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Regiospecific Suzuki coupling of 3,5-dichloroisothiazole-4-carbonitrile

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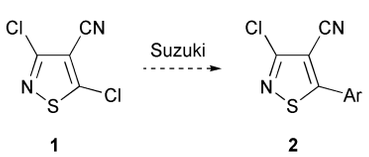
Received 29th May 2003, Accepted 30th June 2003
First published as an Advance Article on the web 14th July 2003

3,5-Dichloroisothiazole-4-carbonitrile **1** reacts with aryl- and methylboronic acids to give in high yields the 3-chloro-5-(aryl and methyl)-isothiazole-4-carbonitrile **2** regiospecifically. The reaction was optimized with respect to base, phase transfer agent and palladium catalyst. Suzuki coupling at C-5 was also achieved in high yield using potassium phenyltrifluoroborate. The regiospecificity of either coupling method is maintained with 3,5-dibromoisothiazole-4-carbonitrile **4** to give exclusively 3-bromo-5-phenylisothiazole-4-carbonitrile **5**. Suzuki cross-coupling conditions applied to 3-chloro-5-phenylisothiazole-4-carbonitrile **2a** gave 3-phenoxy-5-phenylisothiazole-4-carbonitrile **6**, which was prepared independently, and not the 3-phenyl derivative. All isothiazole products were fully characterized.

A recent series of articles have described the broad antiviral activity of 3-methylthio-5-arylisothiazole-4-carbonitrile derivatives.[1–4] These isothiazoles were prepared by cyclisation of arylmethylene-malononitriles with disulfur dichloride and pyridine to afford the 3-chloro-5-arylisothiazole-4-carbonitriles[1,5] which 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.[1] Both routes require 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.[6]

Whilst working on the synthesis and chemistry of 3-haloisothiazole-4,5-dicarbonitriles[7–9] 3,5-dichloroisothiazole-4-carbonitrile **1** was identified as a possible alternative synthetic precursor to 3-chloro-5-arylisothiazole-4-carbonitriles **2** (Scheme 1).



1 **2**

Scheme 1

3,5-Dichloroisothiazole-4-carbonitrile **1** is readily available by condensation of malononitrile and carbon disulfide, followed by chlorination (55%).[10] The 5-chlorine of isothiazole **1** can be regioselectively displaced by a range of nucleophiles.[10] Activation of the 5-chlorine by both the 4-cyano substituent and the ring nitrogen results in its enhanced activity. Thus a regioselective Suzuki reaction was considered as an alternative route to the above 5-aryl isothiazoles **2**. A search of the literature revealed no Suzuki couplings for the isothiazole system, though palladium catalysed cross-coupling reactions were reported for several bromo and iodo halogenated isothiazoles to give alkenyl and alkynyl substituted isothiazoles.[11,12]

The Suzuki reaction is important for C–C bond formation and continues to be extensively investigated for the formation of biaryls.[13] Regiocontrolled heteroaryl Suzuki couplings are known for several heteroaromatic systems such as pyrimidine,[14,15] quinoline,[16] 1,10-phenanthroline[17] and thiophene[18] and we now report rapid high yielding Suzuki couplings at C-5 of the isothiazole **1**.

Reaction of isothiazole 1 with organoboronic acids

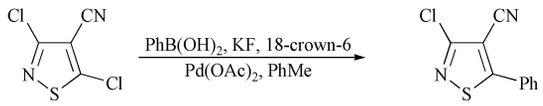
Initial attempts at Suzuki coupling of phenylboronic acid and 3,5-dichloroisothiazole-4-carbonitrile **1** in biphasic mixtures of water and hydrocarbon solvents could not readily be driven to completion without significant reduction in the product yields to 60–70%. A variety of bases and several solvent 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.[19–21] 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,[20,22–24] 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[25] prompted the use of non-aqueous conditions. The use of $Pd(OAc)_2$, 18-crown-6, and vacuum oven-dried KF in dry toluene gave near quantitative conversions of dichloroisothiazole **1** into 3-chloro-5-phenylisothiazole-4-carbonitrile **2a**. 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 1). 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 °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 **1**. Presumably the rate of phenylboronic acid homocoupling increases with temperature and becomes competitive.

