PERKIN 1
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New route to 2-cyanobenzothiazoles *via* *N*-arylimino-1,2,3-dithiazoles †

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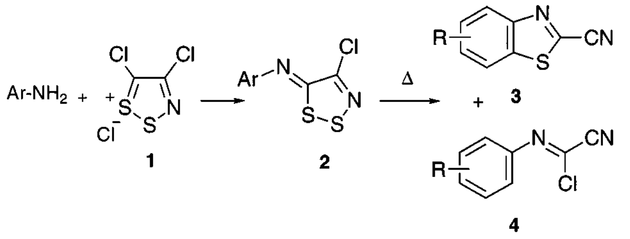
***N*-Arylimino-1,2,3-dithiazole derivatives 2 of 2-bromoanilines are converted in high yield into 2-cyanobenzothiazoles 3 by heating or, more rapidly, by focused microwave irradiation at atmospheric pressure, in pyridine containing cuprous iodide.**

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 easily available from chloroacetonitrile and disulfur dichloride.[1] These iminodithiazoles **2** have proved to be highly versatile intermediates in heterocyclic synthesis.[2] Previous work showed that imino compounds **2** cyclised on vigorous heating to give sulfur, hydrogen chloride and 2-cyanobenzothiazoles **3** (Scheme 1).[3] An electron releasing group (R = *m*-OMe) favoured formation of the benzothiazole **3** whilst a strongly electron withdrawing group (R = *m*- or *p*-NO_2) reduced the yield of **3** dramatically, in favour of the cyanoimidoyl chloride **4** which became the major product (*e.g.* 9% of **3** and 54% of **4** with R = *m*-NO_2).[3] The thermolysis procedures consisted of heating the neat imines **2** under argon at 200–250 °C (metal bath) for 1 to 2 minutes, or exposing these imines to microwave irradiation (neat in a glass vial with a screw-cap lid).[4] In this paper we describe a mild procedure allowing a ready synthesis of 2-cyanobenzothiazoles with electron-withdrawing as well as electron-releasing substituents in the benzene ring. We find that heating *o*-bromophenyl derivatives of imines **2** in the presence of cuprous iodide in pyridine at reflux afforded good yields of 2-cyanobenzothiazoles **3** (Table 1); no cyanoimidoyl chloride derivatives **4** were detected. As part of our work on the application of microwave irradiation to organic synthesis we transposed this reaction in pyridine to a focused microwave reactor (open oven, monomode system)[5] and reduced the reaction times with no loss in yields (Table 1).



Scheme 1

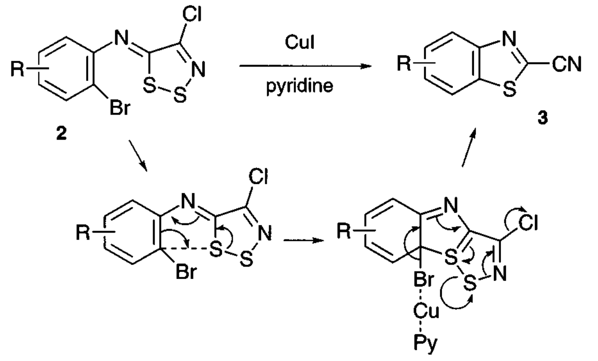
The electrocyclisation and fragmentation process previously suggested[3] (Scheme 2) may be facilitated by halogen complexation as described before for the cyanation of aryl halides by copper(I) cyanide;[6] 2-cyanobenzothiazoles are also formed in the presence of Cu^ICN or Cu^0 but in lower yields.

This new and rapid method for converting 2-bromoanilines into 2-cyanobenzothiazoles in two simple steps is useful for the synthesis of highly substituted derivatives even with electron withdrawing substituents and it provides another example of the utility of focused microwaves for accelerating thermal organic reactions in solution.[7]

Table 1 Preparation of 2-cyanobenzothiazoles **3** from the imino-1,2,3-dithiazoles **2** and CuI in pyridine

Starting imines **2** (R)	Product **3**	Conventional heating[a] *t*/min	Conventional heating[a] Yield (%)[b]	Microwave irradiation (300 W) *t*/min	Microwave irradiation (300 W) Yield (%)[b]
H	**a**	45	67	10	69
4-F	**b**	60	80	10	87
4-Me	**c**	60	84	12	85
4-NO_2	**d**	45	68	10	65
5-CF_3	**e**	45	79	10	82
4,5-di-F	**f**	45	58	10	61

[a] Oil bath. [b] All the reactions were performed three times and yields given are average values.



Scheme 2

Experimental

Spectral data for compounds **2** and **3** were consistent with the assigned structures. Dithiazoles **2** were prepared as described in refs. 2 and 3.

IR spectra were recorded on a Perkin-Elmer Paragon 1000PC instrument. ^1H and ^{13}C-NMR were recorded on a JEOL JNM LA400 (400 MHz) spectrometer (Laboratoire Commun d'Analyse, Université de La Rochelle); chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane ($SiMe_4$), 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. Light petroleum refers to the fraction bp 40–60 °C.

