New regiospecific isothiazole C–C coupling chemistry†‡

Irene C. Christoforou and Panayiotis A. Koutentis*

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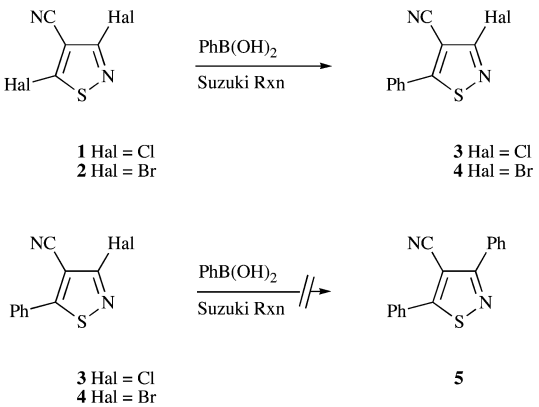
Regioselective palladium catalysed coupling reactions are achieved in good to high yields, starting from either 3,5-dichloro- or 3,5-dibromoisothiazole-4-carbonitriles **1** and **2**, providing 3-halo-5-(hetero/aryl, alkenyl and alkynyl)isothiazoles **3**, **4**, **6**–**9** from Stille couplings, 3-halo-5-(hetero/arylethynyl)-isothiazoles **14**–**19** from Sonogashira and 5,5′-bi(3-chloroisothiazole-4-carbonitrile) (**13**) from an Ullmann type coupling. 3,5-Dibromoisothiazole-4-carbonitrile **2** is more reactive than the dichloroisothiazole-4-carbonitrile **1** and effective enough for Stille, Negishi and Sonogashira couplings. 5,5-Bi(3-chloroisothiazole-4-carbonitrile) (**13**) is prepared by a palladium catalysed Ullmann coupling from 3-chloro-5-iodoisothiazole-4-carbonitrile (**11**). A variety of 3-substituted isothiazoles (3-substituents = Cl, Br, OMs, OTs and OTf) are less reactive and fail to give successful Suzuki couplings at the isothiazole C-3 position. The 3-iodo-5-phenyl-isothiazole-4-carbonitrile (**28**), prepared *via* Sandmeyer iodination, participates successfully in Suzuki, Ullmann type, Stille, Negishi and Sonogashira coupling reactions. All products are fully characterized.

Isothiazoles display wide-ranging biological activity. Commercially important isothiazoles include the Kathon® preservatives, the artificial sweetener saccharin and the antibacterial sulfa drug, sulfasomizole. Isothiazoles are being studied as potential anticancer agents.[1] The chemistry and biological uses of the system has been reviewed extensively.[2–6] Most synthetic strategies involve construction of the isothiazole systems with the desired carbon substituents in place and the routes are therefore product specific.[5] 3,5-Dichloroisothiazole-4-carbonitrile (**1**)[7] is readily available and, in combination with the development of C–C coupling methodology,[8,9] is a potentially useful starting material for the construction of more complex isothiazoles. Surprisingly little, however, has appeared on isothiazole C–C coupling chemistry.[10] Palladium catalysed cross-coupling reactions were reported for several bromo- and iodoisothiazoles to give alkenyl and alkynyl substituted isothiazoles.[11,12] Negishi and Suzuki cross couplings have also been demonstrated on 3-benzyloxy-5-iodoisothiazoles.[13] Furthermore, an attempted Heck coupling between 5-bromo-3-methylisothiazole and styrene gave the 3,3′-dimethyl-5,5′-biisothiazole in almost quantitative yield.[14] We have already shown[15] that 3,5-dichloro- and 3,5-dibromoisothiazole-4-carbonitrile (**1** and **2**)[7] react regiospecifically with either phenylboronic acid or phenyltrifluoroborate to give in high yields 3-halo-5-phenylisothiazole-4-carbonitriles **3** and **4**, respectively. Under analogous reaction conditions both the 3-chloro- and the 3-bromo-5-phenylisothiazole-4-carbonitrile (**3** and **4**) failed to give the desired 3,5-diphenylisothiazole-4-carbonitrile (**5**)[16] (Scheme 1).[15]



Scheme 1

As a logical extension of our earlier work we now present successful regioselective Stille,[17] Negishi,[18] Sonogashira[19] and Ullmann type[20] C–C coupling reactions for 3,5-dihaloisothiazoles and furthermore the work is extended to show for the first time Suzuki,[21] Stille, Negishi, Ullmann and Sonogashira couplings at the C-3 position of 3-halo-5-phenylisothiazole-4-carbonitrile.

Stille coupling reaction at C-5

Initial attempts at Stille coupling of 3,5-dichloroisothiazole-4-carbonitrile (**1**) and tributylphenyltin in toluene with $Pd(OAc)_2$ as catalyst could not be driven to completion and most of the starting isothiazole was recovered. The use of more polar solvent such as THF or MeCN at reflux improved the product ratio (by TLC) but even with excess organotin reagent, complete consumption of starting isothiazole was not achieved. However, complete consumption of the starting isothiazole was possible with the use of tributylphenyltin (1 equiv.) in DMF at 100 °C for 72 h and gave 3-chloro-5-phenylisothiazole-4-carbonitrile (**3**) in moderate yield (68%). The use of excess tributylphenyltin (2 equiv.) under

Department of Chemistry, University of Cyprus, P.O. Box 20537, 1678 Nicosia, Cyprus. E-mail: koutenti@ucy.ac.cy; Fax: 00357 22 892809; Tel: 00357 22 892783

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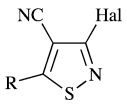
‡ Dedicated to Professor Charles W. Rees on the occasion of his 79th birthday.

