3,4,5-Triarylisothiazoles *via* C–C coupling chemistry†

Irene C. Christoforou and Panayiotis A. Koutentis*

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The regiocontrolled preparation of triarylisothiazoles is presented. 3-Halo-5-phenylisothiazole-4-carbonitriles, **1** (hal = Cl) and **18** (hal = I), are converted into the corresponding 4-bromo derivatives **5** (3-hal = Cl) and **24** (3-hal = I) *via* a Hunsdiecker strategy while the 4-iodo analogues **7** (3-hal = Cl) and **22** (3-hal = I) are prepared *via* a Hoffmann and Sandmeyer strategy. Regioselective Suzuki, Stille and Negishi reactions occur at C-4 with both the 4-bromo- and 4-iodoisothiazoles **5** and **7**, the latter being more reactive than the former. 3-Iodoisothiazoles **22** and **24** fail to give regiocontrolled Suzuki, Stille or Negishi couplings, however, 4-bromo-3-iodo-5-phenylisothiazole **24** gives the regiospecific palladium catalysed Ullmann-type reaction product 3,3′-bi(4-bromo-5-phenylisothiazole) **25**. Alkali hydrolysis of 3-chloro-4,5-diphenylisothiazole **8** gives the 3-hydroxy analogue **12** which is converted into 3-bromo-4,5-diphenylisothiazole **13** with $POBr_3$. 3-Bromoisothiazole **13** reacts with phenylzinc chloride to give 3,4,5-triphenylisothiazole **17** but fails to undergo effective Suzuki or Stille couplings. 3,5-Diphenylisothiazole-4-carbonitrile **26** is converted into the 4-bromo- and 4-iodo-3,5-diphenylisothiazoles **30** and **34** both of which are effective for Suzuki and Stille couplings. A series of triarylisothiazoles are prepared in this manner and fully characterised.

Introduction

1,2-Heteroazoles such as pyrazoles, isoxazoles, and isothiazoles are found in many biologically active compounds and synthetic methods for their preparation are well documented.[1] These 5-membered heterocycles are frequently interchanged as broadly equivalent isosteres. Synthetic routes involving acyclic precursors that afford either 3,4,5-triarylpyrazoles[2–9] or 3,4,5-triarylisoxazoles[10,11] have been reported. Surprisingly, analogous strategies have not been reported for the preparation of 3,4,5-triarylisothiazoles.[12–16] Nevertheless 3,4,5-triphenylisothiazole, the only reported triarylisothiazole, has been prepared from 1,3-dithiazolium[17] and 1,4,2-dithiazolium precursors.[18] Interestingly the very first reported synthesis[19] of 3,4,5-triphenylisothiazole was incorrect.[20]

Our interest in pursuing a new general route to triarylisothiazoles arises due to the growing importance of isothiazoles. Important isothiazoles include the Kathon® preservatives, the artificial sweetener Saccharin and the antibacterial sulfa drug, Sulfasomizole. Recently, isothiazoles have been reported as potential anticancer agents which act *via* inhibition of the MEK-1 and MEK-2 kinases,[21,22] as useful prodrugs for the treatment of hyperproliferative disorders,[23] and as novel active site inhibitors for the hepatitis C virus NS5B polymerase.[24]

Possible strategies to triarylisothiazoles include ring formation *via* 2 + 3 cycloadditions of aryl nitrile sulfides with diarylacetylenes and the oxidative cyclisation of 3-amino-1,2,3-triarylprop-2-ene-1-thiones. These strategies however, have drawbacks since the former cycloaddition route could lead to isomeric mixtures of isothiazoles and the latter route is product-specific. Recently, Pd catalysed cross-coupling methods[25,26] have been used to access 3,4,5-triarylpyrazole 1-oxides *via* sequential metalation and functionalisation of pyrazole 1-oxides[27] and 3,4,5-triarylisoxazoles *via* the modification of suitably substituted isoxazolylsilanols.[28] An analogous approach starting from an appropriately functionalised isothiazole could provide a general route to 3,4,5-triarylisothiazoles. Our work on the development of C–C coupling methods for the readily available 3,5-dichloroisothiazole-4-carbonitrile [29] afforded a route to 5-aryl-3-chloroisothiazole-4-carbonitriles[30] and 3,5-diarylisothiazole-4-carbonitriles.[31] We now report the logical extension of this work to provide two routes to 3,4,5-triarylisothiazoles following the arylation sequence C-5:C-4:C-3 and C-5:C-3:C-4.

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

Synthesis of 3-chloro-4-bromo-5-phenylisothiazole and coupling reactions at C-4

Initially, a sequential arylation of the isothiazole at the C-5, then C-4 and finally the C-3 ring carbons was investigated. Aryl and heteroaryl substituents can be introduced at the isothiazole C-5 position starting from the readily available 3,5-dichloroisothiazole-4-carbonitrile using Suzuki, Stille and Negishi coupling reactions.[30,31] The 4-cyano substituent could be readily converted into either a bromo substituent *via* a Hunsdiecker strategy (Scheme 1) or into an iodo substituent *via* a Sandmeyer strategy (Scheme 2) allowing for the possibility of introducing aryl substituents at the isothiazole C-4 position.

Hydration of the cyano group in concentrated sulfuric acid[32] proceeded smoothly to afford the carboxamide **2** in high yield (97%). Formation of the desired carboxylic acid **3** by addition of aqueous $NaNO_2$ to a solution of carboxamide **2** in concentrated

Department of Chemistry, University of Cyprus, P.O. Box 20537, 1678, Nicosia, Cyprus. E-mail: koutenti@ucy.ac.cy; Fax: +357 22 892809; Tel: +357 22 892783

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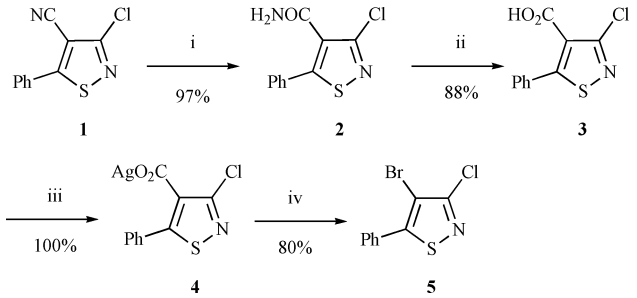
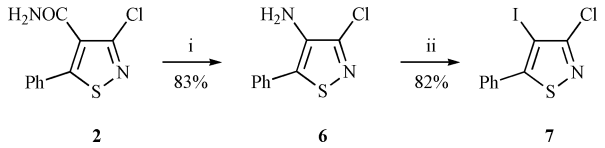


Scheme 1 Reagents and conditions: (i) c. H_2SO_4, 20–100 °C, 2 h + 40 min, 97%; (ii) s. $NaNO_2$ (10 equiv.), c. H_2SO_4, 20–100 °C, 2.5 h, 88%; (iii) KOH (1 equiv.), H_2O, $AgNO_3$ (1 equiv.), 20 °C, 100%; (iv) CCl_4, Br_2 (1.2 equiv.), 20 °C, 1 h, 80%.



Scheme 2 Reagents and conditions: (i) NaOH (5 equiv.), H_2O, Br_2 (1.5 equiv.), 0–70 °C, 1 h, 83%; (ii) isoamylONO (4 equiv.), I_2 (2.5 equiv.), MeCN, 80 °C, 20 min, 82%.

sulfuric acid was complicated by the presence of minor by-products arising from nitration of the phenyl substituents. These nitrated by-products could be avoided if water was eliminated from the reaction mixture. As such, the portionwise addition of solid $NaNO_2$ (10 equiv.) to a solution of carboxamide **2** in concentrated sulfuric acid at 100 °C gave 3-chloro-5-phenylisothiazole-4-carboxylic acid **3** in 88% yield. The silver salt **4** was precipitated quantitatively, thoroughly dried and treated with bromine in tetrachloromethane to give the desired 4-bromo-3-chloro-5-phenylisothiazole **5** in 80% yield.

The conversion of the carboxamide **2** into 3-chloro-4-iodo-5-phenylisothiazole **7** was achieved in two steps. First, a Hoffmann degradation of the carboxamide gave 4-amino-3-chloro-5-phenylisothiazole **6**. Then a Sandmeyer iodination using isoamyl nitrite and I_2 saturated MeCN gave the desired 3-chloro-4-iodo-5-phenylisothiazole **7** in good yield (Scheme 2).

As expected, the 3-chloro-4-iodo-5-phenylisothiazole **7** was more reactive than the analogous 4-bromoisothiazole **5**. The 4-iodoisothiazole **7** readily participated in Suzuki and Stille coupling reactions to afford regioselectively the 4-arylated isothiazole products **8–10** in high yields. The 4-bromoisothiazole **5** gave a successful Suzuki coupling with phenylboronic acid but failed to give the Stille reaction with tributylphenyltin (up to 4 equiv.). Both the 4-bromo- and 4-iodoisothiazoles **5** and **7** did not give the desired Negishi or the homocoupled Ullmann products. In these cases, the bromoisothiazole **5** was unreactive while the iodoisothiazole **7** gave predominantly the protodeiodinated 3-chloro-5-phenyl-isothiazole **11** (Table 1).