DOI: 10.1039/b306005e

Table 1 Reaction of 3,5-dichloroisothiazole-4-carbonitrile **1** (0.3 mmol) with $PhB(OH)_2$, KF, 18-crown-6 (0.5 equiv.) and $Pd(OAc)_2$ (5 mol%)



1 **2a**

$PhB(OH)_2$ (equiv.)	KF (equiv.)	Solvent	Temp.[a] (°C)	Time (h)	Yield **2a** (%)
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 °C. [c] Incomplete reaction.

Table 2 Reaction of 3,5-dichloroisothiazole-4-carbonitrile **1** (0.3 mmol) with $PhB(OH)_2$ (1.5 equiv.), KF (3.5 equiv.), $Pd(OAc)_2$ (5 mol%) and various PTC in PhMe at reflux

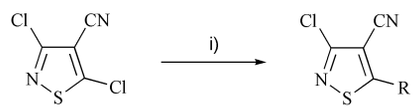
PTC	PTC (equiv.)	Time (h)	Yield **2a** (%)
$Bn(Et)_3N^+Cl^-$	0.5	33	69
$Et_4N^+Br^-$	0.5	24	60
$CH_3(CH_2)_{15}N^+(CH_3)_3Br^-$	0.5	48	70
$Bn(Et)_3N^+I^-$	0.5	8	75
Adogen 464®	1.0	24	[a]
Adogen 464®	0.5	14	86
Adogen 464®	0.25	30	97
Adogen 464®	0.15	27	96
18-Crown-6	0.5	3	96
18-Crown-6	0.25	4.5	90
18-Crown-6	0.15	7	96
18-Crown-6	0.1	9	95
18-Crown-6	0.05	24	[a]

[a] Incomplete reaction.

Next the choice of phase transfer catalyst was examined (Table 2). 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 is not common,[21] but palladium-catalysed aminations of aryl halides[26–28] and Ullmann-type couplings[29] have been performed in good yields with crown ethers.

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 $(PhCN)_2PdCl_2$, $(CH_3CN)_2PdCl_2$, (dibenzylideneacetone)$_3Pd_2$, and [1,1′-bis(Ph_2P)ferrocene]$PdCl_2{\cdot}CH_2Cl_2$ gave significantly better initial activity than $Pd(OAc)_2$, however, with the latter, traces of unreacted isothiazole **1** 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, 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 (Scheme 2, Table 3).

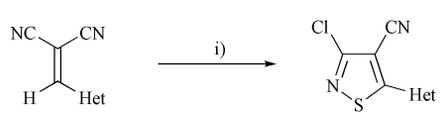
Generally electron rich boronic acids led to faster reactions and substituents in the *ortho* positions had little steric influence on the reaction. Electron poor boronic acid gave lower yields or required further addition of reagents to drive the reaction to



1 **2a-n**

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

completion. Whilst 3-thienylboronic acid reacted in high yield the 2-thienylboronic acid reaction showed no consumption of starting isothiazole. 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.[30–32] Similar problems have been solved by the use of anhydrous conditions.[20,25] 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 were prepared independently from the corresponding thienyl-methylene-malononitriles **3** on treatment with disulfur dichloride and pyridine in *ca.* 30% yields (Scheme 3).



3a Het = 2-Thienyl **2l** 29 %
3b Het = 3-Thienyl **2m** 30 %

Scheme 3 *Reagents and conditions:* i) S_2Cl_2 (4 equiv.), C_5H_5N, 80 °C, 16 h.

Reaction of isothiazole 1 with organotrifluoroborates

For comparison, the above Suzuki couplings were reinvestigated using the readily available and air stable organotrifluoroborates[33] which have recently found use in several such couplings.[15,34–39] The reaction of 3,5-dichloroisothiazole-4-carbonitrile **1** 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 **1** 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 (Scheme 4,

Table 3 Reaction of 3,5-dichloroisothiazole-4-carbonitrile **1** (0.3 mmol) with $RB(OH)_2$ (2 equiv.), KF (3.5 equiv.), $Pd(OAc)_2$ (5 mol%) and 18-crown-6 (0.5 equiv.)