Table 1 Stille coupling reaction of 3,5-dihaloisothiazole-4-carbonitriles **1** and **2** with $Pd(OAc)_2$ (5 mol%) at 20 °C with heating to 100 °C



3,**4**,**6**–**9**

Hal	R	$RSnBu_3$ (equiv.)	Solvent	Time/min	Yield (%)
Cl	Ph	1	DMF	72 h	**3** (68)
Cl	Ph	2	DMF	23 h	**3** (84)
Br	Ph	1.2	MeCN	20	**4** (93)
Br	Ph	1.2	DMF	20	**4** (90)
Br	2-Furyl	1	MeCN	6 h	**6** (86)
Br	2-Furyl	1.2	MeCN	20	**6** (100)
Br	2-Thienyl	1	MeCN	10	**7** (93)
Br	Vinyl	1.2	MeCN	45	**8** (94)
Br	Propynyl	1.2	MeCN	30	**9** (86)
Br	Bu_3Sn	1	MeCN	24 h	[a]

[a] No reaction after 24 h.

the same conditions gave a shorter reaction time (23 h) and an improved yield (84%). 3,5-Dibromoisothiazole-4-carbonitrile (**2**), however, was more reactive and complete consumption of starting isothiazole was observed in both MeCN and DMF. The reaction time and the product yield were also improved. Using MeCN as solvent, $Pd(OAc)_2$ as catalyst and a variety of commercially available organotin reagents aryl, heteroaryl, vinyl and propynyl C-5-substituted isothiazoles **3**, **4**, **6**–**9** were prepared (Table 1). No trace of the 3,5-disubstituted isothiazoles was observed by TLC.

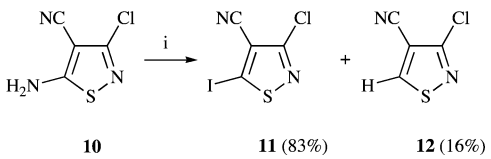
It is worthy of note that the 5-(thien-2-yl)isothiazole (**7**) was synthesised in high yield while, according to our previous work,[15] Suzuki methodology using 2-thienylboronic acid failed to introduce the 2-thienyl substituent at the C-5 position. These results demonstrate that the Stille reaction can be used for regioselective synthesis of C-5-substituted isothiazoles but there are drawbacks; organotin reagents and their residues are toxic,[22] and these residues could not be removed easily by chromatography. Attempts to extract the organotin side products with pentane or hexane[23] failed because the isothiazole products were also soluble. The organotin residues were finally removed after recrystallisation of the isothiazole products from cyclohexane. Another disadvantage of the Stille coupling reaction was the failure to synthesise the 5,5′-biisothiazole **13** using the bis(tributyltin) reagent. This 5,5′-biisothiazole **13** was prepared using palladium catalysed Ullmann type homo-coupling (see below).

Negishi coupling reaction at C-5

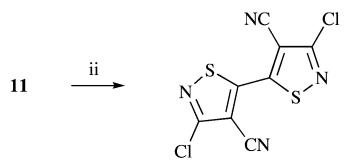
The organozinc reagent used in Negishi couplings is non-toxic and product contamination does not occur readily, and therefore the Negishi coupling reaction is potentially a cleaner alternative to the Stille coupling. Negishi couplings have been conducted with 5-iodoisothiazoles[13] but there are to date no reports of coupling reactions with the less reactive chloro- or bromoisothiazoles. Treatment of 3,5-dichloro- and 3,5-dibromoisothiazole-4-carbonitrile (**1** and **2**) with phenylzinc chloride (1.5 equiv.) and bis(triphenylphosphine)palladium (II) dichloride (5 mol%) in refluxing THF (25 min) gave the desired products **3** and **4** in 84 and 90% yield, respectively. The use of less phenylzinc chloride (1 equiv.) led to incomplete consumption of starting isothiazole; the use of 2 equiv., however, did not affect the product yields or reaction times. As with the Stille and Suzuki reactions no trace of the 3,5-diphenylisothiazole-4-carbonitrile (**5**) was observed. The synthesis of derivatives was not attempted since arylzinc halides have limited commercial availability and their preparation was less attractive.

Ullmann type homocoupling at C-5

Only one example of the 4,4′-biisothiazole[11] and one of the 5,5′-biisothiazole[14] systems have appeared in the literature as byproducts of Heck cross coupling reactions. Attempts to prepare the 5,5′-biisothiazole starting from either 3,5-dichloro- or 3,5-dibromoisothiazole-4-carbonitrile (**1** and **2**) using palladium acetate gave predominantly unreacted starting material. Aryl iodides are known to be more reactive towards homocoupling reactions.[9] Several 5-iodoisothiazoles are known and have been prepared from isothiazoles not substituted at C-5 using both butyllithium and iodine[24] or periodic acid and iodine,[25] or by nucleophilic displacement of 5-bromoisothiazoles[26] or 5-hydrazinoisothiazoles[27] using NaI. Sandmeyer iodination of the readily available 5-amino-3-chloroisothiazole-4-carbonitrile (**10**)[7] was not, however, reported. Diazotization[28] of 3-, 4- and 5-aminoisothiazoles has been reported using nitrosyl tetrafluoroborate in a 1 : 1 mixture of acetic and propionic acids or by treating the amine with sodium nitrite and concentrated acids.[29] Sandmeyer iodination has also been achieved for 4-aminoisothiazoles using standard diazotization conditions.[30] The successful Sandmeyer iodination of 3-amino-5-phenylisothiazole-4-carbonitrile (**29**) using isoamyl nitrite in iodine saturated MeCN (see below) was modified to achieve Sandmeyer iodination at C-5. Treatment of an iodine saturated MeCN solution of the 5-aminoisothiazole **10** with isoamyl nitrite at *ca.* 20 °C gave the 3-chloro-5-iodo-isothiazole-4-carbonitrile **11** (55%) together with a trace of 3-chloroisothiazole-4-carbonitrile **12**. The yield of the 5-iodoisothiazole **11** was significantly improved if the reaction was conducted at higher temperatures in either refluxing MeCN (*ca.* 80 °C, 79% yield) or in refluxing nitromethane (*ca.* 100 °C, 83% yield) (Scheme 2).



