View Article Online / Journal Homepage / Table of Contents for this issue

Published on 03 February 2000. Downloaded by Universitat Politècnica de València on 26/10/2014 01:07:43.

Rapid synthesis of 2-cyanobenzothiazole, isothiocyanate and cyanoformanilide derivatives of dapsone †

Thierry Besson,[a] Jérôme Guillard[a] and Charles W. Rees[b]

[a] *Laboratoire de Génie Protéique et Cellulaire, UPRES 2001, Groupe de Chimie Organique, Pôle Sciences et Technologie, Université de La Rochelle, Avenue Marillac, F-17042 La Rochelle cedex 1, France. E-mail: tbesson@bio.univ-lr.fr*

[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, London, UK SW7 2AY. E-mail: c.rees@ic.ac.uk*

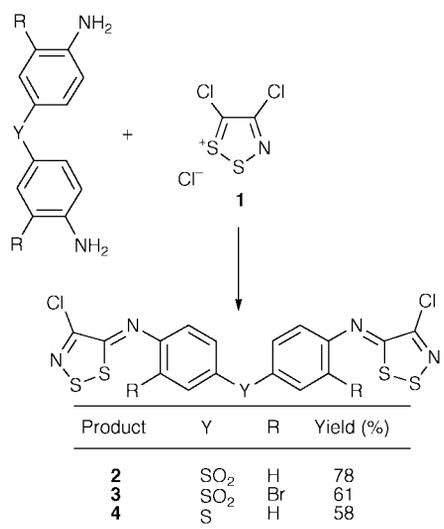
Received (in Cambridge, UK) 2nd November 1999, Accepted 8th December 1999

New derivatives of the leprostatic drug dapsone are prepared by way of imino-1,2,3-dithiazoles obtained by condensation of aromatic primary bisamines, including dapsone, with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt). Reactions, including microwave irradiation, initiated by nucleophilic attack at different sites of the dithiazole ring transform the bisiminodithiazoles into the symmetrical, and some unsymmetrical, title compounds.

Primary aromatic amines are readily converted into stable *N*-arylimino-1,2,3-dithiazoles in high yield.[1,2] We have recently shown that these derivatives are versatile synthetic intermediates undergoing a variety of reactions initiated by nucleophilic attack at different sites on the dithiazole ring.[3] Some of these reactions transform the dithiazole ring only, *e.g.* to give isothiocyanates, whilst others involve cyclisation onto an adjacent aromatic ring. As part of a search for compounds with potential pharmacological value, it seemed that these transformations might provide a simple way to modify the structure of the leprostatic drug dapsone[4] [bis(4-aminophenyl) sulfone], and a new synthesis of the corresponding bisisothiocyanate **8**, the anthelmintic drug centsulphone.[5] Dapsone remains one of the main drugs for the treatment of leprosy, although its action is only bacteriostatic, and it has been used for the treatment of dermatitis herpetiformis. Isothiocyanates like centsulphone are also of pharmacological use as irreversible acylating agents to label proteins and enzymes. Furthermore, these reactions would illustrate the applicability or otherwise of Appel salt chemistry to aromatic diamines; we also hoped to extend our use of a focused microwave oven (open oven, monomode system) as an alternative to the direct thermolysis of dithiazoles.[6]

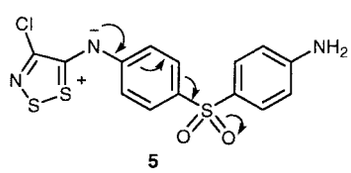
Results and discussion

Using a standard method for the preparation of *N*-arylimino-1,2,3-dithiazoles, the starting bisamines were condensed with 4,5-dichloro-1,2,3-dithiazolium chloride **1**[1] (2 equiv.) in dichloromethane at room temperature, followed by addition of pyridine, to give the desired imines **2**, **3** and **4** in good yields (58–78%) (Scheme 1). To our initial surprise, we did not isolate, or detect, any of the monoimines, *e.g.* **5**. With less than 2 equivalents of Appel salt **1** we simply obtained correspondingly lower yields of the bisimines, **2–4**. This is understandable for the sulfones **2** and **3** where the remaining amino group, *e.g.* in **5**, is probably more nucleophilic than in the starting bisamines because of strong electron release from the iminodithiazole (in its aromatic dipolar form **5**) neutralising electron withdrawal from the sulfone group. The sulfone **2** was also prepared by oxidation of the sulfide **4** with *m*-chloroperbenzoic acid (MCPBA), without oxidation of the dithiazole sulfur atoms.



