-phenylisothiazole-4-carbonitrile **239**. The use of basic solvents such as Py or quinoline have been shown to assist in such cases[327] but the 3-aminoisothiazole **251** was isolated unchanged. Nitrosyl tetrafluoroborate in a 1:1 mixture of acetic and propionic acids gave only traces of the desired 3-iodoisothiazole **245** (by TLC). Similar difficulties in Sandmeyer reactions with the 3-aminoisothiazole **251** have been observed.[320] Iodination of arylamines was known to proceed well under aprotic diazotization conditions using isoamylnitrite in the presence of I_2[328] and similar conditions gave the 3-iodoisothiazole **245** in good yield together with two minor by-products, the methylenemalononitrile **253** and the triazene **254** (Equation 48). The reaction was optimized with respect to I_2 and isoamylnitrite and required dropwise addition of an MeCN solution of the 3-aminoisothiazole **251** into an I_2-saturated MeCN solution of isoamylnitrite.



(48)

251 **245**, 85% **253** **254**

***Reagents and conditions*:** i) IsoamylONO (4 equiv.), I_2 (2.5 equiv.), MeCN, 5 ^oC, 0.5 h.

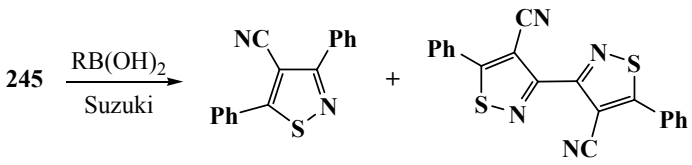
5.3 Suzuki Coupling Reactions at C-3

Having the four new 3-substituted-5-phenylisothiazole-4-carbonitriles **240**-**242** and **245**, Suzuki coupling reactions at C-3 were attempted again starting with the *O*-sulfonylated isothiazoles **240**-**242**. Our *O*-sulfonylated isothiazoles **240**-**242** showed no tendency to isomerization to their sulfonamide isothiazolone derivatives but unfortunately were hydrolytically labile in both MeCN and more so in DMF to a variety of Suzuki reaction conditions affording the starting 3-hydroxyisothiazole **239**. The compounds were stable to hydrolysis in 1,4-dioxane but gave mainly unreacted starting material after 24 h at reflux.

The more reactive (with respect to C-C coupling reactions) 3-iodo-5-phenyl-isothiazole-4-carbonitrile **245** provided a new opportunity to attempt the Suzuki reaction at the isothiazole C-3 position. The conditions [PhMe, KF, 18-crown-6, $Pd(OAc)_2$] that were successfully used for Suzuki couplings at C-5 (Section 4.2.2)[307] did not work with the 3-iodoisothiazole **245**. Replacing PhMe with dry and degassed DMF did, however, afford for the first time the 3,5-diphenylisothiazole-4-carbonitrile **237** in 34% yield together with a minor amount of the 3,3'-bi(5-phenylisothiazol-4-carbonitrile) **255**.

In light of this promising result the reaction was optimized first with respect to base, then with respect to boronic acid and finally with respect to catalyst in DMF. Strong bases such as KOH and Cs_2CO_3 led to decomposition of the starting isothiazole **245** whilst Li_2CO_3, $KHCO_3$ and KF gave longer reaction times. Na_2CO_3 and K_2CO_3 both afforded reasonable yields of the diphenylisothiazole **237** in less than 24 h. Of the two carbonates K_2CO_3 gave the higher yields and was chosen for further optimization studies. It was found that freshly and finely powdered (pestle and mortar) K_2CO_3 greatly reduced the reaction times but also the product yields (Table 17). Similar surface area effects on the reaction rate have been reported for Buchwald-Hartwig aminations with Cs_2CO_3.[329]

Table 17. Reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (0.160 mmol) with $PhB(OH)_2$ (2 equiv.), base (3.5 equiv.), Pd $(OAc)_2$ (5 mol%), DMF (3 ml) and 18-crown-6 (0.5 equiv.) at 140 °C, under Ar.



237 **255**

Base	Time (h)	Yields (%)	
		237	**255**
Li_2CO_3	46	nd[c]	[c]
Na_2CO_3	>18	44	trace
KOH[a]	1	-	-
$KHCO_3$	35	55	3
K_2CO_3	24	60	4
K_2CO_3[b]	3	30	trace
KF	>42	34	5
Cs_2CO_3[a]	1	-	-

[a]Decomposition of starting isothiazole **245**; [b]Powdered; [c]Incomplete reaction.

Considering K_2CO_3 to be the best base, the equivalents of K_2CO_3 were examined (Table 18). With phenylboronic acid (2 equiv.), $Pd(OAc)_2$ (5 mol%) in DMF at 140 ^oC for 2.5 h under an Ar atmosphere, 1.5 equivalents of powdered K_2CO_3 gave a consistent 70% yield of the diphenylisothiazole **237** and traces of the biisothiazole **255**. More than (up to 3.5 equiv.) or less than (down to 0.5 equiv.) 1.5 equivalents of powdered K_2CO_3 was detrimental to both yield and reaction time. The elimination of 18-crown-6 did not affect the reaction at all.

Table 18. Reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (0.160 mmol) with $PhB(OH)_2$ (2 equiv.), K_2CO_3, $Pd(OAc)_2$ (5 mol%), DMF (3 ml) and 18-crown-6 (0.5 equiv.) at 140 °C, under Ar.

K_2CO_3 (equiv.)	Time (h)	Yields (%) **237**	**255**
3.5	24	60	4
3.5[a]	3	30	nd
2[a]	8	52	3
1.5[a]	2.5	70	nd
1.5[a,b]	8	71	trace
1.5[a,c]	1.5	64[c]	trace
1[a]	24	46	trace
0.5[a]	29	55	3

[a]Powdered; [b]Without 18-crown-6; [c]DMF (2 ml)/H_2O (1 ml) & without 18-crown-6.

The equivalents of phenylboronic acid were then screened; with 3 equivalents of $PhB(OH)_2$ the reaction time was reduced to 50 min and yields of the diphenylisothiazole **237** raised to 80% (Table 19). A further increase in phenylboronic acid (4 equiv.) did not change either reaction times or product yields.

Table 19. Reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (0.160 mmol) with $PhB(OH)_2$, powder K_2CO_3 (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), DMF at 140 °C, under Ar.

$PhB(OH)_2$ (equiv.)	Time (h)	Yields (%) **237**	**255**
1	7	35	trace
2	8	30	trace
3	50 min	80	trace
4	50 min	79	trace

The DMF was then examined to determine tolerances in water, air and heating. Wet DMF gave marginally lower yields (75%) but the reaction time was unaffected (50 min). Dry but non-degassed DMF gave similar results. A significant reduction in the reaction time (15 min) was observed when the oil bath was preheated to 140°C, although the product yields were marginally reduced (71%) (Table 20). In light of these results with the iodo compound, the 3-bromo- and 3-chloro-5-phenylisothiazole-4-carbonitriles **223** and **207** were reinvestigated, however, only the 3-bromoisothiazole **223** showed any of

the 3,5-diphenylisothiazole **237** (by TLC) and the reaction was slow and could not be driven to completion.

Table 20. Reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (0.160 mmol) with $PhB(OH)_2$ (3 equiv.), powdered base (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), Solvent (3 ml), under Ar.

Reaction Conditions	Base	Solvent	Temp. (°C)	Time (min)	Yields (%) **237**	**255**
[a]	K_2CO_3	DMF	20-140	50	79	1
[a,b]	K_2CO_3	DMF	20-140	50	79	3
[c]	K_2CO_3	DMF	20-140	50	75	1
[a,d]	K_2CO_3	THF	65	> 24 h	[f]	
[a,d]	K_2CO_3	Dioxane	100	> 24 h	[f]	
[a,d]	K_2CO_3	DMF	100	30	81	1
[a,d]	K_2CO_3	PhMe	110	> 24 h	[f]	
[a,d]	$NaHCO_3$	DMF	140	> 24 h	[f]	
[a,d]	$NaCO_3$	DMF	140	> 24 h	[f]	
[a,d]	KOH	DMF	140	> 24 h	[f]	
[a,d]	$KHCO_3$	DMF	140	40	57	1
[a,d]	K_2CO_3	DMF	140	15	71	1
[e]	K_2CO_3	DMF	140	10	72	2
[a,d]	KF	DMF	140	> 24 h	[f]	
[a,d]	$CsCO_3$	DMF	140	> 24 h	[f]	

[a]Dry and degased DMF; [b]0.5 equiv. of 18-crown-6 was added in the reaction; [c]Wet DMF; [d]Preheated oil; [e]Dry but not degased solvent; [f]Incomplete reaction after 24 h

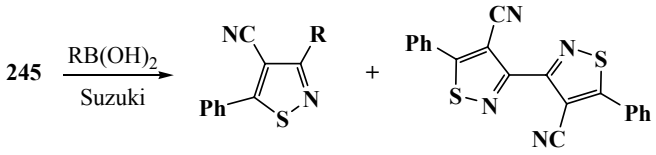
Finally a range of commercially available catalysts was investigated; interestingly three catalysts, $(PPh_3)_2PdCl_2$, $(PPh_3)_4Pd$ and $(dppf)PdCl_2$, showed no formation of the 3,3'-biisothiazole **255** but gave significantly lower yields of the diphenylisothiazole **237** (61-68%) and longer reaction times. $(MeCN)_2PdCl_2$, $(PhCN)_2PdCl_2$, and $PdCl_2$ gave both long reaction times (3-4 h) and reduced yields (60-61%) of the diphenylisothiazole **237** together with significant traces of the biisothiazole **255** (3-5%) whilst $(dba)_3Pd_2$ gave comparable yields to $Pd(OAc)_2$ but at a cost of reaction time (2.5 h) (Table 21).

Table 21. Reaction 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (0.160 mmol) with $PhB(OH)_2$ (3 equiv.), powder base (1.5 equiv.), catalyst (5 mol%), DMF (3 ml) at 140 ^oC, under Ar.

Catalyst	Time	Yields (%)	
	(h)	**237**	**255**
$Pd(OAc)_2$	10 min	75	1
$(PPh_3)_2PdCl_2$	2h 10 min	61	-
$(PPh_3)_4Pd$	2h	67	-
$(dppf)PdCl_2$	2h 20 min	68	-
$(dba)_3Pd_2$	2h 20 min	81	1
$(MeCN)_2PdCl_2$	3h 10 min	60	3
$(PhCN)_2PdCl_2$	3h 50 min	61	3
$PdCl_2$	3.5h	61	5

Having partially optimized the reaction conditions for the Suzuki coupling reaction at the isothiazole C-3 position, a variety of 3-arylsubstituted isothiazoles **237**, **256-265** were synthesized (Table 22). The electron deficient 3-nitrobenzeneboronic acid gave a relatively low yield (58%) of the desired isothiazole **256** despite the addition of further boronic acid. Electron rich arylboronic acids ($MeOC_6H_4$, and 3-thienyl) gave high yields. Sterically hindered boronic acids such as 2-tolyl- and 2-chlorobenzeneboronic acids gave either a low yield of the desired isothiazole or could not be driven to completion within 24 h. As with the C-5 coupling chemistry the 2-thienylboronic acid failed to react presumably due to protodeboronation of the boronic acid. However unlike the coupling at C-5, methylboronic acid failed to react at C-3. 3,3'-Biisothiazole **255** was formed in trace quantities in all reactions.

Table 22. Reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (0.160 mmol) with $RB(OH)_2$ (3-4 equiv.), powdered K_2CO_3 (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), in dry degassed DMF (2 ml) at 20 °C and heated to 140 °C, under Ar.



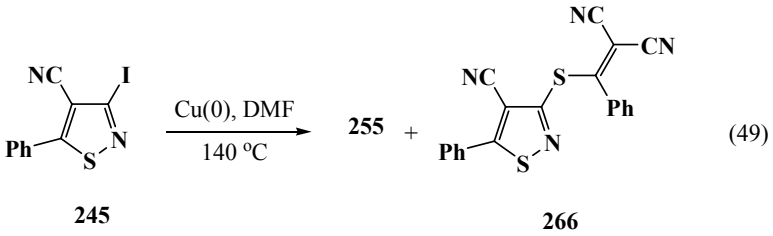
237, **256-265** **255**

R	$RB(OH)_2$ (equiv.)	Time (h)	Yields (%) **237**, **255-264**	**255**
Ph	3	1	**237** (80)	1
3-$NO_2C_6H_4$	3.5	1.17	**256** (58)	6
4-$MeOC_6H_4$	3.5	1.75	**257** (95)	5
3-$MeOC_6H_4$	3	1	**258** (84)	6
2-$MeOC_6H4$	4	0.34	**259** (95)	5
4-Tol	3.5	0.42	**260** (75)	nd[c]
3-Tol	3.5	0.5	**261** (91)	4
2-Tol	4	24	[a]	[a]
4-ClC_6H_4	3.5	0.34	**262** (82)	4
3-ClC_6H_4	3.5	0.34	**263** (75)	3
2-ClC_6H_4	3.5	0.34	**264** (58)	7
3-Thienyl	3	0.5	**265** (91)	2
2-Thienyl	3	24	[b]	[b]
Me	3	24	[b]	[b]

[a] Incomplete reaction after 24 h; [b]no reaction; [c]nd = no data.

5.4 Ullmann Type Homocoupling Reactions at C-3

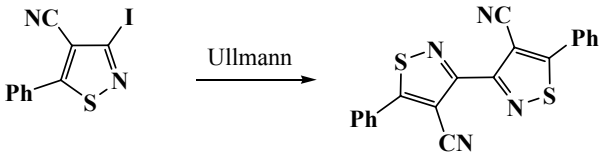
Whilst 4,4'- and 5,5'-biisothiazoles have been reported[44, 330] only the 3,3'-bibenzo-isothiazole moiety has appeared in the literature.[331] Therefore an independent synthesis of the 3,3'-biisothiazole **255** was attempted *via* the traditional copper catalysed Ullmann reaction starting from the 3-iodoisothiazole **245**. Treatment of the 3-iodoisothiazole **245** with either stoichiometric or excess copper powder in refluxing MeCN, PhH, PhMe or xylene gave slow reactions and only traces of product (by TLC). The reaction went to completion when DMF was used as solvent but the dimer **255** was isolated in moderate yield (31%) together with an unexpected isomeric by-product **266** (34%) which could only arise from degradation of one isothiazole ring (Equation 49). A similar 3-[(*Z*)-(2-cyano-2-phenylethenyl)thio]-5-phenylisothiazole was isolated during electrosynthesis of isothiazoles starting from 3-aryl-2-phenylsulfonylpropenonitriles (Chapter 1, Section 1.2.5.1.1, Equation 9).[332]



245 266 (49)

Replacing the copper catalyst with $Pd(OAc)_2$ (5 mol%) in dry degassed DMF failed to give more than a trace of the 3,3'-biisothiazole **255**. The use of triarylphosphine ligands Ph_3P or $(2\text{-tolyl})_3P$, reductive conditions (Zn/H_2O), basic conditions (Hünig's base) or the introduction of either Et_4NBr or CuI did not improve the yield of the 3,3'-biisothiazole **255**. The reaction times and product yields were improved with additional $Pd(OAc)_2$ and after 16.5 h with 1 equiv. of $Pd(OAc)_2$ the desired product **255** was obtained in 76% yield (Table 23). Significant decrease in the reaction time was observed under microwave conditions at 140 ^oC although the yield remained unchanged. Harsher microwave conditions, at 170 or 200 ^oC, provided a further decrease in the reaction time but the product yield dropped to 56%.

Table 23 Reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (0.160 mmol) with $Pd(OAc)_2$ in dry DMF (2 ml), under Ar.



245 **255**

Special Conditions	$Pd(OAc)_2$ (equiv.)	Temp. (^oC)	Time (h)	Yield (%) **255**
	0.05	20-100	24	*f*
a	0.05	20-100	24	*f*
b	0.05	20-100	24	*f,g*
	0.5	20-140	4d	65*h*
	1	20-140	16.5	76
c	1	20-140	18	65
d	1	20-140	96	40
e	1	20-140	5	71
e	1	140	5	77
e	1	200	5min	56

*a*0.5 equiv. R_4NBr or 1 equiv. Hünig's base or 5 mol% of Ph_3P or 5 mol% (*o*-tolyl)$_3$P; *b*3 equiv. Zn, 1 ml H_2O; *c*5 mol% (2-tolyl)$_3$P; *d*With 10 mol% CuI; *e*In microwave reactor, 255 W, Ramp.Temp. 10 sec, stirring; *f*Trace of 3,3'-biisothiazole **255**; *g*Decomposition of 3-iodoisothiazole **245** after 2 h; *h*18% of 3-iodoisothiazole **245** left unreacted, the yield of 3,3'-biisothiazole **255** was based on recovered 3-iodoisothiazole **245**.

Several other commercial palladium catalysts were compared with $Pd(OAc)_2$ but no appreciable benefits could be discerned. $(MeCN)_2PdCl_2$, $(PhCN)_2PdCl_2$ and $PdCl_2$ (1 or 2 equiv.) led to complete consumption of the starting iodoisothiazole **245** but gave lower yields (32-71%) compared to $Pd(OAc)_2$. With $(PPh_3)_2PdCl_2$ a complex reaction mixture was observed while $(dba)_3Pd_2$ gave no trace of biisothiazole **255** (Table 24). With (dppf)$PdCl_2$ no reaction was observed.

Table 24. Reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (0.160 mmol) with catalyst in dry DMF (2 ml) at 140 ^{o}C, under Ar.

Catalyst (equiv.)	Yield (%) **255**
$Pd(OAc)_2$ (2 equiv.)	83
$Pd(OAc)_2$ (1 equiv.)	76
$Pd(OAc)_2$ (5 mol%)	*a*
$(dba)_3Pd_2$ (2 equiv.)	*b*
$(MeCN)_2PdCl_2$ (2 equiv.)	71
$(MeCN)_2PdCl_2$ (1 equiv.)	56
$(MeCN)_2PdCl_2$ (5 mol%)	*b*
$(PhCN)_2PdCl_2$ (2 equiv.)	57
$(PhCN)_2PdCl_2$ (1 equiv.)	32
$(PhCN)_2PdCl_2$ (5 mol%)	*b*
$PdCl_2$ (2 equiv.)	63
$(Ph_3P)_2PdCl_2$ (2 equiv.)	*c*
(dppf)$PdCl_2$.DCM (2 equiv.)	*d*

[a]Only trace of 3,3'-biisothiazole **255**; [b]No 3,3'-biisothiazole **255**, traces of other products were observed; [c]Complex reaction; [d]No reaction.

5.5 Stille Coupling Reactions at C-3

The readiness of 3-chloro-, 3-bromo- and 3-iodoisothiazoles **207**, **223**, and **245** to participate in Stille coupling reactions was investigated. Treatment of either the 3-chloro- or the 3-bromo-5-phenylisothiazole-4-carbonitriles **207** and **223** with tributylphenyltin (up to 3 equiv.) gave only incomplete reactions (by TLC) even after 24 h. On the other hand addition of tributylphenyltin (1 equiv.) and $Pd(OAc)_2$ (5 mol%) to 3-iodo-5-phenyl-isothiazole-4-carbonitrile **245** in DMF at 100 ^{o}C gave the desired 3,5-diphenyl-isothiazole **237** in 94% yield together with traces of the 3,3'-biisothiazole **255**. Under these reaction conditions heteroaryl, including the 2-thienyl, vinyl and propynyl isothiazole derivatives **267-270**, were synthesized in high yields (Table 25). In all the reaction mixtures the 3,3'-biisothiazole **255** was observed in trace quantities. Recrystallization (cyclohexane) of the products isolated by chromatography was sufficient to remove the toxic organotin residues.

Table 25. Reaction of 3-halo-5-phenylisothiazole-4-carbonitriles **207**, **223** and **245** with $RSnBu_3$ and $Pd(OAc)_2$ (5 mol%) in dry degassed DMF (2 ml) at 20 ^oC heated to 100 ^oC, under Ar.

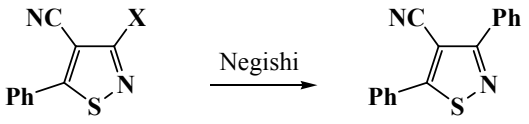
Hal	R	$RSnBu_3$ (equiv.)	Time (h)	Yields (%) **237**, **267-270**	**255**
Cl	Ph	3	24	**237** ([a])	[a]
Br	Ph	3	24	**237** ([a])	[a]
I	Ph	1	1.34	**237** (94)	trace
I	2-Thienyl	1	0.5	**267** (87)	trace
I	2-Furyl	1	1.67	**268** (91)	trace
I	Vinyl	1	24	**269** (96)	trace
I	Propynyl	1	24	**270** (73)	trace

[a] Incomplete reaction (by TLC) after 24 h.

5.6 Negishi Coupling Reactions at C-3

A comparison of the reactivity of the 3-halo-5-phenylisothiazole-4-carbonitriles **207**, **223** and **245** with respect to the Negishi coupling reactions showed that in the presence of $(PPh_3)_2PdCl_2$ (5 mol%) in dry degassed DMF the 3-chloroisothiazole **207** failed to react completely even when an excess of phenylzinc chloride (3 equiv.) was used (Table 26). Under analogous conditions both the 3-bromoisothiazole **223** and 3-iodoisothiazole **245** afforded the 3,5-diphenylisothiazole-4-carbonitrile **237** in 74 and 78% yields respectively in only 20 min. The use of less than 3 equivalents of phenylzinc chloride resulted in incomplete reactions in all cases.

Table 26. Negishi coupling reaction of 3-halo-5-phenylisothiazole-4-carbonitrile **207**, **223** and **245** with PhZnCl, $(Ph_3P)_2PdCl_2$ (5 mol%) in DMF (2 ml) at 20 heated to 100 ^oC, under Ar.



207, **223** and **245** **237**

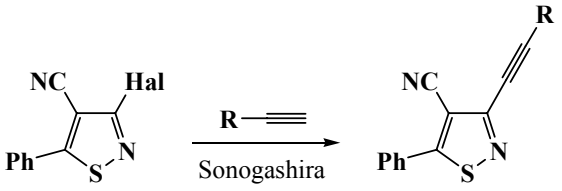
X	PhZnCl (equiv.)	Time (min)	Yield (%) **237**
Cl	2		[a]
Cl	3		[a]
Br	2	120	[a]
Br	3	20	74
I	2		[a]
I	3	20	78

[a]Incomplete reaction after 24 h.

5.7 Sonogashira Coupling Reactions at C-3

The three 3-haloisothiazoles **207**, **223** and **245** were investigated with respect to the Sonogashira reaction using an alkyne, triethylamine (2 equiv.), $(PPh_3)_2PdCl_2$ (5 mol%) and copper iodide (10 mol%) in dry degassed DMF and the order of reactivity was determined to follow I > Br > Cl. 3-Chloro-5-phenylisothiazole-4-carbonitrile **207** gave incomplete reactions even when an excess of phenylacetylene (3 equiv.) was used. In contrast, 3-bromo- and 3-iodo-isothiazoles **223** and **245** gave complete reactions with 2 and 1 equivalent of phenylacetylene respectively. Several 3-substituted-acetyleneisothiazoles **271-275** were prepared from the 3-iodoisothiazole **245** in good yields (Table 27). Surprisingly and in contrast with the 3-chloro-5-iodoisothiazole-4-cabonitrile **204** which gave moderate yield of the 5-(pyridin-2-ylethynyl)isothiazole derivative **232** the analogous 3-(pyridin-2-ylethynyl)isothiazole derivative **274** was prepared in excellent yield starting with 3-iodo-5-phenylisothiazole-4-carbonitrile **245**.

Table 27. Reaction of 3-halo-5-phenylisothiazole-4-carbonitriles **207**, **223** and **245** with Et_3N (2 equiv.), $(PPh_3)_2PdCl_2$ (5 mol %), CuI (10 mol %) in dry degassed DMF (2 ml) at 20 ^oC heated to 100 ^oC, under Ar.



207, **223** and **245** **271-275**

Hal	R	R≡ (equiv.)	Time (h)	Yield (%)
Cl	Ph	1.2	24	**271** ([a])
Cl	Ph	2	24	**271** ([a])
Cl	Ph	3	24	**271** ([a])
Br	Ph	2	2.85	**271** (87)
I	Ph	1	1.25	**271** (92)
I	TMS	1.5	4.25	**272** (70)
I	3-Thienyl	1.2	1.5	**273** (91)
I	2-Pyridyl	1.2	0.5	**274** (92)
I	Ferrocenyl	2	0.5	**275** (100)

[a] Incomplete reaction after 24 h, mainly isothiazole **207** (TLC).

5.8 Summary

Successful Suzuki, Stille, Negishi, Sonogashira, and Ullmann type C-C coupling reactions were achieved at the C-3 position for first time.[311] The couplings at C-3 were less readily achieved in comparison with the couplings at C-5 and the preparation of the more reactive of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** was required. This synthesis, of the first 3-iodo substituted isothiazole, was achieved *via* a Sandmeyer iodination of the 3-amino precursor **251**. 3-Iodo-5-phenylisothiazole-4-carbonitrile **245** was sufficiently reactive to undergo Suzuki, Stille, Negishi, Sonogashira and Ullmann type coupling reactions at the C-3 position. The reactivity of haloisothiazoles towards the coupling methods followed the anticipated order I > Br > Cl. The work described demonstrates the synthetic usefulness of the readily available 3,5-dichloroisothiazole-4-carbonitrile **5** when combined with powerful palladium catalysed C-C coupling.

CHAPTER 6

3,4,5-Triarylisothiazoles *via* C-C Coupling Chemistry

Sections

6.1 Introduction

Synthetic routes involving acyclic precursors that afford either 3,4,5-triarylpyrazoles[333-340] or 3,4,5-triarylisoxazoles[341, 342] have been reported. Surprisingly, analogous strategies have not been reported for the preparation of 3,4,5-triarylisothiazoles.[20-24] Nevertheless 3,4,5-triphenylisothiazole, the only reported triarylisothiazole, has been prepared from 1,3-dithiolium[171] and 1,4,2-dithiazolium precursors.[343] Interestingly the very first reported synthesis[344] of 3,4,5-triphenylisothiazole was also incorrect.[345]

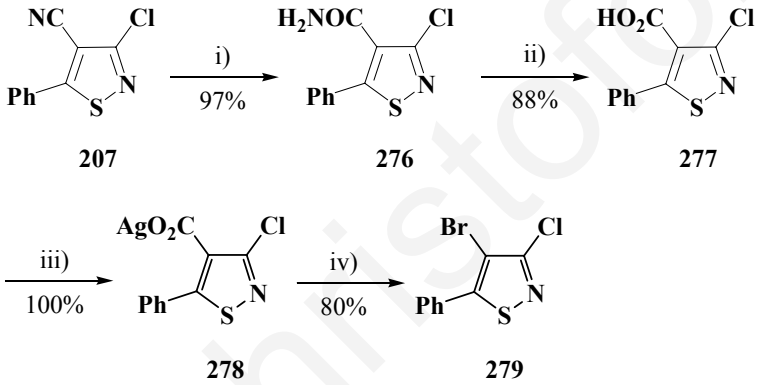
Possible strategies to triarylisothiazoles include ring formation *via* 2+3 cycloadditions of aryl nitrile sulfides with diarylacetylenes and the oxidative cyclization of 3-amino-1,2,3-triarylprop-2-ene-1-thiones. These strategies, however, have drawbacks since the former cycloaddition route could lead to isomeric mixtures of isothiazoles and the latter route is product-specific. Recently, Pd catalysed cross-coupling methods[280, 346] have been used to access 3,4,5-triarylpyrazole 1-oxides, *via* sequential metalation and functionalization of pyrazole 1-oxides,[347] and 3,4,5-triarylisoxazoles, *via* the modification of suitably substituted isoxazolylsilanols.[348] An analogous approach starting from an appropriately functionalised isothiazole could provide a general route to 3,4,5-triaryl-isothiazoles. Our work on the development of C-C coupling methods from the readily available 3,5-dichloroisothiazole-4-carbonitrile **5**[54] afforded a route to 5-aryl-3-chloro-isothiazole-4-carbonitriles[307] and 3,5-diarylisothiazole-4-carbonitriles (Chapters 4 and 5).[311] The logical extension of this work, to provide two routes to 3,4,5-triarylisothiazoles following the arylation sequence C-5 : C-4 : C-3 and C-5 : C-3 :C-4, is reported below.

6.2 Arylation Sequence C-5 : C-4 : C-3

6.2.1 Synthesis of 4-Bromo-3-chloro-5-phenylisothiazole **279** and Coupling Reactions at C-4

Initially, a sequential arylation of the isothiazole at the C-5, then C-4 and finally the C-3 ring carbons was investigated. Aryl and heteroaryl substituents can be introduced at the isothiazole C-5 position starting from the readily available 3,5-dichloroisothiazole-4-carbonitrile **5** using Suzuki, Stille and Negishi coupling techniques.[307, 311] The 4-cyano substituent could be readily converted into either a bromo substituent *via* a Hunsdiecker strategy (Scheme 62) or into an iodo substituent *via* a Sandmeyer strategy (Scheme 63) allowing for the possibility of introducing aryl substituents at the isothiazole C-4 position.

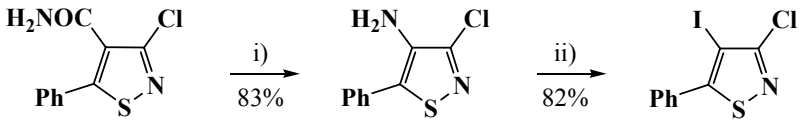
Hydration of the cyano group in concentrated sulfuric acid[60] proceeded smoothly to afford the carboxamide **276** in high yield (97%) (Scheme 62). Formation of the desired carboxylic acid **277** by addition of aqueous $NaNO_2$ to a solution of carboxamide **276** in concentrated sulfuric acid was complicated by the presence of minor by-products arising from nitration of the phenyl substituents. These nitrated by-products could be avoided if water was eliminated from the reaction mixture. As such, the portionwise addition of solid $NaNO_2$ (10 equiv.) to a solution of carboxamide **276** in concentrated sulfuric acid at 100 ^oC gave 3-chloro-5-phenylisothiazole-4-carboxylic acid **277** in 88% yield. The silver salt **278** was precipitated quantitatively, thoroughly dried and treated with Br_2 in CCl_4 to give the desired 4-bromo-3-chloro-5-phenylisothiazole **279** in 80% yield.



***Reagents and conditions*:** i) c. H_2SO_4, 20-100 ^oC, 2 h + 40 min; ii) s. $NaNO_2$ (10 equiv.), c. H_2SO_4, 20-100 ^oC, 2.5 h; iii) KOH (1 equiv.), H_2O, $AgNO_3$ (1 equiv.), 20 ^oC; iv) CCl_4, Br_2 (1.2 equiv.), 20 ^oC, 1 h.

Scheme 62

The conversion of the carboxamide **276** into 3-chloro-4-iodo-5-phenylisothiazole **281** was achieved in two steps (Scheme 63). First, a Hoffmann degradation of the carboxamide gave 4-amino-3-chloro-5-phenylisothiazole **280**. Then a Sandmeyer iodination using isoamyl nitrite and I_2 saturated MeCN gave the desired 3-chloro-4-iodo-5-phenylisothiazole **281** in good yield.



276 **280** **281**

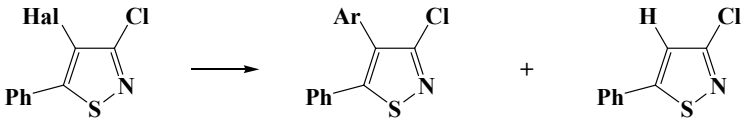
***Reagents and conditions*:** i) NaOH (5 equiv.), H_2O, Br_2 (1.5 equiv.), 0-70 ^oC, 1 h; ii) isoamylONO (4 equiv.), I_2 (2.5 equiv.), MeCN, 80 ^oC, 20 min.

Scheme 63

6.2.2 Coupling reactions at the C-4 isothiazole position

As expected, 3-chloro-4-iodo-5-phenylisothiazole **281** was more reactive than the analogous 4-bromoisothiazole **279**. The 4-iodoisothiazole **281** readily participated in Suzuki and Stille coupling reactions to afford regioselectively the 4-arylated isothiazole products **282**-**284** in high yields. The 4-bromoisothiazole **279** gave a successful Suzuki coupling with phenylboronic acid but failed to give the Stille reaction with tributylphenyltin (up to 4 equiv.). Both the 4-bromo- and 4-iodoisothiazoles **279** and **281** did not give the desired Negishi or the homocoupled Ullmann products. In these cases, the bromoisothiazole **279** was unreactive while the iodoisothiazole **281** gave predominantly the protodeiodinated 3-chloro-5-phenylisothiazole **285** (Table 28).

Table 28. Pd catalysed C-C coupling reactions of 3-chloro-4-halo-5-phenylisothiazole **279** or **281** (0.094 mmol) in anhydrous DMF (2 ml) heated from 20 to 100 °C, under Ar.



279 Hal = Br
281 Hal = I

282-284

285

Hal	Reagent (equiv.)	Catalyst (mol%)	Base (equiv.)	Time (min)	Yields (%)
Br	$PhB(OH)_3$ (3)	$Pd(OAc)_2$ (5)	K_2CO_3 (1.5)	75	**282** (96)
I	$PhB(OH)_3$ (3)	$Pd(OAc)_2$ (5)	K_2CO_3 (1.5)	40	**282** (98)
Br	$PhSnBu_3$ (4)	$Pd(OAc)_2$ (5)	-	> 24 h	[a]
I	$PhSnBu_3$ (1.2)	$Pd(OAc)_2$ (5)	-	25	**282** (99)
I	2-Thienyl$SnBu_3$ (1.2)	$Pd(OAc)_2$ (5)	-	15	**283** (100)
I	2-Furyl$SnBu_3$ (1.2)	$Pd(OAc)_2$ (5)	-	15	**284** (100)
Br	PhZnCl (3)	$(PPh_3)_2PdCl_2$ (5)	-	> 24 h	[a]
I	PhZnCl (1.5)	$(PPh_3)_2PdCl_2$ (5)	-	> 24 h	[a]
I	PhZnCl (3)	$(PPh_3)_2PdCl_2$ (5)	-	35	**282** (20) + **285** (80)
Br[b]	-	$Pd(OAc)_2$ (100)	-	> 24 h	[a]
I[b]	-	$Pd(OAc)_2$ (100)	-	48 h	**285** (98)

[a] Mainly unreacted isothiazole by TLC after 24 h; [b] Heated from 20 to 140 °C.

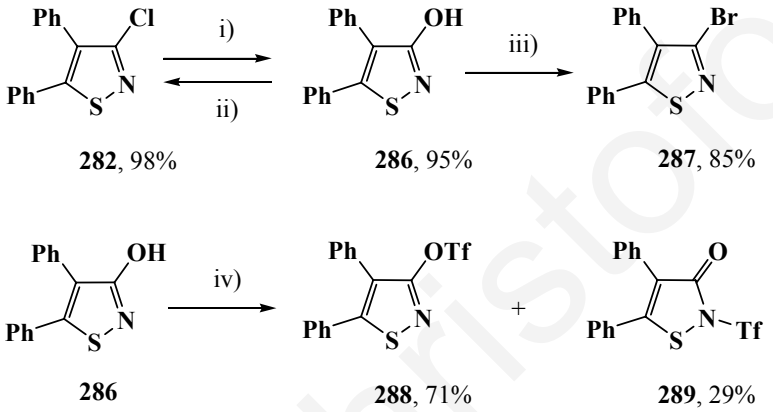
6.2.3 Coupling Reactions at the Less Reactive C-3 Isothiazole Position

6.2.3.1 Activation of 3-Chloro-4,5-diphenylisothiazole **282**

Palladium catalysed C-C coupling reactions at the isothiazole C-3 position were recently reported for 3-halo-5-phenylisothiazole-4-carbonitriles[311] and required either a bromo or iodo halogen since a chloro substituent at C-3 was not sufficiently reactive. Not surprisingly, 3-chloro-4,5-diphenylisothiazole **282** also failed to give successful Suzuki, Stille, Negishi and Ullmann type C-C coupling reactions. Consequently, the introduction of a more reactive group at the isothiazole C-3 position was investigated.

The introduction of a 3-bromo substituent was achieved in two steps starting from 3-chloro-4,5-diphenylisothiazole **282** *via* the 3-hydroxy-4,5-diphenylisothiazole **286**. Unlike 3-chloro-5-phenylisothiazole-4-carbonitrile **207** which can be readily transformed into the 3-hydroxy with $NaNO_2$ in refluxing DMF,[320] 3-chloro-4,5-diphenylisothiazole **282** did not react. Hydrolysis of 3-chloro-4,5-diphenylisothiazole **282** was nevertheless achieved using aqueous KOH at 200 °C and 250 psi in a pressure reactor to afford the

desired 3-hydroxyisothiazole **286** in 95% yield (Scheme 64). The reaction of 3-hydroxy-4,5-diphenyl-isothiazole **286** with $POBr_3$ gave the desired 3-bromo-4,5-diphenyl-isothiazole **287** in 85% yield. 3-Hydroxy-4,5-diphenylisothiazole **286** was resistant to $POCl_3$ at 100 °C and was recovered unreacted after 24 h. Conversion of the hydroxyisothiazole **286** back into the 3-chloroisothiazole **282** was however, achieved after 72 h at 150 °C in a sealed tube. 3-Hydroxy-4,5-diphenylisothiazole **286** reacted with trifluoromethanesulfonic anhydride to give the potentially useful 4,5-diphenylisothiazol-3-yl trifluoromethanesulfonate **288** in 71% yield together with the *N*-trifluoro-methylsulfonylated isothiazolone **289** (29%).



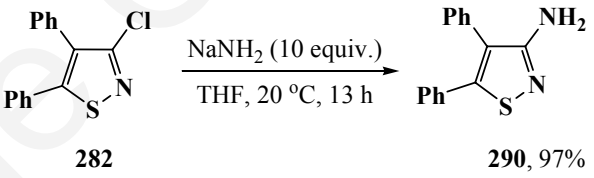
***Reagents and conditions*:** i) KOH (4 equiv.), 200 °C, 250 psi, pressure reactor, 24 h; ii) $POCl_3$, 20-150 °C, sealed tube, 72 h; iii) $POBr_3$, 20-100 °C, 24 h; iv) Tf_2O (1 equiv.), Et_3N (1 equiv.), DCM, 0-10 °C, 30 min.

Scheme 64

Attempts to introduce a 3-iodo substituent to the 4,5-diphenyl substituted isothiazoles **282** (3-Cl) and **286** (3-OH) failed. Lithiation of the 3-chloro-4,5-diphenylisothiazole **282** with n-BuLi at -78 °C in Et_2O followed by an I_2 quench led to a complex reaction mixture and on workup a strong odour of H_2S was detected. No reaction was observed when the reaction was repeated with Li, LDA or MeMgCl in either Et_2O or THF at -78 to 40 °C. Treatment of 3-hydroxy-4,5-diphenylisothiazole **286** with neat HI, HI-KI at 100 °C, excess of KI-I_2 in refluxing THF, Ph_3P-I_2 in DMF at 50 °C, P_2I_4 in CS_2 or PI_3 in refluxing DCM also gave only unreacted 3-hydroxy-4,5-diphenylisothiazole **286** while the use of neat PI_3 at 100 °C led to decomposition of the starting material. No reaction

was observed when the 3-chloro- or 3-bromo-4,5-diphenylisothiazoles **282** and **287** were treated with KI or KI-Et_4NI in refluxing acetone or THF.

Iodine at the isothiazole C-3 position has been introduced *via* 3-amino-5-phenylisothiazole-4-carbonitrile **247** by a Sandmeyer iodination.[311] The introduction of the 3-amino substituent in isothiazole **207** was achieved in two steps by heating a mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **207** in neat benzylamine at 80 ^oC to afford the 3-(*N*-benzylamino)isothiazole **248** followed by oxidative debenzylation with Br_2 (Chapter 5, Section 5.2). A heated mixture of 3-chloro-4,5-diphenylisothiazole **282** and neat benzylamine, however, gave no reaction probably owing to reduced electrophilicity of 3-chloro-4,5-diphenylisothiazole **282** in comparison to that of the analogous 4-cyano-5-phenylisothiazole **207**. The use of aqueous or gaseous ammonia at 80 ^oC and an attempted Gabriel synthesis with potassium phthalimide gave only unreacted starting material. 3-Amino-4,5-diphenylisothiazole **290** was eventually prepared from 3-chloro-4,5-diphenylisothiazole **282** using sodamide (10 equiv.) in THF at 20 ^oC for 13 h (Equation 50). The use of only 2 equiv. of sodamide in refluxing THF led to incomplete reactions after 24 h while at these higher temperatures the use of between 4-10 equiv. increased reaction times but reduced yields (59-67%). In contrast, 3-chloro-5-phenyl-isothiazole-4-carbonitrile **207** and sodamide in refluxing THF gave a complex reaction mixture.[311]



282 **290**, 97% (50)

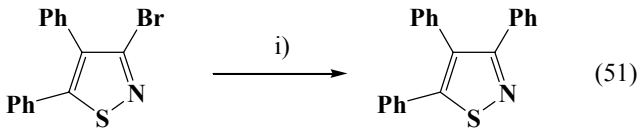
The Sandmeyer iodination of 3-amino-4,5-diphenylisothiazole **290** using KI (1.5 equiv.) and $NaNO_2$ (1.5 equiv.) in sulfuric acid gave 3-hydroxy-4,5-diphenylisothiazole **286** as the main product. Diazotization using nitrosyl tertafluoroborate in a 1 : 1 mixture of acetic and propionic acids gave a complex reaction mixture. The reaction of 3-amino-4,5-diphenylisothiazole **290** with isoamyl nitrite (4 equiv.) in the presence of various sources of iodine (I_2, NIS, $BnEt_3NI$) (3 equiv.) in MeCN at 0 or 80 ^oC gave incomplete reactions, however one main colourless product was observed by TLC. Isolation of this product by chromatography and subsequent spectroscopic analysis revealed the colourless material to be a mixture of inseparable compounds. Mass spectrometry gave a

weak peak for the expected molecular ion at 363 (19%), a stronger peak at 331 (33%) and a base peak at 204 Da (100%). IR spectroscopy supported the presence of a nitrile ν(C≡N) at 2208 cm^{-1} that indicated cleavage of the isothiazole ring. ^{1}H NMR spectroscopy gave a poorly resolved set of multiplets in the range of 7.60-7.14 ppm which was not informative; however ^{13}C NMR spectroscopy indicated 22 carbon signals in the range of 142.0-115.8 ppm, 12 of which in the range of 130.7-128.3 ppm could be assigned to C*H*s by DEPT-90 NMR. The signals at 116.8 and 115.8 ppm supported the presence of at least 1 cyano group. Based on the above data the mixture was very tentatively proposed to be that of 3-iodo-2,3-diphenylacrylonitrile and the desired 3-iodoisothiazole.

6.2.3.2 C-C Coupling Chemistry at the Isothiazole C-3 Position

The C-C coupling chemistry of 4,5-diphenylisothiazol-3-yl trifluoromethanesulfonate **288** and 3-bromo-4,5-diphenylisothiazole **287** was then examined following procedures developed for C-C coupling reactions of 3-bromo- and 3-iodo-5-phenylisothiazole-4-carbonitrile **223** and **245** respectively.[311] Suzuki, Stille, and Ullmann-type reactions on 4,5-diphenylisothiazol-3-yl trifluoromethanesulfonate **288** gave mainly unreacted starting material while the Negishi reaction was complex (by TLC) and the presence of 3-hydroxy-4,5-diphenylisothiazole **286** suggested a competing hydrolysis of the triflate. Similarly, 3-bromo-4,5-diphenylisothiazole **287** did not participate effectively in either the Suzuki or the Stille reactions. Although the desired 3,4,5-triphenylisothiazole **291** could be identified by TLC neither reaction could be driven to completion even with excess reagents and prolonged reaction times (>24 h). Furthermore, no reaction was observed when an Ullmann-type homocoupling with $Pd(OAc)_2$ (1 equiv.) was attempted in DMF at 140 ^{o}C.

Nevertheless the Negishi reaction gave 3,4,5-triphenylisothiazole **291** in 72% yield when 3-bromo-4,5-diphenylisothiazole **287** was treated with phenylzinc chloride (4 equiv.) and $(PPh_3)_2PdCl_2$ (5 mol%) in DMF at 100 ^{o}C under argon (Equation 51).

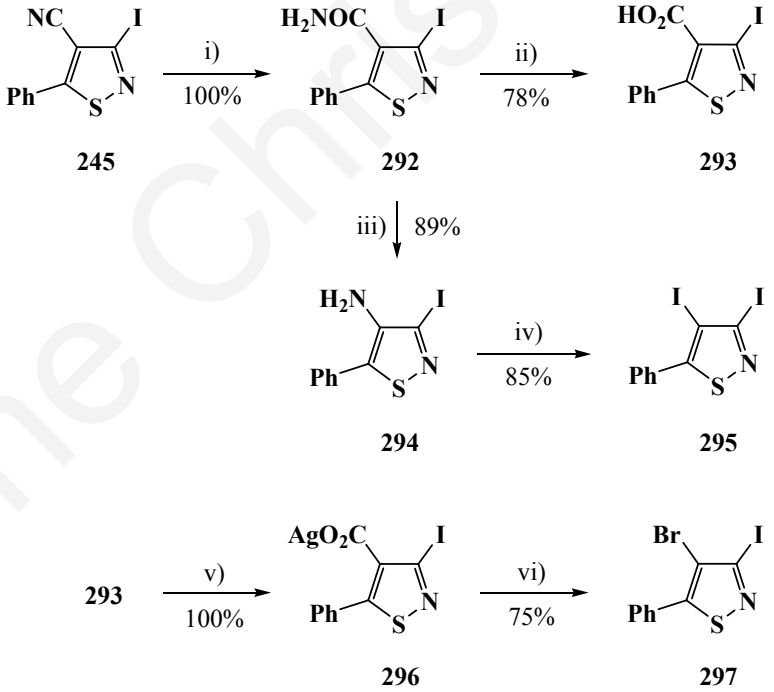


287 **291**, 72% (51)

Reagents and conditions: i) PhZnCl (4 equiv.), $(PPh_3)_2PdCl_2$ (5 mol%) DMF, Ar, 20-100 ^oC, 40 min.

The triarylation of the isothiazole ring system was achieved but the failure to perform both Suzuki and Stille reactions was limiting. As such, an additional effort was made to prepare the potentially more reactive 3-iodo-4,5-diphenylisothiazole starting from the known 3-iodo-5-phenylisothiazole-4-carbonitrile **245**.[311]

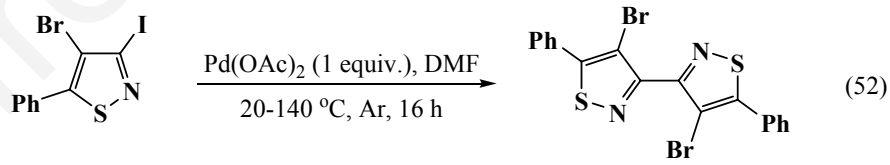
4-Bromo-3-iodo- and 3,4-diiodo-5-phenylisothiazoles **297** and **295** were therefore prepared (Scheme 65) following similar routes for the preparation of 4-bromo-3-chloro and 3-chloro-4-iodo-5-phenylisothiazoles **279** and **281**.