10 **11** (83%) **12** (16%)



13

Scheme 2 Reagents and conditions: (i) I_2 (3 equiv.), $MeNO_2$, *i*-amylONO (4 equiv.), 120 °C, 1 h; (ii) $Pd(OAc)_2$ (5 mol%), DMF, 140 °C, 27.5 h, 86%, Ar; or $Pd(OAc)_2$ (5 mol%), (*o*-Tolyl)$_3$P (5 mol%), DMF, 140 °C, 9 h, 72%, Ar; or $Pd(OAc)_2$ (1 equiv.), DMF, 140 °C, 2.5 h, 85%, Ar.

With catalytic $Pd(OAc)_2$ (5 mol%) in DMF at 140 °C the 5-iodoisothiazole (**11**) could be converted into

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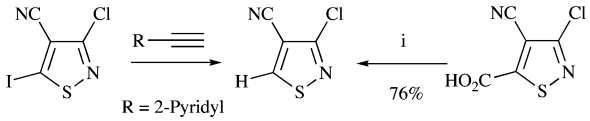
5,5′-bi(3-chloroisothiazole-4-carbonitrile) (**13**) in 86% yield although the reaction required heating for over 27 h. The addition of catalytic amount of tri-*o*-tolylphosphine as ligand significantly reduced the reaction time (9 h) but gave a slightly lower yield (72%). A faster reaction time (2.5 h) was observed when 1 equivalent of $Pd(OAc)_2$ was used and this had no adverse effect on the product yield (Scheme 2).

Sonogashira coupling reaction at C-5

The reaction of 3,5-dichloroisothiazole-4-carbonitrile (**1**) with phenylacetylene, triethylamine (2 equiv.), bis(triphenylphosphine)palladium(II) dichloride (5 mol%) and copper iodide (10 mol%) was investigated in several solvents. MeCN and DMF were suitable with the former giving slightly improved reaction times and yields. In toluene at least 2 equivalents of phenylacetylene were required to drive the reaction with the 3,5-dichloroisothiazole-4-carbonitrile (**1**) to completion. The more reactive 3,5-dibromoisothiazole-4-carbonitrile (**2**), however, could be converted completely to the 5-(phenylethynyl)isothiazole (**14**) even in toluene with only 1.2 equivalents of phenylacetylene. Starting with 3,5-dibromoisothiazole-4-carbonitrile (**2**) the 3-thienyl, ferrocenyl and trimethylsilyl derivatives **16**, **18** and **19** of 5-ethynylisothiazoles were synthesized in good yields, although the trimethylsilyl derivative **19** suffered some desilylation to afford 3-bromo-5-ethynylisothiazole-4-carbonitrile (**20**; Table 2).

The reaction involving the 3,5-dibromoisothiazole-4-carbonitrile (**2**) with 2-pyridinylacetylene (1.2 equiv.) failed to reach completion even with additional equivalents of 2-pyridinylacetylene (up to 3 equiv.) after 24 h. The reaction was therefore repeated with 3-chloro-5-iodoisothiazole-4-carbonitrile (**11**), but when run in either DMF or MeCN the starting isothiazole was consumed rapidly (1 h) to give only 3-chloroisothiazole-4-carbonitrile (**12**) as major product (38%). The structure of 3-chloroisothiazole-4-carbonitrile (**12**) was confirmed by thermal decarboxylation of the known 3-chloro-4-cyanoisothiazole-5-carboxylic acid (**21**)[31] at 200 °C (Scheme 3).



11 **12** **21**

Scheme 3 Reagents and conditions: (i) sealed tube, 200 °C, 15 min, 76%.

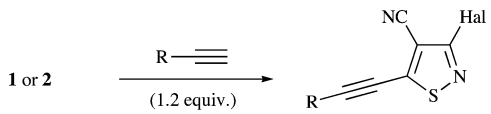
When the reaction of 3-chloro-5-iodoisothiazole-4-carbonitrile (**11**) and 2-pyridylacetylene (2 equiv.) was performed in toluene the desired product was obtained in moderate yield together with 3-chloroisothiazole-4-carbonitrile (**12**). A similar result was obtained when phenylacetylene (2 equiv.) was used. Increasing the equivalents of 2-pyridylacetylene reduced the reaction time but did not significantly change the product yields (Table 3).

Clearly under the reaction conditions the 5-iodoisothiazole **11** was labile to reductive hydrodeiodination however, the equivalent Sonogashira reactions at the C-3 position (see Table 8) did not show any hydrodeiodination and gave high yields of the desired 3-ethynylisothiazole.

Coupling at the less reactive isothiazole C-3

An earlier attempt to achieve the Suzuki coupling reaction at the C-3 position of 3-chloro- and 3-bromo-5-phenylisothiazole-4-carbonitrile (**3** and **4**) resulted in the unexpected synthesis of 3-phenoxy-5-phenylisothiazole-4-carbonitrile and gave no isolable trace of the desired 3,5-diphenylisothiazole-4-carbonitrile (**5**).[15] This result indicated the need for more reactive 3-substituted isothiazoles. For this purpose, the 3-mesylate, tosylate, and triflate isothiazoles **23**, **24** and **25** were synthesized (Table 4) starting from the readily available 3-hydroxy-5-phenylisothiazole-4-carbonitrile (**22**).[32] In addition 2-mesyl, and 2-tosylisothiazol-3-one (**26** and **27**) were isolated as secondary minor byproducts.

