Supplementary Material (ESI) for Organic and Biomolecular Chemistry

ELECTRONIC SUPPLEMENTARY INFORMATION

New Regiospecific Isothiazole C-C Coupling Chemistry

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Experimental

Solvents PhH and PhMe were freshly distilled from CaH_2 under argon. DMF was azeotropically distilled with PhH then redistilled under vacuum from anhydrous $MgSO_4$ and stored over 4Å molecular sieves under argon. THF was freshly distilled from potassium under argon. Anhydrous K_2CO_3 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. Anhydrous $MgSO_4$ was used for drying organic extracts, and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial 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). 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. ^{1}H 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. 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. 3,5-Dichloroisothiazole-4-carbonitrile **1**,[7] 3,5-dibromoisothiazole-4-carbonitrile **2**,[7] 3-chloro-5-phenylisothiazole-4-carbonitrile **3**,[15] 3-bromo-5-phenylisothiazole-4-carbonitrile **4**,[15] 5-amino-3-chloroisothiazole-4-carbonitrile **10**,[7] 3-chloro-4-cyanoisothiazole-5-carboxylic acid **21**[31] and 3-hydroxy-5-phenylisothiazole-4-carbonitrile **22**[32] were prepared according to literature procedures.

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

(typical Stille coupling conditions at C-5: Table 1)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **1** (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^{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 the volatiles evaporated. The residue obtained was absorbed on silica and chromatography (hexane–DCM, 7:3) gave the title compound **3** (31.1 mg, 84%) as colourless needles, mp 87–88^{o}C (from cyclohexane) identical to an authentic sample.

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

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with tributylphenyltin (1.2 equiv.) and $Pd(OAc)_2$ in DMF gave the title compound **4** (90%) as colourless needles, mp 93–94°C (from cyclohexane) identical to an authentic sample.

3-Bromo-5-(fur-2-yl)isothiazole-4-carbonitrile 6

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with 2-(tributylstannyl)-furan (1.2 equiv.) and $Pd(OAc)_2$ in MeCN (2 ml) gave the *title compound* **6** (100%) as colourless needles, mp 100-101°C (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 7

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with 2-(tributylstannyl)-thiophene (1 equiv.) and $Pd(OAc)_2$ in MeCN (2 ml) gave the *title compound* **7** (93%) as colourless needles, mp 134-135°C (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 8

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with tributyl(vinyl)tin (1.2 equiv.) and $Pd(OAc)_2$ in MeCN (2 ml) gave the *title compound* **8** (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 9

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with tributyl(1-propynyl)tin (1.2 equiv.) and $Pd(OAc)_2$ in MeCN (2 ml) gave the *title compound* **9** (86%) as colourless needles, mp 50-51°C (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 3

(typical Negishi coupling conditions at C-5)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **1** (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°C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20°C and the volatiles were evaporated. The residue was absorbed on silica and chromatography (hexane–DCM, 7:3) gave the title compound **3** (34.5 mg, 93%) as colourless needles, mp 87–88°C (from cyclohexane) identical to an authentic sample.

3-Bromo-5-phenylisothiazole-4-carbonitrile 4 (*via* Negishi coupling)

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with phenylzinc chloride and $(PPh_3)_2PdCl_2$ gave the title compound **4** (90%) as colourless needles, mp 93–94°C (from cyclohexane) identical to an authentic sample.

3-Chloro-5-iodoisothiazole-4-carbonitrile 11

To a stirred and heated (*ca.* 110°C) mixture of iodine (238.5 mg, 0.94 mmol, 3 equiv.) and isoamyl nitrite (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 **10** (50 mg, 0.313 mmol). The reaction mixture was kept at *ca.* 110°C until no starting material remained (TLC) and then allowed to cool to *ca.* 20°C and absorbed on silica. Chromatography (hexane–DCM, 7:3) gave the *title compound* **11** (70 mg, 83%) as colourless needles, mp 117-118°C (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* **12** (7 mg, 16%) as colourless needles, mp 50-51°C (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; decoupled $CDCl_3$) 158.4 (*C*-5), 151.2, 111.0, 109.7; δ_C(75 MHz;

coupled $CDCl_3$) 158.4 (d, *J* 192.3, *C*-5), 151.2 (d, *J* 12.3, *C*-3), 111.0 (d, *J* 2.9, *C*≡N or *C*-4), 109.7 (d, *J* 3.4, *C*-4 or *C*≡N); 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) (Found: M^+, 143.9549, C_4HClN_2S requires *M*, 143.9549).