***Reagents and conditions*:** i) c. H_2SO_4, 20-100 ^oC, 2 h; ii) $NaNO_2$ (25 equiv.), c. H_2SO_4, 20-100 ^oC, 3 h; iii) NaOH (5 equiv.), H_2O, Br_2 (1.5 equiv.), 0-70 ^oC, 1 h; iv) isoamylONO (4 equiv.), I_2 (2.5 equiv.), MeCN, 80 ^oC, 20 min; v) KOH (1.2 equiv.), $AgNO_3$ (1.2 equiv.), H_2O, 20 ^oC; vi) Br_2 (1.2 equiv.), CCl_4, 20 ^oC, 1 h.

Scheme 65

Despite the successful syntheses of these 3,4-dihalogenated isothiazoles both the 3,4-diiodo- and the 4-bromo-3-iodo-5-phenylisothiazoles **295** and **297** gave mixtures of mono-, di- and sometimes triphenylated isothiazoles with either phenylboronic acid or tributylphenyltin in DMF. Nevertheless some regioselectivity was observed with the Suzuki coupling reaction between 4-bromo-3-iodo-5-phenylisothiazole **297** and phenylboronic acid. A spectroscopic analysis of the product mixture, that was inseparable by chromatography or recrystallization, supported the mixture to be predominantly 4-bromo-3,5-diphenylisothiazole **287** (an independent synthesis of this compound is presented later in Section 6.3.1) together with a trace of 3-iodo-4,5-diphenylisothiazole. Mass spectrometry indicated the presence of two parent ions, with a weak peak at 363 (15%) corresponding to the 3-iodoisothiazole and two strong peaks supporting a monobromine isotope pattern at 317 (100%) and 315 Da (93%), corresponding to the 4-bromo-3,5-diphenylisothiazole **287**. ^{1}H NMR of this mixture gave three multiplets in the range of 7.86-7.83 (2H), 7.69-7.65 (2H) and 7.54-7.40 ppm (4H) and elemental analysis after one recrystallization gave the percentages C: 55.76; H: 3.05; N: 4.01 which also favoured the 4-bromo-3,5-diphenylisothiazole **287** to be the major product over the 3-iodo-4,5-diphenylisothiazole. At elevated reaction temperatures (140 ^{o}C) 3,3'-bi(4-bromo-5-phenylisothiazole) **298** was also identified in the reaction mixture and the structure of this 3,3'-biisothiazole **298** was supported by a semi-independent synthesis *via* an Ullmann-type reaction of 4-bromo-3-iodo-5-phenylisothiazole **297** with $Pd(OAc)_2$ (1 equiv.) in DMF at 140 ^{o}C under argon in 74% yield (Equation 52). The analogous Ullmann reaction of 3,4-diiodo-5-phenylisothiazole **295** gave a complex mixture of products (by TLC) presumably owing to reduced regiocontrol in comparison to the 4-bromo-3-iodo- analogue.



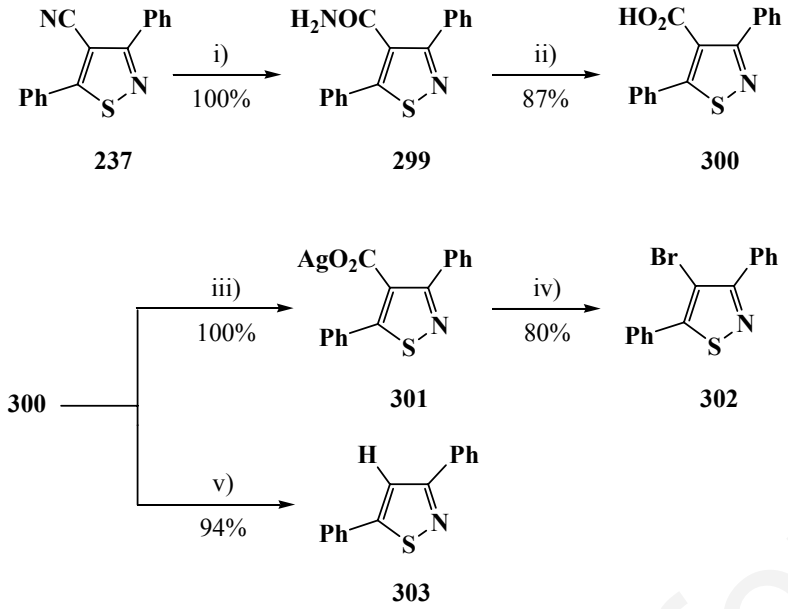
297 **298**, 74% (52)

6.3 Arylation sequence C-5 : C-3 : C-4

The triarylation described above follows the sequence C-5, then C-4 and finally C-3, however difficulties were encountered in the final arylation at C-3 since only the Negishi reagent phenylzinc chloride (4 equiv.) reacted with 3-bromo-4,5-diphenylisothiazole **287** to afford the desired triphenylisothiazole **291**. Furthermore, the synthetic route to the potentially more reactive 3-iodo-4,5-diphenylisothiazole failed. As such, an alternative sequential arylation was pursued which followed the triarylation sequence C-5 then C-3 and finally C-4. This triarylation sequence offered several advantages since Suzuki, Stille, Negishi and Ullmann type couplings have all been successfully employed to prepare a variety of 3,5-diarylisothiazole-4-carbonitriles starting from 3,5-dihalo-isothiazole-4-carbonitriles (Chapters 4 and 5).[311] Furthermore this route avoided the issue of regioselectivity between the isothiazole C-3 and C-4 positions since the C-4 position was "protected" as a nitrile group which could later readily be converted into either a bromo substituent *via* a Hunsdiecker strategy or into an iodo substituent *via* a Sandmeyer strategy using methods similar to those described above (Sections 6.2.1 and 6.2.3.2).

6.3.1 Synthesis of 4-Bromo- and 4-Iodo-3,5-diphenylisothiazoles **302** and **306**

Treatment of 3,5-diphenylisothiazole-4-carbonitrile **237** with concentrated sulfuric acid gave 3,5-diphenylisothiazole-4-carboxamide **299** in quantitative yield. The portionwise addition of solid sodium nitrite to a solution of the carboxamide in concentrated sulfuric acid gave 3,5-diphenylisothiazole-4-carboxylic acid **300** in 87% yield. As before, it was necessary to avoid the use of aqueous sodium nitrite since this led to some undesired nitration on the phenyl substituents. The Hunsdiecker reaction was applied to the 3,5-di-phenylisothiazole-5-carboxylic acid **300** to afford 3,5-diphenyl-4-bromoisothiazole **302** in 80% (Scheme 66).



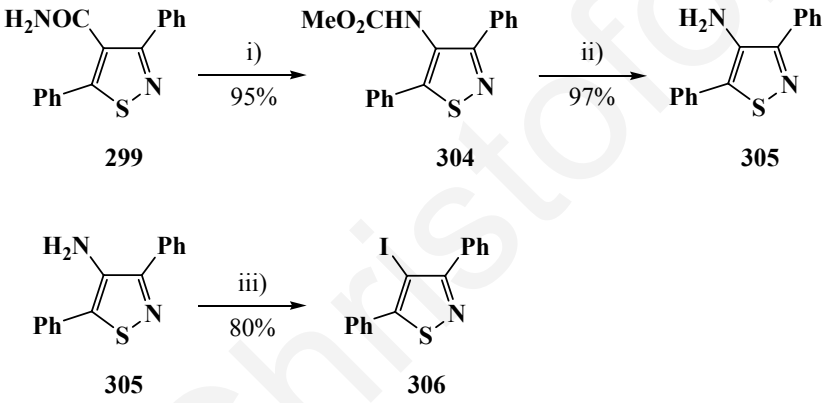
***Reagents and conditions*:** i) c. H_2SO_4, 20-100 ^oC, 3 h; ii) $NaNO_2$ (10 equiv.), c. H_2SO_4, 20-100 ^oC, 1 h; iii) KOH (1.2 equiv.), $AgNO_3$ (1.2 equiv.), H_2O, 20 ^oC; iv) Br_2 (1.2 equiv.), CCl_4, 20 ^oC, 1 h; (v) $TsOH.H_2O$ (10 mol%), Ph_2, 20-250 ^oC, 20.5 h.

Scheme 66

An alternative strategy to the 4-bromo-3,5-diphenylisothiazole **302** *via* electrophilic bromination of the 3,5-diphenylisothiazole **303** was also investigated. The thermal decarboxylation of 3,5-diphenylisothiazole-4-carboxylic acid **300** required prolonged heating at 250 ^oC in biphenyl in the presence of catalytic $TsOH.H_2O$ (Scheme 66) and the resulting 3,5-diphenylisothiazole **303** was unreactive to Br_2 in refluxing AcOH and to NBS in refluxing CCl_4. Iodination at C-4 using I_2 in hydrogen peroxide at 20 ^oC or *N*-iodosuccinimide in refluxing CCl_4 gave only unreacted 3,5-diphenylisothiazole **303** while iodination on phenyl substituents was observed with the use of I_2 in concentrated HNO_3 at 100 ^oC. Attempted nitration of the 3,5-diphenylisothiazole C-4 position with HNO_3 in concentrated H_2SO_4 at 0-5 ^oC also led to undesired nitration on the phenyl substituents.

Owing to these difficulties in controlling the regiochemistry of the above electrophilic substitution reactions, the preparation of the 4-iodo-3,5-diphenylisothiazole **306** was subsequently attempted in a two-step procedure involving first a Hoffmann degradation to afford the 4-amino-3,5-diphenylisothiazole **305** followed by the Sandmeyer iodination. Initially, Hoffmann degradation of 3,5-diphenylisothiazole-4-

carboxamide **299** with NaOH (4 equiv.) and Br_2 (1.5 equiv.) was attempted but the reaction was incomplete and quite complex. Modified Hoffmann degradation conditions using MeOH as solvent, sodium (4 equiv.) and Br_2 (1.2 equiv.), however, gave methyl 3,5-diphenylisothiazole-4-carbamate **304** in 95% yield based on recovered unreacted carboxamide **299** (3-5%), the presence of which could not be overcome. Treatment of the isothiazolecarbamate **304** with aqueous HBr (48%) at 100 ^oC gave 4-amino-3,5-diphenylisothiazole **305** in 97%. Diazotization of the 4-aminoisothiazole **305** with isoamyl nitrite (4 equiv.) and I_2 (3 equiv.) in refluxing nitromethane gave the 4-iodo-3,5-diphenylisothiazole **306** in 80% yield (Scheme 67). Lower reaction temperatures led to more complicated reaction mixtures and reduced yields of the 4-iodoisothiazole **306**.



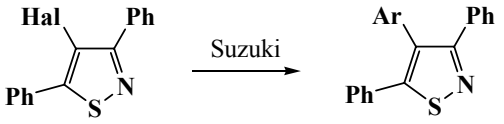
***Reagents and conditions*:** i) Na (4 equiv.), Br_2 (1.2 equiv.), MeOH, 20-70 ^oC, 1 h; ii) aq. HBr (48%), 100 ^oC, 7 h; iii) isoamylONO (4 equiv.), I_2 (3 equiv.), $MeNO_2$, 110 ^oC, 1 h.

Scheme 67

6.3.2 Coupling Reactions of 4-Bromo- and 4-Iodo-3,5-diphenylisothiazoles **302** and **306**

Both the 4-bromo- and 4-iodo-3,5-diphenylisothiazoles **302** and **306** readily undergo the Suzuki reaction with phenylboronic acid (3 equiv.), powdered K_2CO_3 (1.5 equiv.) and $Pd(OAc)_2$ (5 mol%) in DMF at 110 ^oC under argon atmosphere to provide a route to triphenylisothiazole **291**. The 4-iodoisothiazole **306** reacted marginally faster than the 4-bromoisothiazole **302**. A variety of arylboronic acids were subsequently screened to provide a non-product specific route to triarylisothiazoles in good yields (Table 29).

Table 29. Reaction of 4-halo-3,5-diphenylisothiazole **302** and **306** with arylboronic acid (3 equiv.), powdered K_2CO_3 (1.5 equiv.), $Pd(OAc)_2$ (5 mol%) in DMF (2 ml) at 20-110 ^oC under Ar.

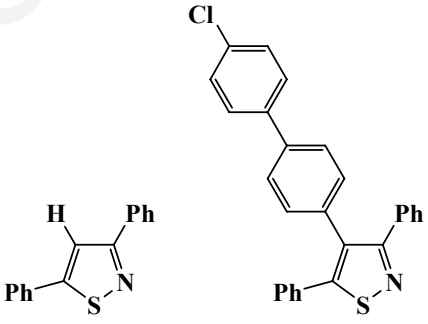


302 (Hal = Br)
306 (Hal = I)

291, 307-318

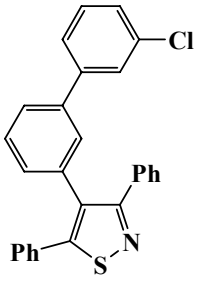
Hal	Ar	Time (min)	Yields (%)	
Br	Ph	60	**291**, (98)	
I	Ph	40	**291**, (100)	
Br	3-$NO_2C_6H_4$	55	**307**, (99)	
Br	4-$MeOC_6H_4$	40	**308**, (98)	
Br	3-$MeOC_6H_4$	40	**309**, (98)	
Br	2-$MeOC_6H_4$	30	**310**, (99)	
Br	4-Tol	45	**311**, (98)	
Br	3-Tol	30	**312**, (99)	
Br	2-Tol	4.5 h	**313**, (49)	**303**, (51)
I	2-Tol	80	**313**, (41)	**303**, (59)
Br	4-ClC_6H_4	30	**314**, (89)	**319**, (11)
Br	3-ClC_6H_4	50	**315**, (83)	**320**, (11)
Br	2-ClC_6H_4	1.5 h	**316**, (81)	**303**, (19)
I	2-ClC_6H_4	60	**316**, (12)	**303**, (88)
Br	3-Thienyl	25	**317**, (100)	
Br	2-Thienyl	[a]		
I	2-Thienyl	6 h	**318**, (99)	

[a]Incomplete reaction after 24h.



303

319

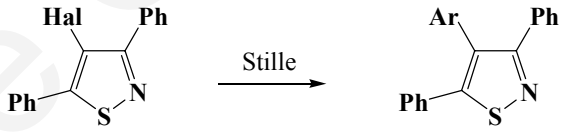


320

When the 4-bromo-3,5-diphenylisothiazole **302** reacted with the sterically more demanding 2-tolylboronic acid or the 2-chlorobenzeneboronic acid, protodebromination gave 3,5-diphenylisothiazole **303** in 51 and 19% yields respectively. A similar result was observed between the reaction of 4-iodo-3,5-diphenylisothiazole **306** and 2-tolylboronic acid, however pronounced protodeiodination occurred with 2-chlorobenzeneboronic acid affording 3,5-diphenylisothiazole **303** in 88% yield. Despite this, 4-iodo-3,5-diphenyl-isothiazole **306** reacted cleanly with 2-thienylboronic acid to give 3,5-diphenyl-4-(thien-2-yl)isothiazole **318** while the 4-bromo anologue failed to reach completion within 24 h. In case of 3- and 4-chlorobenzeneboronic acids the expected triarylisothiazoles reacted further with the excess boronic acid reagents to give minor amounts of isothiazoles **319** and **320** both in 11% yield. No reaction was observed with methylboronic acid.

Unlike the above Suzuki reactions where both the 4-bromo- and 4-iodo-3,5-diphenyl-isothiazoles **302** and **306** showed similar reactivities there was a significant difference with the Stille reaction. The reaction of 4-bromo-3,5-diphenylisothiazole **302** with tributylphenyltin (3 equiv.) and $Pd(OAc)_2$ (5 mol%) in DMF at 100 ^oC remained incomplete after 24 h while the 4-iodo-3,5-diphenylisothiazole **306** gave the desired Stille products in high yield (Table 30).

Table 30. Reaction of 4-halo-3,5-diphenylisothiazoles **302** and **306** with aryltributyltin in the presence of $Pd(OAc)_2$ (5 mol%) in DMF (2 ml) at 20-100 ^oC under Ar.



302 (Hal = Br)
306 (Hal = I)

291, **318** & **321**

Hal	Ar	$RSnBu_3$ (equiv.)	Time (h)	Yields (%)
Br	Ph	3	[a]	
I	Ph	1	24	**291** (99[b])
I	Ph	1.5	0.75	**291** (98)
I	2-Thienyl	1.5	16.25	**318** (99)
I	2-Furyl	1.5	4.25	**321** (98)

[a] Incomplete reaction after 24h; [b] Based on recovered 4-iodo-3,5-diphenylisothiazole **306** (11%).

Both 4-bromo- and 4-iodo-3,5-diphenylisothiazoles **302** and **306** reacted with the Negishi reagent phenylzinc chloride (4 equiv.) and $(PPh_3)_2PdCl_2$ (5 mol%) in DMF at 100 ^oC for 4 h under argon to give 3,4,5-triphenylisothiazole **291** in 29 and 18% yields, respectively. The Negishi reactions gave considerable amounts of the protodehalogenation product 3,5-diphenylisothiazole **303** (71 and 77% respectively) accounting for the low yields of triphenylisothiazole **291**. The Ullmann-type homocoupling of $Pd(OAc)_2$ (1 equiv.) with 4-bromoisothiazole **302** gave a complex reaction mixture, however, with 4-iodoisothiazole **306** only the protodeiodination product 3,5-diphenylisothiazole **303** was isolated in 43% yield.

6.4 Summary

Successful synthetic methods for triarylation on the isothiazole ring system, with C-C coupling reactions, were demonstrated following the arylation sequences C-5 then C-4 and finally C-3 and also C-5 then C-3 and finally C-4 with the latter triarylation sequence proving to be more versatile.[349] Several new 3,4,5-triarylisothiazoles were synthesized in high yields. In general, the reactivity of haloisothiazoles towards the coupling methods followed the anticipated order I > Br > Cl. Methods for converting the cyano substituent at the isothiazole C-4 position to bromo or iodo using Hunsdiecker or Hofmann degradation followed by Sandmeyer iodination techniques were developed. Several novel 3,5-diphenyl-4-haloisothiazoles and 3,4-dihalo-5-phenylisothiazoles were synthesized in good yield.

CHAPTER 7

Experimental

Sections

7.1 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. Potassium salts PhOK, K_2CO_3 and KF (for Suzuki coupling reactions at C-5 position, Chapter 4) were powdered and vacuum dried at 130 ^oC / 2 Torr. Anhydrous K_2CO_3 (for Suzuki coupling reactions at C-3 and C-4 positions, Chapters 5 & 6) was freshly powdered using an agate pestle and mortar before use. Reactions were protected by $CaCl_2$ drying tubes or performed under an argon atmosphere. 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). A Hastelloy B-2 Parr pressure vessel with a teflon sleeve and a 600 ml capacity (3000 psi limit) was used for the autoclave reactions. Microwave mediated chemistry was performed with a CEM Discover Microwave Reactor and reaction temperatures were controlled using standard IR thermometry. Melting points were determined using a PolyTherm-A, Wagner & Munz, Koefler-Hotstage Microscope apparatus. 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 Shimidazu FTIR-NIR Prestige-21 spectrometer with Pike *Miracle* Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w, respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz respectively). *C*H and *C*H_2 assignments were supported by ^{13}C NMR DEPT 90 and 135 experiments respectively. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GCMS with direct inlet probe whilst high resolution spectra were recorded on a VG Autospec "Q" mass spectrometer. Petrol refers to light petroleum, bp 40-60 ^oC. 4,5-Dichloro-1,2,3-dithiazolium chloride **124**,[216] 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylid-ene)malononitrile **120**,[201] (*Z*)-ethyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyano-acetate **137**,[216] *tert*-butyl 2-cyanoacetate,[350] 1,2-bis(4-chloro-5*H*-1,2,3-dithiazol-5-ylid-

ene)hydrazine **181**,[241] 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)acetonitrile **182**,[198] 3,5-dichloroisothiazole-4-carbonitrile **5**,[54] 3,5-dibromoisothiazole-4-carbonitrile **6**,[54] 5-amino-3-chloroisothiazole-4-carbonitrile **203**,[7] 3-chloro-4-cyanoisothiazole-5-carboxylic acid **236**,[200] 2-(2-thienylmethylene)-malononitrile **221**,[351] 2-(3-thienylmethylene)malononitrile **222**,[352] potassium phenyl-trifluoroborate,[298] 3-hydroxy-5-phenylisothiazole-4-carbonitrile **239**[320] and NIS[353] were prepared according to literature procedures.

7.2 Compounds Related to Chapter 2

(*Z*)-*tert*-Butyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate 138

To a stirred suspension of 4,5-dichloro-1,2,3-dithiazolium chloride **124** (10 g, 47.96 mmol) in DCM (200 ml) at *ca.* 20 ^{o}C, tert-butyl 2-cyanoacetate (6.76 g, 47.96 mmol) was added. After 4 h pyridine (7.76 ml, 95.92 mmol) was added dropwise and the mixture was left to stir for a further 2 h. TLC indicated one main orange product. The mixture was absorbed on silica and chromatography (petrol-DCM 3 : 7) gave the *title compound* **138** (6.37 g, 48%) as yellow plates, mp 178-182 ^{o}C (decomp.) (from cyclohexane); (Found: C, 39.0; H, 3.3; N, 10.2. $C_9H_9ClN_2O_2S_2$ requires C, 39.1; H, 3.3; N, 10.1%); λ_{max}(DCM)/nm 414 inf. (log ε 3.15), 432 (3.21), 454 inf. (3.01); ν_{max}/cm^{-1} 3003w, 2990w and 2941w (CH_3), 2208m (C≡N), 1648s (C=O), 1479m, 1473m, 1456w, 1449w, 1391w, 1375w, 1370w, 1307s, 1257m, 1228m, 1154s, 1110m, 964w, 950w, 880m, 844m, 835s, 792m, 769m; δ_H(300 MHz; $CDCl_3$) 1.58 (1H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 166.6 (*C*=O), 161.9 (*C*-5), 144.4 (*C*-4), 113.4 (*C*≡N), 92.8 (*C*C≡N), 84.9 [*C*(CH$_3$)$_3$], 28.0 (*C*H$_3$); δ_C(75 MHz; DEPT 45, $CDCl_3$) 28.0 (*C*H$_3$); *m*/*z* (EI) 278 (M$^+$+2, 8%), 276 (M$^+$, 21), 222 (40), 220 (M$^+$-CCH$_3$, 92), 203 [M$^+$-OC(CH$_3$)$_3$, 21], 185 (83), 114 (7), 110 (6), 99 (7), 82 (NCCO$_2^+$, 10), 64 (S_2, 15), 57 [C(CH$_3$)$_3^+$, 100], 41 (49).

(*Z*)-2-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile 139

To a stirred solution of (*Z*)-tert-butyl 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetate **138** (500 mg, 1.81 mmol) in PhCl (20 ml) at *ca.* 20 ^{o}C, 4-toluenesulfonic acid (9.5 mg, 10 mol%) was added and the reaction was heated to *ca.* 132 ^{o}C. During the heating a yellow-orange precipitate was formed which later dissolved. The mixture was kept at *ca.* 132 ^{o}C until no starting material remained (TLC) and allowed to cool to *ca.*

20 °C. Filtration and wash with DCM gave *(Z)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetic acid* **140** (23.95 mg, 6%) as yellow-orange precipitate, mp 151-152 °C (from PhCl); (Found: C, 27.1; H, 0.5; N, 12.8. $C_5HClN_2O_2S_2$ requires C, 27.2; H, 0.5; N, 12.7%); λ_{max}(EtOH)/nm 416 inf. (log ε 3.09), 430 (3.13), 447 inf. (3.99); ν_{max}/cm^{-1} 3038w, 2942w, 2825w, 2657w, 2531w, 2224m (C≡N), 1643m (C=O), 1467m, 1442w, 1414s, 1270s, 1229s, 1180w, 1126w, 1112m, 1037w, 1009w, 958w, 945w, 876s, 827s, 772w, 767w, 731s; δ_C(75 MHz; DMSO-d_6) 168.4 (*C*=O), 163.6 (*C*-5), 142.5 (*C*-4), 114.6 (*C*≡N), 88.4 (*C*C≡N); *m*/*z* (EI) 222 (M^++2, 12%), 220 (M^+, 29), 187 (9), 185 (M^+-Cl, 100), 178 (3), 176 (M^+-CO_2H, 7), 115 (12), 93 ($ClCNS^+$, 22), 83 ($NCCCO_2H^+$, 16), 82 (25), 77 ($NCC{=}CCN^+$, 23), 70 (22), 64 (S_2, 38), 56 (7), 46 (10), 45 (31), 44 (13). The filtrate was absorbed on silica and chromatography (petrol-DCM 6 : 4) gave the *title compound* **139** (300.30 mg, 94%) as yellow needles, mp 113-114 °C (from cyclohexane); (Found: C, 27.2; H, 0.5; N, 15.8; $C_4HClN_2S_2$ requires C, 27.2; H, 0.6; N, 15.9%); λ_{max}(DCM)/nm 304 (log ε 2.31), 389 (3.07); ν_{max}/cm^{-1} 3077w and 3035w (CH), 2205s (C≡N), 1534s, 1505w, 1497w, 1367w, 1280w, 1262w, 1177s, 882s, 874m, 794, 749m; δ_H(300 MHz; $CDCl_3$) 5.81 (1H, s, C*H*); δ_C(75 MHz; $CDCl_3$) 158.2 (*C*-5), 144.0 (*C*-4), 117.9 (*C*≡N), 83.2 (*C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 83.2 (*C*H); *m*/*z* (EI) 178 (M^++2, 43%), 176 (M^+, 100), 141 (M^+-Cl, 5), 115 (60), 114 (6), 105 (6), 102 (dithiazole ring, 4), 95 (15), 93 ($ClCNS^+$, 38), 88 (10), 83 (34), 82 ($NCC{=}CS^+$, 14), 77 (5), 76 ($NCC{=}CCN^+$, 9), 70 (21), 64 (S_2, 40), 58 (6), 57 (8), 56 (6), 51 (10), 45 (18).

Conversion of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetic acid 140 to (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile 139

To a stirred solution of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-cyanoacetic acid **140** (500 mg, 2.27 mmol) in PhCl (20 ml) at *ca.* 20 °C, 4-toluenesulfonic acid (43.13 mg, 10 mol%) was added and the reaction was heated to *ca.* 132 °C. The mixture was kept at *ca.* 132 °C until no starting material remained (TLC), allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (petrol-DCM 6 : 4) gave the title compound **139** (348.57 mg, 87%) as yellow needles, mp 113-114 °C (from cyclohexane) identical to that described above.

2-Chloro-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile 129

To a stirred solution of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139** (300 mg, 1.70 mmol) in PhCl (15 ml) at *ca.* 20 °C, *N*-chlorosuccinimide (453.90 mg, 3.40 mmol, 2 equiv.) was added and the reaction was heated to *ca.* 132 °C. The mixture was kept at *ca.* 111 °C until no starting material remained (TLC), allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (petrol-DCM 6 : 4) gave the title compound **129** (279.79 mg, 78%) as yellow needles, mp 164-165 °C (lit.,[354] 166-168 °C) (from cyclohexane); (Found: C, 22.8; N, 13.1; $C_4Cl_2N_2S_2$ requires C, 22.8; N, 13.3%); λ_{max}(DCM)/nm 255 (log ε 2.62), 293 (2.14), 396 (3.10); ν_{max}/cm^{-1} 2201m (C≡N), 1518m, 1488w, 1204m, 1164w, 1087w, 1074w, 1034w, 913w, 901m, 882w, 862m, 815w, 782s; δ_C(75 MHz; $CDCl_3$) 155.1 (*C*-5), 139.2 (*C*-4), 113.1 (*C*≡N), 90.3 (*C*C≡N); *m*/*z* (EI) 214 (M^++4, 17%), 212 (M^++2, 71), 210 (M^+, 100), 175 (M^+-Cl, 18), 151 (19), 159 (M^+-ClCN, 44), 119 (9), 117 [NC(Cl)CS^+, 26], 114 (15), 111 [NC(Cl)C=CCN^+, 6], 107 (9), 105 (28), 102 (dithiazole ring, 8), 95 (24), 94 (20), 93 (67), 88 (9), 85 (5), 82 (NCC=CS^+, 55), 81 (15), 79 (39), 76 (NCC=CCN^+, 22), 70 (55), 68 (9), 67 (11), 64 (S_2, 66), 58 (10), 56 (10), 50 (12), 47 (8), 46 (21).

(*Z*)-2-Bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile 142

To a stirred solution of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139** (300 mg, 1.70 mmol) in PhH (15 ml) at *ca.* 20 °C, *N*-bromosuccinimide (302.60 mg, 1.70 mmol, 1 equiv.) was added and the reaction was heated to *ca.* 80 °C. The mixture was kept at *ca.* 80 °C until no starting material remained (TLC), allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (petrol-DCM 6 : 4) gave the *title compound* **142** (403.95 mg, 93%) as yellow needles, mp 176-177 °C (from cyclohexane); (Found: C, 19.0; N, 10.9. $C_4BrClN_2S_2$ requires C, 18.8; N, 11.0%); λ_{max}(DCM)/nm 256 (log ε 2.69), 291 (2.09), 400 (3.11); ν_{max}/cm^{-1} 2192s (C≡N), 1513s, 1486w, 1195s, 1156w, 1057w, 1021w, 894s, 845m, 811w, 770s; δ_C(75 MHz; $CDCl_3$) 157.6 (*C*-5), 138.7 (*C*-4), 113.8 (*C*≡N), 74.6 (*C*C≡N); *m*/*z* (EI) 258 (M^++2, 49%), 257 (M^++1, 11), 256 (M^+, 100), 254 (98), 221 (M^+-Cl, 2), 219 (2), 195 [NC(Br)C=CSS^+, 18], 193 (17), 177 (29), 175 (71), 163 [NC(Br)C=CS^+, 6], 161 (6), 114 (35), 111 [NC(Cl)C=CCN^+, 3], 95 (5), 94 (5), 93 (11), 82 (NCC=CS^+, 12), 70 (8), 64 (S_2, 7).

3,4-Dibromoisothiazole-5-carbonitrile 10

To a stirred solution of (*Z*)-2-Bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-acetonitrile **142** (50 mg, 0.196 mmol) in PhH (3 ml) at *ca.* 20 °C large excess of anhydrous HBr gas was added. The mixture was kept at *ca.* 20 °C until no starting material remained (TLC). Chromatography (petrol-DCM 7 : 3) gave the title compound **10** (22.1 mg, 42%) as colourless plates, mp 104-105 °C (lit.,[57] 107.5-108.5 °C) (from cyclohexane); δ_C(75 MHz; $CDCl_3$) 141.7, 133.3, 121.7, 108.7 (*C*≡N).

Reaction of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile 139 with benzyltriethylammonium chloride

To a stirred solution of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139** (100 mg, 0.567 mmol) in DCM (2 ml) at *ca.* 20 °C, benzyltriethylammonium chloride (12.90 mg, 10 mol%) was added and the reaction was heated to *ca.* 40 °C using preheated oil. The mixture was kept at *ca.* 40 °C until no starting material remained (TLC), allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (petrol-DCM 8 : 2) gave the *title compound* 3,4-dichloromoisothiazole-5-carbonitrile **145** (3.04 mg, 3%) as colourless needles, mp 88-90 °C (lit.,[27] 84-85 °C) (from cyclohexane); ν_{max}/cm^{-1} 2236w (C≡N), 1495w, 1370w, 1349w, 1318s, 1299w, 1162m, 978w, 961m, 943w, 829w, 812m; δ_C(75 MHz; $CDCl_3$) 149.8, 130.9, 130.9, 108.2 (*C*≡N); *m*/*z* (EI) 182 (M^++3, 13%), 180 (M^++2, 70), 178 (M^+, 100), 143 (M^+-Cl, 2), 134 (4), 132 (6), 119 (29), 117 [ClC=C(S)CN^+, 82], 108 (M^+-2Cl, 7), 97 (4), 95 (7), 93 ($ClCNS^+$, 19), 91 (4), 85 (ClC=CCN^+, 6), 82 (isothiazole ring, 33),76 (NCC=CCN^+, 7), 70 (18), 67 (5), 62 (4), 58 (CNS^+, 3), 56 (C=CS^+, 3), 50 (C=CCN^+, 6). Further elution (hexane-DCM, 8 : 2) gave the 1,2,3,4,5-pentathiepino[6,7-*c*]isothiazole-8-carbonitrile **146** (3.5 mg, 7%) as colourless needles, mp 141-142 °C (lit.,[165, 218] 143-144 °C) (from pentane); *m*/*z* (EI) 270 (M^++2, 5%), 268 (M^+, 19), 236 (M^+-S, 3), 206 (18), 205 (8), 204 (M^+-S_2, 100), 172 (M^+-S_3, 3), 114 (13), 108 (M^+-S_5, 2), 96 (S_3^+, 11), 94 (8), 90 (7), 88 (4), 82 (isothiazole ring, 9), 76 (NCC=CCN^+, 4), 70 (51), 66 (8), 64 (S_2, 97), 46 (8), 44 (21). Further elution (hexane-DCM, 6 : 4) gave 1,4-dithiino[2,3-*c*]isothiazole-3,5,6-tricarbonitrile **95** (7.73 mg, 11%) as yellow plates, mp 176-177 °C (lit.,[166] 181-182 °C) (from cyclohexane); ν_{max}/cm^{-1} 2230m and 2214w (C≡N), 1534m, 1487w, 1310s, 1162m, 1150w, 1124w, 1044w, 1030w, 1000w, 989w, 949w, 870w, 827w, 807m; δ_C(75 MHz; $CDCl_3$) 153.9, 129.7, 129.2, 121.3, 118.1, 110.9 (*C*≡N), 110.8 (*C*≡N), 107.2 (*C*≡N); *m*/*z* (EI) 250 (M^++2,

14%), 249 (M^++1, 12), 248 (M^+, 100), 222 (M^+-CN, 3), 216 (M^+-S, 21), 190 (M^+-SCN, 21), 178 (M^+-SCCN, 24), 152 (5), 120 (4), 114 (9), 108 (isothiazole ring, 6), 94 (9), 90 (5), 88 (4), 82 (SC=CCN$^+$, 12), 76 (NCC=CCN$^+$, 9), 70 (NCCS$^+$, 68), 64 (17), 46 (5). Further elution (hexane-DCM, 1 : 9) gave *1,2-dithiolo[4,3*-b*][1,4]-thiazine-3,5,6-tricarbonitrile* **147** (4.92 g, 7%) as dark purple crystals, mp 172-173 °C (from cyclohexane); (Found: C, 38.9; H, N, 22.5. $C_8N_4S_3$ requires C, 38.7; N, 22.6%); λ_{max}(DCM)/nm 243 (log ε 3.26), 306 (2.78), 435 (2.51), 471 inf. (2.54), 544 (2.82), 574 inf. (2.74); ν_{max}/cm^{-1} 2232w, 2219w and 2212w (C≡N), 1511m, 1445s, 1257m, 1242w, 1157w, 1124w, 1085w, 970w, 877m, 844m; δ_C(75 MHz; $CDCl_3$) 177.6, 129.4, 128.6, 122.1, 112.5, 110.8, 110.7, 109.8, 108.9, 100.4; *m*/*z* (EI) 250.1 (M^++2, 14%), 249 (M^++1, 13), 248 (M^+, 100), 198 (M^+-C=CCN, 4), 196 (27), 190 (M^+-SCN, 8), 178 (M^+-SCCN, 13), 152 (7), 126 (6), 120 (34), 108 [NCC=C(S)CN$^+$, 14], 102 (8), 100 (dithiole ring, 16), 96 (7), 94 (28), 88 (16), 82 (SC=CCN$^+$, 22), 76 (NCC=CCN$^+$, 12), 70 (SCCN$^+$, 55), 68 (8), 64 (S_2, 51), 58 (SCN$^+$, 5), 56 (6). Further elution (hexane-DCM, 1 : 9) gave 1,4-dithiine-2,3,5,6-tetracarbonitrile **93** (33.07 mg, 54%) as yellow crystals, mp 205-206 °C (lit.,[166] 207-208 °C decomp.) (from DCM); ν_{max}/cm^{-1} 2242w, 2231w and 2218w (C≡N), 1519s, 1178w, 1158w, 1054w, 1026w, 1013m, 978m, 935w, 874w; δ_C(75 MHz; MeOD) 125.4, 112.4 (*C*≡N); *m*/*z* (EI) 218 (M^++2, 7%), 217 (M^++1, 8), 216 (M^+, 74), 190 (M^+-CN, 7), 184 (M^+-S, 9), 164 (6), 140 (M^+-NCC=CCN, 3), 120 (8), 114 (4), 108 [NCC=C(S)CN$^+$, 4], 94 (23), 82 (SC=CCN$^+$, 12), 76 (NCC=CCN$^+$, 11), 70 (SCCN$^+$, 100), 64 (10). Further elution (hexane-ethylacetate, 3 : 7) gave *5,6-dicyano-[1,2]dithiolo[4,3*-b*][1,4]thiazine-3-carboxamide* **148** (2.26 mg, 3%) as dark purple crystals, mp >300 °C (from 1,2-dichloroethane); (Found: C, 36.2; H, 0.7; N, 21.1. $C_8H_2N_4OS_3$ requires C, 36.1; H, 0.8; N, 21.0%); λ_{max}(EtOH)/nm 254 (log ε 2.96), 303 (2.70), 421 (2.57), 553 (2.75); ν_{max}/cm^{-1} 3390w (NH_2), 3337w, 3270w, 3203w, 3161w, 2237w (C≡N), 2203w (C≡N), 1669m (C=O), 1598w, 1559w, 1502m, 1434s, 1374w, 1256s, 1228w, 1120w, 1106w, 1045w, 966w, 875w, 855w, 763w; δ_H(300 MHz; DMSO-d_6) 8.21 (2H, s, N*H*$_2$); δ_C(75 MHz; DMSO-d_6) 180.5 (*C*=O), 161.2, 136.8, 128.6, 124.0, 114.1 (*C*≡N), 113.4 (*C*≡N), 103.9; *m*/*z* (EI) 268 (M^++2, 14%), 267 (M^++1, 11), 266 (M^+, 100), 225 (12), 224 (9), 223 (M^+-CONH, 85), 196 (5), 179 (6), 178 (M^+-SCCONH$_2$, 10), 171 (22), 164 (6), 159 (5), 147 (15), 127 (4), 108 [NCC=C(S)CN$^+$, 8], 102 (8), 101 (6), 100 (dithiole ring, 30), 95 (21), 94 (NCC=CCONH$_2^+$, 10), 90 [NCC=C(N)CN$^+$, 5], 89 (6), 88 (43), 82 (9), 76 (NCC=CCN$^+$, 7), 70 (26), 64 (S_2, 16), 45 (18).

Reaction of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile 139 with Hünig's base

To a stirred solution of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139** (50 mg, 0.283 mmol) in DCM (2 ml) at *ca.* 20 °C, Hünig's base (49.2 μl, 1 equiv.) was added and the reaction was heated to *ca.* 40 °C using preheated oil. The mixture was kept at *ca.* 40 °C until no starting material remained (TLC), allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (petrol-DCM 8 : 2) gave the title compound 3,4-dichloromoisothiazole-5-carbonitrile **145** (1.5 mg, 3%) as colourless needles, mp 88-90 °C (lit.,[27] 84-85 °C) (from cyclohexane) identical to that described above. Further elution (hexane-DCM, 8 : 2) gave 1,2,3,4,5-pentathiepino[6,7-*c*]isothiazole-8-carbonitrile **146** (1.8 mg, 7%) as colourless needles, mp 141-142 °C (lit.,[165, 218] 143-144 °C) (from pentane) identical to that described above. Further elution (hexane-DCM, 6 : 4) gave the title compound 1,4-dithiino[2,3-*c*]isothiazole-3,5,6-tricarbonitrile **95** (18.9 mg, 54%) as yellow plates, mp 176-177 °C (lit.,[166] 181-182 °C) (from cyclohexane) identical to that described above. Further elution (hexane-DCM, 1 : 9) gave 1,2-dithiolo[4,3-*b*][1,4]thiazine-3,5,6-tricarbonitrile **147** (2.1 g, 6%) as dark purple crystals, mp 172-173 °C (from cyclohexane) identical to that described above. Further elution (hexane-DCM, 1 : 9) gave the 1,4-dithiine-2,3,5,6-tetracarbonitrile **93** (12.2 mg, 30%) as yellow crystals, mp 205-206 °C (lit.,[166] 207-208 °C decomp.) (from DCM) identical to that described above.

Reaction of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile 139 with benzyltriethylammonium chloride and 2,3-diphenyl-1,3-butadiene

A stirred mixture of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139** (50 mg, 0.283 mmol), benzyltriethylammonium chloride (6.4 mg, 10 mol%), 2,3-diphenylbutadiene (116.6 mg, 2 equiv.) and PhCl (2ml) in a sealed tube was heated to *ca.* 132 °C (a preheated bath was used) for 1 h. The reaction mixture was allowed to cool to *ca.* 20 °C and diluted with DCM. Chromatography (petrol-DCM 9 :1) gave the title compound 4,5-diphenyl-3,6-dihydro-1,2-dithiine **153** (12.2 mg, 16%) as colourless crystals, mp 98-99 °C (lit.,[355] 101-102 °C) (from pentane); δ_H(300 MHz; $CDCl_3$) 7.14-7.06 (10H, m, Ph C*H*), 3.68 (4H, s, CH_2); δ_C(75 MHz; $CDCl_3$) 142.5, 134.7, 129.2 (Ph *C*H), 127.9 (Ph *C*H), 126.6 (Ph *C*H), 34.6 (*C*H_2); δ_C(75 MHz; DEPT 135, $CDCl_3$) 129.2 (Ph *C*H), 127.9 (Ph *C*H), 126.6 (Ph *C*H), 34.6 (*C*H_2); *m*/*z* (EI) 270 (M^+, 58%), 238 (M^+-

S, 10), 237 (14), 207 (8), 206 (M^+-S_2, 61), 205 (100), 204 (18), 203 (17), 202 (12), 191 (28), 190 (11), 189 (11), 178 (10), 128 (8), 91 (9), 77 ($C_6H_5^+$, 3). Further elution (hexane-DCM, 5 : 5) gave the *unknown compound* **154** (34.4 mg, 22%) as white crystals, mp 271-272 °C (from 1,2-dichloroethane); (Found: C, 76.6; H, 4.7; N, 4.7. $C_{36}H_{28}N_2S_2$ requires C, 78.2; H, 5.1; N, 5.1%); λ_{max}(DCM)/nm 229 (log ε 3.45), 247 inf. (3.05); ν_{max}/cm^{-1} 3080w, 3055w, 3022w, 2235w (C≡N), 1597w, 1574w, 1496w, 1490w, 1451w, 1444w, 1344w, 1293w, 1279w, 1221w, 1179w, 1159w, 1153w, 1125w, 1072w, 1043w, 1033w, 1025w, 992w, 967w, 930w, 915w, 764s, 725w, 708m; δ_H(300 MHz; $CDCl_3$) 3.42-3.39 (2H, m), 3.78 (1H, s), 3.84, (1H, s), 4.02 (1H, t, *J* 2.1), 4.08 (1H, t, *J* 2.3), 7.20-7.13 (12H, m, Ar *H*), 7.08-7.04 (8H, m Ar *H*); δ_C(75 MHz; $CDCl_3$) 140.8, 140.7, 140.1, 140.0, 134.9, 134.0, 133.7, 133.1, 129.1 (Ar *C*H), 129.0 (Ar *C*H), 128.9 (Ar *C*H), 128.9 (Ar *C*H), 128.2 (Ar *C*H), 128.2 (Ar *C*H), 128.2 (Ar *C*H), 127.2 (Ar *C*H), 127.2 (Ar *C*H), 127.2 (Ar *C*H), 127.1 (Ar *C*H), 50.4, 49.1, 40.6 (*C*H_2), 40.2 (*C*H_2), 32.7 (*C*H_2), 32.6 (*C*H_2), 31.0; δ_C(75 MHz; DEPT 135, $CDCl_3$) 129.1 (Ar *C*H), 129.0 (Ar *C*H), 128.9 (Ar *C*H), 128.9 (Ar *C*H), 128.2 (Ar *C*H), 128.2 (Ar *C*H), 128.2 (Ar *C*H), 127.2 (Ar *C*H), 127.2 (Ar *C*H), 127.2 (Ar *C*H), 127.1 (Ar *C*H), 40.6 (*C*H_2), 40.2 (*C*H_2), 32.7 (*C*H_2), 32.6 (*C*H_2); *m*/*z* (EI) 552 (M^+, 21%), 278 (21), 277 (100), 276 (12), 242 (17), 205 (10), 191 (22), 91 (18), 77 (4). Further elution (hexane-ethylacetate, 3 : 7) gave 5,6-dicyano-[1,2]dithiolo[4,3-*b*][1,4]thiazine-3-carboxamide **148** (4.5 mg, 12%) as dark purple crystals, mp >300 °C (from DCE) identical to that described above.

Reaction of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile 139 with Hünig's base and norbornelyne.

A stirred mixture of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139** (200 mg, 1.13 mmol) and norbornene (500 mg) in a sealed tube was heated to *ca.* 100 °C (a preheated bath was used) for 2 h. The reaction mixture was allowed to cool to *ca.* 20 °C and diluted with DCM. Chromatography (petrol-DCM 4 :6) gave the *title compound bicyclo[2.2.1]heptane[3,4-*e*][1,4]dithiine-2,3-dicarbonitrile* **155** (79.33 mg, 30%) as colourless plates, mp 144-145 °C (from cyclohexane); (Found: C, 56.4; H, 4.2; N, 11.9. $C_{11}H_{10}N_2S_2$ requires C, 56.4; H, 4.3; N, 12.0%); λ_{max}(DCM)/nm 232 (log ε 2.93), 353 (2.62); ν_{max}/cm^{-1} 2979w, 2957w, 2933w, 2917w, 2890w and 2878w (CH), 2226w (C≡N), 2212w (C≡N), 1508s, 1477w, 1454w, 1451w, 1315s, 1303m, 1280w, 1259w, 1223w, 1207s, 1184w, 1167m, 1155w, 1149w, 1133w, 1115w, 1051w, 1036w, 1012m, 999w,

993w, 954w, 944w, 927w, 905w, 883m, 881m, 860w, 852w, 830w, 808w, 785w, 769w, 738w; δ_H(300 MHz; $CDCl_3$) 3.55 (2H, d, *J* 1.8, norbornyl *H*-2), 2.52-2.50 (2H, m, norbornyl *H*-1), 2.40 (1H, app. quintet, *J* 10.8, 2.0, 1.9, 1.9, 1.9, CH_2), 1.82-1.73 (2H, m, CH_2), 1.45 (1H, app. quintet, *J* 10.8, 1.5, 1.5, 1.5, 1.4, CH_2), 1.41-1.33 (2H, m, CH_2); δ_C(75 MHz; $CDCl_3$) 127.4 (*C*CN), 113.6 (*C*≡N), 60.2 (*C*H), 44.7 (*C*H), 35.0 (*C*H_2), 29.0 (*C*H_2); δ_C(75 MHz; DEPT 135, $CDCl_3$) 60.2 (*C*H), 44.7 (*C*H), 35.0 (*C*H_2), 29.0 (*C*H_2); *m*/*z* (EI) 236 (M^++2, 16%), 235 (M^++1, 23), 234 (M^+, 100), 206 (M^+-CH_2CH_2, 9), 205 (6), 201 (6), 179 (M^+-$CH_2CH_2CHCH_2$, 7), 168 (5), 167 (5), 166 (1,4-dithiine-2,3-dicarbonitrile, 41), 164 (8), 153 [CHSC(CN)=C(CN)S^+, 13], 125 (8), 94 (norbonyl, 3), 93 ($C_7H_9^+$, 8), 91 (6), 81 (8), 79 (6), 77 (6), 67 (8), 66 (21), 65 (4).