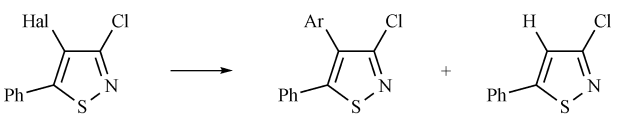
Coupling reactions at the less reactive C-3 isothiazole position

Palladium catalysed C–C coupling reactions at the isothiazole C-3 position were recently reported for 3-halo-5-phenylisothiazole-4-carbonitriles[31] and required either a bromo or iodo halogen since a chloro substituent at C-3 was not sufficiently reactive. Not surprisingly, 3-chloro-4,5-diphenylisothiazole **8** also failed to give successful Suzuki, Stille, Negishi and Ullmann type C–C coupling reactions. Consequently, the introduction of a more reactive group at the isothiazole C-3 position was investigated.

Activation of 3-chloro-4,5-diphenylisothiazole

The introduction of a 3-bromo substituent was achieved in two steps starting from 3-chloro-4,5-diphenylisothiazole **8** *via* the 3-hydroxy-4,5-diphenylisothiazole **12**. Unlike 3-chloro-5-phenylisothiazole-4-carbonitrile **1** which can be readily transformed into the 3-hydroxy derivative with $NaNO_2$ in refluxing DMF,[33] 3-chloro-4,5-diphenylisothiazole **8** did not react. Hydrolysis of 3-chloro-4,5-diphenylisothiazole **8** was nevertheless achieved using aqueous KOH at 200 °C and 250 psi in a pressure reactor

Table 1 Pd catalysed C–C coupling reactions of 3-chloro-4-halo-5-phenylisothiazole **5** or **7** (0.094 mmol) in anhydrous DMF under an argon atmosphere heated from 20 to 100 °C



5 Hal = Br
7 Hal = I

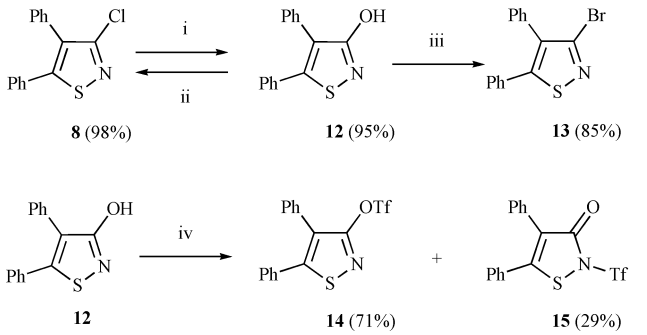
8-10

11

Hal	Reagent (equiv.)	Catalyst (mol%)	Base (equiv.)	Time/min	Yields (%)
Br	$PhB(OH)_3$ (3)	$Pd(OAc)_2$ (5)	K_2CO_3 (1.5)	75	**8** (96)
I	$PhB(OH)_3$ (3)	$Pd(OAc)_2$ (5)	K_2CO_3 (1.5)	40	**8** (98)
Br	$PhSnBu_3$ (4)	$Pd(OAc)_2$ (5)	—	>24 h	[a]
I	$PhSnBu_3$ (1.2)	$Pd(OAc)_2$ (5)	—	25	**8** (99)
I	2-Thienyl$SnBu_3$ (1.2)	$Pd(OAc)_2$ (5)	—	15	**9** (100)
I	2-Furyl$SnBu_3$ (1.2)	$Pd(OAc)_2$ (5)	—	15	**10** (100)
Br	PhZnCl (3)	$(PPh_3)_2PdCl_2$ (5)	—	>24 h	[a]
I	PhZnCl (1.5)	$(PPh_3)_2PdCl_2$ (5)	—	>24 h	[a]
I	PhZnCl (3)	$(PPh_3)_2PdCl_2$ (5)	—	35	**8** (20) + **11** (80)
Br[b]	—	$Pd(OAc)_2$ (100)	—	>24 h	[a]
I[b]	—	$Pd(OAc)_2$ (100)	—	48 h	**11** (98)

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

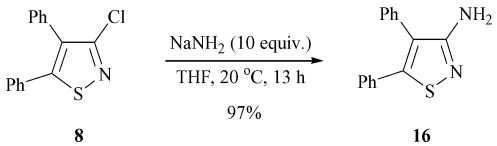
to afford the desired 3-hydroxyisothiazole **12** in 95% yield. The reaction of 3-hydroxy-4,5-diphenylisothiazole **12** with $POBr_3$ gave the desired 3-bromo-4,5-diphenylisothiazole **13** in 85% yield. 3-Hydroxy-4,5-diphenylisothiazole **12** was resistant to $POCl_3$ at 100 °C and was recovered unreacted after 24 h. Conversion of the hydroxyisothiazole **12** back into the 3-chloroisothiazole **8** was however, achieved after 72 h at 150 °C in a sealed tube (Scheme 3). 3-Hydroxy-4,5-diphenylisothiazole **12** reacted with trfluoromethanesulfonic anhydride to give the potentially useful 4,5-diphenylisothiazol-3-yl trifluoromethanesulfonate **14** in 71% yield together with the *N*-trifluoromethylsulfonylated isothiazolone **15** (29%).



Scheme 3 Reagents and conditions: (i) KOH (4 equiv.), 200 °C, 250 psi, pressure reactor, 24 h, 95%; (ii) $POCl_3$, 20–150 °C, sealed tube, 72 h, 98%; (iii) $POBr_3$, 20–100 °C, 24 h, 85%; (iv) Tf_2O (1 equiv.), Et_3N (1 equiv.), DCM, 0–10 °C, 30 min.

Attempts to introduce a 3-iodo substituent to the 4,5-diphenyl substituted isothiazoles **8** (3-Cl) and **12** (3-OH) failed. Lithiation of the 3-chloro-4,5-diphenylisothiazole **8** with n-BuLi at −78 °C in Et_2O followed by an I_2 quench led to a complex reaction mixture and on workup a strong odour of H_2S was detected. No reaction was observed when the reaction was repeated with Li, LDA or MeMgCl in either Et_2O or THF at −78 to 40 °C. Treatment of 3-hydroxy-4,5-diphenylisothiazole **12** with neat HI, HI-KI at 100 °C, excess of KI-I_2 in refluxing THF, Ph_3P-I_2 in DMF at 50 °C, P_2I_4 in CS_2 or PI_3 in refluxing DCM also gave only unreacted 3-hydroxy-4,5-diphenylisothiazole **12** while the use of neat PI_3 at 100 °C led to decomposition of the starting material. No reaction was observed when the 3-chloro- or 3-bromo-4,5-diphenylisothiazoles **8** and **13** were treated with KI or KI-Et_4NI in refluxing acetone or THF.

Iodine at the isothiazole C-3 position has been introduced to 3-amino-5-phenylisothiazole-4-carbonitrile by a Sandmeyer iodination.[31] The introduction of the 3-amino substituent in isothiazole **1** was achieved in two steps by heating a mixture of 3-chloro-5-phenylisothiazole-4-carbonitrile **1** in neat benzylamine at 80 °C to afford the 3-(benzylamino)-isothiazole followed by oxidative debenzylation with bromine. A heated mixture of 3-chloro-4,5-diphenylisothiazole **8** and neat benzylamine however, gave no reaction probably owing to reduced electrophilicity of 3-chloro-4,5-diphenylisothiazole **8** in comparison to that of the analogous 4-cyano-5-phenylisothiazole **1**. The use of aqueous or gaseous ammonia at 80 °C and an attempted Gabriel synthesis with potassium phthalimide gave only unreacted starting material. 3-Amino-4,5-diphenylisothiazole **16** was eventually prepared from 3-chloro-4,5-diphenylisothiazole **8** using sodamide (10 equiv.) in THF at 20 °C for 13 h. The use of only 2 equivalents of sodamide in refluxing THF led to incomplete reactions after 24 h while at these higher temperatures the use of between 4–10 equivalents increased reaction times but reduced yields (59–67%). In contrast 3-chloro-5-phenylisothiazole-4-carbonitrile **1** and sodamide in refluxing THF gave a complex reaction mixture.[31]

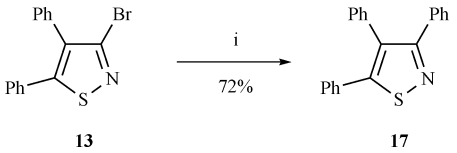


The Sandmeyer iodination of 3-amino-4,5-diphenylisothiazole **16** using KI (1.5 equiv.) and $NaNO_2$ (1.5 equiv.) in sulfuric acid gave 3-hydroxy-4,5-diphenylisothiazole **12** as the main product. Diazotisation using nitrosyl tertafluoroborate in a 1 : 1 mixture of acetic and propionic acids gave a complex reaction mixture. The reaction of 3-amino-4,5-diphenylisothiazole **16** with isoamyl nitrite (4 equiv.) in the presence of various sources of iodine (I_2, NIS, $BnEt_3NI$) (3 equiv.) in MeCN at 0 or 80 °C gave incomplete reactions, however one main colourless product was observed by TLC. Isolation of this product by chromatography and subsequent spectroscopic analysis revealed the colourless material to be a mixture of inseparable compounds. Mass spectrometry gave a weak peak for the expected molecular ion at 363 (19%), a stronger peak at 331 (33%) and a base peak at 204 Da (100%). IR spectroscopy supported the presence of a nitrile ν(C≡N) at 2208 cm^{-1} that indicated cleavage of the isothiazole ring. ^{1}H-NMR spectroscopy gave a poorly resolved set of multiplets in the range of 7.60–7.14 ppm which was not informative, however ^{13}C NMR spectroscopy indicated 22 carbon signals in the range of 142.0–115.8 ppm, 12 of which in the range of 130.7–128.3 ppm could be assigned to C*H*s by DEPT-90 NMR. The signals at 116.8 and 115.8 ppm supported the presence of at least 1 cyano group. Based on the above data the mixture was very tentatively proposed to be a mixture of 3-iodo-2,3-diphenylacrylonitrile and the desired 3-iodoisothiazole.