3-Chloroisothiazole-4-carbonitrile 12 from 3-chloro-4-cyanoisothiazole-5-carboxylic acid 21

A thick walled glass pressure tube was charged with 3-chloro-4-cyanoisothiazole-5-carboxylic acid **21** (100 mg, 0.531 mmol), sealed and heated in a preheated Woods-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 **12** (58.3 mg, 76%) as colourless needles, mp 50-51°C (from pentane) identical to that described above.

5,5'-Bi(3-chloroisothiazole-4-carbonitrile) 13

A stirred mixture of 3-chloro-5-iodoisothiazole-4-carbonitrile **11** (30 mg, 0.11 mmol) and $Pd(OAc)_2$ (24.7 mg, 0.11 mmol) in 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, 1:4) gave the *title compound* **13** (27 mg, 86%) as colourless needles, mp 244-245°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 14

(typical Sonogashira conditions at C-5: Table 2)

A stirred mixture of 3,5-dichloroisothiazole-4-carbonitrile **1** (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 (46.8 μl, 0.336 mmol, 2 equiv.) in DMF (2 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 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* **14** (32.9 mg, 80%) as colourless needles, mp 74–75°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, 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 15

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with CuI, $(PPh_3)_2PdCl_2$, ethynylbenzene and triethylamine in DMF gave the *title compound* **15** (86%) as colourless needles, mp 109-110°C (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 16

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with CuI, $(PPh_3)_2PdCl_2$, 3-ethynylthiophene and triethylamine in MeCN (2 ml) gave the *title compound* **16** (77%) as colourless needles, mp 86-87°C (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 17

Similar treatment of 3-chloro-5-iodoisothiazole-4-carbonitrile **2** 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 **12** (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* **17** (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 18

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with CuI, $(PPh_3)_2PdCl_2$, ethynylferrocene and triethylamine in MeCN (2 ml) gave the *title compound* **18** (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 19

Similar treatment of 3,5-dibromoisothiazole-4-carbonitrile **2** with CuI, $(PPh_3)_2PdCl_2$, ethynyltrimethylsilane (1.5 equiv.) and triethylamine in PhMe (2 ml) gave the *title compound* **19** (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 (*C*-5), 138.0 (*C*-3), 120.0 (*C*≡C), 115.6 (*C*≡N), 111.1 [*C*(C≡N)], 88.2 (*C*≡C),

-0.8 (*C*H_3); *m*/*z* (EI) 286 (13%), 284 (M^+, 12), 271 (100), 269 (M^+-CH_3, 98), 241 (3), 228 (5), 226 (5), 190 (3), 139 (12), 137 (12), 116 (4), 102 (4), 84 (16), 43 (12) (Found: M^+, 283.9442, $C_9H_9BrN_2SSi$ requires *M*, 283.9439). Further elution gave *3-bromo-5-ethynylisothiazole-4-carbonitrile* **20** (14%) as colourless crystals, mp 91-92°C (purified by sublimation) (Found: C, 33.8; H, 0.4; N, 13.1. C_6HBrN_2S requires C, 33.8; H, 0.5; N, 13.2%); 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 decoupled; $CDCl_3$) 155.3, 138.2, 116.6, 110.8, 98.6, 68.8 (*C*≡CH); δ_C(75 MHz coupled; $CDCl_3$) 155.3 (d, $^3J_{CH}$ 4.8, *C*-5), 138.2 (s, *C*-3), 116.6 (*C*≡N), 110.8 [*C*(C≡N)], 98.6 (d, $^1J_{CH}$ 261.8, C≡*C*H) 68.8 (d, $^2J_{CH}$ 51.6, *C*≡CH); 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-Methanesulfonyloxy-5-phenylisothiazole-4-carbonitrile 23