7.3 Compounds Related to Chapter 3

1,3,4-Thiadiazole-2,5-dicarbonitrile 173

To a stirred solution of 1,2-bis(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)hydrazine **181** (100 mg, 0.330 mmol) in PhCl (3 ml) at *ca.* 20 °C, benzyltriethylammonium iodide (105.27 mg, 0.330 mmol, 1 equiv.) was added and the reaction was heated to *ca.* 132 °C. The mixture was kept at *ca.* 132 °C until no starting material remained (TLC) and allowed to cool to *ca.* 20 °C. Chromatography (petrol-DCM 5 : 5) gave the title compound **173** (35.46 mg, 79%) as colourless plates, mp 118-119 °C (lit.,[240] 121 °C) (from cyclohexane); ν_{max}/cm^{-1} 2249w (C≡N), 2182w, 1396w, 1366m, 1340w, 1302w, 1263w, 1227w, 1203s, 1181w, 1157s, 1101w, 892w; δ_C(75 MHz; $CDCl_3$) 142.4, 108.2 (*C*≡N); *m*/*z* (EI) 138 (M^++2, 3%), 137 (M^++1, 4), 136 (M^+, 100), 108 (M^+-N_2, 6), 84 (M^+-NCCN, 44), 82 ($CSCCN^+$, 4), 72 (5), 71 (3), 70 ($SCCN^+$, 100), 58 (10), 56 (CSC^+, 3), 52 ($N{=}CCN^+$, 10), 44 (CS^+, 14). Further elution (hexane-ethylacetate, 3 : 7) gave *5-cyano-1,3,4-thiadiazole-2-carboxamide* **183** (10.77 mg, 21%) as colourless plates, mp 207-208 °C decomp. (from PhH); ν_{max}/cm^{-1} 3401m (NH_2), 3324w, 3294w, 3270m, 3198w, 2260 (C≡N), 1679s (C=O), 1600m, 1454w, 1388w, 1367m, 1330w, 1249w, 1197m, 1179w, 1126m, 1089m, 1081w, 803w; δ_H(300 MHz; DMSO-d_6) 8.91 (1H, br s, N*H*), 8.48 (1H, br s, N*H*); δ_C(75 MHz; DMSO-d_6) 170.0 (*C*=O), 158.1, 143.7, 110.8 (*C*≡N); *m*/*z* (EI) 154 (M^+, 23%), 126 (M^+-N_2, 17), 111 (M^+-CONH, 59), 84 (M^+-$NCCONH_2$, 8), 82 ($CSCCN^+$, 3), 70 ($SCCN^+$, 10), 59 (27), 58 (NCS^+, 12), 53 (6), 52 ($N{=}CCN^+$, 2), 45 (8), 44 ($CONH_2^+$, 100), 43 (9).

1,3,4-Thiadiazole-2,5-dicarbonitrile 173 using polymer bound triphenylphospine

To a stirred solution of 1,2-bis(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)hydrazine **181** (30 mg, 0.099 mmol) in DCM (3 ml) at *ca.* 20 °C, polymer bound triphenylphosphine 3.2mmol/g (185.63 mg, 0.594 mmol, 6 equiv.) was added and the reaction was kept at *ca.* 20 °C until no starting material remained (TLC). The polymer bound triphenylphosphine was filtered off the reaction mixture and the solvent was evaporated to give the title compound **173** (10.64 mg, 79%) as colourless plates, mp 118-119 °C (lit.,[240] 121 °C) (from cyclohexane) identical to that described above.

Thiazole-2,4,5-tricarbonitrile 169

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)acetonitrile **182** (50 mg, 0.153 mmol) in PhCl (3 ml) at *ca.* 20 °C, benzyltriethylammonium chloride (34.88 mg, 0.153 mmol, 1 equiv.) was added and the reaction was kept at *ca.* 132 °C until no starting material remained (TLC) and allowed to cool to *ca.* 20 °C. Chromatography (petrol-DCM, 5 : 5) gave the title compound **169** (17.14 mg, 70%) as colourless plates, mp 122-123 °C (lit.,[231] 127 °C) (from PhH); ν_{max}/cm^{-1} 2246w and 2236w (C≡N), 1477w, 1418m, 1333m, 1205w, 1183w, 1153s, 969w, 950w, 885w, 736w, 703.1m; δ_C(75 MHz; $CDCl_3$) 142.4, 135.4, 119.7, 109.5 (*C*≡N), 109.4 (*C*≡N), 107.0 (*C*≡N); *m*/*z* (EI) 162 (M^++2, 3%), 161 (M^++1, 5), 160 (M^+, 55), 110 (M^+-C=CCN, 5), 109 (6), 108 (M^+-2CN, 100), 91 (4), 83 (3), 82 (thiazole ring, 26), 76 (NCC=CCN$^+$, 9), 72 (3), 71 (5), 70 (SCCN$^+$, 57), 69 (3), 64 (N=CCCN$^+$, 11), 58 (NCS$^+$, 9), 57 (8), 56 (CSC$^+$, 13), 55 (5), 52 (N=CCN$^+$, 8), 50 (C=CCN$^+$, 10), 48 (3), 46 (3), 44 (CS$^+$, 29), 43 (14), 41 (5). Further elution (hexane-ethylacetate, 3 : 7) gave *4,5-dicyanothiazole-2-carboxamide* **184** (4.09 mg, 15%) as colourless needles, mp 162-163 °C (from PhMe); (Found: C, 40.3; H, 1.0; N, 31.3. $C_6H_2N_4OS$ requires C, 40.6; H, 1.1; N, 31.5%); λ_{max}(DCM)/nm 229 (log ε 3.19), 266 (3.03), 276 (3.05); ν_{max}/cm^{-1} 3376w (NH_2), 3297w, 3174w, 2247(C≡N), 2241w (C≡N), 1689s (C=O), 1610w, 1481w, 1458w, 1386m, 1230w, 1130m, 791w, 744w, 735w; δ_H(300 MHz; DMSO-d_6) 8.82 (1H, br s, N*H*), 8.43 (1H, br s, N*H*); δ_C(75 MHz; DMSO-d_6) 171.0 (C=O), 158.7, 134.0, 120.3, 111.8 (*C*≡N), 110.0 (*C*≡N); *m*/*z* (EI) 178 (M^+, 36%), 162 (M^+-NH_2, 3), 135 (M^+-CONH, 50), 126 (M^+-N=CCN, 4), 108 (M^+-SCCN, 27), 83 (9), 82 (thiazole ring, 14), 77 (10), 76 (NCC=CCN$^+$, 7), 71 (5), 70 (N=CCONH$_2^+$ or SCCN$^+$, 23), 69 (N=CCONH$^+$, 3), 64

(NC=CCN$^+$, 5), 59 (10), 58 (N=CS$^+$, 17), 57 (8), 55 (3), 50 (C=CCN$^+$, 4), 45 (4), 44 ($CONH_2^+$, 100).

Thiazole-2,4,5-tricarbonitrile 169 using polymer bound triphenylphospine

To a stirred solution of 2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)acetonitrile **182** (50 mg, 0.153 mmol) in DCM (3 ml) at *ca.* 20 ^oC, polymer bound triphenylphosphine 3.2mmol/g (239.06 mg, 0.765 mmol, 5 equiv.) was added and the reaction was kept at *ca.* 20 ^oC until no starting material remained (TLC). The polymer bound triphenylphosphine was filtered off the reaction mixture and the solvent was evaporated to give the title compound **169** (18.60 mg, 76%) as colourless plates, mp 122-123 ^oC (lit.,[231] 127 ^oC) (from PhH) identical to that described above.

7.4 Compounds Related to Chapter 4

3-Chloro-5-iodoisothiazole-4-carbonitrile 204

To a stirred and heated (*ca.* 110 ^oC) mixture of I_2 (238.9 mg, 0.94 mmol, 3 equiv.) and isoamylnitrite (168 μl, 1.25 mmol, 4 equiv.) in nitromethane (2 ml) was added dropwise a nitromethane (1 ml) solution of 5-amino-3-chloroisothiazole-4-carbonitrile **203** (50 mg, 0.313 mmol). The reaction mixture was kept at *ca.* 110 ^oC until no starting material remained (TLC) and then allowed to cool to *ca.* 20 ^oC and absorbed on silica. Chromatography (hexane-DCM, 7:3) gave the *title compound* **204** (70 mg, 83%) as colourless needles, mp 117-118 ^oC (from pentane); (Found: C, 17.8; N, 10.3. C_4ClIN_2S requires C, 17.8; N, 10.4%); λ_{max}(DCM)/nm 267 (log ε 3.00); ν_{max}/cm^{-1} 2232w (C≡N), 1479m, 1371w, 1360w, 1325s, 1221w, 1076w, 1070w, 953w, 810s, 781m; δ_C(75 MHz; $CDCl_3$). 151.3, 118.8, 112.8, 111.5; *m*/*z* (EI) 272 (M$^+$+2, 35%), 270 (M$^+$, 100), 209 (M$^+$-CClN, 28), 177 (M$^+$-CClNS, 3), 143 (M$^+$-I, 14), 127 (I$^+$, 24), 108 (M$^+$-ClI, 15), 93 (CClNS$^+$, 4), 82 (C_3NS^+, 67), 70 (3), 56 (4) (Found: M$^+$, 269.8510, C_4ClIN_2S requires *M*, 269.8516). Further elution (hexane-DCM, 3:2) gave *3-chloroisothiazole-4-carbonitrile* **205** (7 mg, 16%) as colourless needles, mp 50-51 ^oC (from pentane); (Found: C, 33.3; H, 0.7; N, 19.4. C_4HClN_2S requires C, 33.2; H, 0.7; N, 19.4%); λ_{max}(DCM)/nm 263 (log ε 3.02); ν_{max}/cm^{-1} 3109w and 3098w (CH), 2241w (C≡N), 1497m, 1368w, 1356w, 1335s, 1207w, 1153w, 1144w, 1061m, 1047m, 866m, 841m, 829m, 822m, 816m, 731w; δ_H(300 MHz; $CDCl_3$) 9.23 (1H, s, *H-5*); δ_C(75 MHz; $CDCl_3$) 158.4 (*C*H), 151.2, 111.0, 109.7;

δ_C(75 MHz; DEPT 90, $CDCl_3$) 158.3 (*C*H); *m*/*z* (EI) 146 (M^++2, 37%), 144 (M^+, 100), 108 (M^+-HCl, 1), 93 ($CClNS^+$, 40), 83 (C_3HNS^+, 92), 82 (23), 58 (6), 51 (13). Finally elution (hexane-acetone, 1:4) gave a trace of *5,5'-(triaz-1-ene-1,3-diyl)bis(3-chloro-isothiazole-4-carbonitrile)* **206** (1 mg, 1%) as orange needles, mp > 300 °C (from cyclohexane-EtOH); λ_{max}(EtOH)/nm 203 (log ε 3.23), 245 (2.78), 301 (2.33), 432 (3.19); ν_{max}/cm^{-1} 3402br & w (NH), 2241w (C≡N), 1647w, 1514m, 1493m, 1431w, 1389w, 1360w, 1265s, 1238s, 1180m, 1057s, 1026w, 891m, 874w, 812w, 791w, 772w; δ_H(300 MHz; $CDCl_3$) 9.23 (1H, br s, N*H*); δ_C(75 MHz; DMSO-d_6) 184.7, 170.2, 146.9, 145.6, 113.1 (*C*≡N), 112.7 (*C*≡N), 97.7 [*C*(C≡N)], 91.6 [*C*(C≡N)]; *m*/*z* (EI) 272 (M^++2, 35%), 270 (M^+, 100), 209 (28),177 (3), 145 (5), 143 (14), 127 (24), 108 (15), 93 (4), 84 (3), 83 (3), 82 (67), 70 (3), 56 (4) (Found: M^+, 269.8510, $C_8HCl_2N_7S_2$ requires *M*, 328.9112).

3-Chloro-5-phenylisothiazole-4-carbonitrile 207

(typical Suzuki conditions for coupling at C-5: see Table 9)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **5** (53.4 mg, 0.3 mmol), phenylboronic acid (73.2 mg, 0.6 mmol), KF (61 mg, 1.05 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol%) and 18-crown-6 (40 mg, 0.15 mmol) in toluene (2 ml) was heated to *ca.* 110 °C until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C and chromatography (hexane-DCM, 3 : 1) gave the title compound **207** (60 mg, 91%) as colourless needles, mp 87-88 °C (from cyclohexane) (lit.,[69] 85-86 °C); λ_{max}(DCM)/nm 280 (log ε 4.30); ν_{max}(Nujol)/cm^{-1} 3036m (Ar CH), 2231s (C≡N), 1517s, 1489s, 1447s, 1397s, 1389m, 1348s, 1313m, 1242m, 1108s, 1055s, 1029m, 999m, 951s, 920m, 831s, 817m, 765s, 693s, 685s, 664s; δ_H (300 MHz; $CDCl_3$) 7.78-7.75 (2H, m, Ar *H*), 7.59-7.53 (3H, m, Ar *H*); δ_C (75 MHz; $CDCl_3$) 176.4, 151.3, 132.3 (Ar *C*H), 129.8 (Ar *C*H), 127.3 (Ar *C*), 127.2 (Ar *C*H), 112.1 (*C*≡N), 105.0; δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.3 (Ar *C*H), 129.8 (Ar *C*H), 127.2 (Ar *C*H); *m*/*z* (EI) 220 (M^+,100%), 185 (M^+-Cl, 18), 174 (M^+-NS, 4), 159 (9), 153 (2), 141 (6), 127 (M^+-CClNS, 6), 114 (5), 100 (3), 93 ($CClNS^+$, 5), 77 ($C_6H_5^+$, 7), 69 (3), 51 (8) (Found: M^+, 219.9864, $C_{10}H_5ClN_2S$ requires *M*, 219.9862).

3-Chloro-5-(2-tolyl)isothiazole-4-carbonitrile 208

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 2-tolylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **208** (95%) as colourless crystals, mp 91-92 °C (from cyclohexane) (Found: C, 56.2; H, 2.9; N, 12.0. $C_{11}H_7ClN_2S$ requires

C, 56.3; H, 3.0; N, 11.9%); λ_{max}(DCM)/nm 269 (log ε 4.02); ν_{max}(Nujol)/cm^{-1} 2233s (C≡N), 1516s, 1488s, 1454s, 1391s, 1380m, 1344s, 1243s, 1200m, 1120m, 1058s, 1044m, 1036m, 948m, 837s, 809s, 784m, 762s, 719s, 657m, 600m, 596m; δ_H (300 MHz; $CDCl_3$) 7.49-7.31 (4H, m, Ar *H*), 2.41 (3H, s, C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 177.0, 150.4, 136.35 (Ar *C*), 131.5 (Ar *C*H), 131.4 (Ar *C*H), 129.7 (Ar *C*H), 126.6 (Ar *C*H), 126.4 (Ar *C*), 111.5 (*C*≡N), 108.7, 20.2 (*C*H$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.5 (Ar *C*H), 131.4 (Ar *C*H), 129.7 (Ar *C*H), 126.6 (Ar *C*H); *m*/*z* (EI) 234 (M^+, 49%), 199 (M^+-Cl, 100), 172 (M^+-CHClN, 41), 165 (2), 155 (8), 145 (5), 140 (11), 134 (11), 128 (4), 114 (3), 113 (3), 99 (2), 93 ($CClNS^+$, 4), 91 ($C_7H_7^+$, 4), 89 (4), 75 (4), 63 (6), 51 (5) (Found: M^+, 234.0022, $C_{11}H_7ClN_2S$ requires *M*, 234.0018).

3-Chloro-5-(3-tolyl)isothiazole-4-carbonitrile 209

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 3-tolylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **209** (99%) as colourless crystals, mp 86-87 ^oC (from cyclohexane) (Found: C, 56.3; H, 2.9; N, 11.7; $C_{11}H_7ClN_2S$ requires C, 56.3; H, 3.0; N, 11.9%); λ_{max}(DCM)/nm 281 (log ε 4.32); ν_{max}(Nujol)/cm^{-1} 2233s (C≡N), 1516s, 1486m, 1462m, 1392m, 1379m, 1346s, 1321m, 1265m, 1068s, 919m, 817m, 792s, 773m, 702s, 689m, 596m, 591m; δ_H (300 MHz; $CDCl_3$) 7.56-7.54 (2H, m, Ar *H*), 7.47-7.37 (2H, m, Ar *H*), 2.45 (3H, s, C*H*$_3$); δ_C (75 MHz; $CDCl_3$) 176.7, 151.3, 139.9 (Ar *C*), 133.2 (Ar *C*H), 129.7 (Ar *C*H), 127.7 (Ar *C*H), 127.2 (Ar *C*), 124.3 (Ar *C*H), 112.2 (*C*≡N), 104.8, 21.3 (*C*H$_3$);); δ_C(75 MHz; DEPT 90, $CDCl_3$) 133.2 (Ar *C*H), 129.7 (Ar *C*H), 127.7 (Ar *C*H), 124.3 (Ar *C*H); *m*/*z* (EI) 234 (M^+, 100%), 206 (3), 199 (M^+-Cl, 85), 172 (M^+-CHClN, 31), 165 (4), 155 (11), 145 (5), 140 (12), 134 (6), 128 (6), 117 (6), 114 (5), 113 (4), 93 ($CClNS^+$, 4), 91 ($C_7H_7^+$, 4), 69 (4), 65 (8), 63 (6), 51 (5) (Found: M^+, 234.0019, $C_{11}H_7ClN_2S$ requires *M*, 234.0018).

3-Chloro-5-(2-methoxyphenyl)isothiazole-4-carbonitrile 210

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 2-methoxyphenyl-boronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **210** (89%) as colourless needles, mp 157-158 ^oC (from cyclohexane) (Found: C, 52.8; H, 2.7; N, 11.3. $C_{11}H_7ClN_2OS$ requires C, 52.7; H, 2.8; N, 11.2%); λ_{max}(DCM)/nm 284 (log ε 4.24), 294 (4.17), 331 (4.12); ν_{max}(Nujol)/cm^{-1} 2220s (C≡N), 1600s, 1576s, 1507s, 1468s, 1436s, 1397m, 1340s, 1302s, 1262s, 1234s, 1192m, 1128s, 1057m, 1033s, 1016s, 944m, 837s,

823s, 757s, 741m, 690s, 661s, 603m, 583m, 570m; δ_H (300 MHz; $CDCl_3$) 8.39 (1H, dd, *J* 7.9, 1.6, Ar*H*), 7.54 (1H, ddd, *J* 8.4, 7.4, 1.55, Ar *H*), 7.16 (1H, ddd, *J* 8.0, 7.4, 1.1, Ar *H*), 7.10 (1H, app. d, *J* 8.4, Ar *H*), 4.06 (3H, s, CH_3O); δ_C (75 MHz; $CDCl_3$) 169.9, 156.6, 150.0, 133.4 (Ar *C*H), 127.2 (Ar *C*H), 121.6 (Ar *C*H), 117.2, 113.7 (*C*≡N), 111.5 (Ar *C*H), 103.2, 55.8 (*C*H_3O);); δ_C(75 MHz; DEPT 90, $CDCl_3$) 133.4 (Ar *C*H), 127.2 (Ar *C*H), 121.6 (Ar *C*H), 111.5 (Ar *C*H); *m*/*z* (EI) 250 (M^+, 100%), 235 (M^+-CH_3, 1), 223 (M^+-CHN, 6), 221 (M^+-CHO, 12), 215 (M^+-Cl, 74), 207 (12), 200 (6), 187 (14), 183 (11), 182 (11), 174 (11), 171 (7), 156 (M^+-CHClNS, 5), 146 (35), 137 (6), 133 (7), 127 (5), 120 (7), 114 (12), 109 (5), 102 (6), 93 ($CClNS^+$, 5), 88 (6), 69 (9), 63 (7), 51 (6), 50 (5) (Found: M^+, 249.9956, $C_{11}H_7ClN_2OS$ requires *M*, 249.9968).

3-Chloro-5-(3-methoxyphenyl)isothiazole-4-carbonitrile 211

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 3-methoxyphenyl-boronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **211** (96%) as colourless needles, mp 103-104 °C (from cyclohexane) (Found: C, 52.7; H, 2.7; N, 11.1. $C_{11}H_7ClN_2OS$ requires C, 52.7; H, 2.8; N, 11.2%); λ_{max}(DCM)/nm 247 (log ε 4.18), 280 (4.32), 310 inf. (3.88); ν_{max}(Nujol)/cm^{-1} 3074m, 3013m (Ar CH), 2235s (C≡N), 1605s, 1579s, 1514s, 1483s, 1427m, 1389s, 1345s, 1320m, 1290s, 1275s, 1208s, 1175s, 1105m, 1059s, 1036s, 973s, 886s, 867s, 816s, 795s, 773s, 702s, 689s, 662m, 595m, 565m, 546m; δ_H (300 MHz; $CDCl_3$) 7.47 (1H, app. t, *J* 7.9, Ar *H*), 7.34-7.28 (2H, m, Ar *H*), 7.12 (1H, app. d, *J* 8.3, Ar *H*), 3.89 (3H, d, *J* 1.2, CH_3O); δ_C (75 MHz; $CDCl_3$) 176.3, 160.3, 151.2, 130.95 (Ar *C*H), 128.3 (Ar *C*), 119.5 (Ar *C*H), 118.15 (Ar *C*H), 112.2 (Ar *C*H), 112.1 (*C*≡N), 105.0, 55.5 (*C*H_3O);); δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.95 (Ar *C*H), 119.5 (Ar *C*H), 118.15 (Ar *C*H), 112.2 (Ar *C*H); *m*/*z* (EI) 250 (M^+, 100%), 235 (M^+-CH_3, 1), 221 (M^+-CHO, 24), 215 (M^+-Cl, 1), 207(12), 200 (1), 185 (13), 171 (8), 159 (6), 146 (22), 141 (3), 125 (3), 114 (7), 108 (3), 102 (3), 93 ($CClNS^+$, 4), 88 (3), 69 (5), 63 (6), 51 (3) (Found: M^+, 249.9957, $C_{11}H_7ClN_2OS$ requires *M*, 249.9968).

3-Chloro-5-(4-methoxyphenyl)isothiazole-4-carbonitrile 212

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 4-methoxyphenyl-boronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the title compound **212** (95%) as colourless needles, mp 133-134 °C (from cyclohexane) (lit.,[276] 122-126 °C); λ_{max}(DCM)/nm 285 inf. (log ε 4.01), 320 (4.35); ν_{max}(Nujol)/cm^{-1} 3013m (Ar CH), 2230s

(C≡N), 1603s, 1573s, 1527m, 1495s, 1465s, 1451s, 1404s, 1379m, 1347s, 1315s, 1270s, 1182s, 1151m, 1137m, 1126m, 1048s, 1027s, 1006s, 955s, 834s, 811s, 803s, 781m, 724m, 688s, 629s, 579s, 571s, 516s; δ_H (300 MHz; $CDCl_3$) 7.74 (2H, d, *J* 8.6, Ar *H*-2), 7.04 (2H, d, *J* 8.7, Ar *H*-3), 3.89 (3H, s, C*H*$_3$O); δ_C (75 MHz; $CDCl_3$) 176.15, 162.8, 151.2, 128.8 (Ar *C*H-2 & 6), 119.9, 115.2 (Ar *C*H-3 & 5), 112.6 (C≡N), 103.6, 56.6 (*C*H$_3$O); δ_C(75 MHz; DEPT 90, $CDCl_3$) 128.8 (Ar *C*H-2 & 6), 115.2 (Ar *C*H-3 & 5); *m*/*z* (EI) 250 (M^+, 100%), 235 (M^+-CH_3, 14), 220 (M^+-CHO, 1), 207 (20), 181 (2), 171 (4), 157 (2), 146 (20), 114 (6), 108 (2), 102 (2), 93 ($CClNS^+$, 3), 88 (4), 69 (4), 63 (4), 51 (2) (Found: M^+, 249.9956, $C_{11}H_7ClN_2OS$ requires *M*, 249.9968).

3-Chloro-5-(2-chlorophenyl)isothiazole-4-carbonitrile 213

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 2-chlorophenylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 required after 48 h an extra addition of 2-chlorophenylboronic acid (0.7 equiv.) and $Pd(OAc)_2$ (3 mol%) to drive the reaction to completion and gave the title compound **213** (89%) as colourless needles, mp 99 °C (from cyclohexane) (lit.,[69] 97-98 °C); λ_{max}(DCM)/nm 235 inf. (log ε 3.79), 277 (4.23); ν_{max}(Nujol)/ cm^{-1} 2234s (C≡N), 1589m, 1512m, 1464s, 1436m, 1387m, 1348s, 1076s, 1040s, 950m, 836m, 755s, 719m, 710m, 694m, 648m, 595m, 585m; δ_H (300 MHz; $CDCl_3$) 7.66-7.59 (2H, m, Ar *H*), 7.54-7.43 (2H, m, Ar *H*); δ_C (75 MHz; $CDCl_3$) 173.0, 150.5, 132.8, 132.7 (Ar *C*H), 131.0 (Ar *C*H), 130.7 (Ar *C*H), 127.7 (Ar *C*H), 126.3 (Ar *C*), 111.5 (*C*≡N), 108.9; δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.7 (Ar *C*H), 131.0 (Ar *C*H), 130.7 (Ar *C*H), 127.7 (Ar *C*H); *m*/*z* (EI) 254 (M^+, 100%), 219 (M^+-Cl, 23), 208 (M^+-NS, 4), 193 (M^+-CClN, 8), 184 (M^+-Cl_2, 12), 175 (7), 161 (M^+-CClNS, 10), 158 (14), 139 (2), 126 (4), 114 (9), 111 (4), 99 (6), 93 ($CClNS^-$, 12), 87 (3), 75 (10), 69 (4), 50 (6) (Found: M^+, 253.9462, $C_{10}H_4Cl_2N_2S$ requires *M*, 253.9472).

3-Chloro-5-(3-chlorophenyl)isothiazole-4-carbonitrile 214

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 3-chlorophenylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 required after 48 h an extra addition of 3-chlorophenylboronic acid (0.7 equiv.) and $Pd(OAc)_2$ (3 mol%) to drive the reaction to completion and gave the title compound **214** (91%) as colourless needles, mp 103-104 °C (from cyclohexane) (lit.,[276] 99.5-101 °C); λ_{max}(DCM)/nm 277 (log ε 4.25); ν_{max}(Nujol)/cm^{-1} 3057s (Ar CH), 2237s (C≡N), 1566s, 1512s, 1476s, 1414m, 1392m,

1347s, 1312m, 1106s, 1084s, 1061s, 997m, 905s, 861m, 814m, 795s, 728s, 701s, 683s, 600m, 590m; δ_H (300 MHz; $CDCl_3$) 7.72-7.66 (2H, m, Ar *H*), 7.59-7.49 (2H, m, Ar *H*); δ_C (75 MHz; $CDCl_3$) 174.6, 151.6, 136.0 (Ar *C*), 132.3 (Ar *C*H), 131.2 (Ar *C*H), 128.9 (Ar *C*), 127.3 (Ar *C*H), 125.4 (Ar *C*H), 111.7 (*C*≡N), 105.8; δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.3 (Ar *C*H), 131.2 (Ar *C*H), 127.3 (Ar *C*H), 125.4 (Ar *C*H); *m*/*z* (EI) 254 (M^+, 100%), 219 (M^+-Cl, 21), 208 (M^+-NS, 3), 193 (M^+-CClN, 6), 184 (M^+-Cl_2, 8), 175 (7), 161 (M^+-CClNS, 5), 158 (8), 139 (1), 126 (2), 114 (6), 111 (5), 99 (4), 93 ($CClNS^+$, 9), 87 (2), 75 (10), 69 (4), 50 (5) (Found: M^+, 253.9480, $C_{10}H_4Cl_2N_2S$ requires *M*, 253.9472).

3-Chloro-5-(4-chlorophenyl)isothiazole-4-carbonitrile 215

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 4-chlorophenylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the title compound **215** (97%) as colourless needles, mp 117-119 °C (from cyclohexane) (lit.,[69] 119 °C); λ_{max}(DCM)/nm 285 (log ε 4.44); ν_{max}(Nujol)/cm^{-1} 2229s (C≡N), 1910m, 1595s, 1517s, 1483s, 1404s, 1395s, 1378m, 1341s, 1305m, 1272m, 1251s, 1188m, 1114m, 1098s, 1048s, 1014s, 967m, 842s, 823s, 715s, 690s, 608s, 579m; δ_H (300 MHz; $CDCl_3$) 7.72 (2H, d, *J* 8.8, Ar *H*), 7.54 (2H, d, *J* 8.8, Ar *H*); δ_C (75 MHz; $CDCl_3$) 175.0, 151.6, 138.8 (Ar *C*), 130.2 (Ar *C*H), 128.5 (Ar *C*H), 125.7, (Ar *C*), 111.9 (*C*≡N), 105.4; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.2 (Ar *C*H), 128.5 (Ar *C*H); *m*/*z* (EI) 254 (M^+, 100%), 219 (M+-Cl, 18), 208 (M^+-NS, 4), 193 (M^+-CClN, 6), 184 (M^+-2Cl, 8), 175 (6), 161 (M^+-CClNS, 7), 158 (5), 139 (1), 126 (3), 114 (6), 111 (5), 99 (3), 93 ($CClNS^+$, 8), 87 (2), 75 (9), 69 (4), 50 (5) (Found: M^+, 253.9479, $C_{10}H_4Cl_2N_2S$ requires *M*, 253.9472).

3-Chloro-5-(3-nitrophenyl)isothiazole-4-carbonitrile 216

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 3-nitrophenylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 required after 48 h an extra addition of 3-nitrophenylboronic acid (0.7 equiv.), KF (2 equiv.) and $Pd(OAc)_2$ (5 mol%) to drive the reaction to completion and gave the *title compound* **216** (43%) as colourless needles, mp 135-136 °C (from cyclohexane) (Found: C, 45.0; H, 1.3; N, 15.7. $C_{10}H_4ClN_3O_2S$ requires C, 45.2; H, 1.5; N, 15.8%); λ_{max}(DCM)/nm 265 (log ε 4.38); ν_{max}(Nujol)/cm^{-1} 2233m (C≡N), 1616m, 1532s, 1508s, 1479s, 1463s, 1354s, 1343s, 1293m, 1063s, 908m, 896m, 826m, 810s, 738s, 709s, 698s, 671m; δ_H (300 MHz; $CDCl_3$) 8.56 (1H, t, *J* 2.0, Ar

H-2), 8.46 (1H, app. d, *J* 8.3, Ar *H*), 8.14 (1H, app. d, *J* 7.8, Ar *H*), 7.82 (1H, dd, *J* 8.2, 7.9, Ar *H*-5); δ_C (75 MHz; $CDCl_3$) 173.3, 152.0, 148.8, 132.75 (Ar *C*H), 131.3 (Ar *C*H), 128.8 (Ar *C*), 126.55 (Ar *C*H), 122.5 (Ar *C*H), 111.4 (*C*≡N), 106.8; δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.75 (Ar *C*H), 131.3 (Ar *C*H), 126.55 (Ar *C*H), 122.5 (Ar *C*H); *m*/*z* (EI) 265 (M^+, 100%), 235 (M^+-NO, 5), 219 (18), 207 (18), 199 (3), 184 (23), 158 (25), 146 (8), 114 (34), 93 ($CClNS^+$, 8), 69 (7), 56 (10) (Found: M^+, 264.9720, $C_{10}H_4ClN_3O_2S$ requires *M*, 264.9713).

3-Chloro-5-(4-vinylphenyl)isothiazole-4-carbonitrile 217

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 4-vinylphenylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave after chromatography the crude product together with a co-running insoluble yellow by-product. Repeated fractional crystallization gave the *title compound* **217** (30%) as pale yellow needles, mp 104-105 °C (from cyclohexane) (Found: C, 58.7; H, 2.7; N, 11.5. $C_{12}H_7ClN_2S$ requires C, 58.4; H, 2.8; N, 11.4%); λ_{max}(DCM)/nm 295 inf. (log ε 4.28), 317 (4.46); ν_{max}(Nujol)/cm^{-1} 2229s (C≡N), 1628m, 1600m, 1557m, 1525m, 1496s, 1464m, 1424m, 1401s, 1340s, 1298m, 1245m, 1133m, 1051s, 1035m, 1025m, 992s, 953m, 919s, 840s, 817m, 770m, 692s; δ_H (300 MHz; $CDCl_3$) 7.75 (2H, d, *J* 8.5, Ar *H*), 7.57 (2H, d, *J* 8.5, Ar *H*), 6.51 (1H, dd, *J* 17.6, 10.9, CH=CH_2 *trans*), 5.90 (1H, d, *J* 17.6, C*H*=CH_2), 5.44 (1H, d, *J* 10.9, CH=CH_2 *cis*); δ_C (75 MHz; $CDCl_3$) 176.0, 151.5, 141.6, 135.4 (Ar *C*H or *C*HC=CH_2), 127.5 (Ar *C*H or *C*HC=CH_2), 127.45 (Ar *C*H or *C*HC=CH_2), 126.45 (Ar *C*), 117.25 (CH=*C*H_2), 112.3 (*C*≡N), 104.7; δ_C(75 MHz; DEPT 90, $CDCl_3$) 135.4 (Ar *C*H or *C*HC=CH_2), 127.5 (Ar *C*H or *C*HC=CH_2), 127.45 (Ar *C*H or *C*HC=CH_2), 117.25 (CH=*C*H_2); *m*/*z* (EI) 246 (M^+, 100%), 220 (M^+-CN, 3), 211 (M^+-Cl, 10), 184 (8), 178 (5), 167 (3), 157 (6), 153 (M^+-CNClS, 5), 140 (10), 114 (3), 102 (3), 93 ($CNClS^+$, 6), 82 (2), 77 (6), 70 (5), 63 (5), 51 (6) (Found: M^+, 246.0017, $C_{12}H_7ClN_2S$ requires *M*, 246.0018).

3-Chloro-5-(3-thienyl)isothiazole-4-carbonitrile 219

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with 3-thienylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **219** (93%) as colourless crystals, mp 117-118 °C (from cyclohexane) (Found: C, 42.1; H, 1.1; N, 12.2. $C_8H_3ClN_2S_2$ requires C, 42.4; H, 1.3; N, 12.4%); λ_{max}(DCM)/nm 293 (log ε 4.38); ν_{max}(Nujol)/cm^{-1} 3103s, 3076m, 3070m Ar CH), 2230s (C≡N), 1533s, 1524s, 1508s, 1485m, 1464m,

1456m, 1432s, 1384s, 1360s, 1338s, 1212s, 1058s, 863m, 828m, 812m, 805m, 786s, 759m, 704s, 696s, 632s, 550s; δ_H (300 MHz; $CDCl_3$) 8.10 (1H, dd, *J* 2.8, 1.4, thienyl *H*-2), 7.53 (1H, dd, *J* 5.2, 2.9, thienyl *H*), 7.47 (1H, dd, *J* 5.2, 1.4, thienyl *H*); δ_C (75 MHz; $CDCl_3$) 170.0, 151.0, 128.5 (thienyl *C*H), 127.7 (thienyl *C*H), 127.3 (thienyl *C*), 125.4 (thienyl *C*H), 112.4 (*C*≡N), 104.0; δ_C(75 MHz; DEPT 90, $CDCl_3$) 128.5 (thienyl *C*H), 127.7 (thienyl *C*H), 125.4 (thienyl *C*H); *m*/*z* (EI) 226 (M^+, 100%), 199 (M^+-CHN, 6), 191 (M^+-Cl, 15), 182 (3), 180 (M^+-NS, 2), 165 (M^+-CClN, 37), 147 (13), 133 (M^+-CClNS, 6), 127 (3), 121 (4), 93 ($CClNS^+$, 6), 82 (4), 69 (6), 58 (5) (Found: M^+, 225.9419. $C_8H_3ClN_2S_2$ requires *M*, 225.9426).

3-Chloro-5-methylisothiazole-4-carbonitrile 220

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **5** with methylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **220** (67%) as colourless crystals, mp 53-54 °C (from cyclohexane) (Found: C, 38.0; H, 1.8; N, 17.6. $C_5H_3ClN_2S$ requires C, 37.9; H, 1.9; N, 17.7%); λ_{max}(DCM)/nm 259 (log ε 3.96); ν_{max}(Nujol)/cm^{-1} 2233s (C≡N), 1520m, 1403m, 1380m, 1345s, 1193s, 1105m, 954m, 816m, 645m, 546m; δ_H (300 MHz; $CDCl_3$) 2.74 (3H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 175.2 (*C*-3), 150.0 (*C*-5), 111.0 (*C*≡N), 109.1 (*C*-4), 13.7 (*C*H_3); δ_C (75 MHz; coupled, $CDCl_3$) 175.2 (q, *J* 6.9, *C*-3), 150.0 (q, *J* 1.1, *C*-5), 111.0 (*C*≡N), 109.1 (q, *J* 4.8, *C*-4), 13.7 (q, *J* 132.3, *C*H_3); *m*/*z* (EI) 158 (M^+, 100%), 131 (M^+-CHN, 5), 123 (M^+-Cl, 92), 108 (3), 96 (M^+-CHClN, 20), 93 ($CClNS^-$, 14), 79 (6), 70 (17), 64 (11), 59 (10) (Found: M^+, 157.9717. $C_5H_3ClN_2S$ requires *M*, 157.9705).

3-Chloro-5-(2-thienyl)isothiazole-4-carbonitrile 218 from 2-(2-thienylmethylene)-malononitrile 221

To a stirred solution of 2-(2-thienylmethylene)malononitrile **221** (160 mg, 1 mmol) in pyridine (3 ml) at *ca.* 20 °C, S_2Cl_2 (320 μl, 4 mmol) was added and the mixture was heated to *ca.* 115 °C for 24 h. The mixture was allowed to cool to *ca.* 20 °C and chromatography (hexane-DCM, 3 : 1) gave the *title compound* **218** (29%) as colourless crystals, mp 115-117 °C (from cyclohexane); λ_{max}(DCM)/nm 327 (log ε 4.14), 279 (3.91); ν_{max}(Nujol)/cm^{-1} 3106m, 3082m (thienyl CH), 2227m (C≡N), 1537s, 1523m, 1482s, 1466m, 1418s, 1347s, 1338s, 1231m, 1063m, 1037s, 859m, 850m, 811s, 736m, 710s, 693m; δ_H (300 MHz; $CDCl_3$) 7.76 (1H, dd, *J* 3.8, 1.1, thienyl *H*-3), 7.66 (1H, dd, *J*

5.1, 1.1, thienyl *H*-5), 7.23 (1H, dd, *J* 5.1, 3.8, thienyl *H*-4); δ_C (75 MHz; $CDCl_3$) 168.8, 151.0, 131.2 (thienyl *C*H), 129.7 (thienyl *C*H), 129.0 (thienyl *C*H), 128.4 (thienyl *C*), 112.1 (*C*≡N), 103.6; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.2 (thienyl *C*H), 129.7 (thienyl *C*H), 129.0 (thienyl *C*H); *m*/*z* (EI) 226 (M^+, 100%), 199 (M^+-CHN, 4), 191 (M^+-Cl, 17), 182 (7), 180 (M^+-NS, 4), 165 (M^+-CClN, 10), 159 (2), 147 (17), 133 (M^+-CClNS, 10), 127 (3), 121 (5), 93 ($CClNS^+$, 6), 82 (4), 69 (10), 58 (8) (Found: M^+, 225.9419. $C_8H_3ClN_2S_2$ requires *M*, 225.9426).

3-Chloro-5-(3-thienyl)isothiazole-4-carbonitrile 219 from 2-(3-thienylmethylene)-malononitrile 222

Similar treatment of 2-(3-thienylmethylene)malononitrile **222** with S_2Cl_2 in pyridine gave the title compound **219** (30%) as colourless crystals, mp 117-118 ^oC (from cyclohexane) identical to that described above.

3-Bromo-5-phenylisothiazole-4-carbonitrile 223

A stirred mixture of 3,5-dibromoisothiazole-4-carbonitrile **6** (80.4 mg, 0.3 mmol), phenylboronic acid (73.2 mg, 0.6 mmol), KF (61 mg, 1.05 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol%), 18-crown-6 (0.5 equiv.) in toluene (2 ml) was heated to *ca.* 110 ^oC until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC and chromatography (hexane-DCM, 3 : 1) gave the *title compound* **223** (77 mg, 97%) as colourless crystals, mp 93-94 ^oC (from cyclohexane) (Found: C, 45.6; H, 2.0; N, 10.4. $C_{10}H_5BrN_2S$ requires C, 45.3; H, 1.9; N, 10.6%); λ_{max}(DCM)/nm 281 (log ε 4.26); ν_{max}(Nujol)/cm^{-1} 3034m (Ar CH), 2236s (C≡N), 1517s, 1483s, 1457m, 1445s, 1393s, 1377m, 1337s, 1318m, 1249m, 1240s, 1287m, 1080m, 1040s, 1021m, 998s, 966m, 823m, 789m, 762s, 694s, 667s, 585m, 576m; δ_H (300 MHz; $CDCl_3$) 7.79-7.75 (2H, m, Ar *H*), 7.62-7.53 (3H, m, Ar *H*); δ_C (75 MHz; $CDCl_3$) 176.4, 139.8, 132.3 (Ar *C*H), 129.9 (Ar *C*H), 127.3 (Ar *C*H), 127.2 (Ar *C*), 112.7 (*C*≡N), 108.4; δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.3 (Ar *C*H), 129.9 (Ar *C*H), 127.3 (Ar *C*H); *m*/*z* (EI) 264 (M^+, 100%), 218 (M^+-NS, 4), 185 (38), 184 (M^+-Br, 14), 158 (M^+-CBrN, 18), 153 (6), 141 (21), 127 (6), 114 (12), 100 (4), 84 (53), 77 ($C_6H_5^+$, 7), 69 (4), 63 (4), 51 (4), 49 (68) (Found: M^+, 263.9356. $C_{10}H_5BrN_2S$ requires *M*, 263.9357).

3-Chloro-5-phenylisothiazole-4-carbonitrile 207 (typical organotrifluoroborate procedure)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **5** (53.4 mg, 0.3 mmol), potassium phenyltrifluoroborate (83 mg, 0.45 mmol), powdered K_2CO_3 (62 mg, 0.45 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol%) and 18-crown-6 (40 mg, 0.15 mmol) in PhMe (2 ml) was heated to *ca.* 110 ^oC until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC and chromatography (hexane-DCM, 3 : 1) gave the title compound **207** (65 mg, 99%) as colourless needles, mp 87-88 ^oC (from cyclohexane) identical to that described above.

3-Bromo-5-phenylisothiazole-4-carbonitrile 223

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with potassium phenyltrifluoroborate, K_2CO_3, $Pd(OAc)_2$ and 18-crown-6 gave the title compound **223** (99%) as colourless crystals, mp 93-94 ^oC (from cyclohexane) identical to that described above.

3-Chloro-5-phenylisothiazole-4-carbonitrile 207 (typical Stille coupling conditions at C-5: Table 11)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **5** (30 mg, 0.168 mmol), tributylphenyltin (109.7 μl, 0.336 mmol, 2 equiv.) and $Pd(OAc)_2$ (1.9 mg, 5 mol%) in DMF (2 ml) protected with a $CaCl_2$ drying tube, was heated to *ca.* 100 ^oC, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC, diluted with DCM (15 ml) and washed with H_2O (4 x 10 ml). The organic layer was separated, dried and the volatiles evaporated. The residue obtained was absorbed on silica and chromatography (hexane-DCM, 7:3) gave the title compound **207** (31.1 mg, 84%) as colourless needles, mp 87-88 ^oC (from cyclohexane) identical to that described above.

3-Bromo-5-phenylisothiazole-4-carbonitrile 223

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with tributylphenyltin (1.2 equiv.) and $Pd(OAc)_2$ in DMF gave the *title compound* **223** (90%) as colourless needles, mp 93-94 ^oC (from cyclohexane) identical to that described above.

3-Bromo-5-(fur-2-yl)isothiazole-4-carbonitrile 224

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with 2-(tributylstannyl)-furan (1.2 equiv.) and $Pd(OAc)_2$ in MeCN (2 ml) gave the *title compound* **224** (100%) as colourless needles, mp 100-101 ^oC (from cyclohexane); (Found: C, 37.6; H, 1.2; N, 11.1. $C_8H_3BrN_2OS$ requires C, 37.7; H, 1.2; N, 11.0%); λ_{max}(DCM)/nm 233 (log ε 2.79), 325 (3.18); ν_{max}/cm^{-1} 3136w and 3123 (furyl CH), 2228w (C≡N), 1582m, 1503s, 1477w, 1389w, 1371w, 1340w, 1327m, 1256m, 1225w, 1076w, 1061w, 1053w, 1020s, 986w, 893w, 881m, 827w, 808m, 800m, 748s; δ_H(300 MHz; $CDCl_3$) 7.64 (1H, d, *J* 1.8, furyl *H-5*), 7.39 (1H, d, *J* 3.7, furyl *H-3*), 6.68 (1H, dd, *J* 3.7, 1.8, furyl *H-4*); δ_C(75 MHz; $CDCl_3$) 163.5, 146.0 (furyl *C*H), 142.8, 138.7, 113.9 (furyl *C*H), 113.4 (furyl *C*H), 112.4 (*C*≡N), 104.7 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 146.0 (furyl *C*H), 113.9 (furyl *C*H), 113.4 (furyl *C*H); *m*/*z* (EI) 256 (M^++2, 100), 254 (M^+, 100), 227 (14), 225 (14), 175 (8), 147 (84), 131 (62), 120 (23), 117 (14), 111 (10), 103 (15), 94 (25), 88 (46), 82 (27), 76 (22), 69 (24), 61 (25) (Found: M^+, 253.9159, $C_8H_3BrN_2OS$ requires *M*, 253.9149).