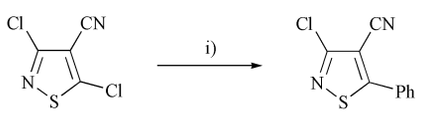
	R	Solvent	Temp. (°C)	Time (h)	Yield **2** (%)
2a	Ph	PhH	80	26	91
2a	Ph	PhMe	110	3	97
2b	2-MeC_6H_4	PhMe	110	1	95
2c	3-MeC_6H_4	PhMe	110	1.5	99
2d	2-$MeOC_6H_4$	PhMe	110	1.5	89
2e	3-$MeOC_6H_4$	PhMe	110	1.5	96
2f	4-$MeOC_6H_4$	PhMe	110	1	80
2f	4-$MeOC_6H_4$	PhH	80	2	95
2g	2-ClC_6H_4	PhMe	110	77[a]	89
2h	3-ClC_6H_4	PhMe	110	74[b]	91
2i	4-ClC_6H_4	PhMe	110	4	97
2j	3-$NO_2C_6H_4$	PhMe	110	30[c]	43
2k	4-Vinylphenyl	PhMe	110	24	30[d]
2l	2-Thienyl	PhMe	110	24	[e]
2m	3-Thienyl	PhMe	110	3	93
2m	3-Thienyl	PhH	80	24	93
2n	Me	PhMe	110	21.5	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 **1** was not consumed.

Table 4 Reaction of dichloroisothiazole **1** (0.3 mmol) with $PhBF_3K$ (1.5 equiv.), K_2CO_3, $Pd(OAc)_2$ (5 mol%) and 18-crown-6 (0.5 equiv.)

Solvent[a]	K_2CO_3 (equiv.)	Temp. (°C)	Time (h)	Yield **2a** (%)
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 reaction.



1 **2a**

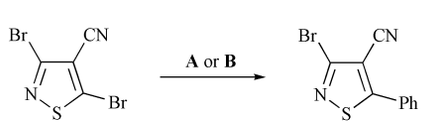
Scheme 4 *Reagents and conditions:* i) $PhBF_3K$ (1.5 equiv.), K_2CO_3 (1–1.5 equiv.), 18-crown-6 (0.5 equiv.), $Pd(OAc)_2$ (5 mol%), PhMe, 110 °C.

Table 4). The reaction required at least 1.5 equivalents of phenyltrifluoroborate and traces of biphenyl were observed by TLC. Interestingly the coupling with trifluoroborates is reported to require water as co-solvent,[34,35] however under the above conditions the reaction between 3,5-dichloroisothiazole-4-carbonitrile **1** and phenyltrifluoroborate proceeded to completion in high yield as rapidly in anhydrous toluene as in undried toluene. 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;[40,41] however, in our reactions added Ag_2O led to an increase in the biphenyl production (TLC) and was not investigated further.

Phenylboronic acid and KF are proposed to yield phenyltrifluoroborate[22,42] 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[34,35,37,39,43] 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 toluene 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.

Coupling reactions of 3,5-dibromoisothiazole-4-carbonitrile 4

3,5-Dibromoisothiazole-4-carbonitrile **4** can be prepared in an analogous manner to dichloroisothiazole **1** but in significantly lower yield 11%.[10] Both the phenylboronic acid and potassium phenyltrifluoroborate couplings proceed regiospecifically at C-5 to afford 3-bromo-5-phenylisothiazole-4-carbonitrile **5** in almost quantitative yield (Scheme 5).