To a stirred solution of 3-hydroxy-5-phenylisothiazole-4-carbonitrile **22** (100 mg, 0.495 mmol) and triethylamine (69 μl, 0.495 mmol, 1 equiv.) in DCM (2 ml) cooled to *ca*. 0°C was added in one portion methanesulfonic anhydride (172.5 mg, 0.99 mmol, 2 equiv.). The reaction mixture was kept at *ca*. 0°C until no starting material remained (TLC). Chromatography (hexane–DCM, 5:3) gave the *title compound* **23** (108 mg, 78%) as colourless needles, mp 104–105°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* **26** (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 24

To a stirred solution of 3-hydroxy-5-phenylisothiazole-4-carbonitrile **22** (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 (188.7 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* **24** (148 mg, 84%) as colourless needles, mp 94–95°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* **27** (21 mg, 12%) as colourless needles, mp 190-191°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 25

To a stirred solution of 3-hydroxy-5-phenylisothiazole-4-carbonitrile **22** (100 mg, 0.495 mmol) and triethylamine (69 μl, 0.495 mmol, 1 equiv.) in DCM (2 ml) cooled to *ca*. 0°C was added dropwise trifluoromethanesulfonic anhydride (167 μl, 0.99 mmol, 2 equiv.). The reaction mixture was kept at *ca*. 0°C until no starting material remained (TLC). Chromatography (hexane–DCM, 5:3) gave the *title compound* **25** (142 mg, 86%) as colourless needles, mp 67–68°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 (8 mg, 8%) as colourless needles, mp 233-234°C (from PhH) (lit.,[32] 235-236°C), identical to an authentic sample.

3-Amino-5-phenylpyrazole-4-carbonitrile 31

A stirred mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **3** (100 mg, 0.454 mmol) in 80% hydrazine hydrate (2 ml) was heated to *ca*. 80°C for 1 h. The mixture was poured onto crushed ice (50 g) to form a white precipitate. Filtration gave the title compound **31** (84 mg, 100%) as white powder, mp 194-195°C (from H_2O-EtOH) (lit.,[35] mp 200°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 32

A stirred solution of 3-chloro-5-phenylisothiazole-4-carbonitrile **3** (50 mg, 0.227 mmol) in benzylamine (2 ml) was heated to *ca*. 80°C 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* **32** (55 mg, 90%) as colourless needles, mp 127–128°C (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 ($BnNH^+$, 37), 91 ($PhCH_2^+$, 80), 77 ($C_6H_5^+$, 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-(4-cyano-5-phenylisothiazole)disulfide* **33** (0.5 mg, 1%) as colourless needles, mp 138–139^{o}C (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 (M^+-HS, 52), 369 (M^+-HS_2, 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 ($C_6H_5^+$, 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)* **34** (0.5 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 (M$^+$-HS, 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 29

A stirred mixture of 3-(benzylamino)-5-phenylisothiazole-4-carbonitrile **32** (50 mg, 0.185 mmol), bromine (14.2 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 **29** (33 mg, 90%) as colourless needles, mp 127-128°C (from cyclohexane) (lit.,[34] 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, NH_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 (M^+-HCN, 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* **35** (1 mg, 1%) as colourless needles, mp 169-170^{o}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 (M^+-CO, 7), 218 (1), 201 (2), 184 (3), 127 (3), 105 ($PhCO^+$, 100), 84 (5), 77 ($C_6H_5^+$, 50), 51 (11) (Found: M^+, 305.0646, $C_{17}H_{11}N_3OS$ requires *M*, 305.0623).

3-Iodo-5-phenylisothiazole-4-carbonitrile 28

To a stirred and cooled (*ca.* 0-5 ^{o}C) mixture of iodine (158 mg, 0.623 mmol, 2.5 equiv.) and isoamyl nitrite (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 **29**

(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* **28** (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 ($C_6H_5^+$, 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* **36** (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 (M^+-I, 100), 126 (16), 100 (7), 77 ($C_6H_5^+$, 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-phenylisothiazole-4-carbonitrile)* **37** (0.5 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^+-HN_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 ($C_6H_5^+$, 29), 51 (12) (Found: M^+-HN_2, 384.0381, $C_{20}H_{10}N_5S_2$ requires *M-HN*$_2$, 384.0378).

