New syntheses of aryl isothiocyanates†

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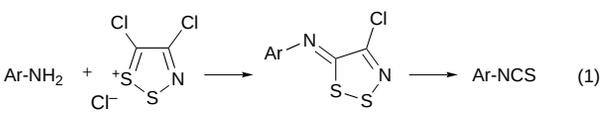
Primary aromatic amines are readily converted into arylimino-1,2,3-dithiazoles 2 and the derived cyanothioformanilides 6, both of which are rapidly cleaved by ethylmagnesium bromide in hot THF to give the corresponding isothiocyanates. The transformation 2→6→ArNCS can be performed as a 'one-pot' operation. The imines 2 are also converted, more slowly, into the isothiocyanates by sodium hydride in hot THF, *via* the cyanothioformanilides 6. Conversion of the anilides 6 into isothiocyanates is much faster under microwave irradiation in 2,6-lutidine. Mechanisms are proposed for these reactions.

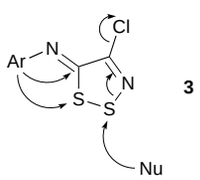
Aryl isothiocyanates are commonly made from primary amines by treatment with carbon disulfide, thiophosgene or thiophosgene-derived reagents, or from monoarylthioureas by thermal decomposition.[1] Most of these methods suffer from the use of environmentally unattractive reagents or reaction conditions. We have discovered a new method for converting aryl amines into isothiocyanates (eqn. 1), free from these disadvantages,



1 **2**

during an investigation of the chemistry of arylimino-1,2,3-dithiazoles **2**.[2]

5-(*N*-Arylimino)-4-chloro-5*H*-1,2,3-dithiazoles **2** are stable crystalline solids readily prepared in high yield from anilines and 4,5-dichloro-1,2,3-dithiazolium chloride **1**, itself readily available from chloroacetonitrile and disulfur dichloride.[3] These iminodithiazoles **2** are reactive towards both inter- and intramolecular nucleophilic attack, at S-1, S-2 and C-5 of the ring, the driving force being the regeneration of the latent cyano group in the dithiazole ring (*cf.* **3**). As a result the iminodi-

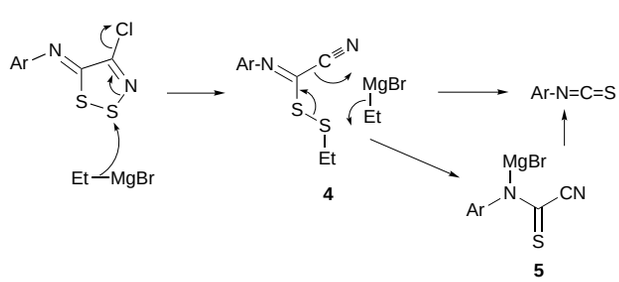


3

thiazoles **2** have proved to be highly versatile intermediates in heterocyclic synthesis. Thus they can be variously converted into 2-cyano derivatives of benzoxazoles,[4] benzothiazoles,[4] benzimidazoles,[5] benzoxazin-4-ones,[6] benzothiazin-4-ones[4] and 4-alkoxyquinazolines,[7] and into the acyclic *N*-arylcyanothioformamides **6**. Opening of the dithiazole ring by aliphatic amines has also been shown by Kim and co-workers to be synthetically useful.[8] In all of these reactions the regenerated cyano group is retained in the products.

We now find that with Grignard reagents, opening of the dithiazole ring is, for the first time, accompanied by elimination of the cyano group. Thus a commercial solution of ethylmagnesium bromide (2 equiv.) in THF was added dropwise to a heated solution of the iminodithiazole **2** in THF under argon, and heated at reflux for 1 h. Hydrolysis followed by extraction of the product with dichloromethane and purification by column chromatography gave the aryl isothiocyanates (45–60%) (method A, Table 1). Similar yields were obtained from reactions run at room temperature overnight. Reaction times and yields were not significantly altered by conducting the reaction under microwave irradiation. An excess of ethylmagnesium bromide (5–6 equiv.) gave more complex reactions with lower yields of the isothiocyanates. This ready conversion of iminodithiazoles **2** into aryl isothiocyanates represents a new reaction of the heterocyclic ring and provides a new two-step conversion of anilines into isothiocyanates.