C–C coupling chemistry at the isothiazole C-3 position

The C–C coupling chemistry of 4,5-diphenylisothiazol-3-yl trifluoromethanesulfonate **14** and 3-bromo-4,5-diphenylisothiazole **13** was then examined following procedures developed for C–C coupling reactions of 3-bromo- and 3-iodo-5-phenylisothiazole-4-carbonitrile.[31] Suzuki, Stille, and Ullmann-type reactions on 4,5-diphenylisothiazol-3-yl trifluoromethanesulfonate **14** gave mainly unreacted starting material while the Negishi reaction was complex (by TLC) and the presence of 3-hydroxy-4,5-diphenylisothiazole **12** suggested a competing hydrolysis of the triflate. Similarly, 3-bromo-4,5-diphenylisothiazole **13** did not participate effectively in either the Suzuki or the Stille reactions. Although the desired 3,4,5-triphenylisothiazole **17** could be identified by TLC neither reaction could be driven to completion even with excess reagents and prolonged reaction times (>24 h). Furthermore, no reaction was observed when an Ullmann-type homocoupling with $Pd(OAc)_2$ (1 equiv.) was attempted in DMF at 140 °C.

Nevertheless the Negishi reaction gave 3,4,5-triphenylisothiazole **17** in 72% yield when 3-bromo-4,5-diphenylisothiazole **13** was treated with phenylzinc chloride (4 equiv.) and $(PPh_3)_2PdCl_2$ (5 mol%) in DMF at 100 °C under argon (Scheme 4).



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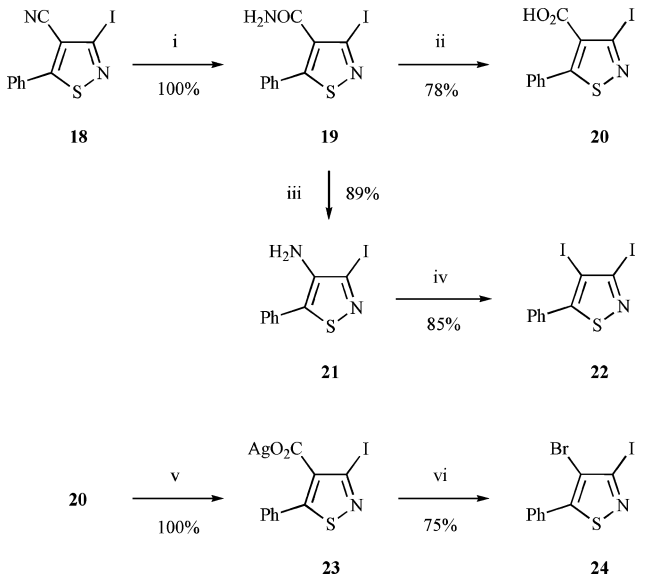
Scheme 4 Reagents and conditions: (i) PhZnCl (4 equiv.), $(PPh_3)_2PdCl_2$ (5 mol%) DMF, Ar, 20–100 °C, 40 min, 72%.

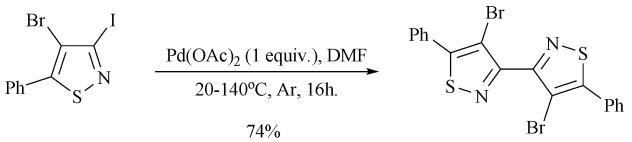
The triarylation of the isothiazole ring system was achieved but the failure to perform both Suzuki and Stille reactions was limiting. As such, an additional effort was made to prepare the potentially more reactive 3-iodo-4,5-diphenylisothiazole starting from the known 3-iodo-5-phenylisothiazole-4-carbonitrile **18**.[31]

4-Bromo-3-iodo- and 3,4-diiodo-5-phenylisothiazoles **24** and **22** were therefore prepared (Scheme 5) following similar routes for the preparation of 4-bromo-3-chloro and 3-chloro-4-iodo-5-phenylisothiazoles **5** and **7**.



Scheme 5 Reagents and conditions: (i) c. H_2SO_4, 20–100 °C, 2 h, 100%; (ii) $NaNO_2$ (25 equiv.), c. H_2SO_4, 20–100 °C, 3 h, 78%; (iii) NaOH (5 equiv.), H_2O, Br_2 (1.5 equiv.), 0–70 °C, 1 h, 89%; (iv) isoamylONO (4 equiv.), I_2 (2.5 equiv.), MeCN, 80 °C, 20 min, 85%; (v) KOH (1.2 equiv.), $AgNO_3$ (1.2 equiv.), H_2O, 20 °C, 100%; (vi) Br_2 (1.2 equiv.), CCl_4, 20 °C, 1 h, 75%.

Despite the successful syntheses of these 3,4-dihalogenated isothiazoles both the 3,4-diiodo- and the 4-bromo-3-iodo-5-phenylisothiazoles **22** and **24** gave mixtures of mono-, di- and sometimes triphenylated isothiazoles with either phenylboronic acid or tributylphenyltin in DMF. Nevertheless some regioselectivity was observed with the Suzuki coupling reaction between 4-bromo-3-iodo-5-phenylisothiazole **24** and phenylboronic acid. A spectroscopic analysis of the product mixture, that was inseparable by chromatography or recrystallisation, supported the mixture to be predominantly 4-bromo-3,5-diphenylisothiazole **30** (an independent synthesis of this compound is presented later in this paper) together with a trace of 3-iodo-4,5-diphenylisothiazole. Mass spectrometry indicated the presence of two parent ions with a weak peak at 363 (15%) corresponding to the 3-iodoisothiazole and two strong peaks supporting a monobromine isotope pattern at 317 (100%) and 315 Da (93%) corresponding to the 4-bromo-3,5-diphenylisothiazole **30**. ^{1}H-NMR of this mixture gave three multiplets in the range of 7.86–7.83 (2H), 7.69–7.65 (2H) and 7.54–7.40 ppm (4H) and elemental analysis after one recrystallization gave the percentages C: 55.76; H: 3.05; N: 4.01 which also favoured the 4-bromo-3,5-diphenylisothiazole **30** to be the major product over the 3-iodo-4,5-diphenylisothiazole. At elevated reaction temperatures (140 °C) 3,3′-bi(4-bromo-5-phenylisothiazole) **25** was also identified in the reaction mixture and the structure of this 3,3′-biisothiazole **25** was supported by a semi-independent synthesis *via* an Ullmann-type reaction of 4-bromo-3-iodo-5-phenylisothiazole **24** with $Pd(OAc)_2$ (1 equiv.) in DMF at 140 °C under argon in 74% yield. The analogous Ullmann reaction of 3,4-diiodo-5-phenylisothiazole **22** gave a complex mixture of products (by TLC) presumably owing to reduced regiocontrol in comparison to the 4-bromo-3-iodo-analogue.