3,5-Diphenylisothiazole-4-carbonitrile 5

(typical Suzuki conditions for coupling at C-3: see Table 5)

A stirred mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** (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 $Pd(OAc)_2$ (1.8 mg, 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 **5** (34 mg, 80%) as white needles, mp 146-147°C (from cyclohexane) (lit.,[16] 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 (M^+-HS, 4), 218 (6), 159 (3), 135 (7), 134 (4), 131 (7), 121 (4), 103 ($PhCN^+$, 6), 77 ($C_6H_5^+$, 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)* **38** (0.3 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 (M^+-CN, 2), 337 (M^+-HS, 4), 305 (2), 290 (5), 274 (2), 242 (2), 211 (4), 205 (2), 185 (M^{2+}, 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 39

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 3-nitrophenyl-boronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **39**

(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 (M^+-NO_2, 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 40

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 4-methoxy-phenylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **40** (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, OCH_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 41

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 3-methoxy-phenylboronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **41** (84%) as colourless needles, mp 75-76^{o}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, OCH_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 42

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 2-methoxyphenylboronic acid (4 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **42** (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, OC*H*$_3$); 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 43

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 4-tolylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **43** (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 (M^+-CH_3, 12), 243 (M^+-HS, 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 44

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 3-tolylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **44** (91%) as colourless needles, mp 94-95°C (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 (M^+-CH_3, 12), 243 (M^+-HS, 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 45

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 4-chloro-phenylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **45** (82%) as colourless needles, mp 168-169^{o}C (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 46

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 3-chlorophenylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **46** (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 47

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 2-chlorophenylboronic acid (3.5 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **47** (58%) as colourless needles, mp 48-49°C (from cyclohexane); (Found: C, 64.7; H, 3.2; N, 9.4. $C_{16}H_9ClN_2S$ requires C, 64.8; H, 3.1; N, 9.4%); 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 48

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 3-thienyl-boronic acid (3 equiv.), powdered K_2CO_3 and $Pd(OAc)_2$ gave the *title compound* **48** (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 (M^+-HS, 4), 224 (4), 211 (2), 159

(3), 141 (M^+-Ph-C≡C-CN, 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) 38

[using Cu(0) catalysed Ullmann conditions]

A stirred mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** (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 **38** (9.2 mg, 31%) as colourless needles, mp 151–152°C (from cyclohexane/PhH) identical to that described above. Further elucidation (hexane–DCM, 1:4) gave *2-[(4-cyano-5-phenylisothiazol-3-ylthio)-(phenyl)methylene]malononitrile* **49** (10 mg, 34%) as colourless needles, mp 118–119°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 (M^+-CN, 4), 337 (M^+-HS, 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 ($PhCS^+$, 50), 114 (9), 100 (6), 90 (6), 84 (7), 77 ($C_6H_5^+$, 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) 38

[using Pd(0) catalysed Ullmann conditions: see Table 6]

A stirred mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** (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°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 **38** (22.5 mg, 76%) as colourless needles, mp 151–152°C (from cyclohexane/PhH) identical to that described above.

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

(typical Stille conditions for coupling at C-3: see Table 7)

A stirred mixture of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** (30 mg, 0.096 mmol), tributylphenyltin (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°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, 7:3) gave the title compound **5** (23.6 mg, 94%) as white needles, mp 146-147°C (from cyclohexane) identical to that described above.

5-Phenyl-3-(thien-2-yl)isothiazole-4-carbonitrile 50

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 2-(tributyl-stannyl)thiophene and $Pd(OAc)_2$ gave the *title compound* **50** (87%) as colourless needles, mp 122–123°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 (M^+-Ph-C≡C-CN, 18), 135 (3), 121 (9), 109 (M^+-Ph-C≡C-CNS, 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 51

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with 2-(tributyl-stannyl)furan and $Pd(OAc)_2$ gave the *title compound* **51** (91%) as pink needles, mp 99-100°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 (M^+-Ph-C≡C-CN, 31), 121 (65), 114 (15), 99 (14), 96 (10), 93 (10), 77 ($C_6H_5^+$, 21), 69 (7), 51 (9) (Found: M^+, 252.0361, $C_{14}H_8N_2OS$ requires *M*, 252.0357).