Table 2 Sonogashira coupling reaction of 3,5-dihaloisothiazole-4-carbonitriles **1** and **2** with $(PPh_3)_2PdCl_2$ (5 mol%), Et_3N (2 equiv.) CuI (10 mol%), 20 °C with heating to 100 °C

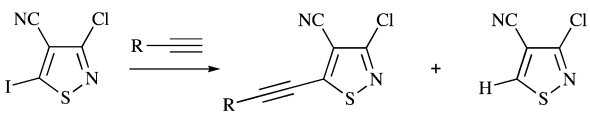


14–19

Hal	R	R–≡ (equiv.)	Solvent	Time/h	Yields (%)
Cl	Ph	1.2	PhMe	24	**14**[a]
Cl	Ph	2.0	PhMe	5.25	**14** (76)
Cl	Ph	1.2	MeCN	1	**14** (91)
Cl	Ph	1.2	DMF	1.5	**14** (80)
Br	Ph	1.2	PhMe	1	**15** (86)
Br	Ph	1.2	MeCN	1	**15** (90)
Br	Ph	1.2	DMF	1	**15** (86)
Br	3-Thienyl	1.2	MeCN	0.5	**16** (77)
Br	2-Pyridyl	1.2	PhMe	24	**17**[a]
Br	2-Pyridyl	1.2	MeCN	24	**17**[a]
Br	2-Pyridyl	1.2	DMF	24	**17**[a]
Br	Ferrocenyl	1.2	MeCN	1.5	**18** (88)
Br	TMS	1.2	PhMe	24	**19**[a]
Br	TMS	1.5	PhMe	0.25	**19** (69)[b]
Br	TMS	1.2	MeCN	24	**19**[a]
Br	TMS	1.2	DMF	24	**19**[a]

[a] Incomplete reaction. [b] 3-Bromo-5-ethynylisothiazole-4-carbonitrile (**20**) was also isolated in 14% yield.

Table 3 Reaction of 3-chloro-5-iodoisothiazole (**11**; 0.113 mmol) with either 2-pyridylacetylene or phenylacetylene in PhMe (2 ml) with Et_3N (2 equiv.), $(PPh_3)_2PdCl_2$ (5 mol%), CuI (10 mol%) at 20 °C with heating to 100 °C

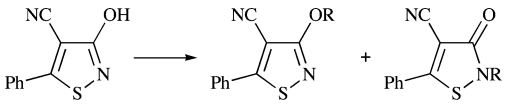


11 **17** (R = 2-Pyridyl) **14** (R = Ph) **12**

R (equiv.)	Time/min	Yields (%)	
2-Pyridyl (1.2)	[a]		
2-Pyridyl (2)	30	**17** (54)	**12** (40)
2-Pyridyl (3)	15	**17** (49)	**12** (43)
Ph (2)	35	**14** (50)	**12** (36)

[a] Incomplete reaction after 24 h.

Table 4 Reaction of 3-hydroxy-5-phenylisothiazole-4-carbonitrile (**22**) with particular reagents (2 equiv.) in DCM at 0–10 °C

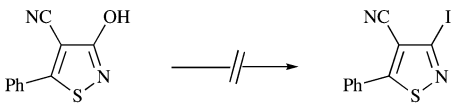


22 **23–25** **26–27**

Reagent (2 equiv.)	Et_3N (equiv.)	Time/h	R	Yields (%) **23–25**	**26–27**
Ms_2O	1	0.3	Ms	**23** (78)	**26** (16)
TsCl	2	1	Ts	**24** (84)	**27** (12)
Tf_2O	1	0.5	Tf	**25** (86)[a]	—

[a] Based on recovered 3-hydroxyisothiazole **22** (8%).

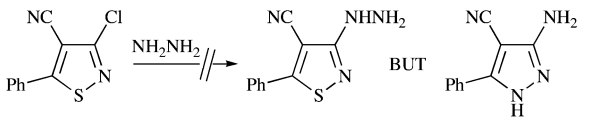
Early studies on the acylation and sulfonylation of 3-hydroxyisothiazoles show a kinetic preference for the formation of the acyloxy and sulfonyloxyisothiazole due to steric reasons; on standing, however, the acyl (but not the sulfonyl) group migrates to the thermodynamically more stable *N*-acylisothiazolone.[33] The *O*-sulfonylated isothiazoles **23**–**25** showed no tendency to isomerisation to their sulfonamide isothiazolone derivatives, but were unfortunately hydrolytically labile in MeCN (and more so in DMF) to a variety of Suzuki reaction conditions, affording the starting 3-hydroxyisothiazole **22**. The compounds were stable to hydrolysis in 1,4-dioxane but unfortunately gave mainly unreacted starting material after 24 h at reflux. Therefore, the synthesis of the previously unknown 3-iodo-5-phenylisothiazole-4-carbonitrile (**28**) was targeted.