Product	Y	R	Yield (%)
2	SO_2	H	78
3	SO_2	Br	61
4	S	H	58

Scheme 1



5

Bis(4-aminophenyl) sulfone (dapsone) derivatives (Scheme 2)

Thermolysis of the neat sulfone **2** at 200 °C gave only the corresponding bis(cyanoimidoyl chloride) **6**. This result accords with our previous work on the thermolysis of *N*-arylimino-1,2,3-dithiazoles; electron-releasing groups on the aryl ring favoured formation of the benzothiazole ring whilst strongly electron-withdrawing groups may lead exclusively to the cyanoimidoyl chloride.[7] However the bis(benzothiazolyl) sulfone **7** was rapidly prepared in good yield (70%) by microwave irradiation of the bis(bromoaryliminodithiazole) **3**[8] in pyridine in the presence of cuprous iodide (CuI) where the aryl *ortho* positions are activated towards attack by the dithiazole ring[6b] (Scheme 2).

Treatment of the bis(imino-1,2,3-dithiazole) **2** with 4 equiv. of ethylmagnesium bromide in THF afforded the bisisothiocyanate **8** (centsulphone[5]) in 38% yield. We recently reported[3a] that various *N*-aryliminodithiazoles may also be reduced with

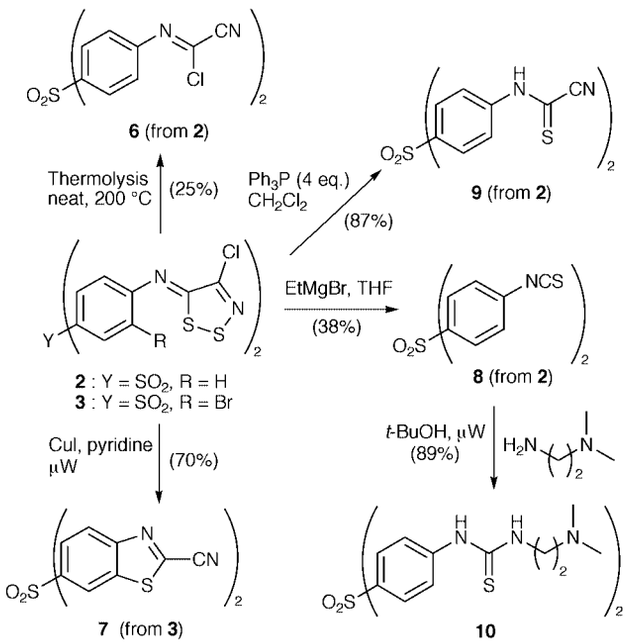
† This work is a part of the PhD thesis of J. G. under the supervision of T. B.

DOI: 10.1039/a908742g

This journal is © The Royal Society of Chemistry 2000

View Article Online

Published on 03 February 2000. Downloaded by Universitat Politècnica de València on 26/10/2014 01:07:43.



Scheme 2

one equivalent of sodium hydride to give the cyanothioformanilides which react further with sodium hydride, with elimination of cyanide, to give isothiocyanates, and this overall transformation can be done in one pot. In the present case the Grignard reagent method gave better results. The sulfone imine **2** was also converted into the corresponding bis(cyanothioformanilide) **9** (87%) with four mole equivalents of triphenylphosphine in dichloromethane at room temperature. Microwave irradiation of a solution of the bisisothiocyanate **8** in *tert*-butyl alcohol, in the presence of three mole equivalents of *N*,*N*-dimethylethylenediamine, gave the corresponding bisthiourea **10** in 98% yield (Scheme 2).

Bis(4-aminophenyl) sulfide derivatives

The bis(iminophenyl) sulfide **4** was similary converted into products (Chart 1) analogous to those shown in Scheme 2 for