A possible mechanism for the reaction is shown in Scheme 1. Opening of the dithiazole ring by the Grignard reagent is presumably initiated by attack at S-2, and generation of the cyano group, since attack at S-1 could hardly result in isothiocyanate formation. Then attack by a second molecule of Grignard reagent on the same sulfur atom could result in formation of the isothiocyanate, diethyl sulfide and cyanide ion, possibly assisted by coordination to magnesium in a cyclic transition state as shown in **4** (Scheme 1). Alternatively the reaction could



4 **5**

Scheme 1

be stepwise, with formation of diethyl sulfide and bromomagnesio derivative **5** of the cyanothioformanilide **6**, followed by elimination of MgBr(CN) to form the isothiocyanate.

We have already shown that iminodithiazoles **2** are readily converted into the cyanothioformanilides **6** in high yield by treatment with triphenylphosphine (2 equiv.) in undried

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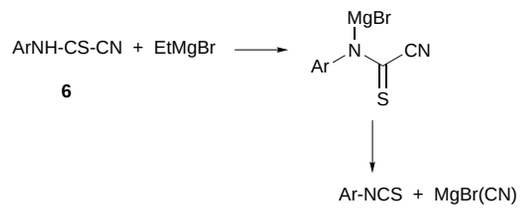
Table 1 Synthesis of aryl isothiocyanates from *N*-arylimino-1,2,3-dithiazoles **2** (methods A, C and D) and from cyanothioformanilides **6** (methods B and E)

Starting material	R	Product	Yield (%)
2a	H	**a**	54 (A)[a]
2b	2-F	**b**	50 (A)
2c	2-CN	**c**	55 (A); 76 (C); 55 (D)
2d,**6d**	4-OMe	**d**	44 (A); 93 (B); 75 (C); 57 (D); 57 (E)[b]
2e	4-CN	**e**	60 (A)
2f	3,4-(OMe)	**f**	50 (A)
2g,**6g**	2-CN, 4,5-$(OMe)_2$[b]	**g**	46 (A); 75 (B); 54 (C); 32 (D)
2h,**6h**	3,4-(OCH_2CH_2O)	**h**	47 (A); 92 (B); 73 (C); 54 (D); 54 (E)

[a] (A, B, *etc.*) = method A, B, *etc.* [b] Treatment of the iminodithiazole **2** with benzylmagnesium bromide gave the same yield of isothiocyanate as ethylmagnesium bromide.

dichloromethane at room temperature.[6] We therefore treated the cyanothioformanilides **6d**, **6g** and **6h** with ethylmagnesium bromide (1 equiv.) in THF at reflux (method B, Table 1) and obtained the corresponding isothiocyanates in high yield (Scheme 2). Furthermore, the two steps, **2**→**6**→ArNCS, were



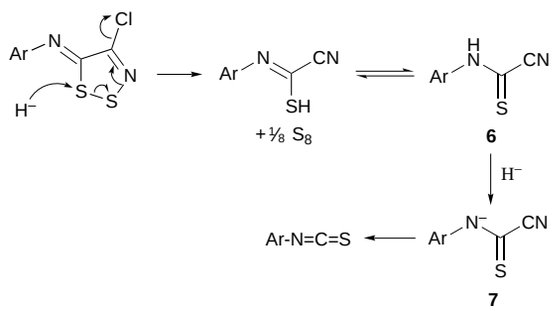
Scheme 2

readily combined in a one-pot procedure (method C, Table 1), starting from **2c**, **2d**, **2g** and **2h**.