22 **28**

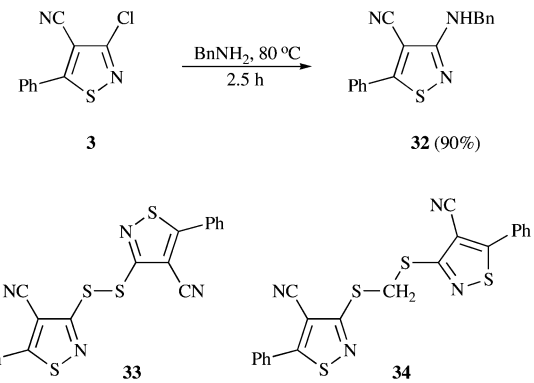
3-Iodoisothiazoles have, to our knowledge, not been reported in the literature. Attempts to convert the 3-hydroxyisothiazole **22** into the 3-iodoisothiazole **28** using neat HI, excess of KI–I_2 in refluxing THF and Ph_3P–I_2 in DMF at 50 °C all failed and gave only unreacted 3-hydroxyisothiazole **22**. The Sandmeyer iodination route was then investigated but this required the synthesis of 3-amino-5-phenylisothiazole-4-carbonitrile (**29**) which has been previously prepared from the reaction of potassium 2,2-dicyano-1-phenylethenethiolate with chloramine.[34] Our strategy, which attempts to avoid product-specific synthetic routes, required the use of the prepared 3-halo-5-phenylisothiazoles **3** or **4**. Unlike the halogen at C-5, which can be displaced readily by anhydrous ammonia in refluxing THF,[7] nucleophilic displacement of the halogen at C-3 requires vigorous conditions. Treatment of 3-chloro-5-phenylisothiazole-4-carbonitrile (**3**) with aqueous ammonia, anhydrous ammonia, potassium phthalimide or sodamide with various solvents and temperatures either failed to react or gave very complex mixtures. An attempt to displace the 3-chloro substituent with hydrazine hydrate or anhydrous hydrazine, in order to prepare the 3-hydrazino-5-phenylisothiazole-4-carbonitrile (**30**), gave instead 3-amino-5-phenyl-1*H*-pyrazole-4-carbonitrile (**31**) in quantitative yield (Scheme 4). Pyrazole **31** has previously been prepared by treating phenylmethylenemalononitrile with hydrazine.[35] Whilst the analogous transformation of isoxazoles into pyrazoles is well documented,[36,37] only one similar report has appeared on the transformation of isothiazoles into pyrazoles using arylhydrazines.[38]

Halogens at the isothiazole C-3 position are known to be labile to alkylamines.[39] Treatment of 3-chloroisothiazole **3** with stoichiometric or excess benzylamine in a variety of solvents (PhMe, PhCl, DCM, THF, DMF, EtOH) gave only a trace of the 3-benzylamino-5-phenylisothiazole-4-carbonitrile (**32**), but when the reaction was repeated in neat benzylamine at 80 °C, the desired product was isolated in 90% yield (Scheme 5). At higher temperatures (150 °C) the yield of **32** was reduced and a second product 3,3′-bis(4-cyano-5-phenylisothiazole-4-carbonitrile) (**33**) was observed indicating partial ring cleavage of the isothiazole possibly initiated by nucleophilic attack of benzylamine on the ring sulfur atom.



3 **30** **31** (100%)

Scheme 4



3 **32** (90%) **33** **34**

Scheme 5

Dimeric isothiazoledisulfides have been previously observed as major products during electrosynthesis of isothiazoles starting from 3-aryl-2-phenylsulfonylpropenonitriles.[40] Disulfide formation was proposed to arise from the oxidative dimerisation of the analogous isothiazole-3-thiolate and it is possible that this also occurs here. Extraction of the benzylamine reaction mixture with hot dichloromethane (DCM) afforded a trace of a new compound, bis(isothiazol-3-ylthio)methane (**34**), and this could have arisen from reaction of the proposed isothiazole-3-thiolate with the DCM.

Cleavage of the benzyl group of 3-(*N*-benzylamino)isothiazole (**32**) was not possible using mild reductive conditions (H_2, Pd/C) or with strong mineral acids possibly due to the amidine nature of the 3-benzylamino nitrogen. A recent publication on the debenzylation of amides using NBS and catalytic AIBN offered an alternative method.[41] With the 3-benzylaminoisothiazole **32**, however, a complex reaction was observed. Replacing the NBS

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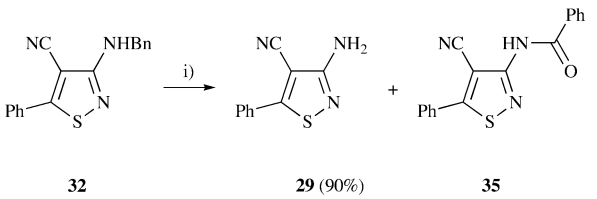
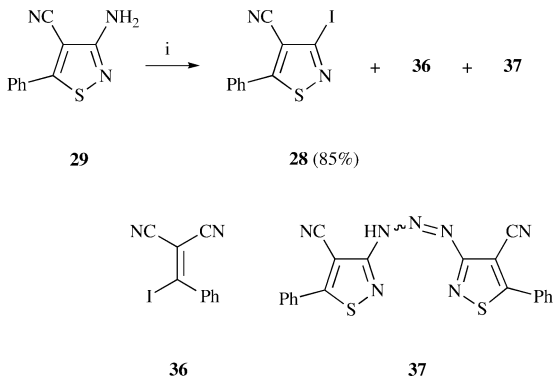
with dibromine gave a much cleaner reaction and the desired 3-aminoisothiazole **29** was isolated in high yield together with traces of 3-(*N*-benzamido)-5-phenylisothiazole-4-carbonitrile (**35**) and benzaldehyde (Scheme 6).



32 **29** (90%) **35**

Scheme 6 Reagents and conditions: (i) Br_2 (1.5 equiv.), AIBN (0.2 equiv.), PhH–H_2O (2 : 1), 0.5 h, 80 °C.

Diazotization of the 3-aminoisothiazole **29** could not be achieved using sodium nitrite with a variety of acids (H_2SO_4, AcOH, HI) and, similarly, nitrous acid (HNO_3–$Na_2S_2O_5$) also failed to affect diazotization. In nearly all cases the 3-aminoisothiazole **29** decomposed or was converted into mainly polar products, *e.g.* 3-hydroxy-5-phenylisothiazole-4-carbonitrile (**22**). The use of basic solvents such as pyridine or quinoline has been shown to assist in such cases,[42] but the 3-aminoisothiazole **29** was isolated unchanged. Nitrosyl tetrafluoroborate in a 1 : 1 mixture of acetic and propionic acids gave only traces of the desired 3-iodoisothiazole **28** (by TLC). Similar difficulties in Sandmeyer reactions with the 3-aminoisothiazole **29** have been observed.[32] Iodination of arylamines is known to proceed well under aprotic diazotization conditions using isoamyl nitrite in the presence of iodine[43] and similar conditions gave the 3-iodo-5-phenylisothiazole-4-carbonitrile (**28**) in good yield together with two minor by-products the methylenemalononitrile **36** and the triazene **37** (Scheme 7). The reaction was optimized with respect to iodine and isoamyl nitrite and required dropwise addition of an MeCN solution of the 3-aminoisothiazole **29** into an iodine-saturated MeCN solution of isoamyl nitrite.