Focused microwave irradiations were carried out at atmospheric pressure with a Synthewave S402 (capacity of the quartz reactor used: 10 and 70 ml) Prolabo microwave reactor (300 W, monomode system) which has a quartz reactor, variable speed rotation, visual control, irradiation (300 W) monitored by PC computer, infrared measurement and continuous feedback temperature control (by PC).[5]

Typical procedure for the synthesis of 2-cyanobenzothiazoles

A stirred mixture of dithiazole **2** (1 mmol) and CuI (1.1 mmol) was heated or irradiated in pyridine (10 ml) for the time shown (Table 1). Dichloromethane (10 ml) was added and the organic layer washed twice with a sodium thiosulfate solution (20%). The crude product was purified by column chromatography on silica gel with light petroleum–dichloromethane as the eluent. No benzothiazole was formed in the absence of CuI.

Selected data for new compounds

6-Methylbenzothiazole-2-carbonitrile 3c. White needles, mp 92 °C (from propan-2-ol) (Found: M^+, 174.0252. $C_9H_6N_2S$ requires *M*, 174.0252); ν_{max}(KBr)/cm^{-1} 2940, 2228 (CN), 1607, 1560, 1474, 1316, 1244 and 816; δ_H (400 MHz, $CDCl_3$) 7.46 (1H, dd, *J* 1.6 and 8.6 Hz, H_{arom}), 7.76 (1H, d, *J* 1.6 Hz, H_{arom}), 8.10 (1H, d, *J* 8.6 Hz, H_{arom}); δ_C (100 MHz, $CDCl_3$) 21.81 (Me), 113.14 (CN), 121.21, 124.71, 129.79, 135.30, 135.69, 139.52 and 150.53; *m*/*z* 174 (M^+, 100%), 146 (3), 121 (18).

5-Trifluoromethylbenzothiazole-2-carbonitrile 3e. White needles, mp 102 °C (from propan-2-ol) (Found: M^+, 277.9966. $C_9H_3N_2SF_3$ requires *M*, 227.9969); ν_{max}(KBr)/cm^{-1} 3046, 2241 (CN), 1939, 1615, 1460, 1339, 1316, 1064 and 927; δ_H (400 MHz, $CDCl_3$) 7.85 (1H, dd, *J* 1.2 and 8.6 Hz, H_{arom}), 8.12 (1H, d, *J* 8.6 Hz, H_{arom}), 8.49 (1H, s, H_{arom}); δ_C (100 MHz, $CDCl_3$) 112.33 (CN), 122.66, 122.76, 123.52 (CF_3), 124.88, 130.86, 138.38, 138.79 and 151.78; *m*/*z* 228 (M^+, 100%), 209 (10), 157 (18), 132 (15).

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Notes and references

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1 R. Appel, H. Janssen, M. Siray and F. Knoch, *Chem. Ber.*, 1985, **118**, 1632.
2 (*a*) T. Besson, K. Emayan and C. W. Rees, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 2097; (*b*) O. A. Rakitin, C. W. Rees and O. G. Vlasova, *Tetrahedron Lett.*, 1996, **37**, 4589; (*c*) T. Besson and C. W. Rees, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 2857; (*d*) C. W. Rees, D. G. Roe and V. Thiéry, *Chem. Commun.*, 1996, 2775; (*e*) T. Besson, G. Guillaumet, C. Lamazzi and C. W. Rees, *Synlett*, 1997, 704.
3 (*a*) C. W. Rees, *J. Heterocycl. Chem.*, 1992, **29**, 639; (*b*) T. Besson and C. W. Rees, *J. Chem. Soc.*, *Perkin Trans. 1*, 1995, 1659; (*c*) R. F. English, O. A. Rakitin, C. W. Rees and O. G. Vlasova, *J. Chem. Soc.*, *Perkin Trans. 1*, 1997, 201.
4 V. Bénéteau, T. Besson and C. W. Rees, *Synth. Commun.*, 1997, **27**, 2275.
5 (*a*) R. Commarmot, R. Didenot and J. F. Gardais, Rhône-Poulenc/Prolabo, Patent 84/03496, 1984, Fr. Pat. FR 2560686, 1985; (*b*) P. Jacquault, Prolabo, Fr. Pat. FR 9116286, 1991.
6 G. P. Ellis and T. M. Romney-Alexander, *Chem. Rev.*, 1987, **87**, 779.
7 T. Besson, M. J. Dozias, J. Guillard, P. Jacquault, M. D. Legoy and C. W. Rees, *Tetrahedron*, 1998, **54**, 6475; For reviews see: S. Caddick, *Tetrahedron*, 1995, **51**, 10403; K. Bougrin, M. Soufiaoui, A. Loupy and P. Jacquault, *New. J. Chem.*, 1995, **19**, 213; S. A. Galema, *Chem. Soc. Rev.*, 1997, **26**, 233.

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