3-Bromo-5-(thien-2-yl)isothiazole-4-carbonitrile 225

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with 2-(tributylstannyl)-thiophene (1 equiv.) and $Pd(OAc)_2$ in MeCN (2 ml) gave the *title compound* **225** (93%) as colourless needles, mp 134-135 ^oC (from cyclohexane); (Found: C, 35.3; 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 3.54), 281 (3.59), 329 (3.84); ν_{max}/cm^{-1} 3105w and 3078w (thienyl CH), 2226w (C≡N), 1568w, 1531m, 1477m, 1418m, 1333m, 1223w, 1063w, 1016m, 858w, 802m, 739w, 710s; δ_H(300 MHz; $CDCl_3$) 7.66 (1H, dd, *J* 3.8, 1.1, thienyl *H-3*), 7.56 (1H, dd, *J* 5.1, 1.1, thienyl *H-5*), 7.13 (1H, dd, *J* 5.1, 3.8 thienyl *H-4*); δ_C(75 MHz; $CDCl_3$) 168.8, 139.4, 131.3 (thienyl *C*H), 129.8 (thienyl *C*H), 129.05 (thienyl *C*H), 128.2, 112.7 (*C*≡N), 106.3 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.3 (thienyl *C*H), 129.8 (thienyl *C*H), 129.05 (thienyl *C*H); *m*/*z* (EI) 272 (M^++2, 100), 270 (M^+, 97), 243 (M^+-HCN, 2), 226 (5), 226 (7), 223 (3), 191 (48), 164 (6), 159 (6), 147 (67), 133 (15), 127 (12), 120 (7), 94 (10), 88 (10), 82 (9), 69 (24), 58 (15) (Found: M^+, 269.8927, $C_8H_3BrN_2S_2$ requires *M*, 269.8921).

3-Bromo-5-vinylisothiazole-4-carbonitrile 226

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with tributyl(vinyl)tin (1.2 equiv.) and $Pd(OAc)_2$ in MeCN (2 ml) gave the *title compound* **226** (94%) as colourless needles, mp 34-35 ^oC (from pentane); (Found: C, 33.6; H, 1.4; N, 13.0. $C_6H_3BrN_2S$ requires C, 33.5; H, 1.4; N, 13.0%); λ_{max}(DCM)/nm 271 (log ε 2.74); ν_{max}/cm^{-1} 2916w (vinyl CH), 2234m (C≡N), 1620w, 1495s, 1379w, 1339s, 1298w, 1211m, 1063w, 974w, 951s, 941m, 826m, 779w, 723w; δ_H(300 MHz; $CDCl_3$) 6.95 (1H, dd, *J* 17.5, 11.1, vinyl *H-gem*), 6.14 (1H, d, *J* 17.5, vinyl *H-trans*), 5.87 (1H, d, 11.1, vinyl *H-cis*); δ_C(75 MHz; $CDCl_3$) 173.8, 138.9, 125.7, 123.5, 111.7, 109.8 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 126.1 (vinyl *C*H); *m*/*z* (EI) 216 (M^++2, 100), 214 (M^+, 99), 172 (6), 170 (7), 139 (11), 137 (14), 135 (75), 109 (44), 108 (36), 103 (12), 91 (24), 82 (35), 76 (38), 69 (31), 64 (27), 58 (30).

3-Bromo-5-(prop-1-ynyl)isothiazole-4-carbonitrile 227

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with tributyl(1-propyn-yl)tin (1.2 equiv.) and $Pd(OAc)_2$ in MeCN (2 ml) gave the *title compound* **227** (86%) as colourless needles, mp 50-51 ^oC (from pentane); (Found: C, 37.0; H, 1.3; N, 12.3. $C_7H_3BrN_2S$ requires C, 37.0; H, 1.3; N, 12.3%); λ_{max}(DCM)/nm 276 (log ε 2.99); ν_{max}/cm^{-1} 2955w, 2922w and 2853w (sp^3 CH), 2243w (C≡N), 2228s (C≡C), 1497s, 1389w, 1337s, 1314w, 1227m, 1011m, 932w, 810s; δ_H(300 MHz; $CDCl_3$) 2.27 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 157.7, 137.8, 114.8, 111.4, 110.5, 66.3 (*C*≡C), 5.6 (*C*H$_3$); *m*/*z* (EI) 228 (M^++2, 94%), 226 (M^+, 85), 149 (19), 147 (100), 120 (28), 103 (19), 94 (28), 88 (30), 83 (30), 82 (31), 81 (20), 71 (29), 69 (28), 61 (19), 57 (33) (Found: M^+, 225.9204, $C_7H_3BrN_2S$ requires *M*, 225.9200).

3-Chloro-5-phenylisothiazole-4-carbonitrile 207 (typical Negishi coupling conditions at C-5: Table 12)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **5** (30 mg, 0.168 mmol), phenylzinc chloride (504 μl, 0.252 mmol, 0.5M in THF, 1.5 equiv.) and $(PPh_3)_2PdCl_2$ (5.9 mg, 5 mol%) in dry and degassed THF (2 ml) under an argon atmosphere, was heated to *ca.* 60 ^oC, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC and the volatiles were evaporated. The residue was absorbed on silica

and chromatography (hexane-DCM, 7:3) gave the title compound **207** (34.5 mg, 93%) as colourless needles, mp 87-88 ^{o}C (from cyclohexane) identical to that described above.

3-Bromo-5-phenylisothiazole-4-carbonitrile 223

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with phenylzinc chloride and $(PPh_3)_2PdCl_2$ gave the *title compound* **223** (90%) as colourless needles, mp 93-94 ^{o}C (from cyclohexane) identical to that described above.

5,5'-Bi(3-chloroisothiazole-4-carbonitrile) 228

A stirred mixture of 3-chloro-5-iodoisothiazole-4-carbonitrile **204** (30 mg, 0.11 mmol) and $Pd(OAc)_2$ (24.7 mg, 0.11 mmol) in DMF (2 ml) was heated to *ca.* 140 ^{o}C until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^{o}C, diluted with DCM (15 ml) and washed with H_2O (4 x 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 1:4) gave the *title compound* **228** (27 mg, 86%) as colourless needles, mp 244-245 ^{o}C (from PhH); (Found: C, 33.5; N, 19.5. $C_8Cl_2N_4S_2$ requires C, 33.5; N, 19.5%); λ_{max}(DCM)/nm 295 (log ε 3.03); ν_{max}/cm^{-1} 2234w (C≡N), 1634w, 1468s, 1356w, 1341s, 1285w, 1240w, 1065s, 887w, 818s, 741s; δ_C(75 MHz; DMSO-d_6) 160.8, 149.8, 111.1, 110.0; *m/z* (EI) 290 (M^++4, 17%), 288 (M^++2, 75), 286 (M^+, 100), 251 (3), 240 (4), 225 (14), 207 (3), 190 (4), 187 (4), 146 (3), 126 (5), 108 (6), 93 (37), 82 (13), 70 (9), 64 (9) (Found: M^+, 285.8944, $C_8Cl_2N_4S_2$ requires *M*, 285.8941).

3-Chloro-5-(phenylethynyl)isothiazole-4-carbonitrile 229 (typical Sonogashira conditions at C-5: Table 13)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **5** (30 mg, 0.168 mmol), CuI (3.2 mg, 10 mol%), $(PPh_3)_2PdCl_2$ (5.9 mg, 5 mol%), ethynylbenzene (22.1 μl, 0.202 mmol, 1.2 equiv.) and triethylamine (31 μl, 0.224 mmol, 2 equiv.) in DMF (2 ml) was heated to *ca.* 100 ^{o}C until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^{o}C, diluted with DCM (15 ml) and washed with H_2O (4 x 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 7:3) gave the *title compound* **229** (32.9 mg, 80%) as colourless needles, mp 74-75 ^{o}C (from pentane); (Found: C, 58.8; H, 2.0; N, 11.3. $C_{12}H_5ClN_2S$ requires C, 58.9; H, 2.1; N, 11.5%); λ_{max}(DCM)/nm 230 (log ε 3.69), 301 inf. (372), 320 (3.85), 336 (3.88);

ν_{max}/cm^{-1} 2236w (C≡N), 2207m (C≡C), 1512m, 1483w, 1443w, 1393w, 1348s, 1279w, 1258w, 1070w, 1026w, 1001w, 993m, 961w, 926w, 876m, 818m, 762s; δ_H(300 MHz; $CDCl_3$) 7.63-7.59 (2H, m, Ph *H*), 7.53-7.40 (3H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) (1 peak missing) 156.7, 149.9, 132.2 (Ph *C*H), 131.0 (Ph *C*H), 128.7 (Ph *C*H), 119.9, 111.4, 110.7, 110.7, 75.0 (*C*≡C); δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.2 (Ph *C*H), 131.0 (Ph *C*H), 128.7 (Ph *C*H); *m*/*z* (EI) 246 (M^++2, 79%), 244 (M^+, 100), 209 (13), 183 (10), 165 (38), 151 (19), 145 (8), 139 (13), 124 (7), 117 (3), 113 (3), 93 (11), 75 (4), 63 (5) (Found: M^+, 243.9871, $C_{12}H_5ClN_2S$ requires *M*, 243.9862).

3-Bromo-5-(phenylethynyl)isothiazole-4-carbonitrile 230

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with CuI, $(PPh_3)_2PdCl_2$, ethynylbenzene and triethylamine in DMF gave the *title compound* **230** (86%) as colourless needles, mp 109-110 ^oC (from cyclohexane); (Found: C, 49.9; H, 1.7; N, 9.6. $C_{12}H_5BrN_2S$ requires C, 49.9; H, 1.7; N, 9.7%); λ_{max}(DCM)/nm 231 (log ε 3.00), 308 inf. (3.05), 320 (3.14), 336 (3.18); ν_{max}/cm^{-1} 2237w (C≡N), 2210m (C≡C), 1514m, 1481w, 1443w, 1393w, 1341m, 1277w, 1242w, 1130w, 1026w, 984m, 957w, 922w, 858w, 800w, 758s; δ_H(300 MHz; $CDCl_3$) 7.63-7.59 (2H, m, Ph C*H*), 7.53-7.40 (3H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$). 156.6, 138.0, 132.2 (Ph *C*H), 131.0 (Ph *C*H), 128.7 (Ph *C*H), 119.9, 114.8, 111.3, 110.9, 74.7 (*C*≡C); δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.2 (Ph *C*H), 131.0 (Ph *C*H), 128.7 (Ph *C*H); *m*/*z* (EI) 290 (M^++2, 98%), 288 (M^+, 100), 209 (17), 182 (6), 177 (5), 165 (71), 157 (5), 151 (19), 145 (25), 138 (16), 124 (9), 111 (6), 106 (4), 101 (8), 100 (5), 99 (10), 98 (4), 93 (9), 87 (6), 77 (10), 75 (8), 63 (8), 51 (12) (Found: M^+, 287.9352, $C_{12}H_5BrN_2S$ requires *M*, 287.9357).

3-Bromo-5-(thien-3-ylethynyl)isothiazole-4-carbonitrile 231

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with CuI, $(PPh_3)_2PdCl_2$, 3-ethynylthiophene and triethylamine in MeCN (2 ml) gave the *title compound* **231** (77%) as colourless needles, mp 86-87 ^oC (from cyclohexane); (Found: C, 40.7; H, 1.0; N, 9.4. $C_{10}H_3BrN_2S_2$ requires C, 40.7; H, 1.0; N, 9.5%); λ_{max}(DCM)/nm 288 (log ε 3.89), 2.89 (3.86), 3.03 (3.88), 3.34 inf. (4.10), 3.43 (4.12); ν_{max}/cm^{-1} 3109w (thienyl CH), 2235w (C≡N), 2210m (C≡C), 2193w, 1533w, 1483m, 1423w, 1373w, 1339m, 1261w, 1244w, 1204w, 1087w, 991m, 972m, 816m, 775s; δ_H(300 MHz; $CDCl_3$) 7.78 (1H, dd, *J* 3.0, 1.1, thienyl *H-2*), 7.39 (1H, dd, *J* 5.0, 3.0, thienyl *H-4*), 7.26 (1H, dd, *J* 5.0, 1.1,

thienyl *H-5*); δ_C(75 MHz; $CDCl_3$) 156.6, 138.0, 133.1 (thienyl *C*H), 129.6 (thienyl *C*H), 126.6 (thienyl *C*H), 119.2, 114.5, 111.4, 106.3 [*C*(C≡N)], 74.7 (*C*≡C); δ_C(75 MHz; DEPT 90, $CDCl_3$) 133.1 (thienyl *C*H), 129.6 (thienyl *C*H), 126.6 (thienyl *C*H); *m*/*z* (EI) 296 (M^++2, 100%), 294 (M^+, 100), 215 (22), 183 (4), 171 (66), 157 (10), 151 (10), 139 (6), 112 (4), 93 (8), 87 (5), 69 (7) (Found: M^+, 293.8924, $C_{10}H_3BrN_2S_2$ requires *M*, 293.8921).

3-Chloro-5-(pyrid-2-ylethynyl)isothiazole-4-carbonitrile 232

Similar treatment of 3-chloro-5-iodoisothiazole-4-carbonitrile **204** with CuI, $(PPh_3)_2PdCl_2$, 2-ethynylpyridine (2 equiv.) and triethylamine in PhMe (2 ml) on chromatography (hexane/DCM, 3:2) gave 3-chloroisothiazole-4-carbonitrile **205** (40%) as colourless needles, mp 50-51 °C (from pentane) identical to that described above. Further elution (hexane/Et_2O, 1:4) gave the *title compound* **232** (54%) as colourless needles, mp 100-101 °C (from cyclohexane); (Found: C, 53.9; H, 1.6; N, 17.0. $C_{11}H_4ClN_3S$ requires C, 53.8; H, 1.6; N, 17.1%); λ_{max}(DCM)/nm 228 (log ε 2.94), 312 (3.14), 330 (3.10); ν_{max}/cm^{-1} 2240w (C≡N), 2218w (C≡C), 1580w, 1505m, 1457w, 1431w, 1389w, 1348s, 1293w, 1279w, 1244w, 1158w, 1152w, 1098w, 1008m, 989m, 965w, 881w, 810m, 779s; δ_H(300 MHz; $CDCl_3$) 8.71 (1H, d, *J* 3.3, Ar *H*), 7.79 (1H, ddd, *J* 7.7, 7.7, 1.7, Ar *H-4* or *H-5*), 7.68 (1H, d, *J* 7.8, Ar *H*), 7.41 (1H, ddd, *J* 7.6, 4.9, 1.1, Ar *H-4* or *H-5*); δ_C(75 MHz; $CDCl_3$) 155.7, 150.7 (Ar *C*H), 150.2, 140.6 (Ar *C*), 136.6 (Ar *C*H), 128.5 (Ar *C*H), 125.0 (Ar *C*H), 112.3, 110.5, 108.0 [*C*(C≡N)], 73.6 (*C*≡C); δ_C(75 MHz; DEPT 90, $CDCl_3$) 150.7 (Ar *C*H), 136.6 (Ar *C*H), 128.5 (Ar *C*H), 125.0 (Ar *C*H); *m*/*z* (EI) 247 (M^++2, 37%), 245 (M^+, 100), 210 (M^+-Cl, 38), 184 (M^+-CNCl, 7), 178 (6), 166 (6), 157 (4), 152 (M^+-CNClS, 4), 139 (5), 125 (3), 99 (6), 93 ($CNClS^+$, 9), 78 (11), 51 (10).

3-Bromo-5-(ferrocenylethynyl)isothiazole-4-carbonitrile 233

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with CuI, $(PPh_3)_2PdCl_2$, ethynylferrocene and triethylamine in MeCN (2 ml) gave the *title compound* **233** (88%) as red cubes, mp 137-138 °C (from cyclohexane); (Found: C, 48.6; H, 2.3; N, 7.2. $C_{16}H_9BrFeN_2S$ requires C, 48.4; H, 2.3; N, 7.1%); λ_{max}(DCM)/nm 288 (log ε 4.03), 278 (3.90), 336 (3.93), 401 (3.14), 501 (3.25); ν_{max}/cm^{-1} 3130w and 3096w, (ferrocenyl CH), 2237w (C≡N), 2193s and 2174m (C≡C), 1513m, 1447m, 1410w, 1387w, 1366m, 1342s,

1281m, 1238w, 1204w, 1169w, 1153w, 1105m, 1059w, 1051w, 1038w, 1028w, 991s, 955w, 916w, 841w, 826s, 783m; δ_H(300 MHz; $CDCl_3$) 4.63 (2H, t, *J* 1.8, cp *H*), 4.44 (2H, t, *J* 1.8, cp *H*), 4.29 (5H, s, cp *H*); δ_C(75 MHz; $CDCl_3$) 157.3, 137.8, 113.8, 113.6, 111.7, 72.4 (cp *C*H), 72.0, 70.9 (cp *C*H), 70.6 (cp *C*H), 60.5; δ_C(75 MHz; DEPT 90, $CDCl_3$) 72.4 (cp *C*H), 70.9 (cp *C*H), 70.6 (cp *C*H); *m*/*z* (EI) 398 (M^++2, 91%), 396 (M^+, 100), 333 (46), 331 (48), 317 (4), 170 (23), 152 (6), 132 (5), 121 (19), 97 (5), 69 (3), 56 (18) (Found: M^+, 395.9019, $C_{16}H_9BrFeN_2S$ requires *M*, 395.9019).

3-Bromo-5-trimethylsilylethynylisothiazole-4-carbonitrile 234

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **6** with CuI, $(PPh_3)_2PdCl_2$, ethynyltrimethylsilane (1.5 equiv.) and triethylamine in PhMe (2 ml) gave the *title compound* **234** (69%) as colourless crystals, mp 54-55 °C (purified by sublimation); (Found: C, 38.0; H, 3.2; N, 9.9. $C_9H_9BrN_2SSi$ requires C, 37.9; H, 3.2; N, 9.8%); λ_{max}(DCM)/nm 228 (log ε 3.23); ν_{max}/cm^{-1} 2959w and 2900w (CH_3) 2234w (C≡N), 1497m, 1383w, 1340m, 1265w, 1253m, 1247m, 1195w, 1172w, 992m, 972w, 852s, 843s, 800m, 763m; δ_H(300 MHz; $CDCl_3$) 0.31 (9H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 156.4, 138.0, 120.0, 115.6, 111.1, 88.2 (*C*≡C), -0.8 (*C*H_3); *m*/*z* (EI) 286 (MH^+, 13%), 284 (12), 271 (MH^+-CH_3, 100), 269 (98), 241 (3), 228 (5), 226 (5), 190 (3), 139 (12), 137 (12), 116 (4), 102 (4), 84 (16), 43 (12). Further elution gave *3-bromo-5-ethynyl-isothiazole-4-carbonitrile* **235** (14%) as colourless crystals, mp 91-92 °C (purified by sublimation); λ_{max}(DCM)/nm 272 (log ε 2.84), 287 inf. (2.64); ν_{max}/cm^{-1} 3209m (≡CH), 2238m (C≡N), 2110m (C≡C), 1496s, 1378w, 1339s, 1250w, 1186w, 1167w, 994w, 972w, 840s, 797w; δ_H(300 MHz; $CDCl_3$) 4.35 (1H, s, C≡C*H*); δ_C(75 MHz; $CDCl_3$) 155.3, 138.2, 116.6, 110.8, 98.6, 68.8 (C≡*C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 68.8 (C≡*C*H); *m*/*z* (EI) 214 (M^++2, 100%), 212 (M^+, 99), 139 (18), 137 (16), 133 (17), 107 (30), 89 (20), 75 (39), 69 (55), 63 (13), 58 (12), 49 (15).

3-Chloroisothiazole-4-carbonitrile 205 from 3-chloro-4-cyanoisothiazole-5-carboxylic acid 236

A thick walled glass pressure tube was charged with 3-chloro-4-cyanoisothiazole-5-carboxylic acid **236** (100 mg, 0.531 mmol), sealed and heated in a preheated Wood's metal bath to *ca*. 200 °C for 15 min. The residue was allowed to cool to *ca*. 20 °C and absorbed on silica. Chromatography (hexane-DCM, 5:5) gave the *title compound* **205**

(58.3 mg, 76%) as colourless needles, mp 50-51 ^{o}C (from pentane) identical to that described above.

3-Phenoxy-5-phenylisothiazole-4-carbonitrile 238 from phenylboronic acid

A stirred mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **207** (66 mg, 0.3 mmol), phenylboronic acid (73.2 mg, 0.6 mmol), KF (61 mg, 1.05 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol%), 18-crown-6 (40 mg, 0.15 mmol) in PhMe (2 ml) was heated to *ca.* 110 ^{o}C. After 24 h a slightly slower running colourless product was observed by TLC. After 48 h additional phenylboronic acid (22 mg, 0.1 mmol), KF (20 mg, 0.35 mmol), $Pd(OAc)_2$ (1 mg, 1.5 mol%), were added. The same addition was repeated every 48 h until no more starting isothiazole remained (TLC); three additions in total. The mixture was allowed to cool to *ca.* 20 ^{o}C and chromatography (hexane-DCM, 3 : 1) gave the *title compound* **238** (79 mg, 95%) as colourless needles, mp 118-119 ^{o}C (from cyclohexane) (Found: C, 69.2; H, 3.5; N, 10.2. $C_{16}H_{10}N_2OS$ requires C, 69.1; H, 3.6; N, 10.1%); λ_{max}(DCM)/nm 281 (log ε 4.36); ν_{max}(Nujol)/cm^{-1} 2221s (C≡N), 1593m, 1541s, 1488s, 1452s, 1436m, 1393s, 1336m, 1312m, 1262m, 1205s, 1161s, 1126m, 1069m, 1023m, 1005m, 929m, 915m, 872s, 771s, 717s, 704s, 685s, 632m; δ_H (300 MHz; $CDCl_3$) 7.83-7.80 (2H, m, Ar *H*), 7.59-7.45 (5H, m, Ar *H*), 7.37-7.29 (3H, m, Ar *H*); δ_C (75 MHz; $CDCl_3$) 175.4, 166.75, 153.1, 131.8 (Ar *C*H), 129.6 (Ar *C*H), 129.55 (Ar *C*H), 128.0 (Ar *C*), 126.9 (Ar *C*H), 125.9 (Ar *C*H), 120.65 (Ar *C*H), 112.45 (*C*≡N), 94.0; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.8 (Ar *C*H), 129.6 (Ar *C*H), 129.55 (Ar *C*H) 126.9 (Ar *C*H), 125.9 (Ar *C*H), 120.65 (Ar *C*H); *m*/*z* (EI) 278 (M^+, 92%), 277 (M^+-H, 100), 265 (4), 250 (7), 237 (4), 222 (3), 204 (4), 180 (8), 159 (6), 139 (4), 125 (6), 121 (9), 93 ($C_6H_5O^+$, 4), 77 ($C_6H_5^+$, 40), 65 (12), 51 (26) (Found: M^+, 278.0503. $C_{16}H_{10}N_2OS$ requires *M*, 278.0514).

3-Phenoxy-5-phenylisothiazole-4-carbonitrile 238 from potassium phenoxide

To a stirred solution of 3-chloro-5-phenylisothiazole-4-carbonitrile **207** (66 mg, 0.3 mmol) in PhMe (2 ml) at *ca.* 20 ^{o}C, anhydrous potassium phenoxide (59.4 mg, 0.45 mmol) and 18-crown-6 (40 mg, 0.15 mmol) were added. The mixture was then heated to 110 ^{o}C until no starting material remained (TLC) (3 h). The mixture was allowed to cool to *ca.* 20 ^{o}C and chromatography (hexane-DCM, 3 : 1) gave the title compound **238** (91%) as colourless needles, mp 118-119 ^{o}C (from cyclohexane) identical to that described above.

7.5 Compounds Related to Chapter 5

3-Methanesulfonyloxy-5-phenylisothiazole-4-carbonitrile 240

To a stirred solution of 3-hydroxy-5-phenylisothiazole-4-carbonitrile **239** (100 mg, 0.495 mmol) and triethylamine (69 μl, 0.495 mmol, 1 equiv.) in DCM (2 ml) cooled to *ca*. 0 ^{o}C was added in one portion methanesulfonic anhydride (172.5 mg, 0.99 mmol, 2 equiv.). The reaction mixture was kept at *ca*. 0 ^{o}C until no starting material remained (TLC). Chromatography (hexane-DCM, 5:3) gave the *title compound* **240** (108 mg, 78%) as colourless needles, mp 104-105 ^{o}C (from cyclohexane); (Found: C, 47.2; H, 2.7; N, 9.9. $C_{11}H_8N_2O_3S_2$ requires C, 47.1; H, 2.9; N, 10.0%); λ_{max}(DCM)/nm 279 (log ε 3.17); ν_{max}/cm^{-1} 2236w (C≡N), 1558w, 1535w, 1495w, 1449w, 1429w, 1387s, 1329w, 1188s, 1126s, 1082w, 978m, 908w, 866m, 781s, 770s, 731m, 714s; δ_H(300 MHz; $CDCl_3$) 7.80-7.76 (2H, m, Ph *H*), 7.64-7.53 (3H, m, Ph *H*), 3.56 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 176.6, 159.0, 132.6 (Ph *C*H), 129.9 (Ph *C*H), 127.4 (Ph *C*), 127.1 (Ph *C*H), 111.2 (*C*≡N), 97.0 [*C*(C≡N)], 40.4 (*C*H$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.5 (Ph *C*H), 129.9 (Ph *C*H), 127.1 (Ph *C*H); *m*/*z* (EI) 280 (M$^+$, 50%), 216 (M$^+$-SO_2, 4), 202 (100), 187 (7), 173 (3), 159 (13), 146 (11), 142 (24), 128 (51), 121 (12), 114 (6), 100 (22), 88 (4), 79 (32), 77(13), 63 (6), 51 (11) (Found: M$^+$, 279.9977, $C_{11}H_8N_2O_3S_2$ requires *M*, 279.9976). Further elution (hexane-*t*-BuOMe, 1:4) gave *4-cyano-2-mesyl-5-phenylisothiazol-3-one* **243** (22 mg, 16%) as colourless needles, mp 182-183 ^{o}C (from t-BuOMe); (Found: C, 47.1; H, 2.8; N, 9.9. $C_{11}H_8N_2O_3S_2$ requires C, 47.1; H, 2.9; N, 10.0%); λ_{max}(DCM)/nm 295 (log ε 3.08); ν_{max}/cm^{-1} 3030w and 3011w (Ar CH), 2930 (CH_3), 2232w (C≡N), 1701s (C=O), 1593w, 1545w, 1489w, 1447w, 1416w, 1368s, 1335m, 1290w, 1171s, 1099m, 1005w, 964s, 939w, 908w, 773s, 758w, 741m; δ_H(300 MHz; $CDCl_3$) 7.80-7.77 (2H, m, Ph *H*), 7.73-7.68 (1H, m, Ph *H*), 7.63-7.58 (2H, m, Ph *H*), 3.59 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 169.4, 162.9, 134.4 (Ph *C*H), 130.2 (Ph *C*H), 128.3, 127.1 (Ph *C*H), 126.8, 111.7 (*C*≡N), 95.8 [*C*(C≡N)], 42.0 (*C*H$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 134.4 (Ph *C*H), 130.2 (Ph *C*H), 127.1 (Ph *C*H); *m*/*z* (EI) 280 (M$^+$, 73%), 215 (6), 202 (M$^+$-CH_2O_2S, 100), 187 (9), 173 (5), 159 (16), 146 (13), 142 (23), 128 (59), 121 (11), 114 (5), 100 (16), 88 (4), 79 ($CH_2O_2S^+$, 21), 77 (11), 69 (3), 63 (5), 51 (10), 46 (11) (Found: M$^+$, 279.9973, $C_{11}H_8N_2O_3S_2$ requires *M*, 279.9976).

3-(4-Toluenesulfonyloxy)-5-phenylisothiazole-4-carbonitrile 241

To a stirred solution of 3-hydroxy-5-phenylisothiazole-4-carbonitrile **239** (100 mg, 0.495 mmol) and triethylamine (69 μl, 0.495 mmol, 1 equiv.) in DCM (2 ml) cooled to *ca*. 0 ^{o}C was added in one portion 4-toluenesulfonyl chloride (377.5 mg, 0.99 mmol, 2 equiv.). The reaction mixture was kept at *ca*. 0 ^{o}C until no starting material remained (TLC). Chromatography (hexane-DCM, 5:3) gave the *title compound* **241** (148 mg, 84%) as colourless needles, mp 94-95 ^{o}C (from cyclohexane); (Found: C, 57.4; H, 3.3; N, 7.8. $C_{17}H_{12}N_2O_3S_2$ requires C, 57.3; H, 3.4; N, 7.9%); λ_{max}(DCM)/nm 214 (log ε 4.87), 278 (4.01); ν_{max}/cm^{-1} 2234w (C≡N), 1597w, 1539m, 1495w, 1449w, 1379s, 1294w, 1217w, 1194m, 1180s, 1123m, 1088m, 1038w, 1016w, 999w, 955w, 910w, 862s, 814m, 800w, 768m, 743s, 712w; δ_H(300 MHz; $CDCl_3$) 8.00 (2H, d, *J* 8.4, Tol *H*), 7.76-7.72 (2H, m, Ph *H*), 7.61-7.50 (3H, m, Ph *H*), 7.41 (2H, d, *J* 8.5, Tol *H*), 2.48 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 176.1, 158.8, 146.6, 132.3 (Ar *C*H), 132.1, 130.0 (Ar *C*H), 129.8 (Ar *C*H), 129.0 (Ar *C*H), 127.6, 127.1 (Ar *C*H), 111.3 (*C*≡N), 97.0 [*C*(C≡N)], 21.8 (*C*H$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.3 (Ar *C*H), 130.0 (Ar *C*H), 129.8 (Ar *C*H), 129.0 (Ar *C*H), 127.1 (Ar *C*H); *m*/*z* (EI) 356 (M$^+$, 0.2%), 292 (M$^+$-SO_2, 20), 155 (47), 127 (8), 100 (4), 91 (100), 77 (5), 65 (24) (Found: M$^+$, 356.0283, $C_{17}H_{12}N_2O_3S_2$ requires *M*, 356.0289). Further elution (hexane-Et_2O, 1:4) gave *4-cyano-5-phenyl-2-(4-tosyl)isothiazol-3-one* **244** (21 mg, 12%) as colourless needles, mp 190-191 ^{o}C (from t-BuOMe); (Found: C, 57.4; H, 3.3; N, 7.8. $C_{17}H_{12}N_2O_3S_2$ requires C, 57.3; H, 3.4; N, 7.9%); λ_{max}(DCM)/nm 230 (log ε 2.86), 296 (3.01); ν_{max}/cm^{-1} 3065w (Ar CH), 2957w, 2922w and 2855 (CH_3), 2228w (C≡N), 1730w, 1701s, 1593w, 1551w, 1487w, 1447w, 1377m, 1329w, 1288w, 1175s, 1123w, 1094w, 1080m, 984w, 928w, 907w, 810w, 800w, 772m, 762m, 743m, 702w; δ_H(300 MHz; $CDCl_3$) 8.05 (2H, d, *J* 8.4, Tol *H*), 7.77-7.73 (2H, m Ph *H*), 7.70-7.64 (1H, m, Ph *H*), 7.61-7.53 (2H, m, Ph *H*), 7.42 (2H, d, *J* 8.1, Tol *H*), 2.48 (C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 168.7, 161.8, 147.3, 134.1 (Ar *C*H), 132.5 (Ar *C*), 130.2 (Ar *C*H), 130.1 (Ar *C*H), 129.1 (Ar *C*H), 127.0 (Ar *C*H), 126.9 (Ar *C*), 111.9 (*C*≡N), 95.9 [*C*(C≡N)], 21.9 (*C*H$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 134.1 (Ar *C*H), 130.2 (Ar *C*H), 130.1 (Ar *C*H), 129.2 (Ar *C*H), 127.0 (Ar *C*H); *m*/*z* (EI) 356 (M$^+$, 0.1%), 292 (M$^+$-SO_2, 17), 155 (53), 128 (4), 127 (7), 100 (4), 91 (100), 77 (6), 65 (27) (Found: M$^+$, 356.0288, $C_{17}H_{12}N_2O_3S_2$ requires *M*, 356.0289).

3-Trifluoromethanesulfonyloxy-5-phenylisothiazole-4-carbonitrile 242

To a stirred solution of 3-hydroxy-5-phenylisothiazole-4-carbonitrile **239** (100 mg, 0.495 mmol) and triethylamine (69 μl, 0.495 mmol, 1 equiv.) in DCM (2 ml) cooled to *ca*. 0 ^{o}C was added dropwise trifluoromethanesulfonic anhydride (167 μl, 0.99 mmol, 2 equiv.). The reaction mixture was kept at *ca*. 0 ^{o}C until no starting material remained (TLC). Chromatography (hexane-DCM, 5:3) gave the *title compound* **242** (142 mg, 86%) as colourless needles, mp 67-68 ^{o}C (from cyclohexane); (Found: C, 39.5; H, 1.5; N, 8.2. $C_{11}H_5F_3N_2O_3S_2$ requires C, 39.5; H, 1.5; N, 8.4%); λ_{max}(DCM)/nm 281 (log ε 3.05); ν_{max}/cm^{-1} 2236w (C≡N), 1541w, 1497w, 1450w, 1414m, 1224s, 1165w, 1134m, 1109m, 1101m, 1032w, 1001w, 951w, 910m, 862m, 791m, 770m, 762m, 692m, 687m; δ_H(300 MHz; $CDCl_3$) 7.82-7.78 (2H, m, Ph *H*), 7.67-7.56 (3H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) (1 peak missing) 177.7, 155.6, 132.9 (Ph *C*H), 130.0 (Ph *C*H), 127.2 (Ph *C*H), 118.5 (1C, q, $^1J_{CF}$ 319.5, *C*F$_3$), 110.3, 96.8; δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.9 (Ph *C*H), 130.0 (Ph *C*H), 127.2 (Ph *C*H); *m*/*z* (EI) 334 (M$^+$, 78%), 270 (M$^+$-SO_2, 45), 201 (4), 196 (100), 186 (7), 176 (8), 159 (10), 146 (8), 127 (39), 114 (3), 100 (8), 84 (5), 77 ($C_6H_5^+$, 8), 69 (58), 63 (4), 51(6) (Found: M$^+$, 333.9695. $C_{11}H_5F_3N_2O_3S_2$ requires *M*, 333.9694). Further elution gave 3-hydroxy-5-phenylisothiazole-4-carbonitrile **239** (8 mg, 8%) as colourless needles, mp 233-234 ^{o}C (from PhH) (lit.,[320] 235-236 ^{o}C), identical to an authentic sample.

3-Amino-5-phenylpyrazole-4-carbonitrile 247

A stirred mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **207** (100 mg, 0.454 mmol) in 80% hydrazine hydrate (2 ml) was heated to *ca*. 80 ^{o}C for 1 h. The mixture was poured onto crushed ice (50 g) to form a white precipitate. Filtration gave the title compound **247** (83 mg, 100%) as white powder, mp 194-195 ^{o}C (from H_2O-EtOH) (lit.,[322] mp 200 ^{o}C); λ_{max}(EtOH)/nm 205 (log ε 4.39), 234 (4.21), 253 inf. (4.11); ν_{max}/cm^{-1} 3348w, 3304w, 3184m, 3169m, 3129w, 3098w, 3049w, 3019w, 2978w, 2953w, 2909w, 2835w, 2232s (C≡N), 1649w, 1580w, 1568w, 1535m, 1501m, 1493m, 1443w, 1422w, 1350w, 1171w, 1140w, 1078m, 1026w, 966w, 916w, 816w, 768s, 725m; δ_H(300 MHz; DMSO-d_6) 12.18 (1H, br s, N*H*), 7.82-7.80 (2H, m, Ph *H*), 7.49-7.37 (3H, m, Ph *H*), 6.45 (2H, br s, NH_2); δ_C(75 MHz; DMSO-d_6) (Ph *C*H peak missing) 154.9 (*C*-3), 150.3 (*C*-5), 132.1 (Ph *C*), 129.0 (Ph *C*H), 125.9 (Ph *C*H), 116.4 (*C*≡N), 69.9 (*C*-4); δ_C(75 MHz; DEPT 90, DMSO-d6) (Ph *C*H peak missing) 129.0 (Ph *C*H), 125.9 (Ph *C*H); *m*/*z* (EI)

184 (M^+, 100%), 167 (1), 155 (10), 142 (10), 128 (13), 121 (3), 115 (3), 106 (11), 102 (4), 91 (25), 77 (15), 65 (4), 63 (3), 51(9), (Found: M^+, 184.0749, $C_{10}H_8N_4$ requires *M*, 184.0749).

3-(Benzylamino)-5-phenylisothiazole-4-carbonitrile 248

A stirred solution of 3-chloro-5-phenylisothiazole-4-carbonitrile **207** (50 mg, 0.227 mmol) in benzylamine (2 ml) was heated to *ca*. 80 ^oC until no starting material remained (TLC). The mixture was diluted with DCM (15 ml) and was washed with 10% aq. HCl (4 x 10 ml) followed by saturated aq. $Na_2S_2O_5$ (4 x 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 7:3) gave the *title compound* **248** (55 mg, 90%) as colourless needles, mp 127-128 ^oC (from cyclohexane); (Found: C, 70.2; H, 4.4; N, 14.4. $C_{17}H_{13}N_3S$ requires C, 70.1; H, 4.5; N, 14.4%); λ_{max}(DCM)/nm 229 (log ε 3.12), 280 (3.05), 338 (2.44); ν_{max}/cm^{-1} 3381m (NH), 3058w and 3025w (Ph CH), 2217m (C≡N), 1556s, 1538m, 1496w, 1458w, 1449w, 1419w, 1349m, 1300w, 1196w, 1160w, 1106w, 1083w, 1065w, 1033w, 1027w, 1011w, 1001w, 956w, 912w, 875w, 771s; δ_H(300 MHz; $CDCl_3$) 7.75-7.72 (2H, m, Ph *H*), 7.55-7.47 (3H, m, Ph *H*), 7.42-7.30 (5H, m, Ph *H*), 5.29 (1H, br s, N*H*), 4.65 (2H, s, CH_2); δ_C(75 MHz; $CDCl_3$) 174.3, 164.3, 138.0 (Ph *C*), 131.3 (Ph *C*H), 129.5 (Ph *C*H), 128.7 (Ph *C*), 128.6 (Ph *C*H), 127.8 (Ph *C*), 127.7 (Ph *C*H), 127.7 (Ph *C*H), 127.1 (Ph *C*H), 114.0 (*C*≡N), 92.2 [*C*(C≡N)], 47.0 (*C*H_2); δ_C(75 MHz; DEPT 135, $CDCl_3$) 131.3 (Ph *C*H), 129.5 (Ph *C*H), 128.7 (Ph *C*H), 127.8 (Ph *C*H), 127.7 (Ph *C*H), 127.1 (Ph *C*H), 47.0 (*C*H_2); *m*/*z* (EI) 291 (M^+, 100%), 290 (30), 275 (3), 258 (3), 218 (4), 214 (5), 186 (5), 159 (3), 155 (3), 146 (3), 141 (3), 128 (5), 121 (7), 106 (37), 91 (80), 79 (4), 77 (9), 65 (11), 51 (5) (Found: M^+, 291.0829. $C_{17}H_{13}N_3S$ requires *M*, 291.0830). Further elution (hexane-DCM, 7:3) gave *3,3'-bis(5-phenylisothiazole-4-carbonitrile)disulfide* **249** (1 mg, 1%) as colourless needles, mp 138-139 ^oC (from EtOH); (Found: C, 55.2; H, 2.3; N, 12.8. $C_{20}H_{10}N_4S_4$ requires C, 55.3; H, 2.3; N, 12.9%); λ_{max}(DCM)/nm 230 (log ε 3.20), 287 (3.30); ν_{max}/cm^{-1} 2224m (C≡N), 1514m, 1483s, 1443m, 1387w, 1325m, 1290w, 1269w, 1240w, 1190w, 1103w, 1076w, 1045m, 1026w, 999w, 955w, 916w, 826m, 766s, 760s; δ_H(300 MHz; $CDCl_3$) 7.79-7.72 (4H, m, Ph *H*), 7.59-7.50 (6H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) 177.0, 162.1, 132.0 (Ph *C*H), 129.7 (Ph *C*H), 127.5 (Ph *C*), 127.4 (Ph *C*H), 112.3 (*C*≡N), 105.1 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.0 (Ph *C*H), 129.7 (Ph *C*H), 127.4 (Ph *C*H); *m*/*z* (EI) 434 (M^+, 68%), 401 (52), 369 (15), 337 (7), 249 (7), 218 (100),

190 (13), 185 (10), 159 (26), 141 (13), 128 (77), 121 (34), 114 (9), 100 (7), 90 (22), 77 (30), 69 (6), 63 (5), 51 (19) (Found: M^+, 433.9790. $C_{20}H_{10}N_4S_4$ requires *M*, 433.9788). If the reaction mixture is initially extracted with hot DCM then chromatography (hexane-DCM, 7:3) of the extracts gave in addition to the above products *3,3′-methylenebis(sulfanediyl)bis(5-phenylisothiazole-4-carbonitrile)* **250** (1 mg, 1%) as colourless needles, mp 134-135 °C (from THF); (Found: C, 56.1; H, 2.5; N, 12.4. $C_{21}H_{12}N_4S_4$ requires C, 56.2; H, 2.7; N, 12.5%); λ_{max}(DCM)/nm 230 (log ε 3.24), 287 (3.34); ν_{max}/cm^{-1} 30098w, (Ar CH), 2222w (C≡N), 1582w, 1510w, 1481s, 1441w, 1381w, 1327m, 1250w, 1223m, 1180w, 1155w, 1101w, 1078w, 1051s, 999w, 961w, 920w, 837s, 785w, 758s, 739m; δ_H(300 MHz; $CDCl_3$) 7.77-7.74 (2H, m, Ph *H*), 7.60-7.50 (3H, m, Ph *H*), 5.16 (1H, s, C*H*$_2$); δ_C(75 MHz; $CDCl_3$) 175.8, 163.7, 131.7 (Ph *C*H), 129.5 (Ph *C*H), 127.5 (Ph *C*), 127.3 (Ph *C*H), 112.2 (*C*≡N), 103.1 [*C*(C≡N)], 32.9 (*C*H$_2$); δ_C[75 MHz; DEPT 135, $CDCl_3$ + Cr(acac)$_3$] (Ph *C*H), 129.5 (Ph *C*H), 127.3 (Ph *C*H), 32.9 (*C*H$_2$); *m*/*z* (EI) 448 (M^+, 38%), 415 (4), 401 (7), 284 (3), 265 (8), 231 (100), 219 (11), 187 (8), 181 (3), 163 (7), 159 (7), 144 (17), 139 (9), 135 (12), 121 (55), 109 (33), 87 (12), 58 (13); (Found: M^+, 447.9961, $C_{21}H_{12}N_4S_4$ requires *M*, 447.9945).

3-Amino-5-phenylisothiazole-4-carbonitrile 251

A stirred mixture of 3-(benzylamino)-5-phenylisothiazole-4-carbonitrile **248** (50 mg, 0.185 mmol), Br_2 (44.5 μl, 0.278 mmol, 1.5 equiv.), AIBN (6 mg, 0.037 mmol, 0.2 equiv.) and PhH/H_2O (2:1, 3 ml) was heated to *ca*. 80 °C until no starting material remained (TLC). The organic layer was separated, dried and then absorbed on silica. Chromatography (hexane-DCM, 4:1) gave the title compound **251** (33 mg, 90%) as colourless needles, mp 127-128 °C (from cyclohexane) (lit.,[136] 128.5 °C); λ_{max}(DCM)/nm 228 (log ε 3.68), 280 (3.83), 325 (3.35); ν_{max}/cm^{-1} 3436w (NH), 3288w and 3193w (Ph CH), 2218m (C≡N), 1618s, 1549s, 1501s, 1465w, 1440w, 1411s, 1337w, 1306w, 1290w, 1270w, 1197w, 1159w, 1100w, 1066w, 1031w, 1002w, 957w, 901w, 844s, 761m; δ_H(300 MHz; $CDCl_3$) 7.73-7.70 (2H, m, Ph *H*), 7.53-7.46 (3H, m, Ph *H*), 5.02 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 174.5, 164.6, 131.4 (Ph *C*H), 129.4 (Ph *C*H), 128.4 (Ph *C*), 127.0 (Ph *C*H), 113.9 (*C*≡N), 92.7 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.4 (Ph *C*H), 129.5 (Ph *C*H), 127.0 (Ph *C*H); *m*/*z* (EI) 201 (M^+, 100%), 174 (10), 159 (15), 153 (13), 128 (49), 114 (7), 100 (11), 88 (5), 77 (18), 74 (41), 63 (5), 51 (13). Further elution (DCM) gave *3-benzoylamino-5-phenylisothiazole-4-carbonitrile* **252** (1 mg, 1%) as

colourless needles, mp 169-170 °C (from cyclohexane); (Found: C, 66.7; H, 3.5; N, 13.7. $C_{17}H_{11}N_3OS$ requires C, 66.9; H, 3.6; N, 13.8%); λ_{max}(DCM)/nm 275 (log ε 3.32); ν_{max}/cm^{-1} 3246w (NH), 2232w (C≡N), 1672s (C=O), 1537s, 1503m, 1472w, 1443w, 1427w, 1381s, 1285m, 1273m, 1254w, 1179w, 1153w, 1101w, 1076w, 1026w, 1001w, 961w, 935w, 920m, 883w, 841m, 795w, 762s, 716s; δ_H(300 MHz; $CDCl_3$) 8.85 (1H, br s, N*H*), 7.98-7.95 (2H, m, Ph *H*), 7.80-7.77 (2H, m, Ph *H*), 7.64-7.49 (6H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$). 175.7, 165.0, 157.3, 133.0 (Ph *C*H), 132.4 (Ph *C*), 131.8 (Ph *C*H), 129.7 (Ph *C*H), 128.9 (Ph *C*H), 127.9 (Ph *C*), 127.7 (Ph *C*H), 127.4 (Ph *C*H), 112.9 (*C*≡N), 99.5 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$). 133.0 (Ph *C*H), 131.8 (Ph *C*H), 129.7 (Ph *C*H), 128.9 (Ph *C*H), 127.7 (Ph *C*H), 127.4 (Ph *C*H); *m*/*z* (EI) 305 (M^+, 16%), 277 (7), 218 (1), 201 (2), 184 (3), 128 (3), 105 (100), 84 (5), 78 (4), 77 (5), 51 (11) (Found: M^+, 305.0646, $C_{17}H_{11}N_3OS$ requires *M*, 305.0623).