29 **28** (85%)

36 **37**

Scheme 7 Reagents and conditions: (i) *i*-AmylONO (4 equiv.), I_2 (2.5 equiv.), MeCN, 5 °C, 0.5 h.

Suzuki coupling reactions at C-3

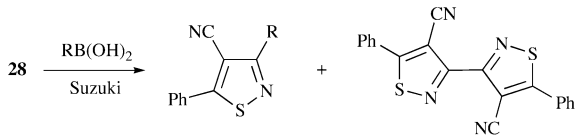
The synthesis of 3-iodo-5-phenylisothiazole-4-carbonitrile (**28**) provided a new opportunity to attempt the Suzuki reaction at the isothiazole C-3 position. The conditions [PhMe, KF, 18-Crown-6, $Pd(OAc)_2$] that were successfully used for Suzuki couplings at C-5[15] did not work with the 3-iodoisothiazole **28**. Replacing toluene with dry and degassed DMF did, however, afford for the first time 3,5-diphenylisothiazole-4-carbonitrile (**5**) in 34% yield together with a minor amount of 3,3′-bi(5-phenylisothiazol-4-carbonitrile) (**38**).

In light of this promising result the reaction was optimized first with respect to base, then with respect to boronic acid and finally with respect to catalyst in DMF. Strong bases, such as KOH and Cs_2CO_3, led to decomposition of the starting isothiazole **28** whilst Li_2CO_3, $KHCO_3$ and KF required longer reaction times. Na_2CO_3 and K_2CO_3 both afforded reasonable yields of the diphenylisothiazole **5** in less than 24 h. Of the two carbonates K_2CO_3 gave the higher yields and was chosen for further optimization studies. It was found that freshly and finely powdered (pestle and mortar) K_2CO_3 greatly reduced the reaction times but also the product yields. Similar surface area effects on the reaction rate have been reported for Buchwald–Hartwig aminations with Cs_2CO_3.[44] The equivalents of K_2CO_3 were then carefully screened. With phenylboronic acid (2 equiv.), $Pd(OAc)_2$ (5 mol%), DMF at 140 °C for 2.5 h under an argon atmosphere with 1.5 equivalents of powdered K_2CO_3 gave a consistent 70% yield of the diphenylisothiazole **5** and traces of the biisothiazole **38**. More than (up to 3.5 equiv.) or less than (down to 0.5 equiv.) 1.5 equivalents of powdered K_2CO_3 was detrimental to both yield and reaction time. The equivalents of phenylboronic acid were then screened; with 3 equivalents of $PhB(OH)_2$ the reaction time was reduced to 50 min and yields of the diphenylisothiazole **5** raised to 80%. A further increase in phenylboronic acid (4 equiv.) did not change either reaction times or product yields. The DMF was then examined to determine tolerances in water, air and heating. Wet DMF gave marginally lower yields but the reaction time was unaffected (50 min). Dry but non-degassed DMF gave similar results. A significant reduction of the reaction time to 10 min was observed when the oil bath was preheated to 140 °C, although the product yields were marginally reduced (70%). In light of these results with the iodo compound the 3-chloro- and 3-bromo-5-phenylisothiazole-4-carbonitriles **3** and **4** were reinvestigated; however only the 3-bromoisothiazole **4** showed any of the 3,5-diphenylisothiazole **5** (by TLC) and the reaction was slow and could not be driven to completion.

Finally a range of commercially available catalysts was investigated; interestingly three catalysts, $(PPh_3)_2PdCl_2$, $(PPh_3)_4Pd$ and $(dppf)PdCl_2$ showed no formation of 3,3′-bi(5-phenylisothiazole-4-carbonitrile) (**38**) but gave significantly lower yields of the diphenylisothiazole **5** (61–68%) and longer reaction times. $(MeCN)_2PdCl_2$, $(PhCN)_2PdCl_2$, and $PdCl_2$ gave both long reaction times (3–4 h) and reduced yields (60–61%) of the diphenylisothiazole **5** together with significant traces of the biisothiazole **38** (3–5%) whilst $(dba)_3Pd_2$ gave comparable yields to $Pd(OAc)_2$ but at a cost of reaction time (2.5 h).

Having partially optimized the reaction conditions for Suzuki coupling reaction at the isothiazole C-3 position a variety of 3-arylsubstituted isothiazoles **5**, **39**–**48** were synthesized (Table 5). The electron deficient 3-nitrobenzeneboronic acid gave a relatively low yield (58%) of the desired isothiazole **39** despite the addition of further boronic acid. Electron rich arylboronic acids ($MeOC_6H_4$, and 3-thienyl) gave higher yields. Sterically hindered boronic acids such as 2-tolyl- and 2-chloro-benzeneboronic acids gave either a low yield of the desired isothiazole or could not be driven to completion within 24 h. As with the C-5 coupling

Table 5 Reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile (**29**) with $RB(OH)_2$ (3–4 equiv.), powdered K_2CO_3 (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), in dry degassed DMF at 20 °C and heated to 140 °C under Ar