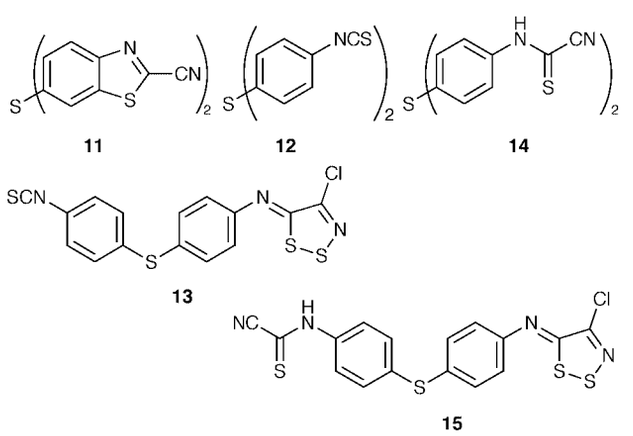


Chart 1

the sulfone **2**, though some of these reactions also gave the unsymmetrical products of reaction at only one dithiazole ring. Microwave irradiation of **4** gave the bisbenzothiazole **11** (66%). Ethylmagnesium bromide (2 equiv.) in THF gave the bisisothiocyanate **12** but in very poor yield (11%), together with the monoisothiocyanate **13** (17%); the yield of the bisisothiocyanate **12** was not improved with 4 or 6 equiv. of the Grignard reagent. Triphenylphosphine (4 equiv.) gave the biscyanothioformanilide **14** (60%), and the monocyanothioformanilide **15** was produced in modest yield (40%) with 2 equiv. of triphenylphosphine.

The results of testing for the biological activity of these compounds will be reported elsewhere.

Experimental

Mps were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Paragon 1000PC instrument. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL JNM LA400 spectrometer (Centre Commun d'Analyse, Université de La Rochelle, France); chemical shifts (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 Mesures Physiques de L'Ouest (C.R.M.P.O.), Université de Rennes, France. Chromatography was carried out on Merck silica gel 60 (70–230 mesh). TLC was performed on Merck Kieselgel 60 F_{254} aluminium-backed plates. Light petroleum refers to the fraction with distillation range 40–60 °C. Focused microwave irradiations were carried out with a Synthewave™ S402 Prolabo® microwave reactor (monomode system, 2450 MHz, 300 W) which has variable-speed rotation, visual control, irradiation monitored by PC computer, IR measurement and continuous feedback temperature control (by PC).[9] Samples were dried over $MgSO_4$.

Bis(4-amino-3-bromophenyl) sulfone[8]

To a solution of bis(4-aminophenyl) sulfone (dapsone) (1.0 g, 4.03 mmol) in acetic acid (20 ml) was added bromine (0.206 ml, 4.03 mmol). The mixture was stirred at room temperature for 40 min then water (20 ml) was added. The white precipitate obtained was filtered off, washed with water and dried. The crude product was purified by column chromatography (dichloromethane–ethyl acetate, 9 : 1) to give the *title compound* (0.142 g, 35%) as colourless needles, mp 192–193 °C (from EtOH) (Found: M^+, 403.8822. $C_{12}H_{10}{}^{79}Br_2N_2O_2S$ requires *M*, 403.8829); ν_{max} (KBr)/cm^{-1} 3364, 1614, 1573, 1557, 1494, 1403, 1320, 1139 and 731; δ_H (400 MHz; acetone-d_6) 5.8 (4H, br s, NH_2), 6.93 (2H, d, *J* 8.5 Hz, H_{arom}), 7.59 (2H, dd, J_1 2.2, J_2 8.5 Hz, H_{arom}), 7.88 (2H, d, *J* 2.1 Hz, H_{arom}); δ_C (100 MHz; acetone-d_6) 107.4, 115.5, 128.9, 131.7, 132.6, 150.6; *m/z* 406 (M^+, 100%), 404 (M^+, 50), 220 (56), 218 (57), 188 (50), 186 (61), 172 (16), 171 (15), 170 (21), 91 (72), 90 (98).