3-Iodo-5-phenylisothiazole-4-carbonitrile 245

To a stirred and cooled (*ca.* 0-5 °C) mixture of I_2 (158 mg, 0.623 mmol, 2.5 equiv.) and isoamylnitrite (134 μl, 0.996 mmol, 4 equiv.) in MeCN (2 ml) was added dropwise an MeCN (1 ml) solution of 3-amino-5-phenylsothiazole-4-carbonitrile **251** (50 mg, 0.249 mmol). The reaction mixture was kept at *ca.* 0-5 °C until no starting material remained (TLC), allowed to warm to *ca.* 20 °C and absorbed on silica. Chromatography (hexane-DCM, 3:7) gave the *title compound* **245** (66 mg, 85%) as colourless needles, mp 123.5-124.5 °C (from cyclohexane); (Found: C, 38.5; H, 1.6; N, 8.9. $C_{10}H_5IN_2S$ requires C, 38.5; H, 1.6; N, 9.0%); λ_{max}(DCM)/nm 229 (log ε 2.95), 285 (3.07); ν_{max}/cm^{-1} 3032w (Ph CH), 2232m (C≡N), 1508w, 1477s, 1445w, 1377m, 1327m, 1233m, 1188w, 1107w, 1080w, 1036m, 1016w, 997m, 962w, 923w, 816s, 770s, 756s; δ_H(300 MHz; $CDCl_3$) 7.77-7.73 (2H, m, Ph *H*), 7.60-7.50 (3H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) 175.7, 132.1, (Ph *C*H), 129.8 (Ph *C*H), 127.4 (Ph *C*H), 126.8, 114.4, 114.1, 113.8; δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.1, (Ph *C*H), 129.8 (Ph *C*H), 127.4 (Ph *C*H); *m*/*z* (EI) 312 (M^+, 100%), 185 (M^+-I, 25), 158 (10), 153 (3), 141 (28), 127 (4), 121 (5), 114 (8), 100 (3), 84 (4), 77 (17), 63 (3), 51 (12) (Found: M^+, 311.9209, $C_{10}H_5IN_2S$ requires *M*, 311.9218). Further elution (hexane-DCM, 3:2) gave *1,1-dicyano-2-iodo-2-phenylethene* **253** (1 mg, 1%) as yellow needles, mp 114-115 °C (from cyclohexane); (Found: C, 42.9; H, 1.7; N, 10.0. $C_{10}H_5IN_2$ requires C, 42.9; H, 1.8; N, 10.0%); λ_{max}(DCM)/nm 282 inf. (log ε 2.85), 319 (3.00); ν_{max}/cm^{-1} 3030w (Ph CH), 2224w (C≡N), 1591w, 1574w, 1537m, 1508m, 1485w,

1441w, 1377w, 1327w, 1233m, 1179w, 1157w, 1076w, 1036w, 999w, 924w, 878w, 833w, 816w, 770w, 752s; δ_H(300 MHz; $CDCl_3$) 7.63-7.58 (2H, m, Ph *H*), 7.57-7.45 (3H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) 142.4, 138.7, 133.1 (Ph *C*H), 129.0 (Ph *C*H), 129.0 (Ph *C*H), 115.3 (*C*≡N), 112.2 (*C*≡N), 96.2 [*C*$(CN)_2$]; δ_C(75 MHz; DEPT 90, $CDCl_3$) , 133.1 (Ph *C*H), 129.0 (Ph *C*H), 129.0 (Ph *C*H); *m*/*z* (EI) 280 (M^+, 39%), 153 (100), 126 (16), 100 (7), 77 (24), 75 (8), 63 (5), 51 (12) (Found: M^+, 279.9500, $C_{10}H_5IN_2$ requires *M*, 279.9498). Further elution (DCM) gave *3,3'-(triaz-1-ene-1,3-diyl)bis(5-phenyl-isothiazole-4-carbonitrile)* **254** (1 mg, 1%) as pale yellow needles, mp 196-197 °C (from cyclohexane); (Found: C, 57.9; H, 2.7; N, 23.6. $C_{20}H_{11}N_7S_2$ requires C, 58.1; H, 2.7; N, 23.7%); λ_{max}(DCM)/nm 296 (log ε 3.55), 335 inf. (3.26); ν_{max}/cm^{-1} 2226w (C≡N), 1584m, 1574m, 1537w, 1522w, 1493w, 1479w, 1423s, 1385m, 1260w, 1227s, 1186w, 1119w, 1080w, 1032w, 1001w, 974w, 883w, 872w, 853w, 764m, 727m, 714m; δ_H(300 MHz; DMSO-d_6) 14.67 (1H, br s, N*H*), 7.86-7.81 (4H, m, Ph *H*), 7.67-7.64 (6H, m, Ph *H*); δ_C(75 MHz; DMSO-d_6) (*C*-4 peak is missing) 176.1, 131.9 (Ph *C*H), 129.7 (Ph *C*H), 128.2 (Ph *C*), 127.5 (Ph *C*H), 127.5 (Ph *C*), 113.1 (*C*≡N); δ_C(75 MHz; DEPT 90, DMSO-d_6) 131.9 (Ph *C*H), 129.7 (Ph *C*H), 127.5 (Ph *C*H); *m*/*z* (EI) 384 (M^+-N_2, 100), 352 (5), 312 (5), 308 (2), 275 (2), 242 (8), 213 (25), 201 (27), 185 (49), 178 (9), 158 (10), 153 (7), 141 (30), 128 (13), 121 (14), 114 (9), 91 (56), 77 (29), 51 (12) (Found: M^+-HN_2, 384.0381, $C_{20}H_{10}N_5S_2$ requires *M*-*H*N_2, 384.0378).

3,5-Diphenylisothiazole-4-carbonitrile 237 (typical Suzuki conditions for coupling at C-3: see Table 22)

A stirred mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (50 mg, 0.16 mmol), phenylboronic acid (58.5 mg, 0.48 mmol, 3 equiv.), powdered K_2CO_3 (33.2 mg, 0.24 mmol, 1.5 equiv.) and $Pd(OAc)_2$ (5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 140 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 x 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 3:2) gave the title compound **237** (34 mg, 80%) as white needles, mp 146-147 °C (from cyclohexane) (lit.,[89] mp 149-150 °C); (Found: C, 73.2; H, 3.7; N, 10.7. $C_{16}H_{10}N_2S$ requires C, 73.3; H, 3.8; N, 10.7%); λ_{max}(DCM)/nm 262 (log ε 3.18); ν_{max}/cm^{-1} 3061w and 3030w (Ph CH), 2226w (C≡N), 1518w, 1481m, 1445m, 1410w, 1364m, 1074w, 1032w, 1001w, 966w, 912m, 839m, 770m, 760m, 718s; δ_H(300

MHz; $CDCl_3$) 8.08-8.03 (2H, m, Ar *H*), 7.83-7.79 (2H, m, Ar *H*), 7.57-7.52 (6H, m, Ar *H*); δ_C(75 MHz; $CDCl_3$) 176.8, 168.9, 132.9 (Ph *C*), 131.5 (Ph *C*H), 130.4 (Ph *C*H), 129.6 (Ph *C*H), 128.8 (Ph *C*H), 128.1 (Ph *C*), 127.9 (Ph *C*H), 127.7 (Ph *C*H), 114.9 (*C*≡N), 103.6 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.5 (Ph *C*H), 130.4 (Ph *C*H), 129.6 (Ph *C*H), 128.8 (Ph *C*H), 127.9 (Ph *C*H), 127.7 (Ph *C*H); *m*/*z* (EI) 262 (M^+, 100%), 261 (6), 229 (4), 218 (6), 159 (3), 135 (7), 134 (4), 131 (7), 121 (4), 103 (6), 77 (13), 51 (8) (Found: M^+, 262.0558, $C_{16}H_{10}N_2S$ requires *M*, 262.0565). Further elution gave *3,3′-bi(5-phenylisothiazole-4-carbonitrile)* **255** (1 mg, 1%) as colourless needles, mp 151-152 °C (from cyclohexane/PhH); (Found: C, 64.6; H, 2.8; N, 15.2. $C_{20}H_{10}N_4S_2$ requires C, 64.8; H, 2.7; N, 15.1%); λ_{max}(DCM)/nm 278 (log ε 3.35); ν_{max}/cm^{-1} 3053w (Ph CH), 2232m (C≡N), 1508w, 1476s, 1443m, 1373m, 1339m, 1331m, 1233w, 1188w, 1105w, 1080w, 1030m, 993m, 962w, 914w, 835s, 764s, 733w; δ_H(300 MHz; CD_2Cl_2) 7.87-7.84 (4H, m, Ph *H*), 7.63-7.59 (6H, m, Ph *H*); δ_C(75 MHz; CD_2Cl_2) 177.5, 160.8, 132.2 (Ph *C*H), 130.1 (Ph *C*H), 128.8 (Ph *C*H), 127.9 (Ph *C*), 113.8 (*C*≡N), 105.6 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, CD_2Cl_2) 132.2 (Ph *C*H), 130.1 (Ph *C*H), 128.8 (Ph *C*H); *m*/*z* (EI) 370 (M^+, 91), 369 (80), 344 (2), 337 (4), 305 (2), 290 (5), 274 (2), 242 (2), 211 (4), 205 (2), 185 (14), 177 (5), 159 (11), 141 (2), 133 (20), 127 (9), 121 (10), 115 (9), 103 (11), 89 (48), 87 (25), 77 (13), 73 (52), 59 (16) (Found: M^+, 370.0354 $C_{20}H_{10}N_4S_2$ requires *M*, 370,0347).

3-(3-Nitrophenyl)-5-phenylisothiazole-4-carbonitrile 256

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 3-nitrophenylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **256** (58%) as colourless needles, mp 162-163 °C (from cyclohexane); (Found: C, 62.6; H, 2.9; N, 13.7. $C_{16}H_9N_3O_2S$ requires C, 62.5; H, 3.0; N, 13.7%); λ_{max}(DCM)/nm 258 (log ε 3.32); ν_{max}/cm^{-1} 3086w (Ar CH), 2226w (C≡N), 1614w, 1595w, 1578w, 1539s, 1516w, 1491w, 1477w, 1447w, 1439w, 1410w, 1348s, 1304w, 1161w, 1094w, 1080w, 1040w, 1001w, 916w, 903w, 883w, 839w, 808m, 758m, 725s, 700s; δ_H(300 MHz; $CDCl_3$) 8.93 (1H, app. t, *J* 1.9, C-3 Ar *H-2*), 8.43 (1H, ddd, *J* 7.8, 1.2, 1.2, Ar *H*), 8.38 (1H, ddd, *J* 8.3, 2.2, 0.9, Ar *H*), 7.85-7.81 (2H, m, Ph *H*), 7.74 (1H, app. t, 8.0, C-3 Ar *H-5*), 7.61-7.57 (3H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) 177.6, 166.0, 148.6, 134.3 (Ar *C*), 133.3 (Ar *C*H), 131.9 (Ar *C*H), 130.0 (Ar *C*H), 129.8 (Ar *C*H), 127.7 (Ar *C*), 127.7 (Ar *C*H), 124.9 (Ar *C*H), 123.2 (Ar *C*H), 114.4 (*C*≡N), 109.6 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$)

133.3 (Ar *C*H), 131.9 (Ar *C*H), 130.0 (Ar *C*H), 129.8 (Ar *C*H), 127.7 (Ar *C*H), 124.9 (Ar *C*H), 123.2 (Ar *C*H); *m*/*z* (EI) 307 (M^+, 100%), 277 (9), 261 (60), 249 (9), 233 (7), 229 (7), 216 (3), 190 (7), 159 (3), 134 (4), 130 (8), 121 (7), 114 (3), 102 (3), 89 (14), 84 (4), 77 (15), 63 (4), 51 (7) (Found: M^+, 307.0426. $C_{16}H_9N_3O_2S$ requires *M*, 307.0415).

3-(4-Methoxyphenyl)-5-phenylisothiazole-4-carbonitrile 257

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 4-methoxyphenylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **257** (95%) as colourless needles, mp 118-119 °C (from cyclohexane); (Found: C, 69.9; H, 4.1; N, 9.6. $C_{17}H_{12}N_2OS$ requires C, 69.8; H, 4.1; N, 9.6%); λ_{max}(DCM)/nm 281 (log ε 3.40); ν_{max}/cm^{-1} 3055w (Ar CH), 2968w, 2922w, and 2841w (CH_3), 2224w (C≡N), 1611w, 1580w, 1514w, 1483m, 1458w, 1445w, 1425w, 1410w, 1364w, 1308w, 1300w, 1252s, 1184w, 1177w, 1117w, 1030w, 1016w, 999w, 966w, 947w, 914w, 846w, 818m, 773w, 752w, 737m, 710w; δ_H(300 MHz; $CDCl_3$) 8.03 (2H, d, *J* 8.9, Ar *H*), 7.82-7.77 (2H, m, Ph *H*), 7.60-7.55 (3H, m, Ph *H*), 7.04 (2H, d, *J* 8.9, Ar *H*), 3.88 (1H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 176.7, 168.5, 161.3, 131.4 (Ar *C*H), 129.6 (Ar *C*H), 129.4 (Ar *C*H), 128.3 (Ar *C*), 127.7 (Ar *C*H), 125. 7 (Ar *C*), 115.2 (*C*≡N), 114.2 (Ar *C*H), 103.2 (*C*-4), 55.4 (*C*H_3); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.4 (Ar *C*H), 129.6 (Ar *C*H), 129.4 (Ar *C*H), 127.7 (Ar *C*H), 114.2 (Ar *C*H); *m*/*z* (EI) 292 (M^+, 100%), 277 (13), 268 (8), 261 (7), 249 (17), 222 (4), 159 (4), 146 (7), 133 (4), 121 (8), 89 (4), 77 (7), 63 (3) (Found: M^+, 292.0679, $C_{17}H_{12}N_2OS$ requires *M*, 292.0670).

3-(3-Methoxyphenyl)-5-phenylisothiazole-4-carbonitrile 258

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 3-methoxyphenylboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **258** (84%) as colourless needles, mp 75-76 °C (from pentane); (Found: C, 69.8; H, 4.1; N, 9.5. $C_{17}H_{12}N_2OS$ requires C, 69.8; H, 4.1; N, 9.6%); λ_{max}(DCM)/nm 228 (log ε 3.20), 263 (3.18), 284 inf. (3.09); ν_{max}/cm^{-1} 3067w (Ar CH), 2999w, 2966w, 2945w and 2832w (CH_3), 2220w (C≡N), 1612w, 1584m, 1516w, 1497w, 1479m, 1456s, 1433w, 1406w, 1395w, 1358w, 1313w, 1288m, 1263w, 1240m, 1152w, 1096w, 1078w, 1057m, 1036m, 1018w, 999w, 918w, 880w, 870w, 841m, 773s, 758m, 725s; δ_H(300 MHz; $CDCl_3$) 7.83-7.79 (2H, m, Ph *H*), 7.66 (1H, ddd, *J* 7.7, 1.5, 1.0, Ar *H*), 7.59-7.53 (4H, m, Ar *H*), 7.44 (1H, app. t, *J* 8.0, Ar *H-5*), 7.07 (1H, ddd, *J* 8.3, 2.6, 1.0, Ar *H*), 3.90 (3H, s, OC*H*$_3$);

δ_C(75 MHz; $CDCl_3$) 176.8, 168.7, 159.8, 134.1 (Ar *C*), 131.5 (Ar *C*H), 129.9 (Ar *C*H), 129.6 (Ar *C*H), 128.1 (Ar *C*), 127.7 (Ar *C*H), 120.2 (Ar *C*H), 116.8 (Ar *C*H), 114.9 (*C*≡N), 112.7 (Ar *C*H), 103.7 [*C*(C≡N)], 55.4 (O*C*H_3); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.5 (Ar *C*H), 129.9 (Ar *C*H), 129.6 (Ar *C*H), 127.7 (Ar *C*H), 120.2 (Ar *C*H), 116.8 (Ar *C*H), 112.7 (Ar *C*H); *m*/*z* (EI) 292 (M^+, 100%), 277 (4), 261 (14), 249 (7), 222 (3), 159 (3), 146 (4), 133 (3), 121 (8), 115 (3), 89 (3), 77 (8), 63 (4), 51 (3) (Found: M^+, 292.0678, $C_{17}H_{12}N_2OS$ requires *M*, 292.0670).

3-(2-Methoxyphenyl)-5-phenylisothiazole-4-carbonitrile 259

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 2-methoxyphenylboronic acid (4 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **259** (95%) as colourless needles, mp 91-92 °C (from pentane); (Found: C, 69.9; H, 4.2; N, 9.5. $C_{17}H_{12}N_2OS$ requires C, 69.8; H, 4.1; N, 9.6%); λ_{max}(DCM)/nm 227 (log ε 2.97), 256 (2.96), 286 (3.05); ν_{max}/cm^{-1} 3032w, (Ar CH), 2959w, 2934w and 2832w (CH_3), 2226w (C≡N), 1601w, 1582w, 1520w, 1497w, 1479w, 1462m, 1445w, 1435w, 1364w, 1302w, 1277w, 1242m, 1182w, 1167w, 1117w, 1078w, 1051w, 1022m, 1007w, 997w, 959w, 864w, 839w, 824w, 775w, 760s, 752m, 721w; δ_H(300 MHz; $CDCl_3$) 7.84-7.81 (2H, m, Ar *H*), 7.56-7.46 (5H, m, Ar *H*), 7.12-7.05 (2H, m, Ar *H*), 3.94 (3H, s, OCH_3); δ_C(75 MHz; $CDCl_3$) 174.8, 168.0, 156.8, 131.8 (Ar *C*H), 131.3 (Ar *C*H), 131.0 (Ar *C*H), 129.5 (Ar *C*H), 128.4 (Ar *C*), 127.7 (Ar *C*H), 122.5 (Ar *C*), 120.9 (Ar *C*H), 114.3 (*C*≡N), 111.4 (Ar *C*H), 106.7 [*C*(C≡N)], 55.4 (O*C*H_3); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.8 (Ar *C*H), 131.3 (Ar *C*H), 131.0 (Ar *C*H), 129.5 (Ar *C*H), 127.7 (Ar *C*H), 120.9 (Ar *C*H), 111.4 (Ar *C*H); *m*/*z* (EI) 292 (M^+, 75%), 291 (84), 275 (5), 263 (100), 261 (24), 248 (4), 231 (6), 218 (3), 203 (3), 190 (3), 159 (3), 146 (5), 121 (13), 102 (4), 89 (5), 77 (11), 76 (3), 63 (5), 51 (6) (Found: M^+, 292.0667, $C_{17}H_{12}N_2OS$ requires *M*, 292.0670).

5-Phenyl-3-(4-tolyl)isothiazole-4-carbonitrile 260

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 4-tolylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **260** (75%) as colourless needles, mp 129-130 °C (from cyclohexane); (Found: C, 73.7; H, 4.5; N, 10.0. $C_{17}H_{12}N_2S$ requires C, 73.9; H, 4.4; N, 10.1%); λ_{max}(DCM)/nm 269 (log ε 3.33); ν_{max}/cm^{-1} 2224w (C≡N), 1614w, 1510w, 1481m, 1443w, 1414w, 1400w, 1360w, 1192w, 1036w, 1023w, 997w, 964w, 851w, 820s, 777w, 762s, 733s, 706w; δ_H(300 MHz; $CDCl_3$) 7.96

(2H, d, *J* 8.2, Tol *H*), 7.83-7.79 (2H, m, Ph *H*), 7.58-7.54 (3H, m, Ph *H*), 7.33 (2H, d, *J* 8.5, Tol *H*), 2.44 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 176.7, 169.0, 140.7 (Ar *C*), 131.4 (Ar *C*H), 130.3 (Ar *C*), 129.6 (Ar *C*H), 129.6 (Ar *C*H), 128.3 (Ar *C*), 127.8 (Ar *C*H), 127.7 (Ar *C*H), 115.0 (*C*≡N), 103.5 [*C*(C≡N)], 21.4 (CH_3); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.4 (Ar *C*H), 129.6 (Ar *C*H), 129.6 (Ar *C*H), 127.8 (Ar *C*H), 127.7 (Ar *C*H); *m*/*z* (EI) 276 (M^+, 100%), 275 (57), 261 (12), 243 (5), 232 (4), 159 (3), 149 (3), 138 (8), 121 (9), 116 (7), 91 (8), 89 (8), 77 (7), 65 (4), 51 (4) (Found: M^+, 276.0716, $C_{17}H_{12}N_2S$ requires *M*, 276.0721).

5-Phenyl-3-(3-tolyl)isothiazole-4-carbonitrile 261

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 3-tolylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **261** (91%) as colourless needles, mp 94-95 ^oC (from cyclohexane); (Found: C, 73.8; H, 4.3; N, 10.1. $C_{17}H_{12}N_2S$ requires C, 73.9; H, 4.4; N, 10.1%); λ_{max}(DCM)/nm 263 (log ε 3.22); ν_{max}/cm^{-1} 3057w and 3030w (Ar CH), 2974w, 2920w and 2855w (CH_3), 2224w (C≡N), 1558w, 1541w, 1520w, 1477m, 1445w, 1406w, 1354m, 1312w, 1171w, 1155w, 1098w, 1078w, 1043w, 999w, 912w, 881w, 833w, 789m, 775w, 756m, 725s; δ_H(300 MHz; $CDCl_3$) 7.87-7.83 (2H, m, Tol *H*), 7.82-7.80 (2H, m, Ph *H*), 7.56-7.55 (3H, m, Ph *H*), 7.43 (1H, app. t, *J* 7.9, Tol *H*), 7.35-7.32 (1H, m, Tol *H*), 2.46 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 176.7, 169.1, 138.7 (Ar *C*), 132.8 (Ar *C*), 131.4 (Ar *C*H), 131.2 (Ar *C*H), 129.6 (Ar *C*H), 128.7 (Ar *C*H), 128.5 (Ar *C*H), 128.2 (Ar *C*), 127.7 (Ar *C*H), 124.9 (Ar *C*H), 114.9 (*C*≡N), 103.7 [*C*(C≡N)], 21.4 (*C*H_3); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.4 (Ar *C*H), 131.2 (Ar *C*H), 129.6 (Ar *C*H), 128.7 (Ar *C*H), 128.5 (Ar *C*H), 127.7 (Ar *C*H), 124.9 (Ar *C*H); *m*/*z* (EI) 276 (M^+, 100%), 275 (42), 261 (12), 243 (35), 232 (3), 216 (3), 159 (3), 149 (3), 137 (11), 121 (15), 116 (14), 102 (3), 89 (16), 77 (16), 65 (12), 63 (10), 51 (14).

3-(4-Chlorophenyl)-5-phenylisothiazole-4-carbonitrile 262

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 4-chlorophenylboronic acid (4 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **262** (82%) as colourless needles, mp 168-169 ^oC (from cyclohexane); (Found: C, 64.6; H, 3.0; N, 9.3. $C_{16}H_9ClN_2S$ requires C, 64.8; H, 3.1; N, 9.4%); λ_{max}(DCM)/nm 268 (log ε 3.34); ν_{max}/cm^{-1} 3057w (Ar CH), 2228w (C≡N), 1597w, 1516w, 1483s, 1447w, 1406s, 1362m, 1273w, 1182w, 1094s, 1018w, 1007w, 966w, 959w, 914w, 846w, 826s, 808m,

758m, 733s, 712w, 704w; δ_H(300 MHz; $CDCl_3$) 8.01 (2H, d, *J* 8.5, Ar *H*), 7.83-7.77 (2H, m, Ph *H*), 7.59-7.54 (3H, m, Ph *H*), 7.50 (2H, d, *J* 8.5, Ar *H*); δ_C(75 MHz; $CDCl_3$) 177.1, 167.6, 136.7 (Ar *C*), 131.6 (Ar *C*H), 131.4 (Ar *C*), 129.7 (Ar *C*H), 129.2 (Ar *C*H), 129.2 (Ar *C*H), 128.0 (Ar *C*), 127.7 (Ar *C*H), 114.8 (*C*≡N), 103.5 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.6 (Ar *C*H), 129.7 (Ar *C*H), 129.2 (Ar *C*H), 129.2 (Ar *C*H), 127.7 (Ar *C*H); *m*/*z* (EI) 298 (M^++2, 39%), 296 (M^+, 100), 261 (11), 169 (7), 148 (3), 137 (9), 121 (6), 102 (3), 89 (3), 77 (8), 69 (3), 51 (7) (Found: M^+, 296.0170, $C_{16}H_9ClN_2S$ requires *M*, 296.0175).

3-(3-Chlorophenyl)-5-phenylisothiazole-4-carbonitrile 263

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 3-chlorophenylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **263** (75%) as colourless needles, mp 153-154 °C (from cyclohexane); (Found: C, 64.9; H, 3.0; N, 9.3. $C_{16}H_9ClN_2S$ requires C, 64.8; H, 3.1; N, 9.4%); λ_{max}(DCM)/nm 261 (log ε 3.12); ν_{max}/cm^{-1} 2224w (C≡N), 1599w, 1572w, 1514w, 1476m, 1443m, 1433m, 1354m, 1261w, 1180w, 1082w, 1038w, 999w, 966w, 917w, 880w, 847w, 829m, 787m, 758m, 739s, 716s; δ_H(300 MHz; $CDCl_3$) 8.04 (1H, m, Ar *H*), 7.98-7.96 (1H, m, Ar *H*), 7.82-7.79 (2H, m, Ph *H*), 7.58-7.56 (3H, m, Ph *H*), 7.51-7.44 (2H, m, Ar *H*); δ_C(75 MHz; $CDCl_3$) 177.1, 167.2, 135.0 (Ar *C*), 134.4 (Ar *C*), 131.6 (Ar *C*H), 131.3 (Ar *C*), 130.5 (Ar *C*H), 130.1 (Ar *C*H), 129.7 (Ar *C*H), 128.1 (Ar *C*H), 127.7 (Ar *C*H), 125.8 (Ar *C*H), 114.6 (*C*≡N), 103.6 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.6 (Ar *C*H), 130.5 (Ar *C*H), 130.1 (Ar *C*H), 129.7 (Ar *C*H), 128.1 (Ar *C*H), 127.7 (Ar *C*H), 125.8 (Ar *C*H); *m*/*z* (EI) 298 (M^++2, 43%), 296 (M^+, 100), 261 (M^+-Cl, 20), 252 (6), 169 (6), 159 (4), 148 (4), 137 (10), 134 (8), 131 (10), 121 (7), 111 (5), 108 (5), 104 (5), 84 (4), 77 (11), 69 (3), 51 (9) (Found: M^+, 296.0168 $C_{16}H_9ClN_2S$ requires *M*, 296.0175).

3-(2-Chlorophenyl)-5-phenylisothiazole-4-carbonitrile 264

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 2-chlorophenylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **264** (58%) as colourless needles, mp 48-49 °C (from cyclohexane); λ_{max}(DCM)/nm 228 (log ε 3.03), 280 (3.11); ν_{max}/cm^{-1} 2224w (C≡N), 1595w, 1570w, 1518w, 1479m, 1431w, 1408w, 1356w, 1179w, 1163w, 1132w, 1070w, 1043w, 1034w, 999w, 968w, 951w, 918w, 839w, 812w, 762m, 737m, 716m, 704m; δ_H(300 MHz; $CDCl_3$) 7.86-7.83 (2H, m,

Ph *H*), 7.58-7.39 (7H, m, Ar *H*); δ_C(75 MHz; $CDCl_3$) 175.4, 167.9, 133.0 (Ar *C*), 132.2 (Ar *C*), 131.6 (Ar *C*H), 131.4 (Ar *C*H), 131.1 (Ar *C*H), 130.3 (Ar *C*H), 129.7 (Ar *C*H), 128.0 (Ar *C*), 127.6 (Ar *C*H), 127.0 (Ar *C*H) 113.7 (*C*≡N), 106.3 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$). 131.7 (Ar *C*H), 131.4 (Ar *C*H), 131.1 (Ar *C*H), 130.3 (Ar *C*H), 129.7 (Ar *C*H), 127.6 (Ar *C*H), 127.0 (Ar *C*H); *m*/*z* (EI) 298 (M^++2, 44%), 296 (M^+, 100), 261 (M^+-Cl, 32), 252 (5), 215 (4), 169 (13), 159 (8), 148 (4), 137 (18), 134 (11), 130 (12), 121 (12), 114 (8), 108 (10), 102 (11), 89 (9), 77 (20), 63 (8), 51 (21).

5-Phenyl-3-(thien-3-yl)isothiazole-4-carbonitrile 265

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 3-thienyl-boronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **265** (91%) as colourless needles, mp 102-103 °C (from cyclohexane); (Found: C, 62.6; H, 2.9; N, 10.4. $C_{14}H_8N_2S_2$ requires C, 62.7; H, 3.0; N, 10.4%); λ_{max}(DCM)/nm 228 (log ε 3.12), 271 (3.29); ν_{max}/cm^{-1} 3109w (Ar CH), 2224w (C≡N), 1531w, 1514w, 1483w, 1445w, 1395w, 1348w, 1337w, 1150w, 1078w, 999w, 962w, 903w, 872w, 845w, 797m, 766m, 723s; δ_H(300 MHz; $CDCl_3$) 8.29 (1H, dd, *J* 2.9, 1.3, thienyl *H-2*), 7.83 (1H, dd, *J* 5.1, 1.3, thienyl *H-4*), 7.82-7.77 (2H, m, Ph *H*), 7.58-7.54 (3H, m, Ph *H*), 7.44 (1H, dd, *J* 5.1, 2.9, thienyl *H-5*); δ_C(75 MHz; $CDCl_3$) 176.5, 163.7, 134.6 (Ar *C*), 131.5 (Ar *C*H), 129.6 (Ar *C*H), 128.1 (Ar *C*), 127.7 (Ar *C*H), 127.0 (Ar *C*H), 126.4 (Ar *C*H), 126.2 (Ar *C*H), 115.1 (*C*≡N), 102.9 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.5 (Ar *C*H), 129.6 (Ar *C*H), 127.7 (Ar *C*H), 127.0 (Ar *C*H), 126.4 (Ar *C*H), 126.2 (Ar *C*H); *m*/*z* (EI) 268 (M^+, 100%), 235 (4), 224 (4), 211 (2), 159 (3), 141 (11), 134 (8), 121 (7), 109 (8), 77 (7), 69 (3), 51 (4) (Found: M^+, 268.0131, $C_{14}H_8N_2S_2$ requires *M*, 268.0129).

3,3'-Bi(5-phenylisothiazole-4-carbonitrile) 255 [using Cu(0) catalysed Ullmann conditions]

A stirred mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (50 mg, 0.16 mmol) and Cu(0) powder (20.3 mg, 0.32 mmol) in DMF (2 ml) under an argon atmosphere, was heated to *ca.* 110 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 x 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 1:4) gave the title compound **255** (9.2 mg, 31%) as colourless needles, mp 151-152 °C (from cyclohexane/PhH) identical to that described above. Further elution

(hexane-DCM, 1:4) gave *2-[(4-cyano-5-phenylisothiazol-3-ylthio)-(phenyl)methylene]-malononitrile* **266** (10 mg, 34%) as colourless needles, mp 118-119 ^{o}C (from cyclohexane); (Found: C, 64.7; H, 2.6; N, 14.9. $C_{20}H_{10}N_4S_2$ requires C, 64.8; H, 2.7; N, 15.1%); λ_{max}(DCM)/nm 228 (log ε 3.92), 302 (4.10); ν_{max}/cm^{-1} 3046w (Ph CH), 2228m (C≡N), 1593w, 1531m, 1510w, 1481m, 1444m, 1379m, 1339w, 1331w, 1288w, 1252w, 1238w, 1190w, 1105w, 1080w, 1049w, 1026w, 1001w, 949w, 926w, 864w, 826m, 804w, 762s, 700m; δ_H(300 MHz; $CDCl_3$) 7.61-7.38 (8H, m, Ph *H*); δ_C(75 MHz; $CDCl_3$) 176.8, 174.2, 156.2, 133.0 (Ph *C*H), 132.5 (Ph *C*H), 132.1 (Ph *C*), 129.9 (Ph *C*H), 129.6 (Ph *C*H), 129.0 (Ph *C*H), 127.3 (Ph *C*H), 126.8 (Ph *C*), 112.0 (C≡N), 112.0 (C≡N), 111.4 (C≡N), 109.1 [*C*(C≡N)], 83.7 [*C*$(CN)_2$]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 133.0 (Ph *C*H), 132.5 (Ph *C*H), 129.9 (Ph *C*H), 129.6 (Ph *C*H), 129.0 (Ph *C*H), 127.3 (Ph *C*H); *m*/*z* (EI) 370 (M^+, 100%), 344 (4), 337 (13), 312 (4), 305 (5), 293 (3), 267 (8), 242 (3), 218 (18), 185 (6), 184 (3), 159 (7), 153 (33), 141 (17), 128 (15), 126 (16), 121 (50), 114 (9), 100 (6), 90 (6), 84 (7), 77 (50), 69 (5), 63 (5), 56 (10), 51 (23) (Found: M^+, 370.0348, $C_{20}H_{10}N_4S_2$ requires *M*, 370.0347).

3,3'-Bi(5-phenylisothiazole-4-carbonitrile) 255 [using Pd(0) catalysed Ullmann conditions: see Table 24]

A stirred mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (50 mg, 0.16 mmol) and $Pd(OAc)_2$ (35.9 mg, 0.16 mmol) in DMF (2 ml) under an argon atmosphere, was heated to *ca.* 140 ^{o}C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^{o}C, diluted with DCM (15 ml) and washed with H_2O (4 x 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 1:4) gave the title compound **255** (22.5 mg, 76%) as colourless needles, mp 151-152 ^{o}C (from cyclohexane/PhH) identical to that described above.

3,5-Diphenylisothiazole-4-carbonitrile 237 *via* Stille coupling reaction at C-3 (typical Stille conditions for coupling at C-3: see Table 25)

A stirred mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (30 mg, 0.096 mmol), tributylphenylstannane (37.6 μl, 0.115 mmol, 1.2 equiv.) and $Pd(OAc)_2$ (1 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 ^{o}C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^{o}C, diluted with DCM (15 ml) and washed with H_2O (4 x 10 ml). The organic layer was

separated, dried and absorbed on silica. Chromatography (hexane-DCM, 7:3) gave the title compound **237** (23.6 mg, 94%) as white needles, mp 146-147 ^{o}C (from cyclohexane) identical to that described above.

5-Phenyl-3-(thien-2-yl)isothiazole-4-carbonitrile 267

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 2-(tributyl-stannyl)thiophene and $Pd(OAc)_2$ gave the *title compound* **267** (87%) as colourless needles, mp 122-123 ^{o}C (from cyclohexane); (Found: C, 62.7; H, 2.9; N, 10.5. $C_{14}H_8N_2S_2$ requires C, 62.7; H, 3.0; N, 10.4%); λ_{max}(DCM)/nm 290 (log ε 3.32); ν_{max}/cm^{-1} 3102w (Ar CH), 2224w (C≡N), 1558w, 1537w, 1508w, 1481m, 1447w, 1437w, 1393w, 1369w, 1339w, 1236w, 1057w, 953w, 847m, 781w, 766m, 719s; δ_H(300 MHz; $CDCl_3$) 8.09 (1H, dd, *J* 3.8, 1.0, thienyl *H-3*), 7.83-7.78 (2H, m, Ph *H*), 7.60-7.54 (3H, m, Ph *H*), 7.51 (1H, dd, *J* 5.1, 1.0, thienyl *H-5*), 7.18 (1H, dd, *J* 5.1, 3.8, thienyl *H-4*); δ_C(75 MHz; $CDCl_3$) (1 peak missing) 176.8, 162.3, 136.2 (Ar *C*), 131.6 (Ar *C*H), 129.7 (Ar *C*H), 129.2 (Ar *C*H), 128.1 (Ar *C*H), 127.9 (Ar *C*), 127.6 (Ar *C*H), 114.7 (*C*≡N), 101.9 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) (1 peak missing) 131.6 (Ar *C*H), 129.7 (Ar *C*H), 129.2 (Ar *C*H), 128.1 (Ar *C*H), 127.6 (Ar *C*H); *m*/*z* (EI) 268 (M^+,100%), 241 (3), 235 (3), 224 (4), 159 (4), 141 (18), 135 (3), 121 (9), 109 (9), 77 (8), 69 (4), 58 (4), 51 (4) (Found: M^+, 268.0120 $C_{14}H_8N_2S_2$ requires *M*, 268.0129).

3-(Fur-2-yl)-5-phenylisothiazole-4-carbonitrile 268

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with 2-(tributyl-stannyl)furan and $Pd(OAc)_2$ gave the *title compound* **268** (91%) as pink needles, mp 99-100 ^{o}C (from cyclohexane); (Found: C, 66.7; H, 3.2; N, 11.3. $C_{14}H_8N_2OS$ requires C, 66.7; H, 3.2; N, 11.1%); λ_{max}(DCM)/nm 284 (log ε 3.39); ν_{max}/cm^{-1} 3132w and 3113w (Ar CH), 2224w (C≡N), 1585w, 1514w, 1497m, 1474w, 1443w, 1412w, 1383w, 1358w, 1260w, 1231w, 1198w, 1150w, 1078w, 1042w, 1028w, 1009m, 961w, 918w, 883w, 843m, 766s, 727m; δ_H(300 MHz; $CDCl_3$) 7.83-7.77 (2H, m, Ph *H*), 7.64 (1H, dd, *J* 1.0, 0.7, furyl *H-5*), 7.61-7.54 (3H, m, Ph *H*), 7.39 (1H, dd, *J* 3.6, 0.7, furyl *H-5*), 6.60 (1H, dd, *J* 3.5, 1.8, furyl *H-4*); δ_C(75 MHz; $CDCl_3$) 176.4, 158.7, 147.4 (Ar *C*), 144.6 (Ar *C*H), 131.7 (Ar *C*H), 129.7 (Ar *C*H), 127.8 (Ar *C*), 127.7 (Ar *C*H), 114.2 (*C*≡N), 112.1 (Ar *C*H), 111.9 (Ar *C*H), 101.6 [*C*(C≡N)]; δ_C(75 MHz; DEPT 90, $CDCl_3$) 144.6 (Ar *C*H), 131.7 (Ar *C*H), 129.7 (Ar *C*H), 127.7 (Ar *C*H), 112.1 (Ar *C*H), 111.9 (Ar *C*H); *m*/*z* (EI)

252 (M^+, 100%), 223 (25), 197 (4), 192 (11), 179 (6), 170 (7), 164 (5), 159 (11), 153 (8), 127 (18), 125 (31), 121 (65), 114 (15), 99 (14), 96 (10), 93 (10), 77 (21), 69 (7), 51 (9) (Found: M^+, 252.0361, $C_{14}H_8N_2OS$ requires *M*, 252.0357).

5-Phenyl-3-vinylisothiazole-4-carbonitrile 269

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with tributyl(vinyl)tin and $Pd(OAc)_2$ gave the *title compound* **269** (96%) as colourless needles, mp 28-29 ^oC (from pentane); (Found: C, 67.8; H, 3.7; N, 13.1. $C_{12}H_8N_2S$ requires C, 67.9; H, 3.8; N, 13.2%); λ_{max}(DCM)/nm 249 (log ε 3.14), 286 (2.98); ν_{max}/cm^{-1} 3030w (Ph CH), 2953w, 2224w (C≡N), 1630w, 1578w, 1514w, 1487w, 1481w, 1447w, 1429w, 1398w, 1385w, 1344w, 1302w, 1184w, 1157w, 1105w, 1080w, 1053w, 1030w, 1020w, 999w, 976w, 949w, 941w, 922w, 839w, 827w, 770w, 750s; δ_H(300 MHz; $CDCl_3$) 7.79-7.72 (2H, m, Ph *H*), 7.56-7.46 (3H, m, Ph *H*), 6.95 (1H, dd, *J* 17.7, 11.1, Vinyl *H-gem*), 6.46 (1H, dd, *J* 17.5, 0.9 Vinyl *H-trans*), 5.71 (1H, dd, *J* 11.1, 0.9, Vinyl *H-cis*); δ_C(75 MHz; $CDCl_3$) 175.4, 166.6, 131.4 (Ph *C*H), 129.5 (Ph *C*H), 127.9 (Ph *C*), 127.8 (=*C*H), 127.4 (Ph *C*H), 122.8 (=*C*H_2), 114.0 (*C*≡N), 103.8 [*C*(C≡N)]; δ_C(75 MHz; DEPT 135, $CDCl_3$) 131.4 (Ph *C*H), 129.5 (Ph *C*H), 127.8 (=*C*H), 127.4 (Ph *C*H), 122.8 (=*C*H_2); *m*/*z* (EI) 212 (M^+, 100%), 211 (96), 185 (32), 179 (8), 168 (16), 159 (8), 153 (3), 140 (4), 134 (3), 127 (6), 121 (6), 115 (4), 106 (3), 85 (6), 77 (4) (Found: M^+, 212.0408, $C_{12}H_8N_2S$ requires *M*, 212.0408).

5-Phenyl-3-propynylisothiazole-4-carbonitrile 270

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with tributyl(1-propynyl)tin and $Pd(OAc)_2$ gave the *title compound* **270** (73%) as white powder, mp 85-86 ^oC (from pentane); (Found: C, 69.7; H, 3.5; N, 12.5. $C_{13}H_8N_2S$ requires C, 69.6; H, 3.6; N, 12.5%); λ_{max}(DCM)/nm 246 (log ε 3.11), 286 (3.); ν_{max}/cm^{-1} 2953w, 2922w and 2853w (CH_3), 2243w (C≡C or C≡N), 2232w, (C≡C or C≡N), 1518w, 1483m, 1449w, 1414w, 1360m, 1339w, 1188w, 1165w, 1152w, 1105w, 1080w, 1032w, 1001w, 918w, 843m, 741s, 719s; δ_H(300 MHz; $CDCl_3$) 7.77-7.74 (2H, m, Ph *H*), 7.54-7.50 (3H, m, Ph *H*), 2.16 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 174.2, 152.9, 131.7 (Ph *C*H), 129.6 (Ph *C*H), 127.6 (Ph *C*), 127.4 (Ph *C*H), 113.3 (*C*≡N), 107.7 [*C*(C≡N)], 92.9 (*C*≡C), 72.4 (*C*≡C), 4.50 (*C*H_3); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.7 (Ph *C*H), 129.6 (Ph *C*H), 127.4 (Ph *C*H); *m*/*z* (EI) 224 (M^+, 100%), 197 (7), 192 (20), 179 (10), 170 (6), 164 (4), 159 (6), 153

(6), 127 (15), 121 (18), 115 (8), 114 (9), 100 (8), 97 (21), 89 (6), 77 (28), 70 (14), 69 (13), 64 (10), 63 (10), 51 (32), 45 (12) (Found: M^+, 224.0408, $C_{13}H_8N_2S$ requires *M*, 224.0408).

3,5-Diphenylisothiazole-4-carbonitrile 237 *via* Negishi coupling reaction at C-3

A stirred mixture of 3-iodo-5-phenyl-4-isothiazolecarbonitrile **245** (30 mg, 0.096 mmol), phenylzinc chloride (580 μl, 0.5 M in THF, 3 equiv.) and $(PPh_3)_2PdCl_2$ (3.4 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 ^oC, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC, diluted with DCM (15 ml) and washed with H_2O (4 x 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 7:3) gave the title compound **237** (19.6 mg, 78%) as white needles, mp 146-147 ^oC (from cyclohexane) identical to that described above.

5-Phenyl-3-(phenylethynyl)isothiazole-4-carbonitrile 271 (typical Sonogashira conditions for coupling at C-3: see Table 27)

A stirred mixture of 3-bromo-5-phenylisothiazole-4-carbonitrile **223** (30 mg, 0.11 mmol), triethylamine (32 μl, 0.23 mmol, 2 equiv.), CuI (2.2 mg, 10 mol%), $(PPh_3)_2PdCl_2$ (4 mg, 5 mol%) and ethynylbenzene (25 μl, 0.22 mmol, 2 equiv.) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 ^oC, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC, diluted with DCM (15 ml) and washed with H_2O (4 x 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 7:3) gave the *title compound* **271** (25 mg, 92%) as pink crystals, mp 122-123 ^oC (from cyclohexane); (Found: C, 75.4; H, 3.4; N, 9.8; $C_{18}H_{10}N_2S$ requires C, 75.5; H, 3.5, N, 9.8%); λ_{max}(DCM)/nm 287 (log ε 3.41), 302 (3.31); ν_{max}/cm^{-1} 3064w (Ph CH), 2230m (C≡N), 2216m (C≡C), 1518m, 1495m, 1481m, 1447m, 1418m, 1362m, 1219w, 1090w, 1080w, 1069w, 1026w, 999w, 961w, 918w, 839m, 770m, 758s, 718m; δ_H(300 MHz; $CDCl_3$) 7.84-7.77 (2H, m, Ph *H*), 7.70-7.66 (2H, m, Ph≡ *H*), 7.60-7.52 (3H, m, Ph *H*), 7.47-7.37 (3H, m, Ph≡ *H*); δ_C(75 MHz; $CDCl_3$) 174.5, 152.6, 132.4 (Ph *C*H), 131.8 (Ph *C*H), 130.0 (Ph *C*H), 129.8 (Ph *C*H), 128.5 (Ph *C*H), 127.5 (Ph *C*), 127.4 (Ph *C*H), 120.7 (Ph *C*), 113.1 (*C*≡N), 108.1 [*C*(C≡N)], 94.7 (*C*≡C), 81.1 (*C*≡C); δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.4 (Ph *C*H), 131.8 (Ph *C*H), 130.0 (Ph *C*H), 129.7 (Ph *C*H), 128.5 (Ph *C*H), 127.4 (Ph *C*H); *m*/*z* (EI)

286 (M^+, 100%), 253 (2), 159 (59), 143 (9), 127 (31), 121 (6), 115 (8), 100 (6), 88 (3), 77 (7), 63 (3), 51 (5) (Found: M^+, 286.0571 $C_{18}H_{10}N_2S$ requires *M*, 286,0565).

5-Phenyl-3-trimethylsilylethynylisothiazole-4-carbonitrile 272

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with triethylamine, CuI, $(PPh_3)_2PdCl_2$ and ethynyltrimethylsilane (1.5 equiv.) gave the *title compound* **272** (70%) as colourless needles, mp 68-69 ^oC (from pentane); (Found: C, 63.8; H, 4.9; N, 9.9. $C_{15}H_{14}N_2SSi$ requires C, 63.8; H, 5.0; N, 9.9%); λ_{max}(DCM)/nm 253 (log ε 3.15), 260 inf. (3.14), 287 (3.01); ν_{max}/cm^{-1} 3057w (Ph CH), 2965w (CH_3), 2234w (C≡N), 1558w, 1539w, 1520w, 1483w, 1447w, 1395w, 1364w, 1252w, 1115w, 883w, 843s, 760s, 721w; δ_H(300 MHz; $CDCl_3$) 7.78-7.74 (2H, m, Ph *H*), 7.56-7.53 (3H, m, Ph *H*), 0.32 (9H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 174.4, 152.4, 131.8 (Ph *C*H), 129.7 (Ph *C*H), 127.5 (Ph *C*), 127.4 (Ph *C*H), 112.8 (*C*≡N), 108.4 [*C*(C≡N)], 101.9 (*C*≡C), 95.2 (*C*≡C), -0.6 (*C*H$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.8 (Ph *C*H), 129.7 (Ph *C*H), 127.4 (Ph *C*H); *m*/*z* (EI) 282 (M^+, 16%), 267 (100), 217 (4), 210 (4), 183 (12), 167 (3), 149 (6), 140 (19), 134 (7), 110 (5), 109 (3), 108 (17), 77 (5) (Found: M^+, 282.0646, $C_{15}H_{14}N_2SSi$ requires *M*, 282.0647).