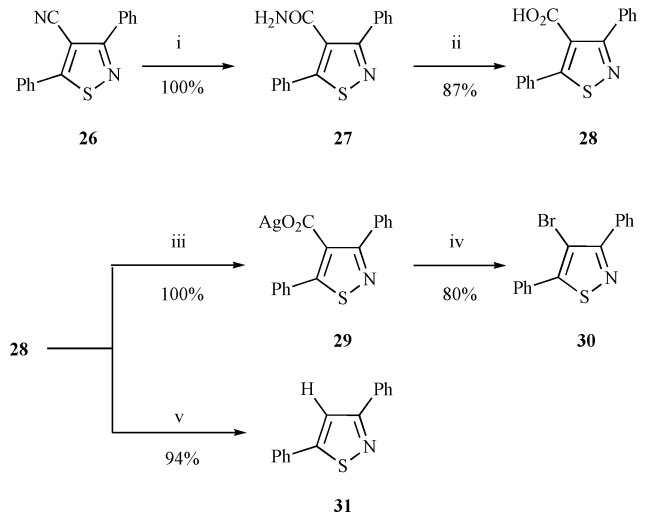
24 25

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

The triarylation described above follows the sequence C-5, then C-4 and finally C-3, however difficulties were encountered in the final arylation at C-3 since only the Negishi reagent phenylzinc chloride (4 equiv.) reacted with 3-bromo-4,5-diphenylisothiazole **13** to afford the desired triphenylisothiazole **17**. Furthermore, the synthetic route to the potentially more reactive 3-iodo-4,5-diphenylisothiazole failed. As such, an alternative sequential arylation was pursued which followed the triarylation sequence C-5 then C-3 and finally C-4. This triarylation sequence offered several advantages since Suzuki, Stille, Negishi and Ullmann-type couplings have all been successfully employed to prepare a variety of 3,5-diarylisothiazole-4-carbonitriles starting from 3,5-dihaloisothiazole-4-carbonitriles.[31] Furthermore this route avoided the issue of regioselectivity between the isothiazole C-3 and C-4 positions since the C-4 position was "protected" as a nitrile group which could later readily be converted into either a bromo substituent *via* a Hunsdiecker strategy or into an iodo substituent *via* a Sandmeyer strategy using methods similar to those described above.

Synthesis of 3,5-diphenyl-4-bromo and 4-iodoisothiazoles

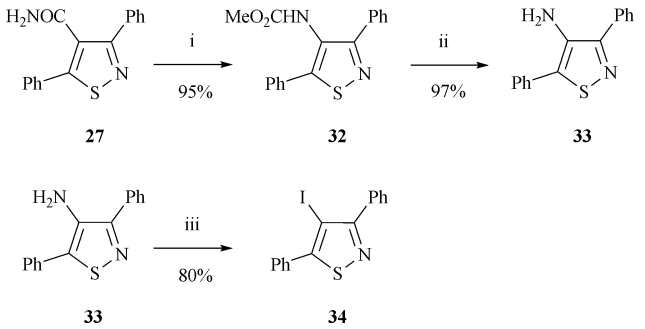
Treatment of 3,5-diphenylisothiazole-4-carbonitrile **26** with concentrated sulfuric acid gave 3,5-diphenylisothiazole-4-carboxamide **27** in quantitative yield. The portionwise addition of solid sodium nitrite to a solution of the carboxamide in concentrated sulfuric acid gave 3,5-diphenylisothiazole-4-carboxylic acid **28** in 87% yield. As before, it was necessary to avoid the use of aqueous sodium nitrite since this led to some undesired nitration on the phenyl substituents. The Hunsdiecker reaction was applied to the 3,5-diphenylisothiazole-5-carboxylic acid **28** to afford 3,5-diphenyl-4-bromoisothiazole **30** in 80% (Scheme 6).



Scheme 6 Reagents and conditions: (i) c. H_2SO_4, 20–100 °C, 3 h, 100%; (ii) $NaNO_2$ (10 equiv.), c. H_2SO_4, 20–100 °C, 1 h, 87%; (iii) KOH (1.2 equiv.), $AgNO_3$ (1.2 equiv.), H_2O, 20 °C, 100%; (iv) Br_2 (1.2 equiv.), CCl_4, 20 °C, 1 h, 80%; (v) $TsOH.H_2O$ (10 mol%), Ph_2, 20–250 °C, 20.5 h, 94%.

An alternative strategy to the 4-bromo-3,5-diphenylisothiazole **30** *via* electrophilic bromination of the 3,5-diphenylisothiazole **31** was also investigated. The thermal decarboxylation of 3,5-diphenylisothiazole-4-carboxylic acid **28** required prolonged heating at 250 °C in biphenyl in the presence of catalytic $TsOH{\cdot}H_2O$ (Scheme 6) and the resulting 3,5-diphenylisothiazole **31** was unreactive to bromine in refluxing acetic acid and to *N*-bromosuccinimide in refluxing tetrachloromethane. Iodination at C-4 using iodine in hydrogen peroxide at 20 °C or *N*-iodosuccinimide in refluxing tetrachloromethane gave only unreacted 3,5-diphenylisothiazole **31** while iodination on phenyl substituents was observed with the use of iodine in concentrated HNO_3 at 100 °C. Attempted nitration of the 3,5-diphenylisothiazole C-4 position with HNO_3 in concentrated H_2SO_4 at 0–5 °C also led to undesired nitration on the phenyl substituents.

Owing to these difficulties in controlling the regiochemistry of the above electrophilic substitution reactions, the preparation of the 4-iodo-3,5-diphenylisothiazole **34** was subsequently attempted in a two step procedure involving first a Hoffmann degradation to afford the 4-amino-3,5-diphenylisothiazole **33** followed by the Sandmeyer iodination. Initially, Hoffmann degradation of 3,5-diphenylisothiazole-4-carboxamide **27** with NaOH (4 equiv.) and bromine (1.5 equiv.) was attempted but the reaction was incomplete and quite complex. Modified Hoffmann degradation conditions using methanol as solvent, sodium (4 equiv.) and bromine (1.2 equiv.) however, gave methyl 3,5-diphenylisothiazole-4-carbamate **32** in 95% yield based on recovered unreacted carboxamide **27** (3–5%), the presence of which could not be overcome. Treatment of the isothiazolecarbamate **32** with aqueous HBr (48%) at 100 °C gave 4-amino-3,5-diphenylisothiazole **33** in 97%. Diazotization of the 4-aminoisothiazole **33** with isoamyl nitrite (4 equiv.) and iodine (3 equiv.) in refluxing nitromethane gave the 4-iodo-3,5-diphenylisothiazole **34** in 80% yield (Scheme 7). Lower reaction temperatures led to more complicated reaction mixtures and reduced yields of the 4-iodoisothiazole **34**.



Scheme 7 Reagents and conditions: (i) Na (4 equiv.), Br_2(1–2 equiv.), MeOH, 20–70 °C, 1 h, 95%; (ii) aq. HBr (48%), 100 °C, 7 h, 97%; (iii) isoamylONO (4 equiv), I_2 (3 equiv.), $MeNO_2$, 110 °C, 1 h, 80%.

Coupling reactions of 3,5-diphenyl-4-bromo- and 4-iodoisothiazoles

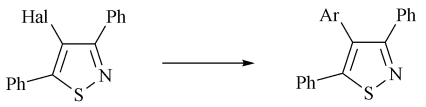
Both the 4-bromo- and 4-iodo-3,5-diphenylisothiazoles **30** and **34** readily undergo the Suzuki reaction with phenylboronic acid (3 equiv.), powdered K_2CO_3 (1.5 equiv.) and $Pd(OAc)_2$ (5 mol%) in DMF at 110 °C under argon atmosphere to provide a route to triphenylisothiazole **17**. The 4-iodoisothiazole **34** reacted marginally faster than the 4-bromoisothiazole **30**. A variety of arylboronic acids were subsequently screened to provide a non-product specific route to triarylisothiazoles in good yields (Table 2).

When 4-bromo-3,5-diphenylisothiazole **30** reacted with the sterically more demanding 2-tolylboronic acid or the 2-chlorobenzeneboronic acid, protodebromination gave 3,5-diphenylisothiazole **31** in 51 and 19% yields respectively. A similar result was observed between the reaction of 4-iodo-3,5-diphenylisothiazole **34** and 2-tolylboronic acid, however pronounced protodeiodination occurred with 2-chlorobenzeneboronic acid affording 3,5-diphenylisothiazole **31** in 88% yield. Despite this, 4-iodo-3,5-diphenylisothiazole **34** reacted cleanly with 2-thienylboronic acid to give 3,5-diphenyl-4-(thien-2-yl)iso-thiazole **46** while the 4-bromo anologue failed to reach completion within 24 h. In the case of 3- and 4-chlorobenzeneboronic acids the expected triarylisothiazoles reacted further with the excess boronic acid reagents to give minor amounts of isothiazoles **48** and **47** both in 11% yield. No reaction was observed with methylboronic acid.

Unlike the above Suzuki reactions where both the 4-bromo- and 4-iodo-3,5-diphenylisothiazoles **30** and **34** showed similar reactivities there was a significant difference with the Stille reaction. The reaction of 4-bromo-3,5-diphenylisothiazole **30** with tributylphenyltin (3 equiv.) and $Pd(OAc)_2$ (5 mol%) in DMF at 100 °C remained incomplete after 24 h while the 4-iodo-3,5-diphenylisothiazole **34** gave the desired Stille products in high yield (Table 3).