Bis[4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenyl] sulfone 2

From bis(4-aminophenyl) sulfone (dapsone). 4,5-Dichloro-1,2,3-dithiazolium chloride **1** (0.416 g, 2 mmol) was added to a solution of dapsone (0.248 g, 1 mmol) in dichloromethane (10 ml) and the mixture was stirred at room temperature until the amine was consumed (TLC). Then pyridine (0.324 ml, 4 mmol) was added and the mixture was stirred for a further 1 h, filtered and the crude product obtained by evaporation of the solution was purified by column chromatography (dichloromethane) to give the *title compound* **2** (0.405 g, 78%) as yellow needles, mp 209 °C (from light petroleum) (Found: M^+, 517.8615. $C_{16}H_8{}^{35}Cl_2N_4O_2S_5$ requires *M*, 517.8628); ν_{max} (KBr)/cm^{-1} 3054, 1570, 1499, 1483, 1399, 1318, 1288, 1221, 1151, 1103 and 867; δ_H (400 MHz; $CDCl_3$) 7.29 (4H, d, *J* 7.9 Hz, H_{arom}), 8.04 (4H, d, *J* 8.4 Hz, H_{arom}); δ_C (100 MHz; $CDCl_3$) 120.1, 129.9, 138.6, 147.8, 155.5, 160.9; *m/z* 520 (M^+, 5%), 518 (M^+, 5), 456 ($M^+ - [S_2]$, 35), 454 ($M^+ - [S_2]$, 4), 427 ($M^+ - [Cl,CN,S]$, 2), 425 ($M^+ - [Cl,CN,S]$, 5), 392 ($M^+ - [Cl_2,CN,S]$, 38), 390 ($M^+ - [Cl_2,CN,S]$, 6), 64 ([S_2], 100).

From bis[4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-phenyl] sulfide 4. To a cooled (0 °C) solution of the bisimino-

View Article Online

Published on 03 February 2000. Downloaded by Universitat Politècnica de València on 26/10/2014 01:07:43.

dithiazole **4** (0.2 g, 0.41 mmol) in dichloromethane (10 ml) was added MCPBA (0.282 g, 0.82 mmol). The mixture was stirred at 0 °C for 1 h. Purification by column chromatography with dichloromethane as eluent afforded the *title compound* (0.129 g, 61%), identical with that described above.

Bis[3-bromo-4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)-phenyl] sulfone 3

A solution of the bis(3-bromo-4-aminophenyl) sulfone (0.519 g, 1 mmol) and pyridine (0.324 ml, 4 mmol) in dichloromethane (20 ml) was stirred at 0 °C for 15 min. 4,5-Dichloro-1,2,3-dithiazolium chloride **1** (0.416 g, 4 mmol) was added and the mixture was stirred for a further 4 h. The crude product was purified by column chromatography (light petroleum–dichloromethane, 3:7) to give the *title compound* (0.413 g, 61%) as yellow needles, mp 196–198 °C (from Pr^{i}OH) (Found: M$^+$, 674.6901. $C_{16}H_6{}^{79}Br_2{}^{35}Cl_2N_4O_2S_5$ requires *M*, 674.6916); ν_{max} (KBr)/cm^{-1} 3075, 1610, 1574, 1463, 1379, 1318, 1232, 1161, 866 and 739; δ_H (400 MHz; $CDCl_3$) 7.22 (2H, d, *J* 8.4 Hz, H_{arom}), 7.96 (2H, dd, J_1 2.1, J_2 8.3 Hz, H_{arom}), 8.26 (2H, d, *J* 2 Hz, H_{arom}); δ_C (100 MHz; $CDCl_3$) 116.1, 119.3, 128.8, 133.4, 139.0, 147.4, 154.6, 162.40; *m*/*z* 678 ([M + H]$^+$, 90%), 676 ([M + H]$^+$, 100), 613 (20), 410 (72), 289 (26), 136 (64).

Bis[4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenyl] sulfide 4

4,5-Dichloro-1,2,3-dithiazolium chloride **1** (0.416 g, 2 mmol) was added to a solution of bis(4-aminophenyl) sulfide (0.216 g, 1 mmol) in dichloromethane (10 ml) and the mixture was stirred at room temperature until the amine was consumed (TLC). Then pyridine (0.324 ml, 4 mmol) was added and the mixture was stirred for a further 1 h, filtered and the crude product obtained by evaporation of the solution was purified by column chromatography (light petroleum–dichloromethane, 1:1) to give the *title compound* (0.283 g, 58%) as orange needles, mp 138–140 °C (from hexane) (Found: M$^+$, 485.8748. $C_{16}H_8{}^{35}Cl_2N_4S_5$ requires *M*, 485.8729); ν_{max} (KBr)/cm^{-1} 3047, 1892, 1697, 1588, 1566, 1543, 1480, 1396, 1226, 1135, 858 and 775; δ_H (400 MHz; $CDCl_3$) 7.22 (4H, d, *J* 8.8 Hz, H_{arom}), 7.44 (4H, d, *J* 8.8 Hz, H_{arom}); δ_C (100 MHz; $CDCl_3$) 120.7, 132.3, 133.7, 148.2, 149.7, 158.3; *m*/*z* 488 (M$^+$, 3%), 486 (M$^+$, 3), 360 (M$^+$ − [2 × S_2], 11), 358 (M$^+$ − [2 × S_2], 15), 258 (10), 256 (35), 160 (37), 128 (36), 96 (25), 64 (S_2, 100).