5, **39**–**48** **38**

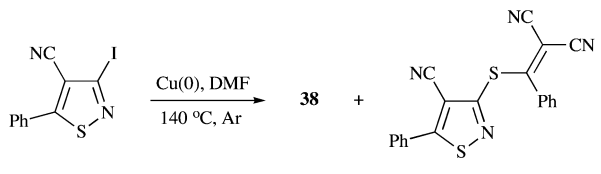
R	$RB(OH)_2$ (equiv.)	Time/h	Yields (%) **5**, **39**–**48**	**38**
Ph	3	1	**5** (80)	1
3-$NO_2C_6H_4$	3.5	1.17	**39** (58)	6
4-$MeOC_6H_4$	3.5	1.75	**40** (95)	5
3-$MeOC_6H_4$	3	1	**41** (84)	6
2-$MeOC_6H_4$	4	0.34	**42** (95)	5
4-Tol	3.5	0.42	**43** (75)	Nd[c]
3-Tol	3.5	0.5	**44** (91)	4
2-Tol	4	24	[a]	[a]
4-ClC_6H_4	3.5	0.34	**45** (82)	4
3-ClC_6H_4	3.5	0.34	**46** (75)	3
2-ClC_6H_4	3.5	0.34	**47** (58)	7
3-Thienyl	3	0.5	**48** (91)	2
2-Thienyl	3	24	[b]	[b]
Me	3	24	[b]	[b]

[a] Incomplete reaction after 24 h. [b] No reaction. [c] Nd = no data.

chemistry the 2-thienyl-boronic acid failed to react presumably due to protodeboronation of the boronic acid. However unlike the coupling at C-5, methylboronic acid failed to react at C-3. 3,3′-Biisothiazole **38** was formed in trace quantities in all reactions.

Ullmann type homocoupling reaction at C-3

Whilst the monocyclic 4,4′- and 5,5′-biisothiazoles have been reported,[11,14] only the 3,3′-bibenzoisothiazole moiety has appeared in the literature.[45] Therefore an independent synthesis of the monocyclic 3,3′-biisothiazole **38** was attempted *via* the traditional copper catalysed Ullmann reaction starting from the 3-iodoisothiazole **28**. Treatment of the 3-iodoisothiazole **28** with either stoichiometric or excess copper powder in refluxing MeCN, benzene, toluene or xylene gave slow reactions and only traces of product (by TLC). The reaction went to completion when DMF was used as solvent but the dimer **38** was isolated in moderate yield (31%) together with an unexpected isomeric by-product **49** (34%) which could only arise from degradation of another isothiazole (Scheme 8). A similar 3-[(*Z*)-(2-cyano-2-phenylethenyl)thio]-5-phenylisothiazole was isolated during electrosynthesis of isothiazoles starting from 3-aryl-2-phenylsulfonylpropenonitriles.[40]



28 **49**

Scheme 8

Table 6 Reaction of 3-iodo-5-phenylisothiazole-4-carbonitrile (**28**) with $Pd(OAc)_2$, in dry DMF, under Ar

$Pd(OAc)_2$ (equiv.)	Temp. (°C)	Time/h	Yield **38** (%)
0.05	20–140	24	[a]
0.5	20–140	5d	52[b]
1	20–140	16.5	76
1	140[c]	5	74
1	170[c]	12 min	57
1	200[c]	5 min	56

[a] Trace of dimer **38** (by TLC) after 24 h. [b] Yield of **38** is based on recovered 3-iodoisothiazole **28** (6%). [c] In microwave reactor, 255 W, ramp time 10 s.

Replacing the copper catalyst with $Pd(OAc)_2$ (5 mol%) in dry degassed DMF failed to give more than a trace of the 3,3′-biisothiazole **38**. The use of triarylphosphine ligands Ph_3P or (*o*-toly)$_3$P, reductive conditions (Zn–H_2O), basic conditions (Hünig's base) or the introduction of either Et_4NBr or CuI did not improve the yield of the 3,3′-biisothiazole **38**. The reaction times and product yields were improved with additional $Pd(OAc)_2$ and after 16.5 h with 1 equiv. of $Pd(OAc)_2$ the desired product **38** was obtained in 76% yield (Table 6). A significant decrease in the reaction time was observed under microwave conditions at 140 °C although the yield remained unchanged. Harsher microwave conditions, at 170 or 200 °C, provided a further decrease in the reaction time but the product yield dropped to 56–57%.

Several other commercial palladium catalysts were compared with $Pd(OAc)_2$ but no appreciable benefits could be discerned. $(MeCN)_2PdCl_2$, $(PhCN)_2PdCl_2$ and $PdCl_2$ (1 or 2 equiv.) led to complete consumption of the starting iodoisothiazole **28** but gave lower yields (32–71%) compared to $Pd(OAc)_2$ and a complex reaction mixture was observed with $(PPh_3)_2PdCl_2$ while $(dba)_3Pd_2$ gave no trace of biisothiazole **38**; with $(dppf)PdCl_2$ no reaction was observed.

Stille coupling reaction at C-3

The readiness of 3-chloro-, 3-bromo- and 3-iodoisothiazoles **3**, **4**, and **28** to participate in Stille coupling reaction was investigated. Treatment of either 3-chloro- or the 3-bromo-5-phenylisothiazole-4-carbonitrile (**3** or **4**) with tributylphenyltin (up to 3 equiv.) gave only incomplete reactions (by TLC) even after 24 h. On the other hand addition of tributylphenyltin (1 equiv.) and $Pd(OAc)_2$ (5 mol%) to 3-iodo-5-phenylisothiazole-4-carbonitrile (**28**) in DMF at 100 °C gave the desired 3,5-diphenylisothiazole **5** in 94% yield together with traces of the 3,3′-biisothiazole **38**. Under these reaction conditions heteroaryl, including the 2-thienyl, vinyl and propynyl isothiazole derivatives **50**–**53**, were synthesised in high yields (Table 7). In all the reaction mixtures the 3,3′-biisothiazole **38** was observed in trace quantities. Recrystallisation (cyclohexane) of the products isolated by chromatography was sufficient to remove the toxic organotin residues.