The smooth elimination of cyanide from the cyanothioformanilides **6** by the Grignard reagent suggested the possibility that this process could be base catalysed. Also, it has been shown that treatment of some cyanothioformanilides **6** with pyrrolidine gave minor amounts of thioureas, where the cyano group had been replaced by the amine, and the corresponding isothiocyanate was proposed as a possible intermediate.[8a] We found two sets of basic conditions which readily gave the isothiocyanates: overnight treatment of the imines **2** with sodium hydride (2.2 equiv.) in hot THF (method D), and brief microwave irradiation of the thioformanilides **6** dissolved in 2,6-lutidine (method E) (Table 1). The thioanilides **6** are intermediates in the sodium hydride reaction, and can be isolated from this reaction if only 1 equiv. of hydride is used. Both methods presumably involve formation of the thioanilide anion **7** and elimination of cyanide ion from this. Since elemental sulfur is formed in the conversion of dithiazoles **2** into thioanilides **6**, it seems likely that initial attack by hydride is now at S-1 (Scheme 3), accompanied by ring opening and extrusion of S-2, possibly *via* the nitrile sulfide. We have observed this ring opening process in several intramolecular reactions.[4] The reactions described in this paper provide simple routes to aryl isothiocyanates, worthy of further investigation and optimisation. The highest yields are obtained from the preformed cyanothioformanilides **6** and ethylmagnesium bromide (method B) though the action of sodium hydride on the imines **2** (method D) is possibly the most attractive in terms of cost and experimental convenience.

Experimental

IR Spectra were recorded on a Perkin-Elmer Paragon 1000PC instrument. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM LA400 (400 MHz) spectrometer (Laboratoire Commun d'Analyse, Université de La Rochelle, France); chemical shifts



Scheme 3

(δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. Mass spectra were recorded on a Varian MAT311 in the Centre Régional de Mesure Physiques de L'Ouest (C.R.M.P.O.), Université de Rennes, France. Focused microwave irradiations were carried out with a Synthewave™ S402 Prolabo® microwave reactor (monomode system) which has a quartz reactor, variable speed rotation, visual control, irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control (by PC). Chromatography was carried out on silica gel 60 at medium pressure with the mixtures preadsorbed onto silica. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} aluminium backed plates. Light petroleum refers to the fraction bp 40–60 °C.

N-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)anilines 2

These were prepared as previously described for aniline,[3] 4-methoxyaniline,[3] anthranilonitrile,[4b] 4,5-dimethoxyanthranilonitrile,[4b] 3,4-dimethoxyaniline[6] and 2-fluoroaniline.[7]

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-2,3-dihydro-1,4-benzodioxin-6-amine 2h.** 4,5-Dichloro-1,2,3-dithiazolium chloride[3] (0.208 g, 1 mmol) was added to 6-amino-2,3-dihydro-1,4-benzodioxine (0.151 g, 1 mmol) in dichloromethane (10 ml) and stirred at room temperature until the amine was consumed (TLC). Then pyridine was added (0.17 ml, 2 mmol) and the mixture stirred for a further 2 h, filtered and the crude product purified by column chromatography (light petroleum–dichloromethane, 1:1) to give the *title compound* (0.191 g, 67%) as yellow needles, mp 134 °C (from ethanol) (Found: C, 41.69; H, 2.42; N, 9.65. $C_{10}H_7N_2ClO_2S_2$ requires C, 41.88; H, 2.46; N, 9.77%); ν_{max}(KBr)/cm^{-1} 2979, 1566, 1501, 1314, 1160, 915 and 824; δ_H(400 MHz, $CDCl_3$) 4.29 (4H, s, OCH_2CH_2O), 6.82 (1H, dd, *J* 2.40 and 8.50 Hz, H_{arom}), 6.86 (1H, d, *J* 2.40 Hz, H_{arom}) and 6.94 (1H, d, *J* 8.80 Hz, H_{arom}); δ_C(100 MHz, $CDCl_3$) 64.36 (2C), 109.00, 113.81, 118.01, 142.33, 143.95, 144.06, 148.32, 160.34; *m*/*z* 286 (M^+, 74%), 193 (M^+ − ClCNS, 68).