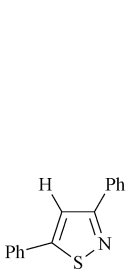
Both 4-bromo- and 4-iodo-3,5-diphenylisothiazoles **30** and **34** reacted with the Negishi reagent phenylzinc chloride (4 equiv.) and $(PPh_3)_2PdCl_2$ (5 mol%) in DMF at 100 °C for 4 h under argon to give 3,4,5-triphenylisothiazole **17** in 29 and 18% yields, respectively. The Negishi reactions gave considerable amounts of the protodehalogenation product 3,5-diphenylisothiazole **31** (71 and 77% respectively) accounting for the low yields of triphenylisothiazole **17**. The Ullmann-type homocoupling of $Pd(OAc)_2$ (1 equiv.) with 4-bromoisothiazole **30** gave a complex reaction mixture, however, with 3-iodoisothiazole **34** only the

Table 2 Reaction of 4-halo-3,5-diphenylisothiazoles **30** and **34** with arylboronic acid (3 equiv.), powdered K_2CO_3 (1.5 equiv.), $Pd(OAc)_2$ (5 mol%) in DMF at 20–110 °C under Ar

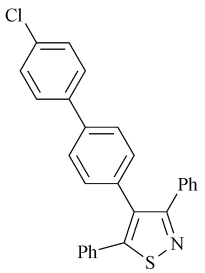


30 (Hal = Br)
34 (Hal = I)

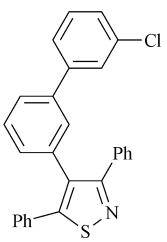
17, **35-46**



31



47

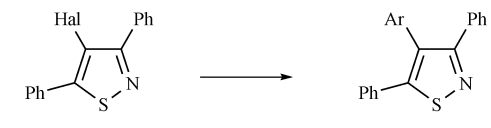


48

Hal	Ar	Time/min	Yields (%)	
Br	Ph	60	**17** (98)	
I	Ph	40	**17** (100)	
Br	3-$NO_2C_6H_4$	55	**35** (99)	
Br	4-$MeOC_6H_4$	40	**36** (98)	
Br	3-$MeOC_6H_4$	40	**37** (98)	
Br	2-$MeOC_6H_4$	30	**38** (99)	
Br	4-Tol	45	**39** (98)	
Br	3-Tol	30	**40** (99)	
Br	2-Tol	4.5 h	**41** (49)	**31** (51)
I	2-Tol	80	**41** (41)	**31** (59)
Br	4-ClC_6H_4	30	**42** (89)	**47** (11)
Br	3-ClC_6H_4	50	**43** (83)	**48** (11)
Br	2-ClC_6H_4	1.5 h	**44** (81)	**31** (19)
I	2-ClC_6H_4	60	**44** (12)	**31** (88)
Br	3-Thienyl	25	**45** (100)	
Br	2-Thienyl	[a]		
I	2-Thienyl	6 h	**46** (99)	

[a] Incomplete reaction after 24 h.

Table 3 Reaction of 4-halo-3,5-diphenylisothiazoles **30** and **34** with aryltributyltin in the presence of $Pd(OAc)_2$ (5 mol%) in DMF at 20–100 °C under Ar



30 (Hal = Br)
34 (Hal = I)

17, **46** & **49**

Hal	Ar	$RSnBu_3$ (equiv.)	Time/h	Yield (%)
Br	Ph	3	[a]	
I	Ph	1	24	**17** (99[b])
I	Ph	1.5	0.75	**17** (98)
I	2-Thienyl	1.5	16.25	**46** (99)
I	2-Furyl	1.5	4.25	**49** (98)

[a] Incomplete reaction after 24 h. [b] Based on recovered 4-iodo-3,5-diphenylisothiazole **34** (11%).

protodeiodination product 3,5-diphenylisothiazole **31** was isolated in 43% yield.

Summary

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

Experimental

CCl_4 and MeOH were freshly distilled from CaH_2 under argon. DMF was azeotropically distilled with PhH then distilled under vacuum from anhydrous $MgSO_4$ and stored over 4 Å molecular sieves. 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 Na_2SO_4 was used for drying organic extracts, and all volatiles were removed under reduced pressure. All reaction mixtures and column eluents were monitored by TLC using commercial 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). A Hastelloy B-2 Parr pressure vessel with a teflon sleeve and a 600 mL capacity (3000 psi limit) was used for the autoclave reactions. Melting points were determined using a PolyTherm-A, Wagner & Munz, Koefler-Hotstage Microscope apparatus. Solvents used for recrystallization are indicated after the melting point. UV spectra were obtained using a Perkin-Elmer Lambda-25 UV/vis spectrophotometer and inflections are identified by the abbreviation "inf". IR spectra were recorded on a Shimidazu FTIR-NIR Prestige-21 spectrometer with Pike *Miracle* Ge ATR accessory, and strong, medium and weak peaks are represented by s, m and w respectively. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 machine (at 300 and 75 MHz respectively). *C*H assignments were supported by ^{13}C NMR DEPT 90 experiments. Deuterated solvents were used for homonuclear lock and the signals are referenced to the deuterated solvent peaks. Low resolution (EI) mass spectra were recorded on a Shimadzu Q2010 GCMS with direct inlet probe whilst high resolution spectra were recorded on a VG Autospec "Q" mass spectrometer. Petrol refers to light petroleum, bp 40–60 °C. 3-Chloro-5-phenylisothiazole-4-carbonitrile **1**,[30] 3-iodo-5-phenylisothiazole-4-carbonitrile **18**[31] and 3,5-diphenylisothiazole-4-carbonitrile **26**[31] were prepared according to literature procedures.

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

To a stirred mixture of 3-chloro-5-phenylisothiazole-4-carboxylic acid **3** (1.0 g, 4.18 mmol) in H_2O (30 ml) was added a solution of

KOH (234 mg, 4.18 mmol, 1 equiv.) in H_2O (10 ml) and the mixture was allowed to stirred at *ca.* 20 °C until the starting material had completely dissolved. To the reaction mixture was added, in one portion, a solution of silver nitrate (710 mg, 4.18 mmol, 1 equiv.) in H_2O (5 ml) to afford a grey-white precipitate. The grey-white precipitate was filtered, washed first with H_2O and then with acetone and dried in a vacuum oven at *ca.* 80 °C for 12 h to give silver 3-chloro-5-phenylisothiazole-4-carboxylate **4** (1.45 g, 100%). To a stirred mixture of silver 3-chloro-5-phenylisothiazole-4-carboxylate **4**, (100 mg, 0.29 mmol) in tetrachloromethane (3 ml) protected with $CaCl_2$ drying tube was added in one portion Br_2 (18 μl, 0.35 mmol, 1.2 equiv.) and the reaction was kept at 20 °C for 1 h. The reaction mixture was filtred and the filtrate was absorbed on silica. Chromatography (hexane–DCM 8 : 2) gave the title compound **5** (63 mg, 80%) as colourless needles, mp 40–41 °C (lit.,[34] 44–46 °C) (from pentane); (Found: C, 39.3; H, 1.9; N, 5.0. $C_9H_5BrClNS$ requires C, 39.4; H, 1.8; N, 5.1%); λ_{max}(DCM)/nm 274 (log ε 3.91); ν_{max}/cm^{-1} 3049w (Ar CH), 1577w, 1559w, 1517w, 1507w, 1476m, 1457w, 1443m, 1388m, 1336w, 1313w, 1294s, 1278m, 1245w, 1217w, 1076w, 1032m, 996m, 920w, 901m, 819m; δ_H(300 MHz; $CDCl_3$) 7.67–7.60 (2H, m, Ph C*H*), 7.53–7.45 (3H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 163.4, 151.0, 130.4 (Ph *C*H), 129.3 (Ph *C*), 129.1 (Ph *C*H), 128.2 (Ph *C*H), 106.2; *m*/*z* (EI) 277 (M$^+$ + 4, 28%), 275 (M$^+$ + 2, 100), 273 (M$^+$, 58), 240 (4), 238 (4), 229 (7), 227 (5), 196 (5), 194 (14), 193 (4), 159 (50), 150 (4), 148 (4), 137 (3), 133 (17), 127 (29), 121 (6), 113 (11), 100 (10), 89 (18), 77 (11), 74 (10), 63 (12), 51 (19) (Found: M$^+$, 272.9015, $C_9H_5BrClNS$ requires *M*, 272.9004).

4-Amino-3-chloro-5-phenylisothiazole 6

To a stirred solution of NaOH (42 mg, 1.05 mmol, 5 equiv.) in water (2 ml) cooled to *ca.* 0 °C was first added Br_2 (13 µl, 0.25 mmol, 1.2 equiv.) and then 3-chloro-5-phenylisothiazole-4-carboxamide **2** (50 mg, 0.21 mmol). The reaction mixture was allowed to warm to *ca.* 20 °C and was kept at this temperature until the starting material had completely dissolved. The reaction mixture was then heated to *ca.* 70 °C for 1 h. The mixture was allowed to cool to *ca.* 20 °C, diluted with water (5 ml) and washed with DCM (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane–DCM, 5 : 5) gave the *title compound* **6** (36.7 mg, 83%) as colourless plates, mp 58–59 °C (from cyclohexane); (Found: C, 51.2; H, 3.2; N, 13.3. $C_9H_7ClN_2S$ requires C, 51.3; H, 3.4; N, 13.3%); λ_{max}(DCM)/nm 315 (log ε 2.79), 262 (2.66); ν_{max}/cm^{-1} 3373w and 3309w (NH_2), 3212w, 3061w (Ph CH), 1623w, 1576w, 1492w, 1445w, 1420m, 1374m, 1316w, 1282w, 1136w, 1086w, 1061w, 1027w, 994w, 974w, 926w, 823m, 764s; δ_H(300 MHz; $CDCl_3$) 7.50–7.37 (5H, m, Ph C*H*), 3.76 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 140.8, 139.8, 134.0, 130.6 (Ph *C*), 129.5 (Ph *C*H), 128.8 (Ph *C*H), 127.1 (Ph *C*H); *m*/*z* (EI) 212 (M$^+$ + 2, 31%), 210 (M$^+$, 82), 175 (11), 148 (29), 142 (62), 121 (100), 104 (16), 93 (9), 89 (14), 77 (63), 69 (14), 63 (15), 62 (15), 53 (14), 51 (37).