Bis{4-*N*-[chloro(cyano)methyleneamino]phenyl} sulfone 6

The bisiminodithiazole **2** (0.10 g, 1.9 mmol) was heated under nitrogen at 200 °C for 6 min (graphite-bath). Purification by column chromatography with dichloromethane as eluent afforded the *title compound* **6** (0.0185 g, 25%) as colourless needles, mp 122–124 °C (from Pr^{i}OH) (Found: M$^+$, 389.9756. $C_{16}H_8{}^{35}Cl_2N_4O_2S$ requires *M*, 389.9745); ν_{max} (KBr)/cm^{-1} 3095, 2241, 1652, 1646, 1587, 1485, 1404, 1321, 1288, 1154, 1103, 1048 and 843; δ_H (400 MHz; $CDCl_3$) 7.17 (4H, d, *J* 8.6 Hz, H_{arom}), 8.05 (4H, d, *J* 8.7 Hz, H_{arom}); δ_C (100 MHz; $CDCl_3$) 111.6, 118.4, 121.3, 129.3, 140.2, 147.7; *m*/*z* 392 (M$^+$, 25%), 390 (M$^+$, 35), 357 (M$^+$ − [Cl_2], 5), 355 (M$^+$ − [Cl_2], 12), 213 (39), 211 (100), 181 (13), 179 (53).

Bis(2-cyanobenzothiazol-6-yl) sulfone 7

A stirred mixture of bis-1,2,3-dithiazole **3** (0.677 g, 1 mmol) and cuprous iodide (0.209 g, 1.1 mmol) in pyridine was placed in a microwave reactor (Synthewave 402) in an open flask. The solution was irradiated (with a delay of 10–15 s to obtain the temperature desired) at 90 °C for 20 min. After cooling of the mixture dichloromethane (10 ml) was added and the organic layer was washed twice with aq. sodium thiosulfate (20%). The crude product was purified by column chromatography to give the *title compound* **7** (0.271 g, 70%) as colourless needles, mp 250–252 °C (from Pr^{i}OH) (Found: M$^+$, 381.9664. $C_{16}H_6N_4O_2S_3$ requires *M*, 381.9653); ν_{max} (KBr)/cm^{-1} 3065, 2236 (CN), 1789, 1587, 1471, 1400, 1321, 1275, 1162, 1134, 1108, 886, 824, 774 and 618; δ_H (400 MHz; $CDCl_3$) 8.18 (2H, dd, J_1 1.8, J_2 8.7 Hz, H_{arom}), 8.36 (2H, d, *J* 8.8 Hz, H_{arom}), 8.74 (2H, d, *J* 1.7 Hz, H_{arom}); δ_C (100 MHz; $CDCl_3$) 112.6, 122.9, 126.7, 126.7, 135.9, 140.9, 141.2, 154.8; *m*/*z* 382 (M$^+$, 40%), 207 (100), 176 (8), 159 (27), 107 (20).

Bis(4-isothiocyanatophenyl) sulfone 8 (centsulfone)

Under an argon atmosphere, commercial ethylmagnesium bromide (4 mmol; 1 M in THF) was added dropwise to a solution of the bisimine **2** (0.519 g, 1 mmol) in THF. The brown mixture obtained was heated at reflux until the starting material was consumed (3 h; TLC). After addition of dichloromethane (20 ml), the solution was washed with water and the organic layer dried over sodium sulfate. The crude product obtained was purified by column chromatography (light petroleum–dichloromethane, 6:4) to give product **8** (0.126 g, 38%) as colourless needles, mp 181 °C (from hexane) (lit.,[5] 180 °C) (Found: M$^+$, 331.9743. $C_{18}H_8N_2O_2S_3$ requires *M*, 331.9748); ν_{max} (KBr)/cm^{-1} 3094, 3035, 2121 (NCS), 1585, 1488, 1406, 1319, 1287, 1152, 1069, 933 and 836; δ_H (400 MHz; $CDCl_3$) 7.32 (4H, d, *J* 8.3 Hz, H_{arom}), 7.91 (4H, d, *J* 8.8 Hz, H_{arom}); δ_C (100 MHz; $CDCl_3$) 126.6, 129.3, 136.8, 139.3, 139.7; *m*/*z* 332 (M$^+$, 100%), 182 (86), 150 (41), 134 (40).