5-Phenyl-3-vinylisothiazole-4-carbonitrile 52

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with tributyl(vinyl)-tin and $Pd(OAc)_2$ gave the *title compound* **52** (96%) as colourless needles, mp 28-29°C (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 53

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with tributyl(1-propynyl)tin and $Pd(OAc)_2$ gave the *title compound* **53** (73%) as white powder, mp 85-86°C (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 (M^+-S, 20), 179 (10), 170 (6), 164 (4), 159 (6), 153 (6), 127 (15), 121 (18), 115 (8), 114 (9), 100 (8), 97 (M^+-Ph-C≡C-CN, 21), 89 (6), 77 ($C_6H_5^+$, 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 5 *via* Negishi coupling reaction at C-3

A stirred mixture of 3-iodo-5-phenyl-4-isothiazolecarbonitrile **28** (30 mg, 0.096 mmol), phenylzinc chloride (576 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°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, 7:3) gave the title compound **5** (19.6 mg, 78%) as white needles, mp 146-147°C (from cyclohexane) identical to that described above.

5-Phenyl-3-(phenylethynyl)isothiazole-4-carbonitrile 54

(typical Sonogashira conditions for coupling at C-3: see Table 8)

A stirred mixture of 3-bromo-5-phenylisothiazole-4-carbonitrile **4** (30 mg, 0.11 mmol), triethylamine (30.7 μl, 0.22 mmol, 2 equiv.), CuI (2.1 mg, 10 mol%), $(PPh_3)_2PdCl_2$ (3.9 mg, 5 mol%) and ethynylbenzene (24.2 μl, 0.22 mmol, 2 equiv.) 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 x 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane–DCM, 7:3) gave the *title compound* **54** (27.4 mg, 77%) as pink crystals, mp 122–123°C (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 (M^+-

Ph-C≡C-CN, 59), 143 (9), 127 (M^+-Ph-C≡C-CNS, 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 55

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with triethylamine, CuI, $(PPh_3)_2PdCl_2$ and ethynyltrimethylsilane (1.5 equiv.) gave the *title compound* **55** (70%) as colourless needles, mp 68-69°C (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 (M^+-CH_3, 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-2-ylethynyl)isothiazole-4-carbonitrile 56

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with triethylamine, CuI, $(PPh_3)_2PdCl_2$ and 2-ethynylthiophene (1.2 equiv.) gave the *title compound* **56** (91%) as colourless needles, mp 123–124°C (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 (M^+-Ph-C≡C-CN, 29), 159 (5), 146 (6), 133 (M^+-Ph-C≡C-CNS, 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 57

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with triethylamine, CuI, $(PPh_3)_2PdCl_2$ and 2-ethynylpyridine (1.2 equiv.) gave the *title compound* **57** (92%) as pale yellow needles, mp 120-121°C (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 (M^+-Ph-C≡C-CN, 19), 144 (5), 128 (12), 121 (4), 115 (4), 108 (4), 101 (6), 78 ($C_5H_4N^+$, 13), 51 (9) [Found (CI): MH^+, 288.0584, $C_{17}H_{10}N_3S$ requires *MH*, 288.0595].

3-(Ferrocenylethynyl)-5-phenylisothiazol-4-carbonitrile 58

Similar treatment of 3-iodo-5-phenylisothiazole-4-carbonitrile **28** with triethylamine, CuI, $(PPh_3)_2PdCl_2$ and ethynylferrocene (2 equiv.) gave the *title compound* **58** (100%) as orange-red needles, mp 121-122°C (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 (M^+-C_5H_5, 46), 215 (3), 202 (6), 197 (6), 170 (2), 158 (8), 146 (6), 121 ($C_5H_5Fe^+$, 13), 88 (4), 56 (10) [Found (CI): MH^+, 395.0293, $C_{22}H_{15}FeN_2S$ requires *MH*, 395.0305).