Negishi coupling reaction at C-3

A comparison of the reactivity of the 3-halo-5-phenylisothiazole-4-carbonitriles **3**, **4** and **28** with respect to the Negishi coupling reactions showed that in the presence of bis(triphenylphosphine)palladium(II) dichloride (5 mol%) in dry degassed DMF the 3-chloroisothiazole **3** failed to react completely even

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Table 7 Reaction of 3-halo-5-phenylisothiazole-4-carbonitriles **3**, **4** and **28** with $RSnBu_3$ and $Pd(OAc)_2$ (5 mol%) in dry degassed DMF at 20 °C heated to 100 °C, under Ar

				Yields (%)	
Hal	R	$RSnBu_3$ (equiv.)	Time/h	**5**, **50**–**53**	**38**
Cl	Ph	3	24	**5**[a]	[a]
Br	Ph	3	24	**5**[a]	[a]
I	Ph	1	1.34	**5** (94)	Trace
I	2-Thienyl	1	0.5	**50** (87)	Trace
I	2-Furyl	1	1.67	**51** (91)	Trace
I	Vinyl	1	24	**52** (96)	Trace
I	Propynyl	1	24	**53** (73)	Trace

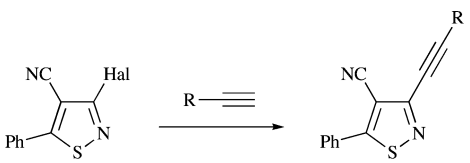
[a] Incomplete reaction (by TLC) after 24 h.

when an excess of phenylzinc chloride (3 equiv.) was used. Under analogous conditions both the 3-bromoisothiazole **4** and 3-iodoisothiazole **28** afforded the 3,5-diphenylisothiazole-4-carbonitrile **5** in 74 and 78% yields, respectively, in only 20 min. The use of less than 3 equivalents of phenylzinc chloride resulted in incomplete reactions in all cases.

Sonogashira coupling reaction at C-3

The three 3-haloisothiazoles **3**, **4** and **28** were investigated with respect to the Sonogashira reaction using an alkyne, triethylamine (2 equiv.), bis(triphenylphosphine)palladium(II) dichloride (5 mol%) and copper iodide (10 mol%) in dry degassed DMF and the order of reactivity was determined to follow I > Br > Cl. 3-Chloro-5-phenylisothiazole-4-carbonitrile (**3**) gave incomplete reactions, even when an excess of phenylacetylene (3 equiv.) was used. In contrast, 3-bromo- and 3-iodoisothiazoles **4** and **28** gave complete reactions with 2 and 1 equivalent of phenylacetylene, respectively. Several 3-substituted-acetyleneisothiazoles **54**–**58** were prepared from the 3-iodoisothiazole **28** in good yields (Table 8). Surprisingly, and in contrast with the 3-chloro-5-iodoisothiazole-4-carbonitrile (**11**), both the TMS and 2-pyridyl derivatives **55** and **57** were prepared in excellent yield.

Table 8 Reaction of 3-halo-5-phenylisothiazole-4-carbonitriles **3**, **4** and **28** with Et_3N (2 equiv.), $(PPh_3)_2PdCl_2$ (5 mol%), CuI (10 mol%) in dry degassed DMF at 20 °C heated to 100 °C, under Ar



3,**4** and **28** **54-58**

Hal	R	R–≡ (equiv.)	Time/h	Yield (%)
Cl	Ph	1.2	24	**54**[a]
Cl	Ph	2	24	**54**[a]
Cl	Ph	3	24	**54**[a]
Br	Ph	2	2.85	**54** (87)
I	Ph	1	1.25	**54** (92)
I	TMS	1.5	4.25	**55** (70)
I	3-Thienyl	1.2	1.5	**56** (91)
I	2-Pyridinyl	1.2	0.5	**57** (92)
I	Ferrocenyl	2	0.5	**58** (100)

[a] Incomplete reaction after 24 h, mainly isothiazole **3** (TLC).

Summary

Regioselective Stille, Negishi, Sonogashira, and Ullmann type C–C coupling reactions were demonstrated with 3,5-dihaloisothiazole-4-carbonitriles **1** and **2** in good to high yields at C-5 position of the isothiazole ring. The analogous couplings at C-3 were much less readily achieved and the preparation of the more reactive 3-iodo-5-phenylisothiazole-4-carbonitrile (**28**) was required. This, the first 3-iodo substituted isothiazole was achieved *via* a Sandmeyer iodination of the 3-amino precursor **29**. 3-Iodo-5-phenylisothiazole-4-carbonitrile (**28**) was sufficiently reactive to undergo Suzuki, Stille, Negishi, Sonogashira and Ullmann type coupling reactions at the C-3 position. The reactivity of haloisothiazoles towards the coupling methodology followed the anticipated order I > Br > Cl. The work described demonstrates the synthetic usefulness of the readily available 3,5-dichloroisothiazole-4-carbonitrile (**1**) when combined with powerful palladium catalysed C–C coupling.

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 4 Å 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 a Pike *Miracle* Ge ATR accessory and strong, medium and weak peaks are represented by s, m and w respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz, respectively). 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 a 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 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and the volatiles evaporated. The residue obtained was absorbed on silica and chromatography (hexane–DCM, 7 : 3) and gave the title compound **3** (31.1 mg, 84%) as colourless needles, mp 87–88 °C (from cyclohexane) identical to an authentic sample.

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) and gave the title compound **3** (34.5 mg, 93%) as colourless needles, mp 87–88 °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} 2232 w (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 × 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 × 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)

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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-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, CH_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 °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, CH_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 °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 °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, CH_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 (CH_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 × 10 ml) followed by saturated aq. $Na_2S_2O_5$ (4 × 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 (CH_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 (CH_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 °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, CH_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 (CH_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 (CH_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 °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).

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

To a stirred and cooled (*ca.* 0–5 °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 × 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, 3700347).

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 × 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 × 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 × 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.

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 × 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 × 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, 2860565).

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