3-Chloro-4-iodo-5-phenylisothiazole 7

To a stirred mixture of I_2 (90.5 mg, 0.358 mmol, 2.5 equiv.) and isoamyl nitrite (77 µl, 0.573 mmol, 4 equiv.) in MeCN (2 ml) protected with a $CaCl_2$ drying tube at *ca.* 80 °C was added dropwise an MeCN (1 ml) solution of 4-amino-3-chloro-5-phenylisothiazole **6** (30 mg, 0.143 mmol). The mixture was kept at *ca.* 80 °C until no starting material remained (TLC), allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (hexane–DCM, 7 : 3) gave the *title compound* **7** (37.7 mg, 82%) as colourless needles, mp 67–68 °C (from pentane); (Found: C, 33.5; H, 1.5; N, 4.3. C_9H_5ClINS requires C, 33.6; H, 1.6; N, 4.4%); λ_{max}(DCM)/nm 275 (log ε 2.70); ν_{max}/cm^{-1} 3046w (Ph CH), 1471m, 1442m, 1381m, 1335w, 1325w, 1286m, 1270s, 1238w, 1207w, 1077w, 1033m, 990m, 966w, 921w, 893m, 841w, 822m, 783w, 750s; δ_H(300 MHz; $CDCl_3$) 7.60–7.57 (2H, m, Ph C*H*), 7.53–7.51 (3H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 168.0, 154.5, 130.7 (Ph *C*), 130.4 (Ph *C*H), 129.1 (Ph *C*H), 128.5 (Ph *C*H), 79.5; *m*/*z* (EI) 323 (M$^+$ + 2, 36%), 321 (M$^+$, 100), 194 (13), 159 (74), 148 (4), 133 (58), 127 (60), 121 (7), 113 (17), 100 (14), 89 (31), 77 (14), 75 (13), 74 (13), 73 (4), 69 (8), 63 (20), 51 (26).

3-Chloro-4,5-diphenylisothiazole 8 *via* Suzuki reaction at C-4

A stirred mixture of 4-bromo-3-chloro-5-phenylisothiazole **5** (30 mg, 0.11 mmol), phenylboronic acid (40 mg, 0.33 mmol, 3 equiv.), powdered K_2CO_3 (22.8 mg, 0.165 mmol, 1.5 equiv.) and $Pd(OAc)_2$ (1.2 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane–DCM, 6 : 4) gave the *title compound* **8** (28.7 mg, 96%) as colourless needles, mp 106–107 °C (from pentane); (Found: C, 66.4; H, 3.6; N, 5.2. $C_{15}H_{10}ClNS$ requires C, 66.3; H, 3.7; N, 5.2%); λ_{max}(DCM)/nm 275 (log ε 2.74); ν_{max}/cm^{-1} 3055w (Ar CH), 1599w, 1574w, 1537w, 1499w, 1477w, 1377w, 1346m, 1312w, 1236m, 1182w, 1143w, 1076w, 1034w, 995w, 988w, 920w, 907w, 843w, 833m, 802m, 770m, 748s, 710w, 694s; δ_H(300 MHz; $CDCl_3$) 7.44–7.22 (10H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 164.4, 150.0, 132.6, 131.8, 130.3 (Ph *C*H), 130.1 (Ph *C*), 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.6 (Ph *C*H), 128.3 (Ph *C*H), 128.2 (Ph *C*H); *m*/*z* (EI) 273 (M$^+$ + 2, 34%), 271 (M$^+$, 100), 258 (7), 256 (19), 236 (27), 203 (30), 190 (20), 178 (12), 165 (13), 135 (3), 104 (15), 89 (4), 77 (15), 63 (4), 51 (10) (Found: M$^+$, 271.0207, $C_{15}H_{10}ClNS$ requires *M*, 271.0222).

3-Chloro-4,5-diphenylisothiazole 8 *via* Stille reaction at C-4 (typical Stille conditions for coupling at C-4: see Table 1)

A stirred mixture of 3-chloro-4-iodo-5-phenylisothiazole **7** (30 mg, 0.093 mmol), tributylphenylstannane (36.6 µl, 0.112 mmol, 1.2 equiv.) and $Pd(OAc)_2$ (1.0 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane–DCM, 6 : 4) gave the *title compound* **8** (25 mg, 99%) as colourless needles, mp 106–107 °C (from pentane) identical to that described above.

3-Chloro-5-phenylisothiazole 11

A stirred mixture of 3-chloro-4-iodo-5-phenylisothiazole **7** (30 mg, 0.093 mmol) and $Pd(OAc)_2$ (20.9 mg, 0.093 mmol, 1 equiv.) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 140 °C, until no starting material remained (TLC). The

mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane–DCM, 6 : 4) gave the *title compound* **11** (17.8 mg, 98%) as colourless needles, mp 50–51 °C (lit.,[34] 56 °C) (from pentane) identical to that described above.

3-Hydroxy-4,5-diphenylisothiazole 12

A mixture of 3-chloro-4,5-diphenylisothiazole **8** (1 g, 3.68 mmol) and KOH (825 mg, 14.7 mmol, 4 equiv.) in H_2O (150 ml) was placed in a bomb reactor with a teflon liner. The bomb reactor was sealed and heated to *ca.* 200 °C (250 psi) for 24 h. The bomb reactor was cooled to *ca.* 20 °C and opened. The reaction mixture was filtered and the filtrate was acidified to give a white precipitate. The white precipitate was filtered, washed (H_2O) and dried to give the title compound **12** (885 mg, 95%) as colourless needles, mp 233–235 °C (lit.,[35] 245–247 °C) (from cyclohexane); (Found: C, 71.0; H, 4.4; N, 5.6. $C_{15}H_{11}NOS$ requires C, 71.1; H, 4.4; N, 5.5%); λ_{max}(DCM)/nm 234 (log ε 3.94), 280 (3.90); ν_{max}/cm^{-1} 3059w (Ar CH), 1607w, 1583w, 1566w, 1500m, 1481m, 1444w, 1342w, 1265m, 1184w, 1081w, 1073w, 1057w, 1033w, 1024w, 943w, 880m, 851w, 844w, 770m, 754s; δ_H(300 MHz; DMSO-d_6) 11.97 (1H, br s, O*H*), 7.34–7.29 (6H, m, Ph C*H*), 7.27–7.21 (4H, m, Ph C*H*); δ_C(75 MHz; DMSO-d_6) 166.8, 160.5, 132.3 (Ph *C*), 131.1 (Ph *C*), 129.8 (Ph *C*H), 129.2 (Ph *C*H), 129.0 (Ph *C*H), 128.3 (Ph *C*H), 127.9 (Ph *C*H), 127.4 (Ph *C*H), 122.1; *m*/*z* (EI) 254 (M$^+$ + 1, 20%), 253 (M$^+$, 100), 252 (54), 238 (6), 219 (7), 209 (17), 205 (10), 190 (6), 178 (29), 165 (32), 152 (10), 139 (4), 126 (6), 121 (4), 104 (12), 89 (8), 77 (11), 63 (6), 51 (10) (Found: M$^+$, 253.0567, $C_{15}H_{11}NOS$ requires *M*, 253.0561).

3-Bromo-4,5-diphenylisothiazole 13

A stirred mixture of 3-hydroxy-4,5-diphenylisothiazole **12** (30 mg, 0.12 mmol) and $POBr_3$ (1.5 g), protected with a $CaCl_2$ drying tube, was heated to *ca.* 100 °C for 24 h. The reaction mixture was cooled to *ca.* 20 °C, diluted with water and extracted with DCM (4 × 10 ml). The organic extracts were combined, dried and absorbed on silica. Chromatography (hexane–DCM, 7 : 3) gave the *title compound* **13** (32 mg, 85%) as colourless crystals, mp 112–113 °C (from pentane); (Found: C, 56.9; H, 3.3; N, 4.3. $C_{15}H_{10}BrNS$ requires C, 57.0; H, 3.2; N, 4.4%); λ_{max}(DCM)/nm 276 (log ε 3.01); ν_{max}/cm^{-1} 1533w, 1498w, 1474w, 1444w, 1372w, 1339m, 1227m, 1182w, 1138w, 1075w, 1034w, 988w, 920w, 898w, 849w, 843w, 825m, 785w, 769m, 747s; δ_H(300 MHz; $CDCl_3$) 7.43–7.40 (3H, m, Ph C*H*), 7.35–7.26 (5H, m, Ph C*H*), 7.22–7.17 (2H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 164.0, 140.0, 135.3, 132.5, 130.4 (Ph *C*H), 130.0, 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.6 (Ph *C*H), 128.3 (Ph *C*H), 128.3 (Ph *C*H); *m*/*z* (EI) 317 (M$^+$ + 2, 97%), 315 (M$^+$, 100), 302 (7), 300 (7), 236 (71), 235 (61), 221 (4), 208 (15), 203 (65), 190 (21), 178 (16), 165 (24), 152 (9), 139 (6), 121 (12), 118 (16), 104 (22), 89 (11), 77 (77), 63 (12), 51 (49).