5-Phenyl-3-(thien-3-ylethynyl)isothiazole-4-carbonitrile 273

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with triethylamine, CuI, $(PPh_3)_2PdCl_2$ and 2-ethynylthiophene (1.2 equiv.) gave the *title compound* **273** (91%) as colourless needles, mp 123-124 ^oC (from cyclohexane); (Found: C, 65.7; H, 2.7; N, 9.7. $C_{16}H_8N_2S_2$ requires C, 65.7; H, 2.8; N, 9.6%); λ_{max}(DCM)/nm 231 (log ε 3.99), 291 (4.30); ν_{max}/cm^{-1} 3105w and 3082w (Ar CH), 2232w (C≡N), 2220m (C≡C), 1528w, 1516w, 1481m, 1449w, 1383w, 1362m, 1227w, 1186w, 1101w, 1094w, 1080w, 1001w, 962w, 947w, 916w, 878w, 854w, 841m, 793s, 762s, 716m; δ_H(300 MHz; $CDCl_3$) 7.82-7.78 (2H, m, Ph *H*), 7.77 (1H, dd, *J* 2.9, 1.2, thienyl *H-3*), 7.58-7.53 (3H, m, Ph *H*), 7.35 (1H, dd, *J* 5.0, 2.9, thienyl *H-4*), 7.31 (1H, dd, *J* 5.0, 1.2, thienyl *H-5*); δ_C(75 MHz; $CDCl_3$) 174.5, 152.6, 132.0 (Ar *C*H), 131.8 (Ar *C*H), 130.0 (Ar *C*H), 129.7 (Ar *C*H), 127.5 (Ar *C*), 127.5 (Ar *C*H), 125.9 (Ar *C*H), 119.8 (Ar *C*), 113.1 (*C*≡N), 107.9 [*C*(C≡N)], 89.9 (*C*≡C), 80.9 (*C*≡C); δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.0 (Ar *C*H), 131.8 (Ar *C*H), 130.0 (Ar *C*H), 129.7 (Ar *C*H), 127.5 (Ar *C*H), 125.9 (Ar *C*H); *m*/*z* (EI)

292 (M^+, 100%), 165 (29), 159 (5), 146 (6), 133 (22), 121 (9), 115 (3), 88 (4), 77 (7), 69 (4), 63 (3), 51 (5) (Found: M^+, 292.0131 $C_{16}H_8N_2S_2$ requires *M*, 292.0129).

5-Phenyl-3-(2-pyridylethynyl)isothiazole-4-carbonitrile 274

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with triethylamine, CuI, $(PPh_3)_2PdCl_2$ and 2-ethynylpyridine (1.2 equiv.) gave the *title compound* **274** (92%) as pale yellow needles, mp 120-121 ^oC (from cyclohexane); (Found: C, 71.0; H, 3.1; N, 14.5. $C_{17}H_9N_3S$ requires C, 71.1; H, 3.2; N, 14.6%); λ_{max}(DCM)/nm 228 (log ε 3.00), 271 inf. (3.18), 291 (3.35); ν_{max}/cm^{-1} 2232w (C≡N), 1580w, 1562w, 1516w, 1483s, 1466m, 1447w, 1431w, 1364m, 1287w, 1263w, 1246w, 1223w, 1186w, 1150w, 1092w, 1043w, 1001w, 989m, 959w, 912w, 891w, 843m, 781m, 768s, 760s, 739w, 716s; δ_H(300 MHz; $CDCl_3$) 8.69 (1H, d, *J* 4.7, Ar *H*), 7.83-7.77 (2H, m, Ph *H*), 7.73 (1H, dd, *J* 7.5, 1.7, Ar *H*), 7.69 (1H, app. d, *J* 7.7, Ar *H*), 7.60-7.52 (3H, m, Ph *H*), 7.35 (1H, ddd, *J* 7.3, 5.0, 1.5, Ar *H*); δ_C(75 MHz; $CDCl_3$) 174.7, 151.7, 150.4 (Ar *C*H), 141.3 (Ar *C*), 136.4 (Ar *C*H), 131.9 (Ar *C*H), 129.8 (Ar *C*H), 128.4 (Ar *C*H), 127.5 (Ar *C*H), 127.4 (Ar *C*), 124.2 (Ar *C*H), 112.9 (*C*≡N), 108.4 [*C*(C≡N)], 92.5 (*C*≡C), 80.0 (*C*≡C); δ_C(75 MHz; DEPT 90, $CDCl_3$) 150.3 (Ar *C*H), 136.4 (Ar *C*H), 131.9 (Ar *C*H), 129.8 (Ar *C*H), 128.5 (Ar *C*H), 127.5 (Ar *C*H), 124.2 (Ar *C*H); *m*/*z* (EI) 287 (M^+, 100%), 160 (19), 144 (5), 128 (12), 121 (4), 115 (4), 108 (4), 101 (6), 78 (13), 51 (9).

3-(Ferrocenylethynyl)-5-phenylisothiazole-4-carbonitrile 275

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** with triethylamine, CuI, $(PPh_3)_2PdCl_2$ and ethynylferrocene (2 equiv.) gave the *title compound* **275** (100%) as orange-red needles, mp 121-122 ^oC (from cyclohexane); (Found: C, 67.0; H, 3.5; N, 7.2. $C_{22}H_{14}FeN_2S$ requires C, 67.0; H, 3.6; N, 7.1%); λ_{max}(DCM)/nm 228 (log ε 3.21), 259 (3.19), 293 (3.31), 350 (2.24), 451 (2.03); ν_{max}/cm^{-1} 2230w (C≡N), 2214m (C≡C), 1518w, 1491w, 1477w, 1447w, 1412w, 1395w, 1360m, 1234w, 1184w, 1105w, 1082w, 1030w, 1001w, 962w, 928w, 839m, 829m, 820m, 764s, 716m; δ_H(300 MHz; $CDCl_3$) 7.83-7.75 (2H, m, Ph C*H*), 7.58-7.53 (3H, m, Ph C*H*), 4.66 (2H, app. s, cp C*H*), 4.36 (2H, app. s, cp C*H*), 4.31 (5H, app. s, cp C*H*); δ_C(75 MHz; $CDCl_3$) 174.2, 153.1, 131.7 (Ph *C*H), 129.7 (Ph *C*H), 127.7 (Ph *C*), 127.4 (Ph *C*H), 113.3 (*C*≡N), 107.9 [*C*(C≡N)], 95.8 (*C*≡C), 77.9 (*C*≡C), 72.4 (cp *C*H), 70.5 (cp *C*H), 70.1 (cp *C*H), 61.8; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.7 (Ph *C*H), 129.7 (Ph *C*H), 127.4 (Ph *C*H), 72.4 (cp *C*H), 70.4 (cp

*C*H), 70.0 (cp *C*H); *m*/*z* (EI) 394 (M^+, 100%), 329 (46), 215 (3), 202 (6), 197 (6), 170 (2), 158 (8), 146 (6), 121 (13), 88 (4), 56 (10).

7.6 Compounds Related to Chapter 6

3-Chloro-5-phenylisothiazole-4-carboxamide 276

A stirred solution of 3-chloro-5-phenylisothiazole-4-carbonitrile **207** (1.5 g, 6.82 mmol) in c. H_2SO_4 (25 ml) protected with $CaCl_2$ drying tube, was heated to *ca.* 100 ^oC until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC and then was poured into ice-water to afford a white precipitate. The white precipitate was filtered, washed (H_2O) and dried under vacuum to give the *title compound* **276** (1.57 g, 97%) as colourless needles, mp 168-171 ^oC (from PhH); (Found: C, 50.4; H, 3.0; N, 11.6. $C_{10}H_7ClN_2OS$ requires C, 50.3; H, 3.0; N, 11.7%); λ_{max}(DCM)/nm 269 (log ε 3.90); ν_{max}/cm^{-1} 3380w (NH), 3184w (Ar CH), 1642s (C=O), 1618m, 1529w, 1491m, 1446w, 1403w, 1321w, 1295m, 1275m, 1103w, 1039m, 1018w, 1000w, 917w, 846m, 793w, 762m; δ_H(300 MHz; DMSO-d_6) 8.08 (1H, br s, N*H*), 7.80 (1H, br s, N*H*), 7.60-7.56 (2H, m, Ph C*H*), 7.49-7.46 (3H, m, Ph C*H*); δ_C(75 MHz; DMSO-d_6) 165.6, 163.6, 146.3, 129.5 (Ph *C*H), 128.8, 128.3 (Ph *C*H), 128.1, 126.7 (Ph *C*H); δ_C(75 MHz; DEPT 90, DMSO-d_6) 129.5 (Ph *C*H), 128.3 (Ph *C*H), 126.7 (Ph *C*H); *m*/*z* (EI) 240 (M^++2, 25%), 239 (M^++1, 44), 238 (M^+, 68), 237 (M^+-H, 100), 224 (27), 223 (13), 222 (72), 221 (13), 219 (3), 203 (M^+-Cl, 4), 186 (3), 159 (12), 133 (18), 129 (11), 127 (15), 121 (4), 114 (4), 101 (4), 100 (3), 89 (18), 77 (13), 75 (5), 63 (6), 51 (10) (Found: M^+, 237.9959, $C_{10}H_7ClN_2OS$ requires *M*, 237.9968).

3-Chloro-5-phenylisothiazole-4-carboxylic acid 277

To a stirred solution of 3-chloro-5-phenylisothiazole-4-carboxamide **276** (1.5 g, 6.29 mmol) in c. H_2SO_4 (250 ml) cooled to *ca.* 0 ^oC and protected with $CaCl_2$ drying tube, was added in portions sodium nitrite (4.34 g, 62.9 mmol, 10 equiv.). The reaction mixture then was heated to *ca.* 100 ^oC, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC and was poured into ice-water to afford a white precipitate. The white precipitate was filtered out, washed (H_2O) and dried under vacuum to give the *title compound* **277** (1.33 g, 88%) as colourless crystals, mp 162-164 ^oC (from cyclohexane); (Found: C, 50.0; H, 2.4; N, 5.7. $C_{10}H_6ClNO_2S$ requires C, 50.1; H, 2.5; N,

5.8%); λ_{max}(DCM)/nm 268 (log ε 3.98); ν_{max}/cm^{-1} 2847br (OH), 1695s (C=O), 1517m, 1479m, 1436m, 1391m, 1345m, 1290w, 1283w, 1246m, 1221m, 1077w, 1043m, 1023w, 926w, 847m, 791w, 757w; δ_H(300 MHz; CD_2Cl_2) 10.72 (1H, br s, CO_2H), 7.54-7.45 (5H, m, Ph C*H*); δ_C(75 MHz; CD_2Cl_2) 175.3 (*C*=O), 166.4, 150.3, 131.0 (Ph *C*H), 129.4 (Ph *C*), 129.2 (Ph *C*H), 129.0 (Ph *C*H), 123.1; δ_C(75 MHz; DEPT 90, CD_2Cl_2) 131.0 (Ph *C*H), 129.2 (Ph *C*H), 129.0 (Ph *C*H); *m*/*z* (EI) 241 (M^++2, 37%), 240 (M^++1, 39), 239 (M^+, 100), 238 (M^+-1, 79), 224 (23), 222 (63), 204 (M+-Cl, 2), 186 (6), 176 (5), 159 (10), 133 (19), 129 (8), 127 (17), 121 (6), 114 (8), 100 (6), 89 (22), 77 (19), 63 (12), 51 (20) (Found: M^+, 238.9803, $C_{10}H_6ClNO_2S$ requires *M*, 238.9808).

4-Bromo-3-chloro-5-phenylisothiazole 279

To a stirred mixture of 3-chloro-5-phenylisothiazole-4-carboxylic acid **277** (1.0 g, 4.18 mmol) in H_2O (30 ml) was added a solution of KOH (234 mg, 4.18 mmol, 1 equiv.) in H_2O (10 ml) and the mixture was allowed to stir at *ca.* 20 ^oC until the starting material had completely dissolved. To the reaction mixture was added, in one portion, a solution of silver nitrate (710 mg, 4.18 mmol, 1 equiv.) in H_2O (5 ml) to afford a grey-white precipitate. The grey-white precipitate was filtered, washed first with H_2O and then with acetone and dried in a vacuum oven at *ca.* 80 ^oC for 12 h to give silver 3-chloro-5-phenylisothiazole-4-carboxylate **278** (1.45 g, 100%). To a stirred mixture of silver 3-chloro-5-phenylisothiazole-4-carboxylate **278**, (100 mg, 0.29 mmol) in tetrachloro-methane (3 ml) protected with $CaCl_2$ drying tube was added in one portion Br_2 (18 μl, 0.35 mmol, 1.2 equiv.) and the reaction was kept at 20 ^oC for 1 h. The reaction mixture was filtred and the filtrate was absorbed on silica. Chromatography (hexane-DCM 8 : 2) gave the title compound **279** (63 mg, 80%) as colourless needles, mp 40-41 ^oC (lit.,[356] 44-46 ^oC) (from pentane); (Found: C, 39.3; H, 1.9; N, 5.0. $C_9H_5BrClNS$ requires C, 39.4; H, 1.8; N, 5.1%); λ_{max}(DCM)/nm 274 (log ε 3.91); ν_{max}/cm^{-1} 3049w (Ar CH), 1577w, 1559w, 1517w, 1507w, 1476m, 1457w, 1443m, 1388m, 1336w, 1313w, 1294s, 1278m, 1245w, 1217w, 1076w, 1032m, 996m, 920w, 901m, 819m; δ_H(300 MHz; $CDCl_3$) 7.67-7.60 (2H, m, Ph C*H*), 7.53-7.45 (3H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 163.4, 151.0, 130.4 (Ph *C*H), 129.3 (Ph *C*), 129.1 (Ph *C*H), 128.2 (Ph *C*H), 106.2; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.4 (Ph *C*H), 129.1 (Ph *C*H), 128.2 (Ph *C*H); *m*/*z* (EI) 277 (M^++4, 28%), 275 (M^++2, 100), 273 (M^+, 58), 240 (4), 238 (4), 229 (7), 227 (5), 196 (5), 194 (14), 193 (4), 159 (50), 150 (4), 148 (4), 137 (3), 133 (17), 127 (29), 121 (6), 113 (11), 100 (10),

89 (18), 77 (11), 74 (10), 63 (12), 51 (19) (Found: M^+, 272.9015, $C_9H_5BrClNS$ requires *M*, 272.9004).

4-Amino-3-chloro-5-phenylisothiazole 280

To a stirred solution of NaOH (42 mg, 1.05 mmol, 5 equiv.) in water (2 ml) cooled to *ca.* 0 °C was first added Br_2 (13 μl, 0.25 mmol, 1.2 equiv.) and then 3-chloro-5-phenylisothiazole-4-carboxamide **276** (50 mg, 0.21 mmol). The reaction mixture was allowed to warm to *ca.* 20 °C and was kept at this temperature until the starting material had completely dissolved. The reaction mixture was then heated to *ca.* 70 °C for 1 h. The mixture was allowed to cool to *ca.* 20 °C, diluted with water (5 ml) and washed with DCM (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 5 : 5) gave the *title compound* **280** (36.7 mg, 83%) as colourless plates, mp 58-59 °C (from cyclohexane); (Found: C, 51.2; H, 3.2; N, 13.3. $C_9H_7ClN_2S$ requires C, 51.3; H, 3.4; N, 13.3%); λ_{max}(DCM)/nm 315 (log ε 2.79), 262 (2.66); ν_{max}/cm^{-1} 3373w and 3309w (NH_2), 3212w, 3061w (Ph CH), 1623w, 1576w, 1492w, 1445w, 1420m, 1374m, 1316w, 1282w, 1136w, 1086w, 1061w, 1027w, 994w, 974w, 926w, 823m, 764s; δ_H(300 MHz; $CDCl_3$) 7.50-7.37 (5H, m, Ph C*H*), 3.76 (2H, br s, NH_2); δ_C(75 MHz; $CDCl_3$) 140.8, 139.8, 134.0, 130.6 (Ph *C*), 129.5 (Ph *C*H), 128.8 (Ph *C*H), 127.1 (Ph *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.5 (Ph *C*H), 128.8 (Ph *C*H), 127.1 (Ph *C*H); *m*/*z* (EI) 212 (M^++2, 31%), 210 (M^+, 82), 175 (11), 148 (29), 142 (62), 121 (100), 104 (16), 93 (9), 89 (14), 77 (63), 69 (14), 63 (15), 62 (15), 53 (14), 51 (37).

3-Chloro-4-iodo-5-phenylisothiazole 281

To a stirred mixture of I_2 (90.5 mg, 0.358 mmol, 2.5 equiv.) and isoamyl nitrite (77 μl, 0.573 mmol, 4 equiv.) in MeCN (2 ml) protected with $CaCl_2$ drying tube at *ca.* 80 °C was added dropwise an MeCN (1 ml) solution of 4-amino-3-chloro-5-phenylisothiazole **280** (30 mg, 0.143 mmol). The mixture was kept at *ca.* 80 °C until no starting material remained (TLC), allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (hexane-DCM, 7 : 3) gave the *title compound* **281** (37.7 mg, 82%) as colourless needles, mp 67-68 °C (from pentane); (Found: C, 33.5; H, 1.5; N, 4.3. C_9H_5ClINS requires C, 33.6; H, 1.6; N, 4.4%); λ_{max}(DCM)/nm 275 (log ε 2.70); ν_{max}/cm^{-1} 3046w (Ph CH), 1471m, 1442m, 1381m, 1335w, 1325w, 1286m, 1270s, 1238w, 1207w, 1077w, 1033m, 990m, 966w, 921w, 893m, 841w, 822m, 783w, 750s; δ_H(300 MHz; $CDCl_3$) 7.60-7.57

(2H, m, Ph C*H*), 7.53-7.51 (3H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 168.0, 154.5, 130.7 (Ph *C*), 130.4 (Ph *C*H), 129.1 (Ph *C*H), 128.5 (Ph *C*H), 79.5; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.4 (Ph *C*H), 129.1 (Ph *C*H), 128.5 (Ph *C*H); *m*/*z* (EI) 323 (M^++2, 36%), 321 (M^+, 100), 194 (13), 159 (74), 148 (4), 133 (58), 127 (60), 121 (7), 113 (17), 100 (14), 89 (31), 77 (14), 75 (13), 74 (13), 73 (4), 69 (8), 63 (20), 51 (26).

3-Chloro-4,5-diphenylisothiazole 282 *via* Suzuki reaction at C-4

A stirred mixture of 4-bromo-3-chloro-5-phenylisothiazole **279** (30 mg, 0.11 mmol), phenylboronic acid (40 mg, 0.33 mmol, 3 equiv.), powdered K_2CO_3 (22.8 mg, 0.165 mmol, 1.5 equiv.) and $Pd(OAc)_2$ (1.2 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 6 : 4) gave the *title compound* **282** (28.7 mg, 96%) as colourless needles, mp 106-107 °C (from pentane); (Found: C, 66.4; H, 3.6; N, 5.2. $C_{15}H_{10}ClNS$ requires C, 66.3; H, 3.7; N, 5.2%); λ_{max}(DCM)/nm 275 (log ε 2.74); ν_{max}/cm^{-1} 3055w (Ar CH), 1599w, 1574w, 1537w, 1499w, 1477w, 1377w, 1346m, 1312w, 1236m, 1182w, 1143w, 1076w, 1034w, 995w, 988w, 920w, 907w, 843w, 833m, 802m, 770m, 748s, 710w, 694s; δ_H(300 MHz; $CDCl_3$) 7.44-7.22 (10H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 164.4, 150.0, 132.6, 131.8, 130.3 (Ph *C*H), 130.1 (Ph *C*), 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.6 (Ph *C*H), 128.3 (Ph *C*H), 128.2 (Ph *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.3 (Ph *C*H), 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.6 (Ph *C*H), 128.3 (Ph *C*H), 128.2 (Ph *C*H); *m*/*z* (EI) 273 (M^++2, 34%), 271 (M^+, 100), 258 (7), 256 (19), 236 (27), 203 (30), 190 (20), 178 (12), 165 (13), 135 (3), 104 (15), 89 (4), 77 (15), 63 (4), 51 (10) (Found: M^+, 271.0207, $C_{15}H_{10}ClNS$ requires *M*, 271.0222).

3-Chloro-4,5-diphenylisothiazole 282 *via* Stille reaction at C-4 (typical Stille conditions for coupling at C-4: see Table 28)

A stirred mixture of 3-chloro-4-iodo-5-phenylisothiazole **281** (30 mg, 0.093 mmol), tributylphenylstannane (36.6 μl, 0.112 mmol, 1.2 equiv.) and $Pd(OAc)_2$ (1.0 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was

separated, dried and absorbed on silica. Chromatography (hexane-DCM, 6 : 4) gave the *title compound* **282** (25 mg, 99%) as colourless needles, mp 106-107 °C (from pentane) identical to that described above.

3-Chloro-5-phenyl-4-(thien-2-yl)isothiazole 283

Similar treatment of 3-chloro-4-iodo-5-phenylisothiazole **281** (30 mg, 0.093 mmol) with 2-(tributylstannyl)thiophene and $Pd(OAc)_2$ gave the *title compound* **283** (25.8 mg, 100%) as colourless needles, mp 90-91 °C (from pentane); (Found: C, 56.2; H, 2.7; N, 5.0. $C_{13}H_8ClNS_2$ requires C, 56.2; H, 2.9; N, 5.0%); λ_{max}(DCM)/nm 251 (log ε 3.10), 274 inf. (3.00); ν_{max}/cm^{-1} 3087w (Ar CH), 1486w, 1447w, 1431w, 1381w, 1364w, 1353w, 1326w, 1316w, 1306w, 1284w, 1238w, 1216w, 1221w, 1109w, 1077w, 1043w, 1031w, 984w, 967w, 927w, 882w, 852m, 821m, 779w, 759s; δ_H(300 MHz; $CDCl_3$) 7.41-7.28 (6H, m, Ar C*H*), 7.09-7.06 (2H, m, Ar C*H*); δ_C(75 MHz; $CDCl_3$) 165.5, 150.4, 131.7, 129.9, 129.9 (Ar *C*H), 129.3 (Ar *C*H), 129.0 (Ar *C*H), 128.3 (Ar *C*H), 127.5 (Ar *C*H), 127.2 (Ar *C*H), 126.1; δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.9 (Ar *C*H), 129.3 (Ar *C*H), 129.0 (Ar *C*H), 128.3 (Ar *C*H), 127.5 (Ar *C*H), 127.2 (Ar *C*H); *m*/*z* (EI) 279 (M^++2, 41%), 277 (M^+, 100), 264 (3), 262 (6), 244 (16), 242 (21), 241 (23), 234 (7), 232 (18), 209 (31), 208 (9), 196 (14), 184 (9), 171 (14), 164 (5), 139 (14), 121 (18), 107 (10), 93 (8), 77 (28), 69 (13), 63 (7), 51 (19).

3-Chloro-5-phenyl-4-(fur-2-yl)isothiazole 284

Similar treatment of 3-chloro-4-iodo-5-phenylisothiazole **281** (30 mg, 0.093 mmol) with 2-(tributylstannyl)furan and $Pd(OAc)_2$ gave the *title compound* **284** (24.3 mg, 100%) as colourless needles, mp 71-72 °C (from pentane); (Found: C, 59.6; H, 3.2; N, 5.5. $C_{13}H_8ClNOS$ requires C, 59.7; H, 3.1; N, 5.4%); λ_{max}(DCM)/nm 238 (log ε 3.00), 272 inf. (2.79), 303 inf. (2.70); ν_{max}/cm^{-1} 3146w, 3125w and 3060w (Ar CH), 1577w, 1517w, 1498w, 1464w, 1442w, 1397w, 1379w, 1338m, 1316w, 1256w, 1222w, 1172w, 1140w, 1078w, 1033w, 1022w, 996m, 948w, 920w, 887w, 876w, 830w, 822m, 790w, 757s, 711m; δ_H(300 MHz; $CDCl_3$) 7.46-7.36 (4H, m, Ar C*H*), 7.33-7.29 (2H, m, Ar C*H*), 6.64, (1H, app. d, *J* 3.6, furyl *H*-3), 6.48 (1H, dd, *J* 3.4, 2.0, furyl *H*-4); δ_C(75 MHz; $CDCl_3$) 165.6, 149.2, 144.7, 143.0 (Ar *C*H), 130.1 (Ar *C*), 129.9 (Ar *C*H), 128.9 (Ar *C*H), 128.2 (Ar *C*H), 123.1 (Ar *C*), 111.3 (Ar *C*H), 111.2 (Ar *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 143.0 (Ar *C*H), 129.9 (Ar *C*H), 128.9 (Ar *C*H), 128.2 (Ar *C*H), 111.3 (Ar *C*H), 111.2 (Ar

*C*H); *m*/*z* (EI) 263 (M^++2, 37%), 261 (M^+, 100), 236 (6), 234 (14), 226 (28), 208 (7), 198 (33), 196 (29), 193 (29), 171 (28), 153 (18), 139 (23), 127 (23), 121 (35), 104 (13), 99 (21), 95 (15), 93 (24), 85 (25), 77 (79), 69 (34), 63 (24), 51 (50).

3-Chloro-4,5-diphenylisothiazole 282 *via* Negishi reaction at C-4 position

A stirred mixture of 3-chloro-4-iodo-5-phenylisothiazole **281** (30 mg, 0.093 mmol), phenylzinc chloride (0.558 μl, 0.5 M in THF, 3 equiv.) and $(PPh_3)_2PdCl_2$ (3.3 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 6 : 4) gave 3-chloro-5-phenylisothiazole **285** (14.6 mg, 80%) as colourless needles, mp 50-51 °C (lit.,[356] 56 °C) (from pentane); ν_{max}/cm^{-1} 3092w (isothiazole CH), 3065w, 3052w and 3028w (Ph CH), 1616w, 1524m, 1483s, 1447m, 1395m, 1333m, 1312m, 1220w, 1137m, 1103w, 1074w, 1031w, 1001w, 980m, 916w, 876m, 834m, 814m, 754s, 719m; δ_H(300 MHz; $CDCl_3$) 7.58-7.53 (2H, m, Ph *H*), 7.50-7.43 (3H, m, Ph *H*), 7.23 (1H, s, isothiazole *H*-4); δ_C(75 MHz; $CDCl_3$) 169.4, 150.0, 130.3 (Ph *C*H), 129.8 (Ph *C*), 129.4 (Ph *C*H), 126.3 (Ph *C*H), 119.0 (isothiazole *H*-4); δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.3 (Ph *C*H), 129.4 (Ph *C*H), 126.3 (Ph *C*H), 119.0 (isothiazole *C*-4); *m*/*z* (EI) 197 (M^++2, 37%), 195 (M^+, 100), 160 (25), 149 (12), 133 (9), 128 (6), 127 (10), 116 (17), 102 (10), 93 (9), 89 (15), 77 (18), 63 (12), 51 (24). Further elution (hexane-DCM, 6 : 4) gave the *title compound* **282** (5.0 mg, 20%) as colourless needles, mp 106-107 °C (from pentane) identical to that described above.

3-Chloro-5-phenylisothiazole 285

A stirred mixture of 3-chloro-4-iodo-5-phenylisothiazole **281** (30 mg, 0.093 mmol) and $Pd(OAc)_2$ (20.9 mg, 0.093 mmol, 1 equiv.) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 140 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 6 : 4) gave the *title compound* **285** (17.8 mg, 98%) as colourless needles, mp 50-51 °C (lit.,[356] 56 °C) (from pentane) identical to that described above.

3-Hydroxy-4,5-diphenylisothiazole 286

A mixture of 3-chloro-4,5-diphenylisothiazole **282** (1 g, 3.68 mmol) and KOH (825 mg, 14.7 mmol, 4 equiv.) in H_2O (150 ml) was placed in a bomb reactor with a teflon liner. The bomb reactor was sealed and heated to *ca.* 200 °C (250 psi) for 24 h. The bomb reactor was cooled to *ca.* 20 °C and opened. The reaction mixture was filtered and the filtrate was acidified to give a white precipitate. The white precipitate was filtered, washed (H_2O) and dried to give the title compound **286** (885 mg, 95%) as colourless needles, mp 233-235 °C (lit.,[357] 245-247 °C) (from cyclohexane); (Found: C, 71.0; H, 4.4; N, 5.6. $C_{15}H_{11}NOS$ requires C, 71.1; H, 4.4; N, 5.5%); λ_{max}(DCM)/nm 234 (log ε 3.94), 280 (3.90); ν_{max}/cm^{-1} 3059w (Ar CH), 1607w, 1583w, 1566w, 1500m, 1481m, 1444w, 1342w, 1265m, 1184w, 1081w, 1073w, 1057w, 1033w, 1024w, 943w, 880m, 851w, 844w, 770m, 754s; δ_H(300 MHz; DMSO-d_6) 11.97 (1H, br s, O*H*), 7.34-7.29 (6H, m, Ph C*H*), 7.27-7.21 (4H, m, Ph C*H*); δ_C(75 MHz; DMSO-d_6) 166.8, 160.5, 132.3 (Ph *C*), 131.1 (Ph *C*), 129.8 (Ph *C*H), 129.2 (Ph *C*H), 129.0 (Ph *C*H), 128.3 (Ph *C*H), 127.9 (Ph *C*H), 127.4 (Ph *C*H), 122.1; δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.8 (Ph *C*H), 129.2 (Ph *C*H), 129.0 (Ph *C*H), 128.3 (Ph *C*H), 127.9 (Ph *C*H), 127.4 (Ph *C*H); *m*/*z* (EI) 254 (M^++1, 20%), 253 (M^+, 100), 252 (54), 238 (6), 219 (7), 209 (17), 205 (10), 190 (6), 178 (29), 165 (32), 152 (10), 139 (4), 126 (6), 121 (4), 104 (12), 89 (8), 77 (11), 63 (6), 51 (10) (Found: M^+, 253.0567, $C_{15}H_{11}NOS$ requires *M*, 253.0561).

3-Bromo-4,5-diphenylisothiazole 287

A stirred mixture of 3-hydroxy-4,5-diphenylisothiazole **286** (30 mg, 0.12 mmol) and $POBr_3$ (1.5 g), protected with $CaCl_2$ drying tube, was heated to *ca.* 100 °C for 24 h. The reaction mixture was cooled to *ca.* 20 °C, diluted with water and extracted with DCM (4 × 10 ml). The organic extracts were combined, dried and absorbed on silica. Chromatography (hexane-DCM, 7 : 3) gave the *title compound* **287** (32 mg, 85%) as colourless crystals, mp 112-113 °C (from pentane); (Found: C, 56.9; H, 3.3; N, 4.3. $C_{15}H_{10}BrNS$ requires C, 57.0; H, 3.2; N, 4.4%); λ_{max}(DCM)/nm 276 (log ε 3.01); ν_{max}/cm^{-1} 1533w, 1498w, 1474w, 1444w, 1372w, 1339m, 1227m, 1182w, 1138w, 1075w, 1034w, 988w, 920w, 898w, 849w, 843w, 825m, 785w, 769m, 747s; δ_H(300 MHz; $CDCl_3$) 7.43-7.40 (3H, m, Ph C*H*), 7.35-7.26 (5H, m, Ph C*H*), 7.22-7.17 (2H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 164.0, 140.0, 135.3, 132.5, 130.4 (Ph *C*H), 130.0, 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.6 (Ph *C*H), 128.3 (Ph *C*H), 128.3 (Ph *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.4 (Ph

*C*H), 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.6 (Ph *C*H), 128.3 (Ph *C*H), 128.3 (Ph *C*H); *m*/*z* (EI) 317 (M^++2, 97%), 315 (M^+, 100), 302 (7), 300 (7), 236 (71), 235 (61), 221 (4), 208 (15), 203 (65), 190 (21), 178 (16), 165 (24), 152 (9), 139 (6), 121 (12), 118 (16), 104 (22), 89 (11), 77 (77), 63 (12), 51 (49).

3-Chloro-4,5-diphenylisothiazole 282 from 3-hydroxy-4,5-diphenylisothiazole 286

A stirred mixture of 3-hydroxy-4,5-diphenylisothiazole **286** (20 mg, 0.079 mmol) and $POCl_3$ (1 ml) was placed in a sealed tube and heated to *ca.* 150 °C for 72 h. The reaction mixture was cooled to *ca.* 20 °C, diluted (H_2O) and extracted with DCM (4 × 10 ml). The organic extracts were combined, dried and absorbed on silica. Chromatography (hexane-DCM, 7 : 3) gave the *title compound* **282** (21 mg, 98%) as colourless needles, mp 106-107 °C (from pentane) identical to that described above.

4,5-Diphenylisothiazol-3-yl trifluoromethanesulfonate 288

To a stirred solution of 3-hydroxy-4,5-diphenylisothiazole **286** (30 mg, 0.118 mmol) and triethylamine (16.5 μl, 0.118 mmol, 1 equiv.) in DCM (2 ml) cooled to *ca*. 0 °C and protected with $CaCl_2$ drying tube was added dropwise trifluoromethanesulfonic anhydride (20 μl, 0.118 mmol, 1 equiv.). The reaction mixture was kept at *ca*. 0 °C until no starting material remained (TLC). Chromatography (hexane-DCM, 7 : 3) gave the *title compound* **288** (32.3 mg, 71%) as colourless crystals mp 66-67 °C (from pentane) (Found: C, 50.1; H, 2.7; N, 3.7. $C_{16}H_{10}F_3NO_3S_2$ requires C, 49.9; H, 2.6; N, 3.6%); λ_{max}(DCM)/nm 277 (log ε 2.94); ν_{max}/cm^{-1} 1449w, 1424m, 1409w, 1374m, 1274w, 1233s, 1220s, 1162w, 1132m, 1080w, 1042m, 1018w, 1000w, 941m, 922w, 877m, 856m, 802s, 773w, 763m, 751m, 736m; δ_H(300 MHz; $CDCl_3$) 7.42-7.31 (6H, m, Ph C*H*), 7.27-7.24 (4H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 166.2, 154.4, 130.1 (Ph *C*H), 129.8 (Ph *C*H), 129.8 (Ph *C*), 129.4 (Ph *C*), 129.1 (Ph *C*H), 128.9 (Ph *C*H), 128.8 (Ph *C*H), 128.2 (Ph *C*H), 125.4, 118.3 (1C, q, $^1J_{CF}$ 321.0, *C*F$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.1 (Ph *C*H), 129.8 (Ph *C*H), 129.1 (Ph *C*H), 128.9 (Ph *C*H), 128.8 (Ph *C*H), 128.2 (Ph *C*H); *m*/*z* (EI) 386 (M^++1, 16%), 385 (M^+, 77), 252 (100), 234 (10), 219 (19), 210 (11), 190 (16), 178 (43), 176 (20), 152 (14), 139 (4), 126 (6), 121 (6), 89 (4) 77 (10), 69 (19). Further elution (hexane-Et_2O, 2 : 8) gave *4,5-diphenyl-2-(trifluoromethylsulfonyl)isothiazol-3(2*H*)-one* **289** (13.2 mg, 29%) as colourless crystals mp 96-97 °C (from pentane) (Found: C, 50.1; H, 2.7; N, 3.5. $C_{16}H_{10}F_3NO_3S_2$ requires C, 49.9; H, 2.6; N, 3.6%);

λ_{max}(DCM)/nm 236 (log ε 3.05), 307 (2.83); ν_{max}/cm^{-1} 1715s (C=O), 1653w, 1599w, 1579w, 1564w, 1560w, 1506w, 1487w, 1451w, 1445w, 1415s, 1397w, 1337w, 1235s, 1200s, 1170w, 1138s, 1131s, 1081w, 1030w, 1001s, 976w, 971w, 933w, 925w, 855w, 840w, 796m, 768m, 754s, 729m; δ_H(300 MHz; $CDCl_3$) 7.52-7.47 (1H, m, Ph C*H*), 7.43-7.29 (9H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 163.9, 157.3, 131.8 (Ph *C*H), 129.8 (Ph *C*), 129.7 (Ph *C*H), 129.6 (Ph *C*H), 128.9 (Ph *C*H), 128.6 (Ph *C*H), 128.0 (Ph *C*H), 121.0, 119.2 (1C, q, $^1J_{CF}$ 324.3, CF_3); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.8 (Ph *C*H), 129.7 (Ph *C*H), 129.6 (Ph *C*H), 128.9 (Ph *C*H), 128.6 (Ph *C*H), 128.0 (Ph *C*H); *m*/*z* (EI) 386 (M^++1, 12%), 385 (M^+, 59), 252 (100), 234 (9), 219 (20), 210 (12), 190 (12), 178 (45), 176 (21), 165 (20), 152 (14), 139 (4), 126 (5), 121 (7), 89 (6) 77 (11), 69 (23), 63 (5), 51 (9).

3-Amino-4,5-diphenylisothiazole 290

A stirred mixture of 3-chloro-4,5-diphenylisothiazole **282** (50 mg, 0.184 mmol) and sodium amide (71.8 mg, 1.84 mmol, 10 equiv.) in dry THF (2 ml) was kept to *ca.* 20 °C, under argon, until no starting material remained (TLC). Chromatography (hexane-DCM, 3 : 7) gave the *title compound* **290** (45 mg, 97%) as colourless needles, mp 130-131 °C (from cyclohexane); (Found: C, 71.4; H, 4.8; N, 10.9. $C_{15}H_{12}N_2S$ requires C, 71.4; H, 4.8; N, 11.1%); λ_{max}(DCM)/nm 276 (log ε 3.71); ν_{max}/cm^{-1} 3458w and 3302w (NH), 3196 (Ar CH), 1622m, 1576w, 1558w, 1541w, 1506w, 1495m, 1458m, 1443w, 1402m, 1339w, 1161w, 1072w, 1053w, 1028w, 999w, 934w, 924w, 851w, 843m, 772m, 756s, 739w, 704s; δ_H(300 MHz; $CDCl_3$) 7.42-7.23 (10H, m, Ph C*H*), 4.37 (2H, br s, NH_2); δ_C(75 MHz; $CDCl_3$) 162.9, 161.5, 133.0 (Ph *C*), 131.0 (Ph *C*), 129.9 (Ph *C*H), 129.2 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.2 (Ph *C*H), 128.1 (Ph *C*H), 122.7; δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.9 (Ph *C*H), 129.2 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.2 (Ph *C*H), 128.1 (Ph *C*H); *m*/*z* (EI) 253 (M^++1, 27%), 252 (M^+, 100), 251 (59), 234 (5), 218 (12), 209 (7), 190 (13), 178 (10), 176 (10), 165 (28), 152 (7), 139 (4), 126 (6), 121 (4), 104 (8), 89 (8), 77 (12), 74 (9), 69 (3), 63 (5), 51 (10) (Found: M^+, 252.0718, $C_{15}H_{12}N_2S$ requires *M*, 252.0721).

Sandmeyer iodination reaction of 3-amino-4,5-diphenylisothiazole 290

To a stirred mixture of benzyltriethylammonium iodide (113.9 mg, 0.357 mmol, 3 equiv.) and isoamyl nitrite (63.9 μl, 0.476 mmol, 4 equiv.) in MeCN (2 ml) protected with $CaCl_2$ drying tube at *ca.* 20 °C was added dropwise an MeCN (1 ml) solution of

3-amino-4,5-diphenylisothiazole **290** (30 mg, 0.119 mmol). The mixture was kept at *ca.* 20 °C for 30 min and then was heated to *ca.* 80 °C for 1 h. The mixture was allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (hexane-DCM, 7 : 3) gave a colourless material which was a mixture of inseparable compounds: ν_{max}/cm^{-1} 2954w, 2923m, 2854w, 2208w (C≡N), 1594w, 1582w, 1576w, 1564w, 1485w, 1467w, 1457w, 1444m, 1378w, 1363w, 1331w, 1262w, 1222w, 1180w, 1157w, 1134w, 1078w, 1046w, 1031w, 998w, 985w, 969w, 919w, 900w, 873w, 854w, 822w, 793w, 768s, 746m, 738s; δ_H(300 MHz; $CDCl_3$) 7.63-7.60 (m, Ph C*H*), 7.54-7.40 (m, Ph C*H*), 7.26-7.12 (m, PhC*H*); δ_C(75 MHz; $CDCl_3$) 142.0, 141.1, 137.9, 133.8, 130.7 (Ph *C*H), 130.4 (Ph *C*H), 129.6 (Ph *C*H), 129.6, 129.1 (Ph *C*H), 129.1 (Ph *C*H), 128.9 (Ph *C*H), 128.8 (Ph *C*H), 128.7 (Ph *C*H), 128.6 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H), 128.3 (Ph *C*H), 125.1, 121.1, 121.0, 116.8, 115.8; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.7 (Ph *C*H), 130.4 (Ph *C*H), 129.6 (Ph *C*H), 129.1 (Ph *C*H), 129.1 (Ph *C*H), 128.9 (Ph *C*H), 128.8 (Ph *C*H), 128.7 (Ph *C*H), 128.6 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H), 128.3 (Ph *C*H); *m*/*z* (EI) 364 (M^++1%), 363 (M^+, 19), 332 (6), 331 ($C_{15}H_{10}IN^+$, 33), 236 (8), 205 (17), 204 (100), 203 (37), 202 (7), 177 (22), 176 (17), 127 (8), 102 (10), 88 (13), 77 (33), 51 (29).

3,4,5-Triphenylisothiazole 291

A stirred mixture of 3-bromo-4,5-diphenylisothiazole **287** (30 mg, 0.095 mmol), phenylzinc chloride (570 μl, 0.5 M in THF, 3 equiv.) and $(PPh_3)_2PdCl_2$ (3.3 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 5 : 5) gave the title compound **291** (21.4 mg, 72%) as colourless crystals, mp 210-211 °C (lit.,[171] 211.5-212.5 °C) (from cyclohexane); (Found: C, 80.5; H, 4.8; N, 4.4. $C_{21}H_{15}NS$ requires C, 80.5; H, 4.8; N, 4.5%); λ_{max}(DCM)/nm 241 (log ε 4.06), 284 (3.85); ν_{max}/cm^{-1} 3063w (Ph CH), 1601w, 1576w, 1539w, 1533w, 1499w, 1479w, 1440w, 1398w, 1363w, 1291w, 1272w, 1188w, 1179w, 1159w, 1153w, 1073w, 1030w, 977w, 920w, 908w, 842w, 802w, 782w, 764m, 748s, 726m, 701m; δ_H(300 MHz; $CDCl_3$) 7.44-7.41 (2H, m, Ph C*H*), 7.37-7.23 (11H, m, Ph C*H*), 7.13-7.10 (2H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 167.6, 164.0, 135.7, 134.2, 134.1, 131.0, 130.6 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.7 (Ph *C*H), 128.7 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H), 128.0 (Ph *C*H), 127.5 (Ph *C*H);

δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.6 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.7 (Ph *C*H), 128.7 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H), 128.0 (Ph *C*H), 127.5 (Ph *C*H); *m*/*z* (EI) 314 (M^++1, 30%), 313 (M^+, 98), 312 (100), 297 (3), 280 (3), 278 (3), 236 (4), 210 (5), 208 (5), 178 (10), 165 (24), 155 (7), 149 (10), 139 (4), 126 (3), 121 (4), 103 (4), 89 (5), 77 (14), 63 (4), 51 (9).

3-Iodo-5-phenylisothiazole-4-carboxamide 292

A stirred solution of 3-iodo-5-phenylisothiazole-4-carbonitrile **245** (2 g, 6.41 mmol) in c. H_2SO_4 (50 ml), protected with $CaCl_2$ drying tube, was heated to *ca.* 100 °C until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C and then was poured into ice-water to form a white precipitate. The white precipitate was filtered out, washed (H_2O) and dried under vacuum to give the *title compound* **292** (2.12 g, 100%) as colourless crystals, mp 184-185 °C (from PhH); (Found: C, 36.4; H, 2.1; N, 8.5. $C_{10}H_7IN_2OS$ requires C, 36.4; H, 2.1; N, 8.5%); λ_{max}(DCM)/nm 274 (log ε 3.90); ν_{max}/cm^{-1} 3375w (NH), 3186w (Ph CH), 1643s (C=O), 1617w, 1522w, 1485w, 1415m, 1363w, 1289w, 1259m, 1228w, 1119w, 1080w, 1036w, 993w, 940w, 917w, 830w, 787w, 772m, 756w; δ_H(300 MHz; CD_2Cl_2) 7.58-7.55 (2H, m, Ph C*H*), 7.51-7.45 (3H, m, Ph C*H*), 5.91 (1H, br s, N*H*), 5.69 (1H, br s, N*H*); δ_C(75 MHz; CD_2Cl_2) 166.7, 165.1, 130.9 (Ph *C*H), 129.7 (Ph *C*H), 128.7, 128.6, 128.4 (Ph *C*H), 111.0; δ_C(75 MHz; DEPT 90, CD_2Cl_2) 130.9 (Ph *C*H), 129.7 (Ph *C*H), 128.4 (Ph *C*H); *m*/*z* (EI) 331 (M^++1, 15%), 330 (M^+, 100), 329 (80), 314 (46), 202 (10), 187 (10), 159 (24), 133 (16), 127 (18), 121 (13), 116 (11), 100 (6), 89 (27), 77 (29), 63 (9), 51 (22).

3-Iodo-5-phenylisothiazole-4-carboxylic acid 293

To a stirred solution of 3-iodo-5-phenylisothiazole-4-carboxamide **292** (49.5 mg, 0.15 mmol) in c. H_2SO_4 (1 ml) cooled to *ca.* 0 °C and protected with $CaCl_2$ drying tube, was added in portions sodium nitrite (259 mg, 3.75 mmol, 25 equiv.). The reaction mixture was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C and then was poured into ice-water to form a white precipitate. The white precipitate was filtered out, washed (H_2O) and dried under vacuum to give the *title compound* **293** (38.7 mg, 78%) as colourless neadles, mp 156-157 °C (from cyclohexane); (Found: C, 36.3; H, 1.8; N, 4.3. $C_{10}H_6INO_2S$ requires C, 36.3; H, 1.8; N, 4.2%); λ_{max}(DCM)/nm 230 (log ε 2.78), 273 (2.86); ν_{max}/cm^{-1} 1689s (C=O),

1537w, 1507m, 1473s, 1445w, 1433m, 1371m, 1337m, 1282w, 1267w, 1220m, 1076w, 1034w, 1006w, 962w, 915w, 828s, 788w, 773w, 754w, 735s; δ_H(300 MHz; CD_2Cl_2) 8.83 (1H, br s, O*H*), 7.55-7.45 (5H, m, Ph C*H*); δ_C(75 MHz; CD_2Cl_2) 173.1, 166.6, 130.9 (Ph *C*H), 129.9, 129.1 (Ph *C*H), 129.0 (Ph *C*H), 128.9, 112.6; δ_C(75 MHz; DEPT 90, CD_2Cl_2) 130.9 (Ph *C*H), 129.1 (Ph *C*H), 129.0 (Ph *C*H); *m*/*z* (EI) 332 (M^++1, 13%), 331 (M^+, 100), 330 (24), 314 (35), 187 (4), 186 (5), 159 (13), 133 (13), 127 (14), 121 (7), 116 (12), 100 (5), 89 (22), 77 (28), 69 (5), 63 (7), 51 (23).