Bis[4-(cyanothioformamido)phenyl] sulfone 9

Stirring of the bisimine **2** (0.519 g, 1 mmol) with triphenylphosphine (1.072 g, 4 mmol) in dichloromethane (10 ml) at room temperature for 3 h, followed by column chromatography (dichloromethane–ethyl acetate, 1:1), gave the title compound **9** (0.336 g, 87%) as orange needles, mp 106 °C (from EtOH); ν_{max} (KBr)/cm^{-1} 3262, 3064, 2235, 1592, 1493, 1376, 1299, 1154, 1106, 839 and 725; δ_H (400 MHz; DMSO-d_6) 8.06 (4H, d, *J* 8.9 Hz, H_{arom}), 8.11 (4H, d, *J* 8.4 Hz, H_{arom}), 13.72 (2H, br s, NH-CSCN); δ_C (100 MHz; $CDCl_3$) 113.7, 123.3, 128.7, 138.7, 142.1, 162.6; *m*/*z* 386 (M$^+$, not detected), 332 (M$^+$ − 2[HCN], 52%), 277 (100), 199 (37), 182 (34).

Bis(4-{N^3-[2-(dimethylamino)ethyl]thioureido}phenyl) sulfone 10

A stirred mixture of bis(4-isothiocyanatophenyl) sulfone **8** (0.332 g, 1 mmol) and *N*,*N*-dimethylethylenediamine (0.264 g, 3 mmol) in *tert*-butyl alcohol (2 ml) was placed in a microwave reactor in an open flask. The solution was irradiated (with a delay of 10–15 s to obtain the reflux) for 5 min. The hot solution obtained was filtered, the solvent evaporated off, and the crude product purified by column chromatography (ethyl acetate–dichloromethane, 1:1) to give the *title compound* **10** (0.452 g, 89%) as colourless needles, mp 198–200 °C (from Pr^{i}OH) (Found: MH$^+$, 509.1820. $C_{22}H_{32}N_6O_2S_3$ requires *MH*, 509.1827); ν_{max} (KBr)/cm^{-1} 2950, 2774, 1625, 1593, 1537, 1494, 1317, 1156, 1105, 1045, 944, 842 and 742; δ_H (400 MHz; DMSO-d_6) 1.02 (3H, s, CH_3), 1.03 (3H, s, CH_3), 2.41 [2H, t, *J* 6 Hz, $NH_2CH_2CH_2N(CH_3)_2$], 3.53 [2H, m, $NH_2CH_2CH_2$-$N(CH_3)_2$], 7.76–7.83 (4H, m, H_{arom}), 7.97 (1H, br s, NHCS), 10.1 (1H, br s, NHCS); δ_C (100 MHz; DMSO-d_6) 41.7, 44.95 (2 × Me), 56.9, 121.1, 127.9, 135.0, 144.4, 179.8; *m*/*z* 509 ([M + H]$^+$, 100%), 421 ([M + H]$^+$ − [$NH_2CH_2CH_2N(CH_3)_2$], 36), 376 (47), 289 (15).

Bis(2-cyanobenzothiazol-6-yl) sulfide 11

A solution of the bisimine **4** (0.1 g, 0.2 mmol) in toluene (1 ml) was placed in a microwave oven in a glass 10 ml vial with a screw-cap lid. The irradiation was programmed for 7 min with a delay of 5 s to obtain 100% power output (300 W). The temperature (IR measurement) was constant over a period of 30 s

View Article Online

Published on 03 February 2000. Downloaded by Universitat Politècnica de València on 26/10/2014 01:07:43.

to 2 min followed by a sharp increase in temperature, over a period of 1 min, which appeared to reach a plateau (80 °C) for 1 min. Thereafter the temperature increased over a period of 3 min to 140 °C. After cooling, the brown reaction mixture (oil) was purified by column chromatography (light petroleum–ethyl acetate, 9:1) to give the *title compound* **11** (0.25 g, 66%) as yellow needles, mp 250–252 °C (from light petroleum) (Found: M^+, 349.9760. $C_{16}H_6N_4S_3$ requires *M*, 349.9755); ν_{max} (KBr)/cm^{-1} 2228 (CN), 1582, 1538, 1463, 1397, 1144, 1087 and 810; δ_H (400 MHz; $CDCl_3$) 7.62 (2H, dd, J_1 1.9, J_2 9 Hz, H_{arom}), 7.94 (2H, d, *J* 2 Hz, H_{arom}), 8.18 (2H, d, *J* 8.8 Hz, H_{arom}); δ_C (100 MHz; $CDCl_3$) 112.7, 123.6, 126.0, 130.9, 136.6, 136.7, 137.1, 151.6; *m/z* 350 (M^+, 100%), 266 (5), 253 (5), 191 (3), 175 (3), 139 (7), 127 (5), 107 (6).