3-Amino-4,5-diphenylisothiazole 16

A stirred mixture of 3-chloro-4,5-diphenylisothiazole **8** (50 mg, 0.184 mmol) and sodium amide (71.8 mg, 1.84 mmol, 10 equiv.) in dry THF (2 ml) was kept to *ca.* 20 °C, under argon, until no starting material remained (TLC). Chromatography (hexane–DCM, 3 : 7) gave the *title compound* **16** (45 mg, 97%) as colourless needles, mp 130–131 °C (from cyclohexane); (Found: C, 71.4; H, 4.8; N, 10.9. $C_{15}H_{12}N_2S$ requires C, 71.4; H, 4.8; N, 11.1%); λ_{max}(DCM)/nm 276 (log ε 3.71); ν_{max}/cm^{-1} 3458w and 3302w (NH), 3196 (Ar CH), 1622m, 1576w, 1558w, 1541w, 1506w, 1495m, 1458m, 1443w, 1402m, 1339w, 1161w, 1072w, 1053w, 1028w, 999w, 934w, 924w, 851w, 843m, 772m, 756s, 739w, 704s; δ_H(300 MHz; $CDCl_3$) 7.42–7.23 (10H, m, Ph C*H*), 4.37 (2H, br s, N*H*$_2$); δ_C(75 MHz; $CDCl_3$) 162.9, 161.5, 133.0 (Ph *C*), 131.0 (Ph *C*), 129.9 (Ph *C*H), 129.2 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.2 (Ph *C*H), 128.1 (Ph *C*H), 122.7; *m*/*z* (EI) 253 (M$^+$ + 1, 27%), 252 (M$^+$, 100), 251 (59), 234 (5), 218 (12), 209 (7), 190 (13), 178 (10), 176 (10), 165 (28), 152 (7), 139 (4), 126 (6), 121 (4), 104 (8), 89 (8), 77 (12), 74 (9), 69 (3), 63 (5), 51 (10) (Found: M$^+$, 252.0718, $C_{15}H_{12}N_2S$ requires *M*, 252.0721).

Sandmeyer iodination reaction of 3-amino-4,5-diphenylisothiazole 16

To a stirred mixture of benzyltriethylammonium iodide (113.9 mg, 0.357 mmol, 3 equiv.) and isoamyl nitrite (63.9 µl, 0.476 mmol, 4 equiv.) in MeCN (2 ml) protected with a $CaCl_2$ drying tube at *ca.* 20 °C was added dropwise an MeCN (1 ml) solution of 3-amino-4,5-diphenyl-isothiazole **16** (30 mg, 0.119 mmol). The mixture was kept at *ca.* 20 °C for 30 min and then was heated to *ca.* 80 °C for 1 h. The mixture was allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (hexane–DCM, 7 : 3) gave a colourless material which was a mixture of inseparable compounds: ν_{max}/cm^{-1} 2954w, 2923m, 2854w, 2208w (C≡N), 1594w, 1582w, 1576w, 1564w, 1485w, 1467w, 1457w, 1444m, 1378w, 1363w, 1331w, 1262w, 1222w, 1180w, 1157w, 1134w, 1078w, 1046w, 1031w, 998w, 985w, 969w, 919w, 900w, 873w, 854w, 822w, 793w, 768s, 746m, 738s; δ_H(300 MHz; $CDCl_3$) 7.63–7.60 (m, Ph C*H*), 7.54–7.40 (m, Ph C*H*), 7.26-7.12 (m, PhC*H*); δ_C(75 MHz; $CDCl_3$) 142.0, 141.1, 137.9, 133.8, 130.7 (Ph *C*H), 130.4 (Ph *C*H), 129.6 (Ph *C*H), 129.6, 129.1 (Ph *C*H), 129.1 (Ph *C*H), 128.9 (Ph *C*H), 128.8 (Ph *C*H), 128.7 (Ph *C*H), 128.6 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H), 128.3 (Ph *C*H), 125.1, 121.1, 121.0, 116.8, 115.8; *m*/*z* (EI) 364 (M$^+$ + 1%), 363 (M$^+$, 19), 332 (6), 331 ($C_{15}H_{10}IN^+$, 33), 236 (8), 205 (17), 204 (100), 203 (37), 202 (7), 177 (22), 176 (17), 127 (8), 102 (10), 88 (13), 77 (33), 51 (29).

3,4,5-Triphenylisothiazole 17

A stirred mixture of 3-bromo-4,5-diphenylisothiazole **13** (30 mg, 0.095 mmol), phenylzinc chloride (570 µl, 0.5 M in THF, 3 equiv.) and $(PPh_3)_2PdCl_2$ (3.3 mg, 5 mol%) in dry and degassed DMF (2 ml) under an argon atmosphere, was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with DCM (15 ml) and washed with H_2O (4 × 10 ml). The organic layer was separated, dried and absorbed on silica. Chromatography (hexane–DCM, 5 : 5) gave the title compound **17** (21.4 mg, 72%) as colourless crystals, mp 210–211 °C (lit.,[17] 211.5–212.5 °C) (from cyclohexane); (Found: C, 80.5; H, 4.8; N, 4.4. $C_{21}H_{15}NS$ requires C, 80.5; H, 4.8; N, 4.5%); λ_{max}(DCM)/nm 241 (log ε 4.06), 284 (3.85); ν_{max}/cm^{-1} 3063w (Ph CH), 1601w, 1576w, 1539w, 1533w, 1499w, 1479w, 1440w, 1398w,

1363w, 1291w, 1272w, 1188w, 1179w, 1159w, 1153w, 1073w, 1030w, 977w, 920w, 908w, 842w, 802w, 782w, 764m, 748s, 726m, 701m; δ_H(300 MHz; $CDCl_3$) 7.44–7.41 (2H, m, Ph C*H*), 7.37–7.23 (11H, m, Ph C*H*), 7.13–7.10 (2H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 167.6, 164.0, 135.7, 134.2, 134.1, 131.0, 130.6 (Ph *C*H), 128.9 (Ph *C*H), 128.7 (Ph *C*H), 128.7 (Ph *C*H), 128.7 (Ph *C*H), 128.5 (Ph *C*H), 128.4 (Ph *C*H), 128.0 (Ph *C*H), 127.5 (Ph *C*H); *m*/*z* (EI) 314 (M^+ + 1, 30%), 313 (M^+, 98), 312 (100), 297 (3), 280 (3), 278 (3), 236 (4), 210 (5), 208 (5), 178 (10), 165 (24), 155 (7), 149 (10), 139 (4), 126 (3), 121 (4), 103 (4), 89 (5), 77 (14), 63 (4), 51 (9).

3,3′-Bi(4-bromo-5-phenylisothiazole) 25

A stirred mixture of 4-bromo-3-iodo-5-phenylisothiazole **24** (30 mg, 0.082 mmol) and $Pd(OAc)_2$ (18.4 mg, 0.082 mmol, 1 equiv.) in DMF (2 ml) under an argon atmosphere, was heated to *ca.* 140 °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, 2 : 8) gave the *title compound* **25** (14.5 mg, 74%) as colourless needles, mp 208–209 °C (from cyclohexane); (Found: C, 45.4; H, 2.2; N, 6.0. $C_{18}H_{10}Br_2N_2S_2$ requires C, 45.2; H, 2.1; N, 5.9%); λ_{max}(DCM)/nm 285 (log ε 4.09); ν_{max}/cm^{-1} 3062w (Ph CH), 1684w, 1653w, 1576w, 1559w, 1539w, 1506w, 1473m, 1445m, 1357w, 1288w, 1243s, 1213w, 1181w, 1159w, 1077w, 1056w, 1035w, 1000w, 977w, 967w, 912w, 882s, 846w, 829m, 754m, 746s, 728w, 724w; δ_H(300 MHz; $CDCl_3$) 7.74–7.66 (4H, m, Ph C*H*), 7.59-7.48 (6H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 163.0, 161.3, 130.1 (Ph *C*H), 129.4 (Ph *C*), 129.1 (Ph *C*H), 128.7 (Ph *C*H), 107.3; *m*/*z* (EI) 480 (M^+ + 2, 54%), 478 (M^+ + 2, 100), 476 (M^+, 50), 399 (3), 397 (3), 318 (15), 239 (8), 214 (4), 159 (18), 145 (8), 133 (42), 127 (10), 121 (13), 101 (4), 89 (40), 77 (10), 63 (6), 51 (8).