4-Amino-3-iodo-5-phenylisothiazole 294

To a stirred solution of sodium hydroxide (18.2 mg, 0.455 mmol, 5 equiv.) in water (2 ml) cooled to *ca.* 0 °C was first added Br_2 (5.6 μl, 0.109 mmol 1.2 equiv.) and then 3-iodo-5-phenylisothiazole-4-carboxamide **292** (30 mg, 0.091 mmol). The reaction mixture was allowed to warm to *ca.* 20 °C and was kept at this temperature until the starting material had completely dissolved. The reaction mixture was then heated to *ca.* 70 °C for 1 h. The mixture was allowed to cool to *ca.* 20 °C, diluted with water (2 ml) and extracted with DCM (4 × 10 ml). The organic extracts were combined, dried and absorbed on silica. Chromatography (hexane-DCM, 5 : 5) gave the *title compound* **294** (24.5 mg, 89%) as orange cubes, mp 74-76 °C (from cyclohexane); (Found: C, 35.9; H, 2.3; N, 9.3. $C_9H_7IN_2S$ requires C, 35.8; H, 2.3; N, 9.3%); λ_{max}(DCM)/nm 231 (log ε 2.76), 266 (2.68), 320 (2.86); ν_{max}/cm^{-1} 3368w and 3308 (NH), 1622w, 1597w, 1572w, 1538w, 1487w, 1442w, 1400m, 1347m, 1316w, 1275w, 1182w, 1157w, 1117w, 1078w, 1040m, 999w, 992w, 970w, 926w, 859w, 807m, 773m, 761s; δ_H(300 MHz; CD_2Cl_2) 7.52-7.37 (5H, m, Ph C*H*), 3.96 (2H, br s, N*H*); δ_C(75 MHz; CD_2Cl_2) 140.4, 138.1, 130.6 (Ph *C*), 129.8 (Ph *C*H), 129.1 (Ph *C*H), 127.7 (Ph *C*H), 108.5; δ_C(75 MHz; DEPT 90, CD_2Cl_2) 129.8 (Ph *C*H), 129.1 (Ph *C*H), 127.7 (Ph *C*H); *m*/*z* (EI) 303 (M^++1, 11%), 302 (M^+, 100), 175 (15), 148 (31), 142 (78), 127 (4), 121 (83), 89 (6), 77 (39), 69 (6), 63 (6), 51 (16).

3,4-Diiodo-5-phenylisothiazole 295

To a stirred mixture of I_2 (62.9 mg, 0.248 mmol, 2.5 equiv.) and isoamyl nitrite (53.2 μl, 0.396 mmol, 4 equiv.) in MeCN (2 ml) protected with $CaCl_2$ drying tube at *ca.* 80 °C was added dropwise an MeCN (1 ml) solution of 4-amino-3-iodo-5-phenylisothiazole **294** (30 mg, 0.099 mmol). The mixture was kept at *ca.* 80 °C until no starting material remained

(TLC), allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (hexane-DCM, 7 : 3) gave the *title compound* **295** (34.8 mg, 85%) as colourless plates, mp 84-85 °C (from pentane); (Found: C, 26.2; H, 1.2; N, 3.4. $C_9H_5I_2NS$ requires C, 26.2; H, 1.2; N, 3.4%); λ_{max}(DCM)/nm 281 (log ε 3.72); ν_{max}/cm^{-1} 3046w (Ph CH), 1459s, 1439m, 1356m, 1317w, 1290w, 1235s, 1217m, 1202w, 1076w, 1033m, 971m, 920w, 870s, 841w, 800m, 766s, 745s; δ_H(300 MHz; $CDCl_3$) 7.56-7.44 (5H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 166.9, 130.6, 130.3 (Ph *C*H), 128.9 128.9 (Ph *C*H), 128.7 (Ph *C*H), 125.5; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.3 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H); *m*/*z* (EI) 414 (M^++1, 12%), 413 (M^+, 100), 286 (M^+-I, 2), 254 (2), 206 (3), 159 (M^+-2I, 89), 133 (5), 127 (26), 115 (11), 100 (7), 89 (8), 77 (12), 69 (5), 63 (8), 51 (17).

4-Bromo-3-iodo-5-phenylisothiazole 297

To a stirred mixture of 3-iodo-5-phenylisothiazole-4-carboxylic acid **293** (1.0 g, 3.02 mmol) in H_2O (50 ml) was added aqueous solution of KOH (169.5 mg, 3.02 mmol, 1 equiv.) and the mixture was allowed to stir at *ca.* 20 °C until the complete solution of the starting material. To the reaction mixture was added, in one portion, a solution of silver nitrate (513 mg, 3.02 mmol, 1 equiv.) in H_2O (5 ml) to form a white-grey precipitate. The white-grey precipitate was filtered out, washed first with H_2O and then with acetone and dried in a vacuum oven at *ca.* 80 °C for 12 h to give the *title compound* **296** (1.32 g, 100%). To a stirred mixture of silver 3-iodo-5-phenylisothiazole-4-carboxylate **296** (50 mg, 0.114 mmol) in tetrachloromethane (3 ml) protected with $CaCl_2$ drying tube was added in one portion Br_2 (7.02 μl, 0.137 mmol, 1.2 equiv.) and the reaction was kept at 20 °C for 1 h. The reaction mixture was filtered and the filtrate was absorbed on silica. Chromatography (hexane-DCM 8 : 2) gave the *title compound* **297** (31.3mg, 75%) as pale yellow oil; (Found: C, 29.5; H, 1.8; N, 3.8. C_9H_5BrINS requires C, 29.5; H, 1.4; N, 3.8%); λ_{max}(DCM)/nm 280 (log ε 2.82); ν_{max}/cm^{-1} 3062w (Ph CH), 2921w, 1575w, 1521w, 1467s, 1442m, 1361w, 1250s, 1224w, 1210w, 1075w, 1032w, 977w, 917w, 884s, 802m, 767m, 744s; δ_H(300 MHz; $CDCl_3$) 7.62-7.56 (2H, m, Ph C*H*), 7.54-7.47 (3H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 161.9, 130.3 (Ph *C*H), 129.1 (Ph *C*H), 129.0 (Ph *C*), 128.4 (Ph *C*H), 119.7, 115.4; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.3 (Ph *C*H), 129.0 (Ph *C*H), 128.4 (Ph *C*H); *m*/*z* (EI) 367 (M^++2, 83%), 365 (M^+, 81), 240 (3), 238 (M^+-I, 3), 159 (100), 127 (34), 121 (7), 115 (13), 114 (11), 100 (9), 89 (10), 77 (24), 69 (10), 63 (13), 51 (35).

Suzuki reaction on 4-bromo-3-iodo-5-phenylisothiazole 297

A stirred mixture of 4-bromo-3-iodo-5-diphenylisothiazole **297** (30 mg, 0.082 mmol), phenylboronic acid (30.0 mg, 0.246 mmol, 3 equiv.), powdered K_2CO_3 (17.0 mg, 0.123 mmol, 1.5 equiv.) and $Pd(OAc)_2$ (0.9 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 140 ^oC, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 7 : 3) gave a colourless material which was (tentatively) an inseparable mixture of mainly 4-bromo-3,5-diphenylisothiazole 3**02** (see below for independent synthesis and characterization) and a trace of 3-iodo-4,5-diphenylisothiazole; (Found: C, 55.8; H, 3.1; N, 4.0.); δ_H(300 MHz; $CDCl_3$) 7.86-7.83 (2H, m, Ph C*H*), 7.68-7.65 (2H, m, Ph C*H*), 7.54-7.42 (6H, m, PhC*H*); *m*/*z* (EI) 364 (M^++1, 3%), 363 (M^+, $C_{15}H_{10}INS$, 15), 318 (17), 317 (M^+, $C_{15}H_{10}Br_{81}NS$, 100), 316 (19), 315 (M^+, $C_{15}H_{10}Br_{79}NS$, 93), 237 (32), 236 (77), 235 (27), 204 (10), 203 (17), 189 (11), 135 (11), 134 (26), 133 (31), 118 (25), 104 (11), 89 (52), 77 (31), 63 (11), 57 (8), 51 (21).

3,3'-Bi(4-bromo-5-phenylisothiazole) 298

A stirred mixture of 4-bromo-3-iodo-5-phenylisothiazole **297** (30 mg, 0.082 mmol) and $Pd(OAc)_2$ (18.4 mg, 0.082 mmol, 1 equiv.) in DMF (2 ml) under an argon atmosphere, was heated to *ca.* 140 ^oC, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 2 : 8) gave the *title compound* **298** (14.5 mg, 74%) as colourless needles, mp 208-209 ^oC (from cyclohexane); (Found: C, 45.4; H, 2.2; N, 6.0. $C_{18}H_{10}Br_2N_2S_2$ requires C, 45.2; H, 2.1; N, 5.9%); λ_{max}(DCM)/nm 285 (log ε 4.09); ν_{max}/cm^{-1} 3062w (Ph CH), 1684w, 1653w, 1576w, 1559w, 1539w, 1506w, 1473m, 1445m, 1357w, 1288w, 1243s, 1213w, 1181w, 1159w, 1077w, 1056w, 1035w, 1000w, 977w, 967w, 912w, 882s, 846w, 829m, 754m, 746s, 728w, 724w; δ_H(300 MHz; $CDCl_3$) 7.74-7.66 (4H, m, Ph C*H*), 7.59-7.48 (6H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 163.0, 161.3, 130.1 (Ph *C*H), 129.4 (Ph *C*), 129.1 (Ph *C*H), 128.7 (Ph *C*H), 107.3; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.1 (Ph *C*H), 129.1 (Ph *C*H), 128.7 (Ph *C*H); *m*/*z* (EI) 480 (M^++2, 54%), 478 (M^++2, 100), 476 (M^+,

50), 399 (3), 397 (3), 318 (15), 239 (8), 214 (4), 159 (18), 145 (8), 133 (42), 127 (10), 121 (13), 101 (4), 89 (40), 77 (10), 63 (6), 51 (8).

3,5-Diphenylisothiazole-4-carboxamide 299

A stirred solution of 3,5-diphenylisothiazole-4-carbonitrile **237** (1 g, 3.81 mmol) in c. H_2SO_4 (10 ml), protected with $CaCl_2$ drying tube, was heated to *ca.* 100 °C until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C and then was poured into ice-water to afford a white precipitate. The white precipitate was filtered, washed (H_2O) and dried under vacuum to give the *title compound* **299** (1.07 g, 100%) as colourless needles, mp 210-211 °C (from PhH); (Found: C, 68.6; H, 4.4; N, 9.9. $C_{16}H_{12}N_2OS$ requires C, 68.6; H, 4.3; N, 10.0%); λ_{max}(DCM)/nm 249 (log ε 4.19), 271 (4.11); ν_{max}/cm^{-1} 3398w (NH), 3198w, 1641s (C=O), 1616w, 1560w, 1533w, 1488w, 1446w, 1430w, 1385w, 1348w, 1099w, 1079w, 1029w, 1005w, 992w, 923w, 857w, 790w, 777w, 763w; δ_H(300 MHz; CD_2Cl_2) 7.83-7.77 (2H, m, Ph C*H*), 7.65-7.59 (2H, m, Ph C*H*), 7.53-7.43 (6H, m, Ph C*H*), 5.89 (1H, br s, N*H*), 5.68 (1H, br s, N*H*); δ_C(75 MHz; CD_2Cl_2) 167.4, 167.3, 166.5, 135.1, 130.4 (Ph *C*H), 130.1, 130.1, 129.7 (Ph *C*H), 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H); δ_C(75 MHz; DEPT 90, CD_2Cl_2) 130.4 (Ph *C*H), 129.7(Ph *C*H), 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H); *m*/*z* (EI) 280 (M^+, 91%), 279 (M^+-H, 100), 264 (50), 236 (4), 203 (5), 189 (4), 163 (3), 140 (10), 133 (29), 129 (19), 121 (9), 103 (8), 89 (37), 77 (38), 69 (6), 63 (10), 51 (23).

3,5-Diphenylisothiazole-4-carboxylic acid 300

To a stirred solution of 3,5-diphenylisothiazole-4-carboxamide **299** (1 g, 3.57 mmol) in c. H_2SO_4 (10 ml) cooled to *ca.* 0 °C and protected with $CaCl_2$ drying tube, was added in portions sodium nitrite (2.46 g, 35.7 mmol, 10 equiv.). The reaction mixture was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C and then was poured into ice-water to afford a white precipitate. The white precipitate was filtered, washed (H_2O) and dried under vacuum to give the title compound **300** (0.87 g, 87%) as colourless needles, mp 202-203 °C (lit.,[159] 204-206 °C) (from cyclohexane); (Found: C, 68.5; H, 3.9; N, 5.0. $C_{16}H_{11}NO_2S$ requires C, 68.3; H, 3.9; N, 5.0%); λ_{max}(DCM)/nm 251 (log ε 4.00); ν_{max}/cm^{-1} 3055w (Ph CH), 1679s (C=O), 1559w, 1539w, 1533w, 1510m, 1476s, 1442m, 1356m, 1296m, 1208w, 1151w, 1077w,

1025w, 1005w, 990w, 953w, 917w, 856m, 821w, 801w, 769w, 755s; δ_H(300 MHz; CD_2Cl_2) 7.65-7.62 (2H, m, Ph C*H*), 7.56-7.53 (2H, m, Ph C*H*), 7.52-7.39 (6H, m, Ph C*H*) OH peak missing; δ_C(75 MHz; CD_2Cl_2) 171.8, 168.4, 167.5, 135.6, 130.4 (Ph *C*H), 130.0, 129.7 (Ph *C*H), 129.2 (Ph *C*H), 129.0 (Ph *C*H), 128.7 (Ph *C*H), 128.7 (Ph *C*H), 125.8; δ_C(75 MHz; DEPT 90, CD_2Cl_2) 130.4 (Ph *C*H), 129.7 (Ph *C*H), 129.2 (Ph *C*H), 129.0 (Ph *C*H), 128.7 (Ph *C*H), 128.7 (Ph *C*H); *m*/*z* (EI) 282 (M^++1, 24%), 281 (M^+, 100), 280 (57), 264 (21), 252 (5), 248 (7), 237 (57), 220 (3), 204 (7), 190 (4), 178 (3), 176 (3), 165 (7), 141 (7), 134 (19), 133 (20), 129 (14), 121 (16), 103 (15), 89 (32), 77 (44), 69 (8), 63 (13), 51 (28).

4-Bromo-3,5-diphenylisothiazole 302

To a stirred mixture of 3,5-diphenylisothiazole-4-carboxylic acid **300** (0.5 g, 1.78 mmol) in H_2O (50 ml) was added an aqueous solution of KOH (99.9 mg, 1.78 mmol, 1 equiv.) in H_2O (10 ml) and the mixture was allowed to stir at *ca.* 20 ^oC until the starting material had completely dissolved. To the reaction mixture was added, in one portion, a solution of silver nitrate (302 mg, 1.78 mmol, 1 equiv.) in water (5 ml) to afford a white-grey precipitate. The white-grey precipitate was filtered, washed first with water and then with acetone and dried in a vacuum oven at *ca.* 80 ^oC for 12 h to give the *title compound* **301** (0.69 g, 100%). To a stirred mixture of silver 3,5-diphenylisothiazole-4-carboxylate **301** (100 mg, 0.258 mmol) in tetrachloromethane (3 ml) protected with $CaCl_2$ drying tube was added in one portion Br_2 (15.9 μl, 0.31 mmol, 1.2 equiv.) and the reaction was kept at 20 ^oC for 1 h. The reaction mixture was filtred and the filtrate was absorbed on silica. Chromatography (hexane-DCM 8 : 2) gave the *title compound* **302** (65.3 mg, 80%) as colourless needles, mp 114-115 ^oC (from pentane); (Found: C, 57.2; H, 3.2; N, 4.6. $C_{15}H_{10}BrNS$ requires C, 57.0; H, 3.2; N, 4.4%); λ_{max}(DCM)/nm 238 (log ε 4.03), 282 (3.96); ν_{max}/cm^{-1} 3054w (Ph CH), 1684w, 1653w, 1559w, 1539w, 1521w, 1506w, 1474s, 1444s, 1399w, 1343m, 1312w, 1208w, 1143w, 1075w, 1024m, 973w, 923w, 902s, 834m, 789w, 764s, 756s; δ_H(300 MHz; $CDCl_3$) 7.88-7.83 (2H, m, Ph C*H*), 7.69-7.66 (2H, m, Ph C*H*), 7.56-7.45 (6H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 167.0, 162.9, 134.7 (Ph *C*), 130.1 (Ph *C*), 129.8 (Ph *C*H), 129.3 (Ph *C*H), 129.0 (Ph *C*H), 128.9 (Ph *C*H), 128.8 (Ph *C*H), 128.2 (Ph *C*H), 106.0; δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.8 (Ph *C*H), 129.3 (Ph *C*H), 129.0 (Ph *C*H), 128.9 (Ph *C*H), 128.8 (Ph *C*H), 128.2 (Ph *C*H); *m*/*z* (EI) 317 (M^++2,

98%), 315 (M^+, 100), 236 (78), 203 (13), 189 (12), 134 (35), 133 (47), 118 (27), 109 (16), 89 (100), 77 (45), 63 (19), 51 (32).

3,5-Diphenylisothiazole 303

A stirred mixture of 3,5-diphenylisothiazole-4-carboxylic acid **300** (50 mg, 0.178 mmol), TsOH (3.4 mg, 10 mol%) and biphenyl (1 g) protected with $CaCl_2$ drying tube, was heated to *ca.* 250 ^oC until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 ^oC and absorbed on silica. Chromatography (hexane-DCM 8 : 2) gave the title compound **303** (39.7 mg, 94%)as colourless needles, mp 80-81 ^oC (lit.,[188] 81 ^oC) (from pentane); (Found: C, 75.9; H, 4.6; N, 5.8. $C_{15}H_{11}NS$ requires C, 75.9; H, 4.7; N, 5.9%); λ_{max}(DCM)/nm 256 (log ε 4.13), 280 (4.06); ν_{max}/cm^{-1} 3055w (Ph CH), 1530w, 1448m, 1453w, 1447w, 1391w, 1370w, 1337w, 1306w, 1206w, 1188w, 1157w, 1153w, 1087w, 1075w, 1027w, 1000w, 970w, 965w, 920w, 909w, 878m, 851w, 830m, 770w, 759m, 752s; δ_H(300 MHz; $CDCl_3$) 8.03-7.99 (2H, m, Ph C*H*), 7.76 (1H, s, isothiazole C*H*), 7.68-7.64 (2H, m, Ph C*H*), 7.53-7.39 (6H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 168.2, 168.2, 134.8, 130.9 (Ph C*H*), 129.5 (Ph C*H*), 129.2 (Ph C*H*), 128.8 (Ph C*H*), 126.8 (Ph C*H*), 126.5 (Ph C*H*), 117.5 (isothiazole *H*-4) one peak missing; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.9 (Ph C*H*), 129.5 (Ph C*H*), 129.2 (Ph C*H*), 128.8 (Ph C*H*), 126.8 (Ph C*H*), 126.5 (Ph C*H*), 117.5 (isothiazole *H*-4); *m*/*z* (EI) 238 (M^++1, 19%), 237 (M^+, 100), 204 (6), 159 (3), 134 (23), 121 (5), 118 (3), 108 (5), 103 (9), 89 (10), 77 (21), 76 (8), 69 (4), 63 (6), 51 (15).

Methyl 3,5-diphenylisothiazole-4-carbamate 304

To a stirred solution of 3,5-diphenylisothiazole-4-carboxamide **299** (0.2 g, 0.713 mmol) in MeOH (3 ml) at *ca.* 20 ^oC, protected with $CaCl_2$ drying tube, was added sodium (65.6 mg, 2.85 mmol, 4 equiv.) and then Br_2 (43.9 μl, 0.856 mmol, 1.2 equiv.). The reaction mixture was heated to *ca.* 70 ^oC for 1 h. The mixture was allowed to cool to *ca.* 20 ^oC and absorbed on silica. Chromatography (hexane-DCM 5 : 5) gave the *title compound* **304** (0.20 g, 95%) as colourless needles, mp 163-164 ^oC (from cyclohexane); (Found: C, 65.9; H, 4.7; N, 9.2. $C_{17}H_{14}N_2O_2S$ requires C, 65.8; H, 4.6; N, 9.0%); λ_{max}(DCM)/nm 243 (log ε 4.00), 276 inf. (3.90); ν_{max}/cm^{-1} 3286w (NH), 1712s (C=O), 1582w, 1555w, 1522m, 1506m, 1484w, 1451w, 1424w, 1370w, 1251s, 1190w, 1181w, 1157w, 1097m, 1076w, 1037w, 1030w, 1017w, 1000w, 915w, 852w, 840w, 777w, 761s, 746s, 722w;

δ_H(300 MHz; $CDCl_3$) 7.72-7.69 (2H, m, Ph C*H*), 7.51-7.42 (8H, m, Ph C*H*), 6.44 (1H, br s, N*H*), 3.62 (3H, br s, CH_3); δ_C[75 MHz; CD_2Cl_2 with $Cr(acac)_3$] 165.3, 162.0, 155.6, 135.2, 130.3, 130.0, 129.9 (Ph *C*H), 129.5 (Ph *C*H), 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.2 (Ph *C*H), 127.9 (Ph *C*H), 114.8, 1 peak missing; δ_C[75 MHz; DEPT 90, CD_2Cl_2 with $Cr(acac)_3$] 129.9 (Ph *C*H), 129.5 (Ph *C*H), 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.2 (Ph *C*H), 127.9 (Ph *C*H) 1 peak missing; *m*/*z* (EI) 311 (M^++1, 20%), 310 (M^+, 98), 279 (17), 278 (18), 265 (6), 251 (16), 233 (4), 218 (10), 173 (5), 162 (5), 148 (29), 130 (5), 121 (100), 120 (7), 104 (13), 89 (8), 77 (62), 59 (18), 51 (22). Further elution gave 3,5-diphenylisothiazole-4-carboxamide **299** (6 mg, 3%) as colourless needles, mp 210-211 °C (from PhH) identical to that described above.

4-Amino-3,5-diphenylisothiazole 305

A stirred solution of methyl 3,5-diphenylisothiazole-4-carbamate **304** (0.5 g, 1.61 mmol) in 48% aq. HBr (20 ml) was heated to *ca.* 100 °C until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with water (10 ml) and extracted with DCM (4 × 10 ml). The organic extracts were combined, dried and absorbed on silica. Chromatography (hexane-DCM, 5 : 5) gave the *title compound* **305** (394 mg, 97%) as colourless needles, mp 113-114 °C (from cyclohexane); (Found: C, 71.4; H, 4.9; N, 11.0. $C_{15}H_{12}N_2S$ requires C, 71.4; H, 4.8; N, 11.1%); λ_{max}(DCM)/nm 238 (log ε 3.11), 327 (4.01); ν_{max}/cm^{-1} 3430w and 3349 (NH), 3055w (Ph CH), 1734w, 1718w, 1700w, 1684w, 1653w, 1613m, 1559w, 1506w, 1487w, 1449m, 1417s, 1387w, 1340w, 1316w, 1291w, 1278w, 1232w, 1182w, 1116w, 1103w, 1079w, 1042w, 1029m, 1018m, 997w, 974w, 919w, 836m, 774w, 762w, 719w; δ_H(300 MHz; $CDCl_3$) 7.81 (2H, m, Ph C*H*), 7.59-7.37 (8H, m, Ph C*H*), 3.61 (2H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 159.4, 140.7, 136.2, 135.1, 131.3, 129.4 (Ph *C*H), 129.0 (Ph *C*H), 128.9 (Ph *C*H), 128.3 (Ph *C*H), 127.7 (Ph *C*H), 127.7 (Ph *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.4 (Ph *C*H), 129.0 (Ph *C*H), 128.9 (Ph *C*H), 128.3 (Ph *C*H), 127.7 (Ph *C*H), 127.7 (Ph *C*H); *m*/*z* (EI) 253 (M^++1, 19%), 252 (M^+, 100), 180 (2), 149 (22), 121 (68), 104 (51), 89 (8), 77 (31), 51 (10).

4-Iodo-3,5-diphenylisothiazole 306

To a stirred mixture of I_2 (151 mg, 0.594 mmol, 3 equiv.) and isoamyl nitrite (106 μl, 0.794 mmol, 4 equiv.) in $MeNO_2$ (2 ml) protected with $CaCl_2$ drying tube at *ca.* 110 °C

was added dropwise an $MeNO_2$ (1 ml) solution of 4-amino-3,5-diphenylisothiazole **305** (50 mg, 0.198 mmol). The mixture was kept at *ca.* 110 °C until no starting material remained (TLC), allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (hexane-DCM, 7 : 3) gave the *title compound* **306** (57.5 mg, 80%) as colourless plates, mp 138-139 °C (from cyclohexane); (Found: C, 49.7; H, 3.0; N, 3.8. $C_{15}H_{10}INS$ requires C, 49.6; H, 2.8; N, 3.9%); λ_{max}(DCM)/nm 234 (log ε 3.13), 282 (2.96); ν_{max}/cm^{-1} 3054w (Ph CH), 1468m, 1442m, 1396w, 1339w, 1331w, 1308w, 1203w, 1180w, 1140w, 1076w, 1032w, 1024w, 973w, 922w, 893s, 836w, 784w, 762s, 752m; δ_H(300 MHz; $CDCl_3$) 7.80-7.77 (2H, m, Ph C*H*), 7.62-7.60 (2H, m, Ph C*H*), 7.52-7.48 (4H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 170.0, 167.1, 135.8, 131.6, 129.8 (Ph *C*H), 129.4 (Ph *C*H), 129.3 (Ph *C*H), 129.1 (Ph *C*H), 128.9 (Ph *C*H), 128.1 (Ph *C*H), 78.8; δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.8 (Ph *C*H), 129.4 (Ph *C*H), 129.3 (Ph *C*H), 129.1 (Ph *C*H), 128.9 (Ph *C*H), 128.1 (Ph *C*H); *m*/*z* (EI) 364 (M^++1, 18%), 363 (M^+, 100), 236 (40), 203 (8), 189 (6), 165 (3), 163 (3), 133 (15), 118 (14), 109 (9), 89 (23), 77 (10), 63 (5), 51 (8).

3,4,5-Triphenylisothiazole 291 (typical Suzuki conditions for coupling at C-4: see Table 29)

A stirred mixture of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol), phenylboronic acid (57.8 mg, 0.474 mmol, 3 equiv.), powdered K_2CO_3 (32.8 mg, 0.237 mmol, 1.5 equiv.) and $Pd(OAc)_2$ (1.8 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 110 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 7 : 3) gave the title compound **291** (49.5 mg, 98%) as colourless crystals, mp 210-211 °C (from cyclohexane) identical to that described above.

3,5-Diphenyl-4-(3-nitrobenzene)isothiazole 307

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 3-nitrobenzeneboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **307** (56 mg, 99%) as colourless needles, mp 203-204 °C (from cyclohexane); (Found: C, 70.3; H, 3.8; N, 7.9. $C_{21}H_{14}N_2O_2S$ requires C, 70.4; H, 3.9; N, 7.8%); λ_{max}(DCM)/nm 245 (log ε 3.19), 274 inf. (3.09); ν_{max}/cm^{-1} 3076w and 3067w (Ar CH),

1537m, 1518s, 1491w, 1470w, 1443w, 1398w, 1350s, 1275w, 1267w, 1179w, 1163w, 1123w, 1070w, 1028w, 988w, 972w, 939w, 918w, 908w, 864w, 843w, 818w, 800w, 781m, 760m, 743s, 731s, 710m; δ_H(300 MHz; $CDCl_3$) 8.14 (1H, ddd, *J* 7.7, 2.0, 2.0, Ar C*H*), 7.93 (1H, app. t, *J* 1.9, Ar C*H*), 7.46-7.26 (10H, m, Ar C*H*), 7.20-7.17 (2H, m, Ar C*H*); δ_C(75 MHz; $CDCl_3$) 167.3, 165.6, 148.2, 136.8 (Ph *C*H), 136.0, 134.9, 131.7, 130.1, 129.5 (Ph *C*H), 129.3 (Ph *C*H), 129.0 (Ph *C*H), 128.9 (Ph *C*H), 128.8 (Ph *C*H), 128.7 (Ph *C*H), 128.3 (Ph *C*H), 125.4 (Ph *C*H), 122.5 (Ph *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 136.8 (Ph *C*H), 129.5 (Ph *C*H), 129.3 (Ph *C*H), 129.0 (Ph *C*H), 128.9 (Ph *C*H), 128.8 (Ph *C*H), 128.7 (Ph *C*H), 128.3 (Ph *C*H), 125.4 (Ph *C*H), 122.5 (Ph *C*H); *m*/*z* (EI) 359 (M^++1, 25%), 358 (M^+, 100), 357 (31), 328 (4), 311 (36), 296 (3), 278 (3), 237 (3), 208 (5), 190 (2), 176 (3), 165 (8), 155 (12), 135 (5), 121 (3), 103 (3), 89 (9), 77 (8), 73 (7), 51 (4) (Found: M^+, 358.0779, $C_{21}H_{14}N_2O_2S$ requires *M*, 358.0776).

3,5-Diphenyl-4-(4-methoxybenzene)isothiazole 308

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 4-methoxybenzeneboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **308** (53 mg, 98%) as colourless needles, mp 174-175 ^oC (from cyclohexane); (Found: C, 77.0; H, 4.9; N, 4.1. $C_{22}H_{17}NOS$ requires C, 76.9; H, 5.0; N, 4.1%); λ_{max}(DCM)/nm 241 (log ε 3.45), 282 inf. (3.08); ν_{max}/cm^{-1} 3063w (Ar CH) and 2930w, 1611w, 1574w, 1539w, 1508w, 1483w, 1470w, 1456w, 1441w, 1400w, 1364w, 1287m, 1273w, 1248s, 1173m, 1157w, 1103w, 1072w, 1030m, 982w, 966w, 907w, 851w, 822m, 777m, 760m, 733s, 719m; δ_H(300 MHz; $CDCl_3$) 7.41 (2H, app. d, *J* 6.9, Ar C*H*), 7.32-7.21 (8H, m, Ar C*H*), 6.99 (2H, d, *J* 8.6, Ar C*H*), 7.80 (2H, d, *J* 8.50, Ar C*H*), 3.80 (3H, s, OCH_3; δ_C(75 MHz; $CDCl_3$) 167.7, 163.6, 158.9, 135.8, 133.8, 131.7 (Ph *C*H), 131.1, 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.4 (Ph *C*H), 128.0 (Ph *C*H), 126.1, 114.0 (Ph *C*H), 55.1, 1 peak missing; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.7 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.7, (Ph *C*H), 128.4 (Ph *C*H), 128.0 (Ph *C*H), 114.0 (Ph *C*H), 1 peak missing; *m*/*z* (EI) 344 (M^++1, 25%), 343 (M^+, 100), 328 (3), 312 (3), 256 (2), 225 (7), 208 (7), 193 (3), 165 (7), 152 (3), 81 (3), 77 (3), 69 (8), 60 (3), 57 (4), 55 (5), (Found: M^+, 343.1031, $C_{22}H_{17}NOS$ requires *M*, 343.1031).

3,5-Diphenyl-4-(3-methoxybenzene)isothiazole 309

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 3-methoxybenzeneboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **309** (53 mg, 98%) as colourless crystals, mp 132-133 ^oC (from cyclohexane); (Found: C, 76.8; H, 4.8; N, 4.0. $C_{22}H_{17}NOS$ requires C, 76.9; H, 5.0; N, 4.1%); λ_{max}(DCM)/nm 232 (log ε 4.06), 245 inf. (3.98), 282 (3.82); ν_{max}/cm^{-1} 3054w (Ar CH), 2962w, 2943w, 2919w, 2840w, 1700w, 1684w, 1608w, 1576m, 1491w, 1478w, 1455w, 1442w, 1430w, 1395w, 1362w, 1316w, 1285m, 1224s, 1171w, 1109w, 1102w, 1090w, 1075w, 1051m, 1030w, 985w, 971w, 940w, 923w, 915w, 883w, 846m, 832w, 791m, 780m, 773m, 757s, 727s; δ_H(300 MHz; $CDCl_3$) 7.41 (2H, dd, *J* 7.5, 2.0, Ph C*H*), 7.35-7.22 (8H, m, Ph C*H*), 7.17 (1H, dd, *J* 8.0, 8.0, Ar C*H*), 6.83 (1H, dd, *J* 8.4, 2.6, Ar C*H*), 6.68 (1H, app. d, *J* 7.5, Ar C*H*), 6.60 (1H, dd, *J* 2.0, 2.0, Ar C*H*), 3.60 (3H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 167.6, 164.1, 159.5, 135.6, 135.3, 134.0, 131.0, 129.6 (Ar *C*H), 128.8 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.4 (Ar *C*H), 128.0 (Ar *C*H), 123.1 (Ar *C*H), 115.8 (Ar *C*H), 113.5 (Ar *C*H), 55.1 (O*C*H$_3$), 1 peak missing; δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.6 (Ar *C*H), 128.8 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.4 (Ar *C*H), 128.0 (Ar *C*H), 123.1 (Ar *C*H), 115.8 (Ar *C*H), 113.5 (Ar *C*H), 1 peak missing; *m*/*z* (EI) 344 (M^++1, 26%), 343 (M^+, 100), 342 (35), 328 (3), 326 (3), 312 (8), 298 (3), 272 (2), 240 (3), 208 (3), 197 (3), 178 (2), 165 (6), 155 (7), 121 (3), 77 (4), 62 (2), 51 (2) (Found: M^+, 343.1045, $C_{22}H_{17}NOS$ requires *M*, 253.1031).

3,5-Diphenyl-4-(2-methoxybenzene)isothiazole 310

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 2-methoxybenzeneboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **310** (53.7 mg, 99%) as colourless crystals, mp 114-115 ^oC (from pentane); (Found: C, 77.0; H, 4.9; N, 4.0. $C_{22}H_{17}NOS$ requires C, 76.9; H, 5.0; N, 4.1%); λ_{max}(DCM)/nm 235 (log ε 3.19), 279 (3.00); ν_{max}/cm^{-1} 3059w and 3025w (Ar CH), 2835w, 1601w, 1580w, 1559w, 1539w, 1496w, 1479w, 1464w, 1443w, 1433w, 1400w, 1362w, 1265w, 1242m, 1188w, 1161w, 1132w, 1123w, 1105w, 1097w, 1073w, 1046w, 1028m, 973w, 936w, 916w, 906w, 856w, 843w, 809w, 778m, 755s, 746m, 742m, 721w; δ_H(300 MHz; $CDCl_3$) 7.43-7.39 (2H, m, Ar C*H*), 7.33-7.23 (9H, m, Ar C*H*), 7.00 (1H, ddd, *J* 7.5, 1.8, 1.8, Ar C*H*), 6.87 (1H, dd, *J* 8.4, 8.4, Ar C*H*), 6.84 (1H, dd, *J* 7.8, 7.8, Ar C*H*), 3.33 (3H, s, OC*H*$_3$); δ_C(75 MHz; $CDCl_3$) 168.1, 164.1, 157.3, 136.3, 132.0 (Ar

*C*H), 131.5, 130.7, 129.5 (Ar *C*H), 128.6 (Ar *C*H), 128.5 (Ar *C*H), 128.2 (Ar *C*H), 128.2 (Ar *C*H), 127.9 (Ar *C*H), 127.8 (Ar *C*H), 123.3, 120.9 (Ar *C*H), 111.4 (Ar *C*H), 55.0 (O*C*H$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 132.0 (Ar *C*H), 129.5 (Ar *C*H), 128.6 (Ar *C*H), 128.5 (Ar *C*H), 128.2 (Ar *C*H), 128.2 (Ar *C*H), 127.9 (Ar *C*H), 127.8 (Ar *C*H), 120.9 (Ar *C*H), 111.4 (Ar *C*H); *m*/*z* (EI) 344 (M^++1, 23%), 343 (M^+, 100), 342 (24), 328 (5), 312 (20), 207 (7), 197 (5), 165 (9), 155 (8), 121 (4), 77 (6) (Found: M^+, 343.1031, $C_{22}H_{17}NOS$ requires *M*, 343.1031).

3,5-Diphenyl-4-(4-tolyl)isothiazole 311

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 4-tolylboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **311** (50.7 mg, 98%) as colourless needles, mp 203-205 ^oC (from cyclohexane); (Found: C, 80.8; H, 5.3; N, 4.2. $C_{22}H_{17}NS$ requires C, 80.7; H, 5.2; N, 4.3%); λ_{max}(DCM)/nm 231 (log ε 3.24), 284 (2.94); ν_{max}/cm^{-1} 3069w and 3028w (Ar CH), 2922w, 1537w, 1483m, 1443m, 1395m, 1360m, 1273w, 1180w, 1163w, 1109w, 1074w, 1028w, 918w, 907w, 851w, 843w, 818m, 802w, 783m, 775m, 758m, 729s, 716m; δ_H(300 MHz; $CDCl_3$) 7.43-7.40 (2H, m, Ar C*H*), 7.34-7.22 (8H, m, Ar C*H*), 7.08, (2H, d, *J* 7.9, Ar C*H*), 6.97 (2H, d, *J* 6.3, Ar C*H*), 2.35 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 167.7, 163.7, 137.2, 135.8, 134.2, 131.1, 130.9, 130.4 (Ar *C*H), 129.3 (Ar *C*H), 128.9 (Ar *C*H), 128.7 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.3 (Ar *C*H), 128.0 (Ar *C*H), 21.3 (C*H*$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.4 (Ar *C*H), 129.3 (Ar *C*H), 128.9 (Ar *C*H), 128.7 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.3 (Ar *C*H), 128.0 (Ar *C*H); *m*/*z* (EI) 328 (M^++1, 25%), 327 (M^+, 100), 326 (49), 312 (22), 250 (7), 223 (4), 208 (3), 191 (6), 179 (37), 165 (11), 156 (8), 155 (8), 149 (5), 121 (3), 103 (3), 77 (6) (Found: M^+, 327.1072, $C_{22}H_{17}NS$ requires *M*, 327.1082).

3,5-Diphenyl-4-(3-tolyl)isothiazole 312

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 3-tolylboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **312** (51.2 mg, 99%) as colourless needles, mp 162-163 ^oC (from pentane); (Found: C, 80.8; H, 5.2; N, 4.3. $C_{22}H_{17}NS$ requires C, 80.7; H, 5.2; N, 4.3%); λ_{max}(DCM)/nm 237 (log ε 3.89), 283 (3.72); ν_{max}/cm^{-1} 3050w (Ar CH), 2955w, 2922w, 2850w, 1605w, 1586w, 1534w, 1490w, 1476w, 1447w, 1442m, 1394w, 1362m, 1291w, 1275w, 1182w,

1172w, 1154w, 1074w, 1030w, 1004w, 986w, 968w, 941w, 921w, 914w, 892w, 849m, 801m, 780m, 772m, 756s, 705s; δ_H(300 MHz; $CDCl_3$) 7.40 (2H, dd, *J* 7.8, 1.7, Ar C*H*), 7.31-7.21 (8H, m, Ar C*H*), 7.18-7.08 (2H, m, Ar C*H*), 6.89-6.87 (2H, m, Ar C*H*), 2.22 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 167.6, 163.9, 138.1, 135.7, 134.3, 134.0, 131.1 (Ar *C*H), 131.1, 128.8 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.6 (Ar *C*H), 128.4 (Ar *C*H), 128.4 (Ar *C*H), 128.3 (Ar *C*H), 128.0 (Ar *C*H), 127.7 (Ar *C*H), 21.3 (C*H*$_3$); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.1 (Ar *C*H), 128.8 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.6 (Ar *C*H), 128.4 (Ar *C*H), 128.4 (Ar *C*H), 128.3 (Ar *C*H), 128.0 (Ar *C*H), 127.7 (Ar *C*H); *m*/*z* (EI) 328 (M^++1, 27%), 327 (M^+, 100), 326 (56), 312 (17), 224 (4), 208 (4), 192 (5), 179 (4), 165 (7), 155 (8), 148 (4), 121 (3), 103 (2), 77 (5), 51 (3) (Found: M^+, 327.1073, $C_{22}H_{17}NS$ requires *M*, 327.1082).

3,5-Diphenyl-4-(2-tolyl)isothiazole 313

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 2-tolylboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **313** (25.4 mg, 49%) as colourless needles, mp 145-146 ^oC (from cyclohexane); (Found: C, 80.6; H, 5.2; N, 4.3. $C_{22}H_{17}NS$ requires C, 80.7; H, 5.2; N, 4.3%); λ_{max}(DCM)/nm 242 (log ε 3.31), 281 (3.12); ν_{max}/cm^{-1} 3058w and 3028w (Ar CH), 2919w, 1602w, 1576w, 1559w, 1533w, 1491w, 1476w, 1448m, 1443w, 1396m, 1379w, 1363m, 1269mw, 1205w, 1188w, 1178w, 1158w, 1095w, 1075w, 1072w, 1029m, 1003w, 983w, 969w, 950w, 921w, 909m, 846m, 788m, 779m, 765s, 750s, 733m, 723m; δ_H(300 MHz; $CDCl_3$) 7.43-7.40 (2H, m, Ar C*H*), 7.32-7.09 (12H, m, Ar C*H*), 1.87 (3H, s, C*H*$_3$); δ_C(75 MHz; $CDCl_3$) 167.4, 163.9, 137.2, 135.7, 133.9, 133.5, 131.2 (Ar *C*H), 131.1 (Ar *C*H), 130.5, 128.9 (Ar *C*H), 128.8 (Ar *C*H), 128.5 (Ar *C*H), 128.2 (Ar *C*H), 128.1 (Ar *C*H), 128.0 (Ar *C*H), 126.3 (Ar *C*H), 19.9 (C*H*$_3$) 1 peak missing; δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.2 (Ar *C*H), 131.1 (Ar *C*H), 128.9 (Ar *C*H), 128.8 (Ar *C*H), 128.5 (Ar *C*H), 128.2 (Ar *C*H), 128.1 (Ar *C*H), 128.0 (Ar *C*H), 126.3 (Ar *C*H), 1 peak missing; *m*/*z* (EI) 328 (M^++1, 31%), 327 (M^+, 100), 326 (51), 312 (32), 294 (2), 250 (18), 223 (8), 191 (15), 178 (3), 165 (8), 156 (8), 155 (9), 148 (6), 121 (3), 115 (3), 103 (3), 77 (6), 51(3) (Found: M^+, 327.1077, $C_{22}H_{17}NS$ requires *M*, 327.1082). Further elution (hexane-DCM, 7 : 3) gave 3,5-diphenylisothiazole **303** (19.1 mg, 51 %) as colourless needles, mp 80-81 ^oC (from pentane) identical to that described above.

3,5-Diphenyl-4-(4-chlorobenzene)isothiazole 314

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 4-chlorobenzeneboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **314** (48.9 mg, 89%) as colourless needles, mp 205-206 °C (from cyclohexane); (Found: C, 72.5; H, 3.9; N, 4.0. $C_{21}H_{14}ClNS$ requires C, 72.5; H, 4.1; N, 4.0%); λ_{max}(DCM)/nm 237 (log ε 3.25), 280 (2.98); ν_{max}/cm^{-1} 3067w (Ar CH), 2929w, 1598w, 1533w, 1494w, 1479w, 1442w, 1402w, 1394w, 1362w, 1290w, 1273w, 1180w, 1164w, 1113w, 1099w, 1090m, 1074w, 1029w, 1017m, 906w, 825s, 799w, 777m, 760m, 756m, 734m, 721s; δ_H(300 MHz; $CDCl_3$) 7.40-7.20 (12H, m, Ar C*H*), 7.02 (2H, ddd, *J* 9.6, 2.0, 1.9, Ar C*H*); δ_C(75 MHz; $CDCl_3$) 167.5, 164.4, 135.4, 133.6, 132.8, 132.5, 131.9 (Ar *C*H), 130.7, 129.0 (Ar *C*H), 128.9 (Ar *C*H), 128.9 (Ar *C*H), 128.8 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.2 (Ar *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 131.9 (Ar *C*H), 129.0 (Ar *C*H), 128.9 (Ar *C*H), 128.9 (Ar *C*H), 128.8 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.2 (Ar *C*H); *m*/*z* (EI) 349 (M^++2, 36%), 348 (M^++1, 40), 347 (M^+, 100), 327 (3), 312 (13), 244 (5), 212 (8), 208 (5), 199 (3), 176 (4), 165 (12), 156 (13), 155 (13), 135 (5), 121 (3), 103 (2), 77 (6), 51 (3) (Found: M^+, 347.1531, $C_{21}H_{14}ClNS$ requires *M*, 347.0535). Further elution (hexane-DCM, 7 : 3) gave *4-(4-chlorobiphenyl-4-yl)-3,5-diphenylisothiazole* **319** (7.4 mg, 11%) as colourless crystals, mp 224-225 °C (from cyclohexane); (Found: C, 72.4; H, 3.9; N, 4.0. $C_{27}H_{18}ClNS$ requires C, 76.5; H, 4.3; N, 3.3%); λ_{max}(DCM)/nm 269 (log ε 3.54); ν_{max}/cm^{-1} 3058w (Ar CH), 2926w, 2851w, 1488w, 1479w, 1448w, 1442w, 1395w, 1363w, 1272w, 1183w, 1093m, 1077w, 1030w, 1006w, 922w, 910w, 860w, 841w, 821s, 802w, 780m, 767m, 760m, 742w, 722m; δ_H(300 MHz; CD_2Cl_2) 7.57 (4H, ddd, *J* 8.7, 2.3, 2.3, Ar C*H*), 7.50 (2H, ddd, *J* 8.5, 1.8, 1.8, Ar C*H*), 7.41 (4H, ddd, *J* 8.7, 2.3, 2.3, Ar C*H*), 7.34-7.23 (8H, m, Ar C*H*), 7.16 (2H, ddd, *J* 8.5, 1.9, 1.9, Ar C*H*); δ_C(75 MHz; CD_2Cl_2) 167.9, 164.6, 139.1, 139.1, 136.2, 134.1, 134.0, 133.7, 131.5 (Ar C*H*), 131.4, 129.2 (Ar C*H*), 129.2 (Ar C*H*), 129.1 (Ar C*H*), 129.1 (Ar C*H*), 128.8 (Ar C*H*), 128.5 (Ar C*H*), 128.4 (Ar C*H*), 127.2 (Ar C*H*), 1 peak missing; δ_C(75 MHz; DEPT 90, CD_2Cl_2) 131.5 (Ar C*H*), 129.2 (Ar C*H*), 129.2 (Ar C*H*), 129.1 (Ar C*H*), 129.1 (Ar C*H*), 128.8 (Ar C*H*), 128.5 (Ar C*H*), 128.4 (Ar C*H*), 127.2 (Ar C*H*), 1 peak missing; *m*/*z* (EI) 426 (M^++3, 12%), 425 (M^++2, 36), 424 (M^++1, 41), 423 (M^+, 100), 422 (40), 347 (10), 329 (4), 312 (4), 298 (8), 290 (3), 288 (10), 275 (4), 252 (9), 249 (8), 239 (3), 193 (7), 120 (4), 77 (3) (Found: M^+, 423.0866, $C_{21}H_{14}ClNS$ requires *M*, 423.0848).