4 **5**

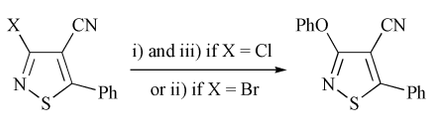
Scheme 5 *Reagents and conditions:* **A**) $PhB(OH)_2$ (2 equiv.), KF (3.5 equiv.), 18-crown-6 (0.5 equiv.), $Pd(OAc)_2$ (5 mol%), PhMe, 110 °C, 2 h, 97%; **B**) $PhBF_3K$ (1.5 equiv.), K_2CO_3 (1–1.5 equiv.), 18-crown-6 (0.5 equiv.), $Pd(OAc)_2$ (5 mol%), PhMe, 110 °C, 18 h, 99%.

Aryl bromides are more reactive than aryl chlorides in Suzuki couplings and the reaction of phenylboronic acid with dibromoisothiazole **4** reached completion slightly faster than with dichloroisothiazole **1**. Contrary to expectations the potassium phenyltrifluoroborate reaction proceeded significantly slower with dibromoisothiazole **4** than with the dichloroisothiazole **1**. 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. This peculiar response is under investigation.

Attempted Suzuki coupling at C-3 of isothiazole 2a

An attempt to perform a Suzuki coupling at C-3 with 3-chloro-5-phenylisothiazole-4-carbonitrile **2a** 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 **2a** was consumed fully after 7 days, 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 is known[44] and could be eliminated by its melting point and the absence of a *ν*(C=O) in the IR, whilst the second possibility, 3-phenoxy-5-phenylisothiazole-4-carbonitrile **6**, was unknown. This ether was prepared independently in high yield by treating 3-chloro-5-phenylisothiazole-4-carbonitrile **2a** with potassium phenoxide in refluxing toluene in the presence of 18-crown-6 (Scheme 6), and the spectral data of the two specimens were identical.



2a X = Cl
5 X = Br

6

Scheme 6 *Reagents and conditions:* i) PhOK (1.5 equiv.), 18-crown-6 (0.5 equiv.), PhMe, 20–140 °C, 3 h, 91%; ii) PhOK (2 equiv.), 18-crown-6 (0.5 equiv.), PhMe, 20–140 °C, 3.5 h, 66%; iii) $PhB(OH)_2$, $PdOAc_2$, KF, 18-crown-6, 95% (see Experimental section).

Phenylboronic acid can afford phenol and this conversion is often effected by hydrogen peroxide.[45–47] 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 **5** with potassium phenoxide (2 equivalents) gave the ether in 66%. 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 byproducts 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.

Summary

To summarize, optimal conditions for high yielding regioselective Suzuki couplings at C-5 of the readily available 3,5-dichloroisothiazole-4-carbonitrile **1** have been achieved using ligandless palladium catalysis and 18-crown-6 as PTC in refluxing toluene with either organoboronic acid–KF or organotrifluoroborate–K_2CO_3. The regioselectivity and high yields are maintained with 3,5-dibromoisothiazole-4-carbonitrile **4**. The use of 18-crown-6 and this relatively high temperature significantly shorten the reaction times. 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 **6** that was prepared independently from 3-chloro-5-phenylisothiazole-4-carbonitrile **2a** and potassium phenoxide. Further attempts to achieve coupling at C-3 are under way.

Experimental

Benzene and toluene were freshly distilled from CaH_2 under argon. Potassium salts PhOK, K_2CO_3 and KF were powdered and vacuum dried at 130 °C/2 Torr. Reactions were protected by $CaCl_2$ drying tubes. Anhydrous sodium sulfate was used for drying organic extracts, and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial glass backed 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). Melting points were determined using a Stuart Scientific SMP 1 apparatus. Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a Shimadzu UV-1601 spectrometer and inflections are identified by the abbreviation "inf". IR spectra were recorded on a Jasco FT/IR-460 plus spectrometer and strong and medium peaks are represented by s and m respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz respectively). Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Mass spectra were recorded on a VG Autospec "Q" mass spectrometer. Petrol refers to light petroleum, bp 40–60 °C. 3,5-Dichloroisothiazole-4-carbonitrile **1**,[10] 2-(2-thienylmethylene)-malononitrile **3a**,[48] 2-(3-thienylmethylene)-malononitrile **3b**,[49] 3,5-dibromoisothiazole-4-carbonitrile **4**[10] and potassium phenyltrifluoroborate[35] were prepared according to literature procedures.