***N*-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4-cyanoaniline 2e.** 4,5-Dichloro-1,2,3-dithiazolium chloride (0.208 g, 1 mmol) was added to 4-cyanoaniline (0.118 g, 1 mmol) in dichloromethane (10 ml) and stirred at room temperature until the amine was

consumed (TLC). Then pyridine was added (0.17 ml, 2 mmol) and the mixture stirred for a further 1 h, filtered and the crude product purified by column chromatography (light petroleum–dichloromethane, 8:2) to give the title compound (0.187 g, 74%) as yellow needles, mp 152 °C (from light petroleum); ν_{max}(KBr)/cm^{-1} 3086, 2229 (CN), 1570, 1494, 1411, 1237, 1014 and 873; δ_H(400 MHz, $CDCl_3$) 7.28 (2H, d, *J* 8.50 Hz, H_{arom}) and 7.76 (2H, d, *J* 8.60 Hz, H_{arom}); *m*/*z* 253 (M^+, 3%), 192 ($M^+ - ClCN$, 15), 160 ($M^+ - ClCNS$, 51).

N-Arylcyanothioformanilides 6

N-(Cyanothioformyl)-4,5-dimethoxyanthranilonitrile **6g**[4b] and *N*-(4-methoxyphenyl)cyanothioformamide **6d**[6] were prepared following procedures previously described.

***N*-(Cyanothioformyl)-2,3-dihydro-1,4-benzodioxin-6-amine 6h.** Stirring of the imine **2h** (0.286 g, 1 mmol) with triphenylphosphine (0.536 g, 2 mmol) in dichloromethane (10 ml) at room temperature for 1 h, followed by column chromatography (light petroleum–dichloromethane), gave the *title compound* (0.176 g, 80%) as red needles, mp 118 °C (from ethanol) (Found: C, 54.37; H, 3.29; N, 12.48. $C_{10}H_8N_2O_2S$ requires C, 54.58; H, 3.66; N, 12.73%); ν_{max}(KBr)/cm^{-1} 3258, 3088, 2229 (CN), 1726, 1604, 1503, 1401, 1297, 1065, 845 and 754; δ_H(400 MHz, $CDCl_3$) 4.29 (4H, m, OCH_2CH_2O), 6.89 (1H, d, *J* 9.00 Hz, H_{arom}), 7.18 (1H, dd, *J* 3.00 and 9.00 Hz, H_{arom}) and 7.52 (1H, d, *J* 3.00 Hz, H_{arom}); δ_C(100 MHz, $CDCl_3$); *m*/*z* 220 (M^+, 23%), 193 ($M^+ - HCN$, 100), 137 ($M^+ + 2 - C_2HN_2S$, 60) and 109 ($M^+ + 2 - C_2HN_2S - C_2H_4$, 37).

Aryl isothiocyanates: typical procedures from *N*-arylimino-4-chloro-5*H*-1,2,3-dithiazoles 2 and cyanothioformanilides 6

Method A. Under an argon atmosphere, a solution of ethylmagnesium bromide (2 mmol, 1 M in THF) was added dropwise to a solution of the imino-1,2,3-dithiazole **2** (1 mmol) in boiling THF (5 ml). The brown mixture obtained was heated for about 1 h, the reaction being followed by TLC. After addition of dichloromethane (20 ml) the solution was washed with water, the organic layer was dried over sodium sulfate and the solvent evaporated. The crude product was then purified by column chromatography with light petroleum–dichloromethane as the eluent.

Method B. Under an argon atmosphere, a solution of ethylmagnesium bromide (1 mmol, 1 M in THF) was added dropwise to a solution of the cyanothioformanilide **6** (1 mmol) in boiling THF (15 ml). The brown mixture obtained was heated for about 30 min, the reaction being followed by TLC. After addition of dichloromethane (20 ml) the solution was washed with water, the organic layer dried over sodium sulfate and the solvent evaporated. The crude product was then purified by column chromatography as above.