3,5-Diphenyl-4-(3-chlorobenzene)isothiazole 315

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 3-chlorobenzeneboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **315** (45.6 mg, 83%) as colourless cotton like needles, mp 175-176 ^oC (from cyclohexane); (Found: C, 72.4; H, 3.9; N, 4.0. $C_{21}H_{14}ClNS$ requires C, 72.5; H, 4.1; N, 4.0%); λ_{max}(DCM)/nm 234 (log ε 3.47), 280 (3.27); ν_{max}/cm^{-1} 3054w (Ar CH), 1597w, 1565w, 1489w, 1468w, 1442w, 1395w, 1361w, 1272w, 1188w, 1119w, 1088w, 1079w, 1072w, 1029w, 999w, 915w, 889w, 843w, 812w, 791m, 778s, 760m, 738s; δ_H(300 MHz; $CDCl_3$) 7.37-7.15 (12H, m, Ar C*H*), 7.06 (1H, dd, *J* 1.7, 1.7, Ar C*H*), 6.95 (1H, ddd, *J* 7.5, 1.3, 1.3, Ar C*H*); δ_C(75 MHz; $CDCl_3$) 167.4, 164.8, 136.0, 135.3, 134.3, 132.6, 130.5, 130.5 (Ar *C*H), 129.8 (Ar C*H*), 129.1 (Ar C*H*), 128.9 (Ar C*H*), 128.8 (Ar C*H*), 128.7 (Ar C*H*), 128.1 (Ar C*H*), 127.8 (Ar C*H*) 2 peak missing; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.5 (Ar *C*H), 129.8 (Ar C*H*), 129.1 (Ar C*H*), 128.9 (Ar C*H*), 128.8 (Ar C*H*), 128.7 (Ar C*H*), 128.1 (Ar C*H*), 127.8 (Ar C*H*) 2 peak missing; *m*/*z* (EI) 349 (M^++2, 39%), 348 (M^++1, 46), 347 (M^+, 100) 346 (64), 312 (18), 310 (11), 244 (3), 212 (5), 208 (7), 199 (4), 176 (4), 165 (12), 156 (13), 155 (14), 135 (4), 121 (3), 77 (7), 51 (4) (Found: M^+, 347.0535, $C_{21}H_{14}ClNS$ requires *M*, 347.0535). Further elution (hexane-DCM, 7 : 3) gave 4-(3-chlorobiphenyl-3-yl)-3,5-diphenylisothiazole **320** (7.4 mg, 11%) as colourless crystals, mp 143-144 ^oC (from pentane); (Found: C, 72.5; H, 4.0; N, 4.0. $C_{21}H_{14}ClNS$ requires C, 72.5; H, 4.1; N, 4.0%); λ_{max}(DCM)/nm 233 (log ε 2.79), 325 (3.18); ν_{max}/cm^{-1} 3068w and 3025w (Ar CH), 1594w, 1565w, 1506w, 1485w, 1473w, 1441w, 1398w, 1388w, 1361w, 1293w, 1250w, 1182w, 1156w, 1100w, 1075w, 1047w, 1029w, 999w, 985w, 968w, 936w, 924w, 914w, 880w, 852w, 828w, 810w, 788m, 777s, 756m, 729s, 708m; δ_H(300 MHz; $CDCl_3$) 7.47-7.07 (14H, m, Ar C*H*); δ_C(75 MHz; $CDCl_3$) 167.7, 164.3, 142.4, 139.9, 135.7, 134.6, 134.5, 133.8, 131.0, 130.0 (Ar *C*H), 129.9 (Ar *C*H), 129.6 (Ar *C*H), 129.1 (Ar *C*H), 129.0 (Ar *C*H), 129.0 (Ar *C*H), 128.9 (Ar *C*H), 128.8, (Ar *C*H), 128.6 (Ar *C*H), 128.2 (Ar *C*H), 127.3 (Ar *C*H), 127.2 (Ar *C*H), 126.2 (Ar *C*H), 125.1 (Ar *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.0 (Ar *C*H), 129.9 (Ar *C*H), 129.6 (Ar *C*H), 129.1 (Ar *C*H), 129.0 (Ar *C*H), 129.0 (Ar *C*H), 128.9 (Ar *C*H), 128.8, (Ar *C*H), 128.6 (Ar *C*H), 128.2 (Ar *C*H), 127.3 (Ar *C*H), 127.2 (Ar *C*H), 126.2 (Ar *C*H), 125.1 (Ar *C*H); *m*/*z* (EI) 425 (M^++2, 42%), 424 (M^++1, 45), 423 (M^+, 100), 422 (39), 387 (3), 347 (5), 310 (5), 309 (3), 298 (7), 288 (9), 284 (4), 275 (4), 252 (10), 239 (4), 192 (6), 186

(7), 165 (3), 155 (3), 120 (5), 103 (3), 77 (9), 51 (4) (Found: M^+, 423.0864, $C_{27}H_{18}ClNS$ requires *M*, 423.0848).

3,5-Diphenyl-4-(2-chlorobenzene)isothiazole 316

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 2-chlorobenzeneboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **316** (44.5 mg, 81%) as colourless crystals, mp 176-177 °C (from cyclohexane); (Found: C, 72.5; H, 4.0; N, 4.0. $C_{21}H_{14}ClNS$ requires C, 72.5; H, 4.1; N, 4.0%); λ_{max}(DCM)/nm 233 (log ε 3.23), 281 (3.01); ν_{max}/cm^{-1} 3061 (Ar CH), 1597w, 1565w, 1489w, 1468w, 1442w, 1419w, 1410w, 1395w, 1361w, 1272w, 1188w, 1119w, 1089w, 1079w, 1073w, 1029w, 888w, 843w, 815w, 792w, 779s, 761m, 744m, 738s, 729m; δ_H(300 MHz; $CDCl_3$) 7.39-7.17 (12H, m, Ar C*H*), 7.08-7.07 (1H, m, Ar C*H*), 6.97 (1H, ddd, *J* 7.5, 1.4, 1.4, Ar C*H*); δ_C(75 MHz; $CDCl_3$) 167.4, 164.8, 136.0, 135.3, 134.3, 132.6, 130.6, 130.5 (Ar *C*H), 129.8 (Ar *C*H), 129.1 (Ar *C*H), 128.9 (Ar *C*H), 128.8 (Ar *C*H), 128.7, (Ar *C*H), 128.7 (Ar *C*H), 128.2 (Ar *C*H), 127.8 (Ar *C*H), 1 peak missing; δ_C(75 MHz; DEPT 90, $CDCl_3$) 130.5 (Ar *C*H), 129.8 (Ar *C*H), 129.1 (Ar *C*H), 128.9 (Ar *C*H), 128.8 (Ar *C*H), 128.7, (Ar *C*H), 128.7 (Ar *C*H), 128.2 (Ar *C*H), 127.8 (Ar *C*H), 1 peak missing; *m*/*z* (EI) 349 (M^++2, 38%), 348 (M^++1, 41), 347 (M^+, 100), 346 (58), 312 (21), 244 (4), 208 (8), 176 (14), 165 (6), 156 (18), 155 (18), 135 (5), 121 (4), 103 (4), 89 (6), 77 (16), 62 (24), 51 (8) (Found: M^+, 347.0544, $C_{21}H_{14}ClNS$ requires *M*, 347.0535). Further elution (hexane-DCM, 7 : 3) gave 3,5-diphenylisothiazole **303** (7.1 mg, 19%) as colourless needles, mp 80-81 °C (from pentane) identical to that described above.

3,5-Diphenyl-4-(thien-3-yl)isothiazole 317

Similar treatment of 4-bromo-3,5-diphenylisothiazole **302** (50 mg, 0.158 mmol) with 3-thienylboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **317** (50.4 mg, 100%) as colourless needles, mp 186-187 °C (from cyclohexane); (Found: C, 71.3; H, 4.1; N, 4.3. $C_{19}H_{13}NS_2$ requires C, 71.4; H, 4.1; N, 4.4%); λ_{max}(DCM)/nm 245 (log ε 4.09), 284 (3.80); ν_{max}/cm^{-1} 3092w and 3057w (Ar CH), 1481w, 1441w, 1418w, 1350w, 1188w, 1072w, 1032w, 856m, 849m, 789s, 775m, 764m, 750s, 722s; δ_H(300 MHz; $CDCl_3$) 7.47-7.43 (2H, m, Ar C*H*), 7.37-7.26 (9H, m, Ar C*H*), 6.95 (1H, dd, *J* 3.0, 1.2, thienyl *H-2*) 6.78 (1H, dd, *J* 5.0, 1.2, thienyl *H-4*); δ_C(75 MHz; $CDCl_3$) 167.7, 164.1, 135.7, 133.6, 131.0, 129.1, 129.1 (Ar *C*H), 128.9 (Ar *C*H),

128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.6 (Ar *C*H), 128.5 (Ar *C*H), 128.1 (Ar *C*H), 125.7 (Ar *C*H), 125.0 (Ar *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.1 (Ar *C*H), 128.9 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.6 (Ar *C*H), 128.5 (Ar *C*H), 128.1 (Ar *C*H), 125.7 (Ar *C*H), 125.0 (Ar *C*H); *m*/*z* (EI) 320 (M^++1, 25%), 319 (M^+, 100), 318 (63), 286 (10), 285 (4), 272 (4), 242 (3), 216 (3), 184 (16), 171 (15), 159 (3), 143 (5), 139 (5), 121 (3), 103 (2), 84 (3), 77 (7), 62 (3) (Found: M^+, 319.0488, $C_{19}H_{13}NS_2$ requires *M*, 319.0489).

3,5-Diphenyl-4-(thien-2-yl)isothiazole 318

Similar treatment of 4-iodo-3,5-diphenylisothiazole **306** (50 mg, 0.138 mmol) with 2-thienylboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **318** (43.6 mg, 99%) as colourless needles, mp 189-190 °C (from cyclohexane); (Found: C, 71.4; H, 4.0; N, 4.3. $C_{19}H_{13}NS_2$ requires C, 71.4; H, 4.1; N, 4.4%); λ_{max}(DCM)/nm 245 (log ε 3.34), 285 (2.96); ν_{max}/cm^{-1} 3065w (Ar CH), 1601w, 1481w, 1447w, 1441w, 1434w, 1389w, 1360w, 1336w, 1309w, 1283w, 1262w, 1220w, 1186w, 1178w, 1155w, 1092w, 1076w, 1062w, 1033w, 970w, 922w, 916w, 906w, 882w, 848w, 831m, 775m, 752m, 745w, 726m, 720m, 707s; δ_H(300 MHz; $CDCl_3$) 7.51-7.47 (2H, m, Ar C*H*), 7.37-7.28 (9H, m, Ar C*H*), 6.97 (1H, dd, *J* 5.1, 3.6, thienyl *H-4*) 6.79 (1H, dd, *J* 3.6, 1.2, thienyl *H-5*); δ_C(75 MHz; $CDCl_3$) 167.9, 165.6, 135.4, 134.4, 130.7, 129.1 (Ar *C*H), 128.9 (Ar *C*H), 128.7 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.6 (Ar *C*H), 128.1 (Ar *C*H), 127.3 (Ar *C*H), 127.0 (Ar *C*H), 126.9; δ_C(75 MHz; DEPT 90, $CDCl_3$) 129.1 (Ar *C*H), 128.9 (Ar *C*H), 128.7 (Ar *C*H), 128.7 (Ar *C*H), 128.6 (Ar *C*H), 128.6 (Ar *C*H), 128.1 (Ar *C*H), 127.3 (Ar *C*H), 127.0 (Ar *C*H); *m*/*z* (EI) 320 (M^++1, 27%), 319 (M^+, 100), 318 (57), 286 (19), 274 (8), 242 (3), 216 (10) 184 (21), 171 (23), 159 (6), 158 (5), 143 (8), 139 (12), 121 (7), 89 (3), 77 (13), 69 (5), 51 (8).

3,4,5-Triphenylisothiazole 291 (typical Stille conditions for coupling at C-4: see Table 30)

A stirred mixture of 3,5-diphenyl-4-iodoisothiazole **306** (30 mg, 0.083 mmol), tributylphenylstannane (40.5 μl, 0.124 mmol, 1.5 equiv.) and $Pd(OAc)_2$ (0.9 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane-DCM, 6 : 4) gave the

title compound **291** (25.5 mg, 98%) as colourless needles, mp 210-211 ^{o}C (from cyclohexane) identical to that described above.

3,5-Diphenyl-4-(thien-2-yl)isothiazole 318 *via* Stille coupling at C-4

Similar treatment of 4-iodo-3,5-diphenylisothiazole **306** (30 mg, 0.083 mmol) with tributyl(2-thienyl)stannane (1.5 equiv.) and $Pd(OAc)_2$ gave the *title compound* **318** (26.2 mg, 99%) as colourless needles, mp 189-190 ^{o}C (from cyclohexane) identical to that described above.

3,5-Diphenyl-4-(fur-2-yl)isothiazole 321

Similar treatment of 4-iodo-3,5-diphenylisothiazole **306** (30 mg, 0.083 mmol) with tributyl(2-furyl)stannane (1.5 equiv.) and $Pd(OAc)_2$ gave the *title compound* **321** (24.6 mg, 98%) as colourless needles, mp 114-115 ^{o}C (from cyclohexane); (Found: C, 75.2; H, 4.2; N, 4.6. $C_{19}H_{13}NOS$ requires C, 75.2; H, 4.3; N, 4.6%); λ_{max}(DCM)/nm 247 (log ε 3.18), 280 (2.86); ν_{max}/cm^{-1} 3125w and 3109w (Ar CH), 1598w, 1525w, 1502w, 1478w, 1447w, 1441w, 1389w, 1352w, 1271w, 1226w, 1181w, 1160w, 1072w, 1031w, 1022w, 1001w, 985w, 940w, 926w, 916w, 885w, 872w, 853w, 842w, 830w, 780m, 767m, 757m, 725s; δ_H(300 MHz; $CDCl_3$) 7.50-7.46 (2H, m, Ar C*H*), 7.44 (1H, dd, *J* 2.0, 0.6, furyl *H*-5), 7.42-7.30 (8H, m, Ar CH), 6.38 (1H, dd, *J* 3.3, 1.8, furyl *H*-4) 6.11 (1H, dd, *J* 3.3, 0.6, furyl *H*-3); δ_C(75 MHz; $CDCl_3$) 168.0, 167.0, 146.2, 142.5 (Ar *C*H), 135.5, 130.6, 129.3 (Ar *C*H), 128.8 (Ar *C*H), 128.8 (Ar *C*H), 128.3 (Ar *C*H), 128.2 (Ar *C*H), 128.2 (Ar *C*H), 124.1, 111.3 (Ar *C*H), 111.0 (Ar *C*H); δ_C(75 MHz; DEPT 90, $CDCl_3$) 142.5 (Ar *C*H), 129.3 (Ar *C*H), 128.8 (Ar *C*H), 128.8 (Ar *C*H), 128.3 (Ar *C*H), 128.2 (Ar *C*H), 128.2 (Ar *C*H), 111.3 (Ar *C*H), 111.0 (Ar *C*H); *m*/*z* (EI) 304 (M^++1, 23%), 303 (M^+, 100), 286 (4), 274 (32), 259 (3), 249 (12), 241 (5), 240 (4), 200 (6), 171 (15), 139 (11), 121 (9), 102 (3), 89 (3), 77 (12), 69 (4), 51 (7).

APPENDIX

Crystallographic data

Introduction

This appendix records relevant data for all the new compounds in this thesis studied by single crystal X-ray diffraction.

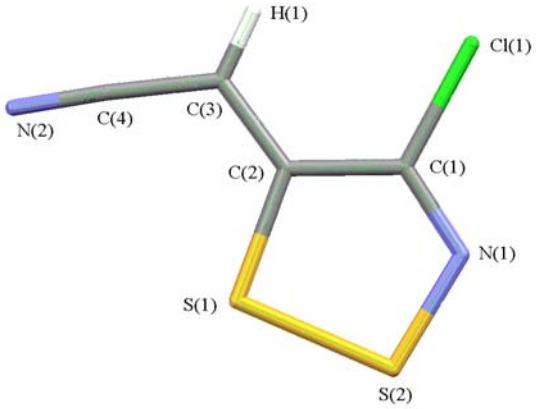


Figure 20 X-ray structure of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139**.

Space Group: P 2_1/c

Cell Lengths (Å): a 7.5167(11), b 11.280(3), c 8.1382(16)

Cell Angles (°): α 89.874(19), β 108.043(15), γ 90.208(16)

Cell Volume: 656.1(2)

Cell Formula Units: Z 4, Z' 0

R factor (%): 5.54

Table 31. Bond lengths of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139** received from x-ray chrystallography.

Atom 1	Atom 2	Length (Å)
N(2)	C(4)	1.148(5)
C(3)	C(2)	1.344(5)
C(3)	C(4)	1.413(5)
S(1)	C(2)	1.730(4)
S(1)	S(2)	2.084(9)
S(2)	N(1)	1.637(3)
Cl(1)	C(1)	1.715(4)
N(1)	C(1)	1.277(5)
C(2)	C(1)	1.456(5)

Table 32. Bond angles of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139** received from X-ray chrystallography.

Atom 1	Atom 2	Atom 3	Angle (°)
C(2)	C(3)	C(4)	120.1(4)
N(2)	C(4)	C(3)	176.5(4)
C(2)	S(1)	S(2)	93.3(1)
N(1)	S(2)	S(1)	97.3(1)
C(1)	N(1)	S(2)	116.0(3)
C(3)	C(2)	C(1)	125.5(4)
C(3)	C(2)	S(1)	123.5(3)
C(1)	C(2)	S(1)	111.0(3)
N(1)	C(1)	C(2)	122.3(4)
N(1)	C(1)	Cl(1)	118.7(3)
C(2)	C(1)	Cl(1)	119.0(3)

Table 33. Non bonding diatomic contacts between nearby molecules of (*Z*)-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **139** received from X-ray chrystallography.

Atom 1 of Molecule 1	Atom 1 of molecule 2	Length (Å)	Length - VdW (Å)
H(1)	N(1)	2.518	-0.232
N(2)	S(2)	2.871	-0.479
S(1)	N(2)	2.896	-0.454
S(1)	C(1)	3.383	-0.117
C(1)	Cl(1)	3.430	-0.020
Cl(1)	C(2)	3.449	-0.001
C(2)	S(1)	3.487	-0.013

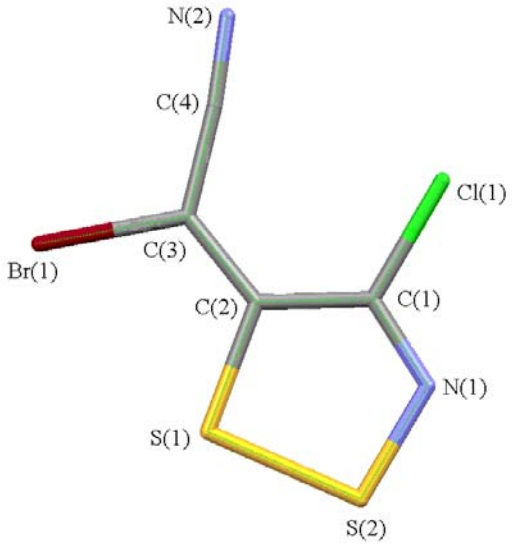


Figure 21 X-ray structure of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **142**.

Space Group: P n m a

Cell Lengths (Å): a 8.1226(8), b 6.7318(7), c 13.5987(11)

Cell Angles (°): α 89.947(8), β 89.928(7), γ 89.901(8)

Cell Volume: 743.571

Cell Formula Units: Z 8, Z' 0

R factor (%): 3.04

Table 34. Bond lengths of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-acetonitrile **142** received from X-ray chrystallography.

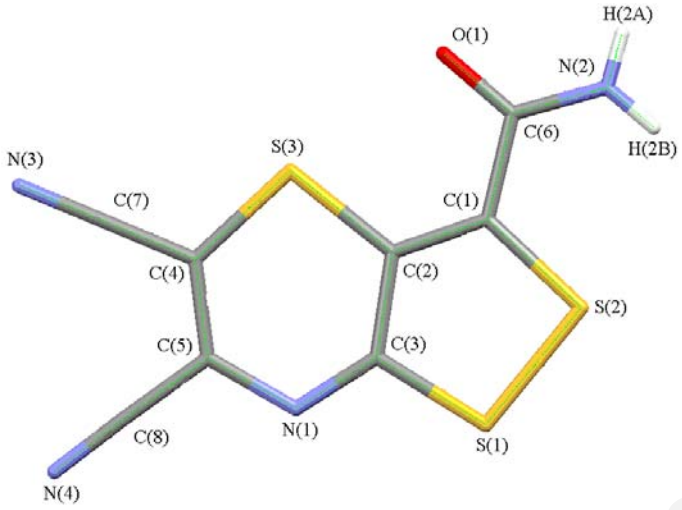
Atom 1	Atom 2	Length (Å)
Br(1)	C(3)	1.890(5)
Cl(1)	C(1)	1.721(5)
S(1)	C(2)	1.738(5)
S(1)	S(2)	2.092(1)
S(2)	N(1)	1.651(4)
N(1)	C(1)	1.284(6)
C(4)	N(2)	1.130(7)
C(4)	C(3)	1.426(7)
C(1)	C(2)	1.454(6)
C(1)	Cl(1)	1.721(5)
C(2)	C(3)	1.376(6)
N(2)	C(4)	1.130(7)

Table 34. Bond angles of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)aceto-nitrile **142** received from X-ray chrystallography.

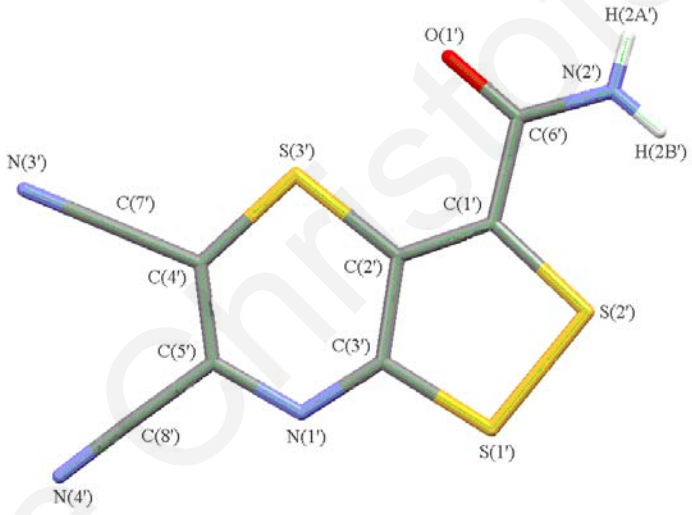
Atom 1	Atom 2	Atom 3	Angle (°)
C(2)	S(1)	S(2)	93.15(14)
N(1)	S(2)	S(1)	96.82(13)
C(1)	N(1)	S(2)	116.9(3)
N(2)	C(4)	C(3)	174.3(4)
N(1)	C(1)	C(2)	121.1(4)
N(1)	C(1)	Cl(1)	117.2(3)
C(2)	C(1)	Cl(1)	121.8(4)
C(3)	C(2)	C(1)	127.5(4)
C(3)	C(2)	S(1)	120.5(3)
C(1)	C(2)	S(1)	112.0(3)
C(2)	C(3)	C(4)	127.4(4)
C(2)	C(3)	Br(1)	118.4(3)
C(4)	C(3)	Br(1)	114.3(3)

Table 36. Non bonding diatomic contacts between nearby molecules of (*Z*)-2-bromo-2-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)acetonitrile **142** received from X-ray chrystallography.

Atom 1 of Molecule 1	Atom 1 of molecule 2	Length (Å)	Length - VdW (Å)
S(1)	N(2)	2.915	-0.435
S(2)	N(2)	2.939	-0.411
S(2)	Cl(1)	3.471	-0.079
N(1)	Cl(1)	3.088	-0.212
Br(1)	N(2)	3.332	-0.068
S(1)	S(2)	3.553	-0.047



Heterocycle A



Heterocycle B

Figure 22 X-ray structure of 5,6-dicyano-[1,2]dithiolo[4,3-*b*][1,4]thiazine-3-carboxamide **148**.

Space Group: P 2_1/n

Cell Lengths (Å): a 14.8359(6), b 8.4726(4), c 25.8165(15)

Cell Angles (^{o}): α 90.079(4), β 95.888(4), γ 89.977(4)

Cell Volume: 3227.98

Cell Formula Units: Z 4, Z' 0

R factor (%): 4.14

Table 37. Bond lengths of 5,6-dicyano-[1,2]dithiolo[4,3-*b*][1,4]thiazine-3-carboxamide **148** (Heterocycle A) received from X-ray chrystallography.

Atom 1	Atom 2	Length (Å)
O(1)	C(6)	1.245(3)
N(2)	C(6)	1.327(4)
C(6)	C(1)	1.479(4)
N(4)	C(8)	1.146(4)
N(3)	C(7)	1.150(4)
C(7)	C(4)	1.435(4)
C(8)	C(5)	1.445(4)
S(1)	C(3)	1.742(3)
S(1)	S(2)	2.0562(11)
S(2)	C(1)	1.751(3)
S(3)	C(4)	1.768(3)
S(3)	C(2)	1.773(3)
C(4)	C(5)	1.355(4)
C(2)	C(1)	1.363(4)
C(2)	C(3)	1.447(4)
N(1)	C(3)	1.300(4)
N(1)	C(5)	1.378(4)

Table 38. Bond lengths of 5,6-dicyano-[1,2]dithiolo[4,3-*b*][1,4]thiazine-3-carboxamide **148** (Heterocycle B) received from X-ray chrystallography.

Atom 1	Atom 2	Length (Å)
O(1')	C(6')	1.241(3)
N(2')	C(6')	1.320(4)
C(6')	C(1')	1.493(4)
N(4')	C(8')	1.153(4)
N(3')	C(7')	1.151(4)
C(7')	C(4')	1.434(4)
C(8')	C(5')	1.452(5)
S(1')	C(3')	1.746(3)
S(1')	S(2')	2.0639(11)
S(2')	C(1')	1.751(3)
S(3')	C(4')	1.774(3)
S(3')	C(2')	1.765(3)
C(4')	C(5')	1.342(4)
C(2')	C(1')	1.360(4)
C(2')	C(3')	1.450(4)
N(1')	C(3')	1.303(4)
N(1')	C(5')	1.391(4)

Table 39. Bond angles of 5,6-dicyano-[1,2]dithiolo[4,3-*b*][1,4]thiazine-3-carboxamide **148** (Heterocycle A) received from X-ray chrystallography.

Atom 1	Atom 2	Atom 3	Angle (°)
O(1)	C(6)	N(2)	123.6(3)
O(1)	C(6)	C(1)	117.8(3)
N(2)	C(6)	C(1)	118.6(3)
N(3)	C(7)	C(4)	179.2(4)
N(4)	C(8)	C(5)	176.9(3)
C(3)	S(1)	S(2)	97.09(11)
C(1)	S(2)	S(1)	94.25(10)
C(4)	S(3)	C(2)	98.10(14)
C(5)	C(4)	C(7)	119.9(3)
C(5)	C(4)	S(3)	125.8(2)
C(7)	C(4)	S(3)	114.3(2)
C(1)	C(2)	C(3)	117.4(3)
C(1)	C(2)	S(3)	122.2(2)
C(3)	C(2)	S(3)	120.3(2)
C(3)	N(1)	C(5)	117.5(3)
C(4)	C(5)	N(1)	127.2(3)
C(4)	C(5)	C(8)	118.6(3)
N(1)	C(5)	C(8)	114.1(3)
C(2)	C(1)	C(6)	122.2(3)
C(2)	C(1)	S(2)	117.7(2)
C(6)	C(1)	S(2)	120.1(2)
N(1)	C(3)	C(2)	130.8(3)
N(1)	C(3)	S(1)	115.6(2)
C(2)	C(3)	S(1)	113.6(2)

Table 40. Bond angles of 5,6-dicyano-[1,2]dithiolo[4,3-*b*][1,4]thiazine-3-carboxamide **148** (Heterocycle B) received from X-ray chrystallography.

Atom 1	Atom 2	Atom 3	Angle (°)
O(1')	C(6')	N(2')	123.3(3)
O(1')	C(6')	C(1')	117.1(3)
N(2')	C(6')	C(1')	119.6(3)
N(3')	C(7')	C(4')	178.3(4)
N(4')	C(8')	C(5')	179.7(4)
C(3')	S(1')	S(2')	97.14(11)
C(1')	S(2')	S(1')	94.94(11)
C(4')	S(3')	C(2')	98.66(14)
C(5')	C(4')	C(7')	121.1(3)
C(5')	C(4')	S(3')	126.2(2)
C(7')	C(4')	S(3')	112.6(2)
C(1')	C(2')	C(3')	117.4(3)
C(1')	C(2')	S(3')	123.2(2)
C(3')	C(2')	S(3')	119.5(2)
C(3')	N(1')	C(5')	117.4(3)
C(4')	C(5')	N(1')	117.4(3)
C(4')	C(5')	C(8')	119.6(3)
N(1')	C(5')	C(8')	113.9(3)
C(2')	C(1')	C(6')	120.7(3)
C(2')	C(1')	S(2')	118.1(2)
C(6')	C(1')	S(2')	121.1(2)
N(1')	C(3')	C(2')	131.6(3)
N(1')	C(3')	S(1')	115.0(2)
C(2')	C(3')	S(1')	113.4(2)

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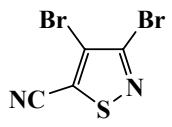
Compound number in bold followed by page number where compound appears in Chapter 7 (Experimental).



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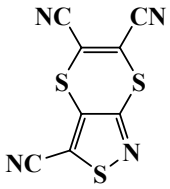

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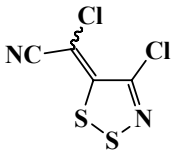

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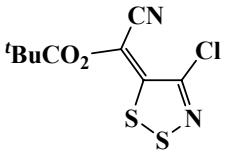

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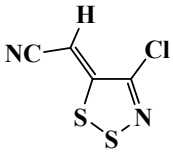

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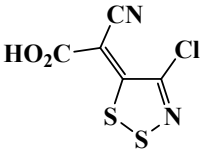

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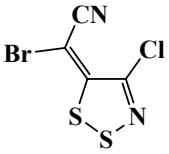

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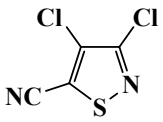

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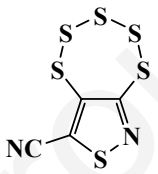

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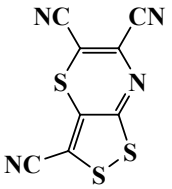

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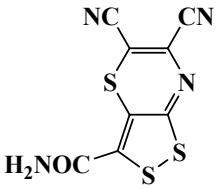

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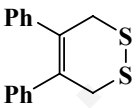

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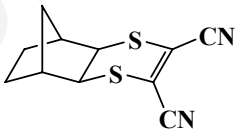

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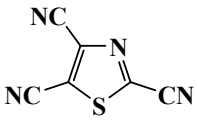

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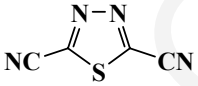

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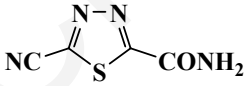

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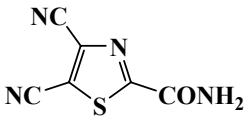

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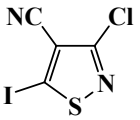

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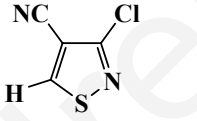

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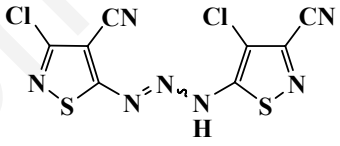

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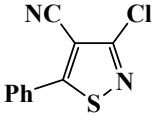

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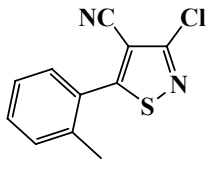

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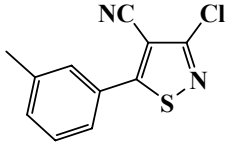

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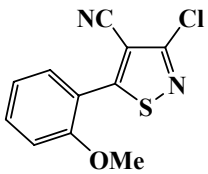

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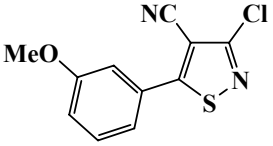

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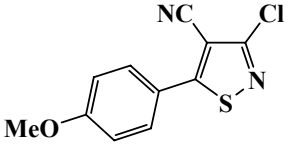

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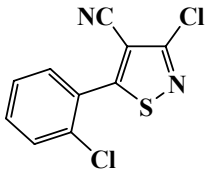

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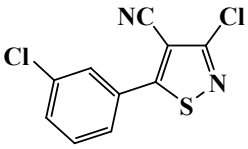

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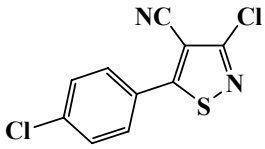

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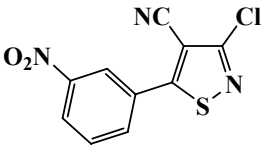

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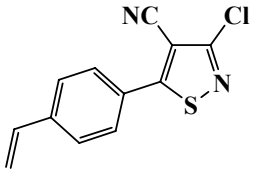

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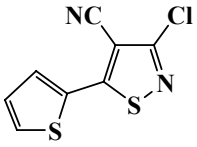

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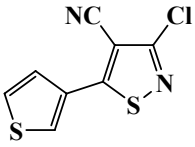

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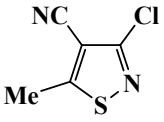

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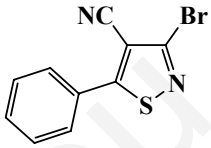

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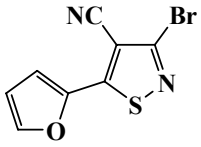

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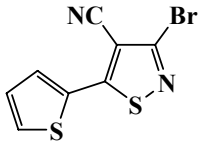

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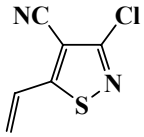

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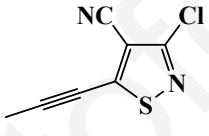

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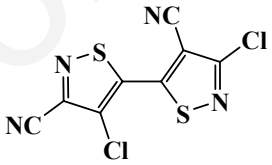

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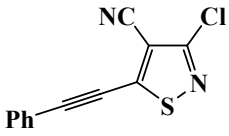

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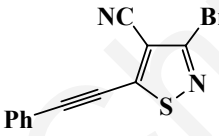

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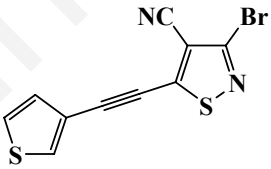

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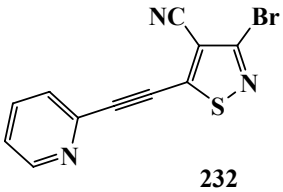

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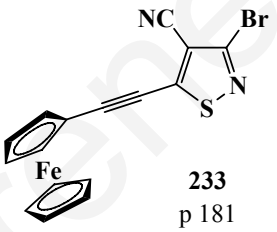

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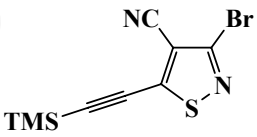

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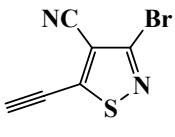

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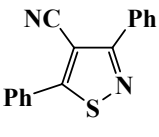

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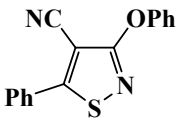

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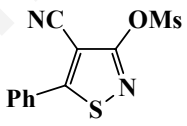

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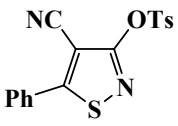

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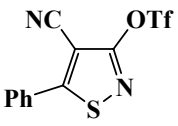

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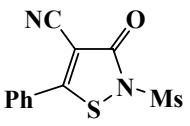

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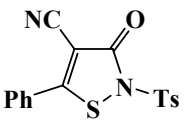

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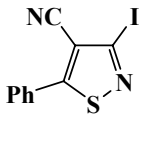

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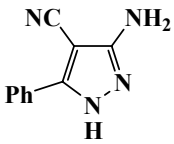

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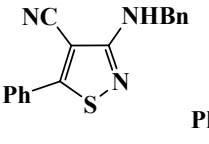

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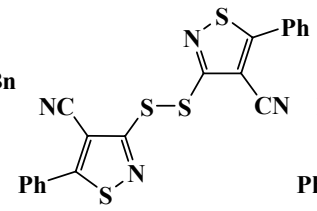

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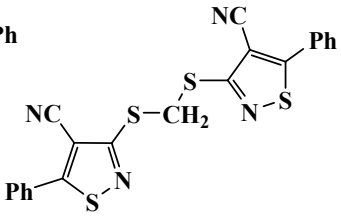

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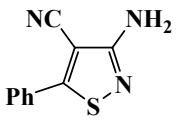

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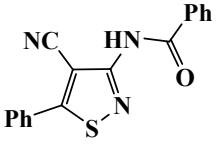

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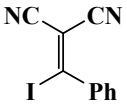

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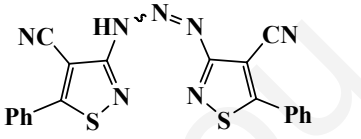

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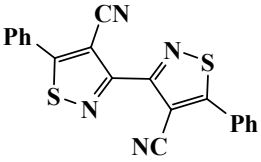

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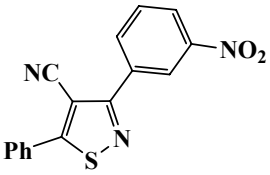

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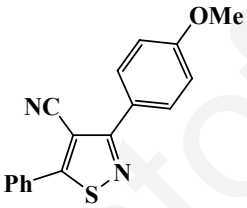

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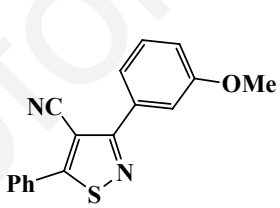

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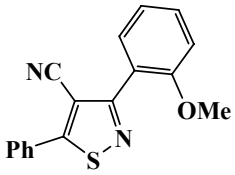

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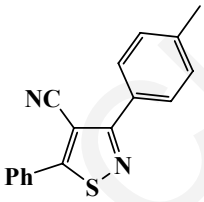

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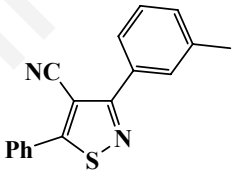

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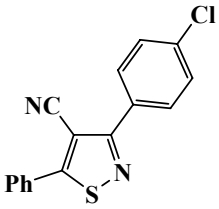

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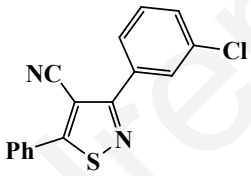

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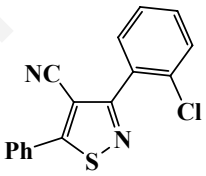

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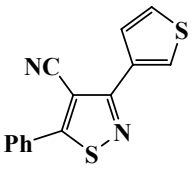

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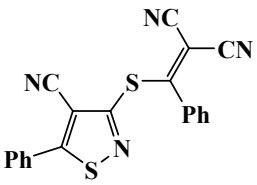

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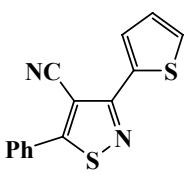

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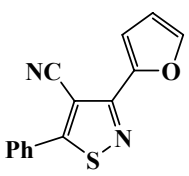

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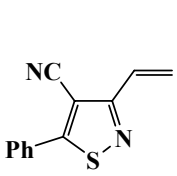

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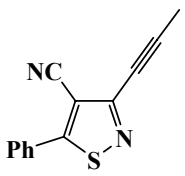

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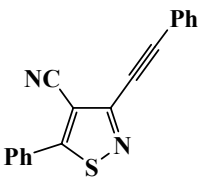

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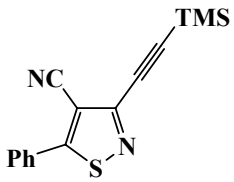

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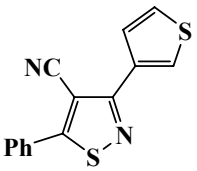

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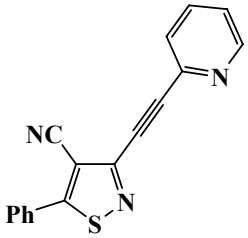

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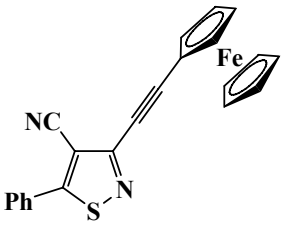

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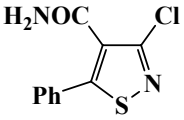

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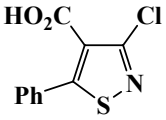

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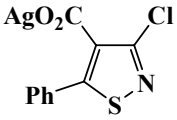

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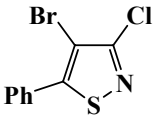

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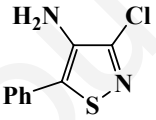

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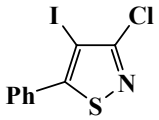

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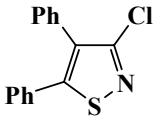

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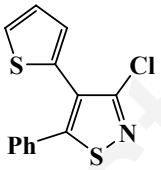

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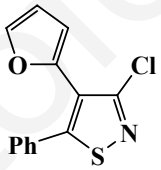

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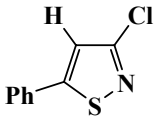

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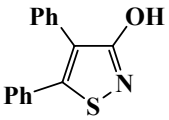

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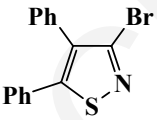

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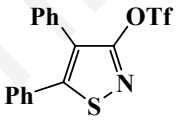

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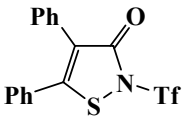

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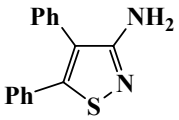

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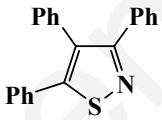

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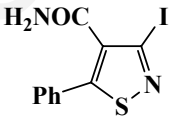

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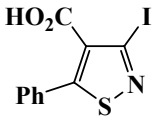

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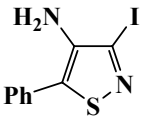

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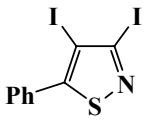

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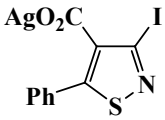

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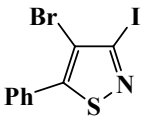

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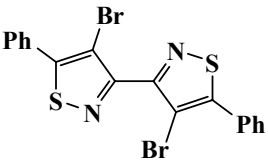

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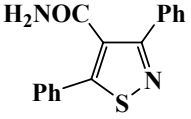

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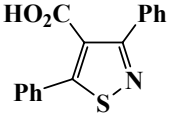

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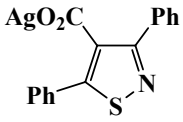

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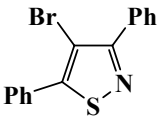

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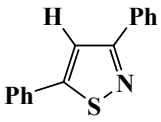

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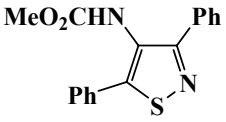

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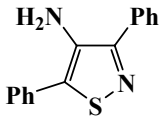

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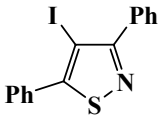

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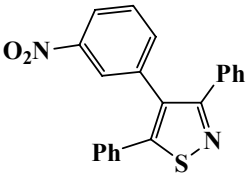

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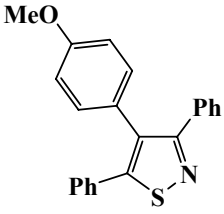

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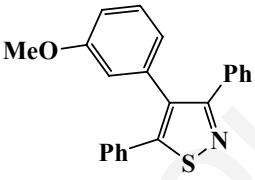

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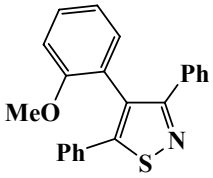

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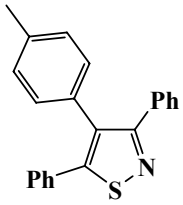

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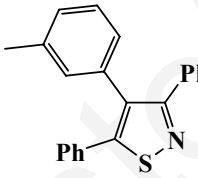

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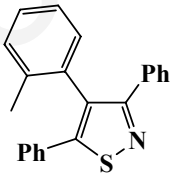

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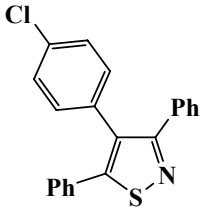

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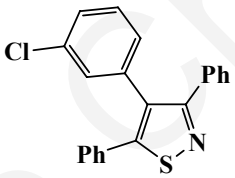

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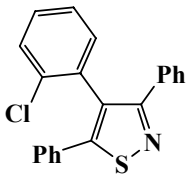

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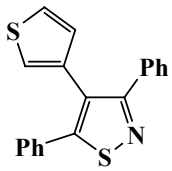

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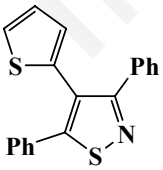

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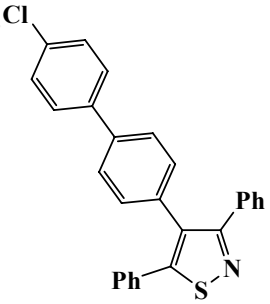

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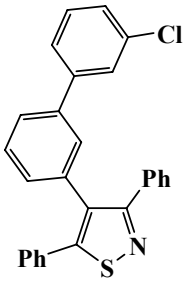

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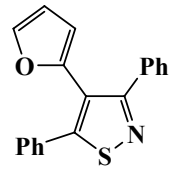

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