3-Chloro-5-phenylisothiazole-4-carbonitrile 2a (typical organoboronic acid procedure)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **1** (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 **2a** (60 mg, 91%) as colourless needles, mp 87–88 °C (from cyclohexane) (lit.,[5] 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; *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 2b

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** with 2-tolylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **2b** (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, CH_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 (CH_3); *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 2c

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** with 3-tolylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **2c** (99%) as colourless crystals, mp 86–87 °C (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, CH_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 (CH_3); *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 2d

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** with 2-methoxyphenylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **2d** (89%) as colourless needles, mp 157–158 °C (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 (CH_3O); *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 2e

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** with 3-methoxyphenylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **2e** (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 (CH_3O); *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 2f

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** with 4-methoxyphenylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the title compound **2f** (95%) as colourless needles, mp 133–134 °C (from cyclohexane) (lit.,[1] 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, CH_3O); 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 (CH_3O); *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 2g

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** 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 **2g** (89%) as colourless needles, mp 99 °C (from cyclohexane) (lit.,[5] 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; *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 2h

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** 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 **2h** (91%) as colourless needles, mp 103–104 °C (from cyclohexane) (lit.,[1] 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; *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 2i

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** with 4-chlorophenylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-

6 gave the title compound **2i** (97%) as colourless needles, mp 117–119 °C (from cyclohexane) (lit.,[5] 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; *m*/*z* (EI) 254 (M^+, 100%), 219 ($M^+ - Cl$, 18), 208 ($M^+ - NS$, 4), 193 ($M^+ - CClN$, 6), 184 ($M^+ - Cl_2$, 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 2j

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** 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* **2j** (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; *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 2k

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** 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* **2k** (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; *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 2m

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** with 3-thienylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **2m** (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; *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 2n

Similar treatment of 3,5-dichloroisothiazole-4-carbonitrile **1** with methylboronic acid, KF, $Pd(OAc)_2$ and 18-crown-6 gave the *title compound* **2n** (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 2l from 2-(2-thienylmethylene)malononitrile 3a

To a stirred solution of 2-(2-thienylmethylene)malononitrile **3a** (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* **2l** (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; *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 2m from 2-(3-thienylmethylene)malononitrile 3b

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

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

A stirred mixture of 3,5-dibromoisothiazole-4-carbonitrile **4** (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 °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* **5** (77 mg, 97%) as colourless crystals, mp 93–94 °C (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; *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 2a (typical organotrifluoroborate procedure)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **1** (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 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 **2a** (65 mg, 99%) as colourless needles, mp 87–88 °C (from cyclohexane) identical to that described above.

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

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

3-Phenoxy-5-phenylisothiazole-4-carbonitrile 6 from phenylboronic acid

A stirred mixture of 3-chloro-5-phenylisothiazole–4-carbonitrile **2a** (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 toluene (2 ml) was heated to *ca.* 110 °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 °C and chromatography (hexane–DCM, 3 : 1) gave the *title compound* **6** (79 mg, 95%) as colourless needles, mp 118–119 °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; *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 6 from potassium phenoxide

To a stirred solution of 3-chloro-5-phenylisothiazole-4-carbonitrile **2a** (66 mg, 0.3 mmol) in toluene (2 ml) at *ca.* 20 °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 °C until no starting material remained (TLC) (3 h). The mixture was allowed to cool to *ca.* 20 °C and chromatography (hexane–DCM, 3 : 1) gave the title compound **6** (91%) as colourless needles, mp 118–119 °C (from cyclohexane) identical to that described above.

Acknowledgements

We thank the following organisations in Cyprus for generous donations of chemicals and glassware: the State General Laboratory, the Agricultural Research Institute and the Ministry of Agriculture. Furthermore we thank the A. G. Leventis Foundation for helping to establish the NMR facility in the University of Cyprus, MDL Information Sytems (UK) Ltd for financial support and the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College. We thank the referees for their valuable comments regarding the formation of phenoxyisothiazole **6**.

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