Method C. A solution of the iminodithiazole **2** (1 mmol) and triphenylphosphine (2 mmol) in undried dichloromethane (10 ml) was stirred at room temperature. The reaction was followed by TLC and when complete the solvent was evaporated, the residue was dried in a stream of argon for 10 min, and dissolved in THF (5 ml). This solution was warmed to 50 °C and ethylmagnesium bromide (1 mmol, 1 M in THF) was added dropwise. The mixture was heated for 30 min and the product was isolated and purified as above.

Method D. A solution of the iminodithiazole **2** (0.7 mmol) in dry THF (5 ml) was stirred at 67 °C for 18 h in the presence of sodium hydride (60% dispersion in mineral oil, 1.54 mmol). The reaction mixture was filtered and the solvent evaporated from the filtrate. The residue was dissolved in ethyl acetate, washed with water, dried over sodium sulfate and purified by column chromatography as above.

Method E. The cyanothioformanilide **6** (1 mmol) in 2,6-lutidine (1 ml) was placed in the microwave oven in a glass vial (10 ml) with a screw-cap lid. The irradiation was programmed for 4 min with a delay of 5 s to obtain 100% power output (300 W). The initial temperature (infra-red measurement) was constant over a period of 15 to 30 s followed by a sharp increase over a period of 1 min. The irradiation was stopped 2 min later. After cooling, the brown reaction mixture was purifed by column chromatography as above.

The following isothiocyanates were prepared by the method indicated.

Phenyl isothiocyanate. A colourless oil (54%, method A); ν_{max}(KBr)/cm^{-1} 2973, 2924, 2062 (N=C=S), 1591, 1488, 1451, 1252, 927 and 750; δ_H(400 MHz, $CDCl_3$) 7.23 (2H, d, *J* 8.39 Hz, H_{arom}), 7.29 (2H, d, *J* 7.59 Hz, H_{arom}) and 7.36 (1H, t, *J* 8.40 Hz, H_{arom}); δ_C(100 MHz, $CDCl_3$) 125.73, 127.29, 129.53, 131.21 and 136.12.

2-Fluorophenyl isothiocyanate. A colourless oil (50%, method A); ν_{max}(KBr)/cm^{-1} 2923, 2851, 2033 (N=C=S), 1607, 1598, 1496, 1458, 1265, 1212, 942 and 809; δ_H(400 MHz, $CDCl_3$) 7.08–7.25 (4H, m, H_{arom}).

2-Cyanophenyl isothiocyanate. Colourless needles (55%, method A) (76%, method C) (55%, method D), mp 64 °C (from light petroleum) (Found: C, 60.28; H, 2.72; N, 17.32. $C_8H_4N_2S$ requires C, 60.05; H, 2.52; N, 17.51%); ν_{max}(KBr)/cm^{-1} 2229 (CN), 2111 (N=C=S), 1651, 1588, 1483, 1445, 1283, 955 and 761; δ_H(400 MHz, $CDCl_3$) 7.35 (1H, td, *J* 1.50 and 7.78 Hz, H_{arom}), 7.36 (1H, dd, *J* 1.50 and 7.99 Hz, H_{arom}), 7.60 (1H, td, *J* 1.50 and 8.05 Hz, H_{arom}), 7.64 (1H, dd, *J* 1.50 and 7.99 Hz, H_{arom}); δ_C(100 MHz, $CDCl_3$) 109.68, 115.48, 115.82, 127.65, 133.45, 133.95, 134.80 (NCS) and 141.08; *m*/*z* 160 (M^+, 100%), 133 ($M^+ - HCN$, 2) and 102 ($M^+ - N=C=S$, 40).

4-Methoxyphenyl isothiocyanate. A colourless oil (44%, method A) (93%, method B) (75%, method C) (57%, method D) (57%, method E); ν_{max}(KBr)/cm^{-1} 2923, 2846, 2108 (N=C=S), 1603, 1504, 1463, 1296, 1250, 1166, 929, 828 and 738; δ_H(400 MHz, $CDCl_3$) 3.81 (3H, s, OMe), 6.85 (2H, dd, *J* 1.99 and 9.19 Hz, H_{arom}), 7.17 (2H, dd, *J* 1.99 and 9.19 Hz, H_{arom}); δ_C(100 MHz, $CDCl_3$) 55.53, 114.77, 123.56, 126.94, 133.86 (NCS) and 158.55.