3,5-Diphenylisothiazole-4-carboxylic acid 28

To a stirred solution of 3,5-diphenylisothiazole-4-carboxamide **27** (1 g, 3.57 mmol) in c. H_2SO_4 (10 ml) cooled to *ca.* 0 °C and protected with a $CaCl_2$ drying tube, was added in portions sodium nitrite (2.46 g, 35.7 mmol, 10 equiv.). The reaction mixture was heated to *ca.* 100 °C, until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C and then was poured into ice–water to afford a white precipitate. The white precipitate was filtered, washed (H_2O) and dried under vacuum to give the title compound **28** (0.87 g, 87%) as colourless needles, mp 202–203 °C (lit.,[36] 204–206 °C) (from cyclohexane); (Found: C, 68.5; H, 3.9; N, 5.0. $C_{16}H_{11}NO_2S$ requires C, 68.3; H, 3.9; N, 5.0%); λ_{max}(DCM)/nm 251 (log ε 4.00); ν_{max}/cm^{-1} 3055w (Ph CH), 1679s (C=O), 1559w, 1539w, 1533w, 1510m, 1476s, 1442m, 1356m, 1296m, 1208w, 1151w, 1077w, 1025w, 1005w, 990w, 953w, 917w, 856m, 821w, 801w, 769w, 755s; δ_H(300 MHz; CD_2Cl_2) 7.65–7.62 (2H, m, Ph C*H*), 7.56–7.53 (2H, m, Ph C*H*), 7.52–7.39 (6H, m, Ph C*H*) OH peak missing; δ_C(75 MHz; CD_2Cl_2) 171.8, 168.4, 167.5, 135.6, 130.4 (Ph *C*H), 130.0, 129.7 (Ph *C*H), 129.2 (Ph *C*H), 129.0 (Ph *C*H), 128.7 (Ph *C*H), 128.7 (Ph *C*H), 125.8; *m*/*z* (EI) 282 (M^+ + 1, 24%), 281 (M^+, 100), 280 (57), 264 (21), 252 (5), 248 (7), 237 (57), 220 (3), 204 (7), 190 (4), 178 (3), 176 (3), 165 (7), 141 (7), 134 (19), 133 (20), 129 (14), 121 (16), 103 (15), 89 (32), 77 (44), 69 (8), 63 (13), 51 (28).

3,5-Diphenylisothiazole 31

A stirred mixture of 3,5-diphenylisothiazole-4-carboxylic acid **28** (50 mg, 0.178 mmol), *p*-toluenesulfonic acid (3.4 mg, 10 mol%) and biphenyl (1 g) protected with a $CaCl_2$ drying tube, was heated to *ca.* 250 °C until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (hexane–DCM, 8 : 2) gave the title compound **31** (39.7 mg, 94%) as colourless needles, mp 80–81 °C (lit.,[37] 81 °C) (from pentane); (Found: C, 75.9; H, 4.6; N, 5.8. $C_{15}H_{11}NS$ requires C, 75.9; H, 4.7; N, 5.9%); λ_{max}(DCM)/nm 256 (log ε 4.13), 280 (4.06); ν_{max}/cm^{-1} 3055w (Ph CH), 1530w, 1448m, 1453w, 1447w, 1391w, 1370w, 1337w, 1306w, 1206w, 1188w, 1157w, 1153w, 1087w, 1075w, 1027w, 1000w, 970w, 965w, 920w, 909w, 878m, 851w, 830m, 770w, 759m, 752s; δ_H(300 MHz; $CDCl_3$) 8.03–7.99 (2H, m, Ph C*H*), 7.76 (1H, s, isothiazole C*H*), 7.68–7.64 (2H, m, Ph C*H*), 7.53–7.39 (6H, m, Ph C*H*); δ_C(75 MHz; $CDCl_3$) 168.2, 168.2, 134.8, 130.9 (Ph C*H*), 129.5 (Ph C*H*), 129.2 (Ph C*H*), 128.8 (Ph C*H*), 126.8 (Ph C*H*), 126.5 (Ph C*H*), 117.5 (isothiazole *H*-4) one peak missing; *m*/*z* (EI) 238 (M^+ + 1, 19%), 237 (M^+, 100), 204 (6), 159 (3), 134 (23), 121 (5), 118 (3), 108 (5), 103 (9), 89 (10), 77 (21), 76 (8), 69 (4), 63 (6), 51 (15).

Methyl 3,5-diphenylisothiazole-4-carbamate 32

To a stirred solution of 3,5-diphenylisothiazole-4-carboxamide **27** (0.2 g, 0.713 mmol) in methanol (3 ml) at *ca.* 20 °C, protected with a $CaCl_2$ drying tube, was added sodium (65.6 mg, 2.85 mmol, 4 equiv.) and then Br_2 (43.9 µl, 0.856 mmol, 1.2 equiv.). The reaction mixture was heated to *ca.* 70 °C for 1 h. The mixture was allowed to cool to *ca.* 20 °C and absorbed on silica. Chromatography (hexane–DCM 5 : 5) gave the *title compound* **32** (0.20 g, 95%) as colourless needles, mp 163–164 °C (from cyclohexane); (Found: C, 65.9; H, 4.7; N, 9.2. $C_{17}H_{14}N_2O_2S$ requires C, 65.8; H, 4.6; N, 9.0%); λ_{max}(DCM)/nm 243 (log ε 4.00), 276 inf (3.90); ν_{max}/cm^{-1} 3286w (NH), 1712s (C=O), 1582w, 1555w, 1522m, 1506m, 1484w, 1451w, 1424w, 1370w, 1251s, 1190w, 1181w, 1157w, 1097m, 1076w, 1037w, 1030w, 1017w, 1000w, 915w, 852w, 840w, 777w, 761s, 746s, 722w; δ_H(300 MHz; $CDCl_3$) 7.72–7.69 (2H, m, Ph C*H*), 7.51–7.42 (8H, m, Ph C*H*), 6.44 (1H, br s, N*H*), 3.62 (3H, br s, CH_3); δ_C[75 MHz; CD_2Cl_2 with $Cr(acac)_3$] 165.3, 162.0, 155.6, 135.2, 130.3, 130.0, 129.9 (Ph *C*H), 129.5 (Ph *C*H), 129.5 (Ph *C*H), 128.9 (Ph *C*H), 128.2 (Ph *C*H), 127.9 (Ph *C*H), 114.8, 1 peak missing; *m*/*z* (EI) 311 (M^+ + 1, 20%), 310 (M^+, 98), 279 (17), 278 (18), 265 (6), 251 (16), 233 (4), 218 (10), 173 (5), 162 (5), 148 (29), 130 (5), 121 (100), 120 (7), 104 (13), 89 (8), 77 (62), 59 (18), 51 (22). Further elution gave 3,5-diphenylisothiazole-4-carboxamide **27** (6 mg, 3%) as colourless needles, mp 210–211 °C (from PhH) identical to that described above.

4-Amino-3,5-diphenylisothiazole 33

A stirred solution of methyl 3,5-diphenylisothiazole-4-carbamate **32** (0.5 g, 1.61 mmol) in 48% aq. HBr (20 ml) was heated to *ca.* 100 °C until no starting material remained (TLC). The mixture was allowed to cool to *ca.* 20 °C, diluted with water (10 ml) and extracted with DCM (4 × 10 ml). The organic extracts were combined, dried and absorbed on silica. Chromatography (hexane–DCM, 5 : 5) gave the *title compound* **33** (394 mg, 97%) as colourless needles, mp 113–114 °C (from cyclohexane); (Found:

C, 71.4; H, 4.9; N, 11.0. $C_{15}H_{12}N_2S$ requires C, 71.4; H, 4.8; N, 11.1%); λ_{max}(DCM)/nm 238 (log ε 3.11), 327 (4.01); ν_{max}/cm^{-1} 3430w and 3349 (NH), 3055w (Ph CH), 1734w, 1718w, 1700w, 1684w, 1653w, 1613m, 1559w, 1506w, 1487w, 1449m, 1417s, 1387w, 1340w, 1316w, 1291w, 1278w, 1232w, 1182w, 1116w, 1103w, 1079w, 1042w, 1029m, 1018m, 997w, 974w, 919w, 836m, 774w, 762w, 719w; δ_H(300 MHz; $CDCl_3$) 7.81 (2H, m, Ph C*H*), 7.59–7.37 (8H, m, Ph C*H*), 3.61 (2H, br s, N*H*); δ_C(75 MHz; $CDCl_3$) 159.4, 140.7, 136.2, 135.1, 131.3, 129.4 (Ph *C*H), 129.0 (Ph *C*H), 128.9 (Ph *C*H), 128.3 (Ph *C*H), 127.7 (Ph *C*H), 127.7 (Ph *C*H); *m*/*z* (EI) 253 ($M^+ + 1$, 19%), 252 (M^+, 100), 180 (2), 149 (22), 121 (68), 104 (51), 89 (8), 77 (31), 51 (10).

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