Bis(4-isothiocyanatophenyl) sulfide 12 and 4-(4-chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenyl] 4-isothiocyanatophenyl sulfide 13

Under an argon atmosphere, a solution of ethylmagnesium bromide (0.82 mmol; 1 M in THF) was added dropwise to a solution of the bisimine **4** (0.2 g, 0.41 mmol) in THF (20 ml). The brown mixture obtained was heated at 50 °C for about 2 h. After addition of dichloromethane (20 ml), the solution was washed with water, the organic layer dried over sodium sulfate and the solvent evaporated off. The crude product was purified by column chromatography (light petroleum–dichloromethane, 7:3) to give the *title compound* **12** (0.007 g, 11%) as colourless needles, mp 120–122 °C (from light petroleum) (Found: M^+, 299.9842. $C_{14}H_8N_2S_3$ requires *M*, 299.9849); ν_{max} (KBr)/cm^{-1} 2100 (NCS), 1584, 1486, 1380, 1221, 1016 and 870; δ_H (400 MHz; $CDCl_3$) 7.16 (4H, d, *J* 8.6 Hz, H_{arom}), 7.28 (4H, d, *J* 8.3 Hz, H_{arom}); δ_C (100 MHz; $CDCl_3$) 126.6, 130.6, 132.1, 134.5, 136.7; *m/z* 300 (M^+, 100%), 268 (18), 242 (M^+ − [NCS], 5), 209 (8), 184 (38), 166 (15), 108 (28).

Further elution (light petroleum–dichloromethane, 1:1) gave the *title compound* **13** (0.014 g, 17%) as red needles, mp 150–152 °C (from light petroleum) (Found: M^+, 392.9288. $C_{15}H_8{}^{35}ClN_3S_4$ requires *M*, 392.9289); ν_{max} (KBr)/cm^{-1} 2088 (NCS), 1583, 1483, 1398, 1222, 1082, 1010, 928, 863 and 822; δ_H (400 MHz; $CDCl_3$) 7.16 (2H, d, *J* 8.8 Hz, H_{arom}), 7.22 (2H, d, *J* 8.8 Hz, H_{arom}), 7.27 (2H, d, *J* 8.4 Hz, H_{arom}), 7.45 (2H, d, *J* 8.8 Hz, H_{arom}); δ_C (100 MHz; $CDCl_3$) 120.8, 126.5, 130.0, 131.2, 132.4, 133.3, 135.8, 137.2, 148.1, 150.3, 159.1; *m/z* 395 (M^+, 26%), 355 (53), 300 (87), 294 (13), 284 (17), 269 (30), 243 (22), 184 (100), 166 (48).

Bis[4-(cyanothioformamido)phenyl] sulfide 14

The bisimine **4** (0.488 g, 1 mmol) and triphenylphosphine (1.072 g, 4 mmol) were stirred in dichloromethane (10 ml) at room temperature for 6 h. Purification by column chromatography (light petroleum–dichloromethane, 7:3) gave the *title compound* **14** (0.213 g, 60%) as red needles, mp 208–210 °C (from MeOH) (Found: $(M - HCN)^+$, 326.9964. $C_{15}H_9N_3S_3$ requires *M*, 326.9958); ν_{max} (KBr)/cm^{-1} 3260, 3103, 2232, 1706, 1654, 1590, 1534, 1490, 1388, 1085, 1009 and 825; δ_H (400 MHz; DMSO-d_6) 7.4–7.51 (4H, m, H_{arom}), 7.94 (4H, dd, J_1 2.5, J_2 8.8 Hz, H_{arom}), 13.5 (2H, br s, NH-CS); δ_C (100 MHz; DMSO-d_6) 113.8, 123.5, 131.2, 133.6, 137.1, 161.1; *m/z* 354 (M^+, not detected), 327 (M^+ − [HCN], 8%), 300 (M^+ − 2[HCN], 63), 184 (M^+ − 2[NHCSCN], 14), 27 (100).