4-Cyanophenyl isothiocyanate. Colourless needles (60%, method A), mp 123 °C (from light petroleum); ν_{max}(KBr)/cm^{-1} 2226 (CN), 2140 (N=C=S), 1600, 1505, 1494, 1174, 934 and 836; δ_H(400 MHz, $CDCl_3$) 7.31 (2H, d, *J* 8.80 Hz, H_{arom}) and 7.66 (2H, d, *J* 8.80 Hz, H_{arom}); δ_C(100 MHz, $CDCl_3$) 110.62, 117.89, 126.48, 133.62, 136.06, and 139.63.

3,4-Dimethoxyphenyl isothiocyanate. A colourless oil (50%, method A); ν_{max}(KBr)/cm^{-1} 3003, 2958, 2934, 2128 (N=C=S), 1657, 1589, 1509, 1438, 1168, 1025 and 839; δ_H(400 MHz, $CDCl_3$) 3.87 (3H, s, OMe), 3.88 (3H, s, OMe) 6.74 (1H, d, *J* 2.40 Hz, H_{arom}), 6.79 (1H, s, H_{arom}) and 6.81 (1H, d, *J* 2.40 Hz, H_{arom}); δ_C(100 MHz, $CDCl_3$) 55.89, 56.58, 111.23, 112.49, 113.48, 121.13, 140.27 (NCS), 150.50 and 153.44.

2-Cyano-4,5-dimethoxyphenyl isothiocyanate. Colourless needles (46%, method A) (75%, method B) (54%, method C) (32%, method D), mp 134 °C (from hexane) (Found: C, 55.10; H, 3.88; N, 12.52. $C_{10}H_8N_2O_2S$ requires C, 54.58; H, 3.66; N, 12.73%); ν_{max}(KBr)/cm^{-1} 2932, 2225 (CN), 2057 (N=C=S), 1731, 1660, 1651, 1593, 1520, 1505, 1282, 1002 and 874; δ_H(400 MHz, $CDCl_3$) 3.90 (3H, s, OMe), 3.93 (3H, s, OMe), 6.76 (1H, s, H_{arom}) and 6.96 (1H, s, H_{arom}); δ_C(100 MHz, $CDCl_3$) 56.46 (CH_3O), 56.50 (CH_3O), 101.04, 107.78, 109.44, 113.58, 115.87, 137.36 (NCS), 148.12 and 153.40; *m*/*z* 220 (M^+, 100%), 205 ($M^+ - CH_3$, 47) and 162 ($M^+ - N=C=S$, 15).

2,3-Dihydro-1,4-benzodioxane 6-isothiocyanate. Colourless needles (47%, method A) (92%, method B) (73%, method C) (54%, method D) (54%, method E), mp 74 °C (from hexane) (Found: C, 55.83; H, 3.51; N, 7.03. $C_9H_7NO_2S$ requires C, 56.00; H, 3.65; N, 7.26%); ν_{max}(KBr)/cm^{-1} 2978, 2163, 2135 (N=C=S), 1636, 1538, 1499, 1313, 1304, 1290, 1064 and 890; δ_H(400 MHz, $CDCl_3$) 4.26 (4H, s, OCH_2CH_2O), 6.74 (1H, dd, *J* 2.40 and 8.50 Hz, H_{arom}), 6.76 (1H, d, *J* 2.40 Hz, H_{arom}) and 6.81 (1H, d, *J* 8.30 Hz, H_{arom}); δ_C(100 MHz, $CDCl_3$) 64.29, 64.31, 114.69, 117.94, 119.19, 123.00, 134.04 (NCS),

143.13 and 143.77; *m*/*z* 193 (M^+, 100%), 178 (6), 137 (53), 109 (34).

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