4-(4-Chloro-5*H*-1,2,3-dithiazol-5-ylideneamino)phenyl 4-(cyanothioformamido)phenyl sulfide 15

The bisimine **4** (0.350 g, 0.72 mmol) and triphenylphosphine (0.377 g, 1.44 mmol) were stirred in dichloromethane (10 ml) at room temperature for 10 h. Purification by column chromatography (dichloromethane) gave the title compound **15** (0.053 g, 40%) as orange needles, mp 138–140 °C (from CH_2Cl_2); ν_{max} (KBr)/cm^{-1} 3266, 2230 (CN), 1589, 1488, 1372, 1222, 1083, 1010, 862 and 826; δ_H (400 MHz; DMSO-d_6 + D_2O) 7.26 (2H, d, *J* 8.4 Hz, H_{arom}), 7.39 (2H, d, *J* 8.4 Hz, H_{arom}), 7.48 (2H, d, *J* 8.4 Hz, H_{arom}), 7.92 (2H, d, *J* 8.4 Hz, H_{arom}); δ_C (100 MHz; DMSO-d_6) 113.7 (CN), 120.9, 123.4, 130.3, 130.8, 133.2, 134.8, 136.7, 146.9, 150.5, 159.9, 160.9; *m/z* 420 (M^+, not detected), 300 (M^+ − [HCN, ClCNS], 44%), 192 (21), 184 (11), 167 (27), 76 (100).

Acknowledgements

We thank the Communauté de Villes de l'Agglomération de La Rochelle (J. G. PhD grant) and the Prolabo company for financial support, and the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College. We also thank Axelle Grélard-Michon, Centre Commun d'Analyse (NMR), Université de La Rochelle, for helpful technical assistance.

References and notes

1 R. Appel, H. Janssen, M. Siray and F. Knoch, *Chem. Ber.*, 1985, **118**, 1632. The salt **1** is a greenish solid, insoluble in organic solvents. It is completely stable in a dry inert atmosphere but reacts slowly with moisture to form 4-chloro-1,2,3-dithiazol-5-one.
2 C. W. Rees, *J. Heterocycl. Chem.*, 1992, **29**, 639.
3 (*a*) T. Besson, J. Guillard, C. W. Rees and V. Thiéry, *J. Chem. Soc., Perkin Trans. 1*, 1998, 889; (*b*) T. Besson, G. Guillaumet, C. Lamazzi and C. W. Rees, *Synlett*, 1997, 704; (*c*) O. A. Rakitin, C. W. Rees and O. G. Vlasova, *Tetrahedron Lett.*, 1996, **37**, 4589.
4 T. Ogino, K. Tsuji, T. Tojo, N. Igari, N. Seki, Y. Sudo, T. Manda, F. Nishigaki and M. Matsuo, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 75; *Merck Index*, 1996, **12**, 478; *Dictionary of Drugs*, eds. J. Elks and C. R. Ganellin, Chapman and Hall, London, 1990, p. 370.
5 *Dictionary of Drugs*, eds. J. Elks and C. R. Ganellin, Chapman and Hall, London, 1990, p. 1131.
6 (*a*) T. Besson, M.-J. Dozias, J. Guillard, P. Jacquault, M. D. Legoy and C. W. Rees, *Tetrahedron*, 1998, **54**, 6475; (*b*) T. Besson, M.-J. Dozias, J. Guillard and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3925; (*c*) V. Bénéteau, T. Besson and C. W. Rees, *Synth. Commun.*, 1997, **27**, 2275.
7 R. F. English, O. A. Rakitin, C. W. Rees and O. G. Vlasova, *J. Chem. Soc., Perkin Trans. 1*, 1997, 201; (*b*) T. Besson and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1659.
8 Bromination of the starting amine (dapsone) always afforded a mixture of polybrominated compounds from which the bis-*ortho*-bromo derivative was isolated in about 35% yield.
9 R. Commarmot, R. Didenot and J. F. Gardais, *Brevet Fr. Pat.*, 2 560 529, 1985 (to Rhône-Poulenc/Prolabo) (*Chem. Abstr.*, 1986, **105**, 17442); P. Jacquault (Prolabo company) *Eur. Pat.*, 545 995 AI (21–12–92), 1992.

Paper a908742g