New routes to 1,2-dithiole-3-thiones and 3-imines

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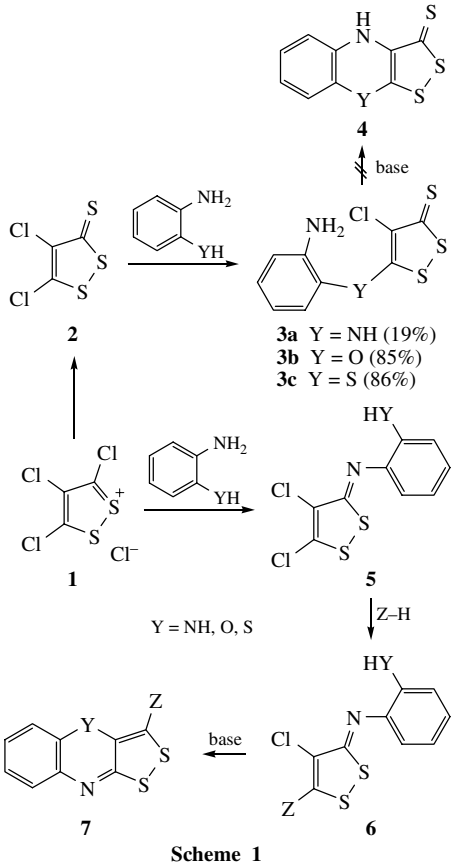
The reaction of readily available 3,4,5-trichloro-1,2-dithiolium chloride 1 and 4,5-dichloro-1,2-dithiole-3-thione 2 with *o*-substituted anilines provides a simple route to 1,2-dithiole-3-thiones and 3-imines, which can be cyclised to give new, more complex heterocyclic systems such as 1,2-dithiolo[4,3-*b*][1,4]benzoxazine of potential value in cancer chemotherapy.

1,2-Dithioles have attracted much interest in the recent years, especially as anticancer agents. This activity is mainly focused on 1,2-dithiole-3-thiones; thus, 4-methyl-5-pyrazinyl-1,2-dithiole-3-thione, Oltipraz, is a promising chemopreventive agent in clinical trials.[1,2] Even the parent 3*H*-1,2-dithiole-3-thione can protect against neoplasia.[3] Bis[1,2]dithiolo[1,4]thiazine-3,5-dione has shown moderate activity for some lines of leukemia, renal cancer, CNS and melanoma,[4] and the 1,2-dithiole ring seems to be crucial for this anticancer activity.

1,2-Dithiole-3-thiones undergo an interesting type of 1,3-dipolar cycloaddition to electron-deficient alkynes,[5] but these reactions convert the 1,2-dithioles into 1,3-dithioles, which may lead to the loss of anticancer activity. There are relatively few examples of the formation of 1,2-dithioles attached to other heterocyclic rings,[6] which are our targets for further anticancer agents. An attractive starting material for the synthesis of such compounds could be readily available 3,4,5-trichloro-1,2-dithiolium chloride **1**.[7] We have explored two routes to condensed 1,2-dithioles from **1** and certain bis(nucleophiles) (Scheme 1).

When **2**, which was readily obtained from **1** and hydrogen sulfide,[8] was treated with two equivalents of *o*-phenylenediamine, *o*-aminophenol or *o*-aminothiophenol in acetonitrile or methanol at room temperature for 20 h, substituted 1,2-dithioles **3a–c** were formed in 19–86% yields (Scheme 1).† Reaction of **2** with *o*-phenylenediamine is more complex than with other amines studied and is under further investigation.



Scheme 1

The base-catalysed cyclization of compounds **3a–c** to linear tricyclic derivatives **4** was attempted with *N*-ethyldiisopropylamine, sodium hydride or potassium carbonate but without success; prolonged heating led to starting material decomposition. Not surprisingly, the chlorine in **3** is insufficiently activated to be replaced by nucleophiles and presumably nucleophilic attack on heterocyclic sulfur supervenes; the inertness of 4-halogen atoms in 1,2-dithiole-3-thiones and 3-ones has been demonstrated before.[8]

To prepare imines **5**, the reaction of 3,4,5-trichloro-1,2-dithiolium chloride **1** with *o*-substituted anilines was studied and

† *General procedure for the preparation of* **3** *and* **5**. A mixture of **1** or **2** (1 mmol), a corresponding *o*-substituted aniline (1 mmol) and a corresponding base (2 or 1 mmol in the case of **1** or **2**, respectively) were stirred for 2 h in THF or dichloromethane for **1** and in acetonitrile or methanol for compound **2**. Solvents were evaporated, and the residue was separated by column chromatography (Silica gel Merck 60).

Synthesis of phenylsulfonyl derivatives **6** (Z = $PhSO_2$). A mixture of **5** (1 mmol) in dichloromethane (20 ml) and sodium benzenesulfinate (2 mmol) in methanol (4 ml) was refluxed for 5–9 h in the case of **5a–c**,**e** or for 66 h in the case of **5d** up to disappearance of **5**. Solvents were evaporated, and the residue was separated by column chromatography (Silica gel Merck 60).

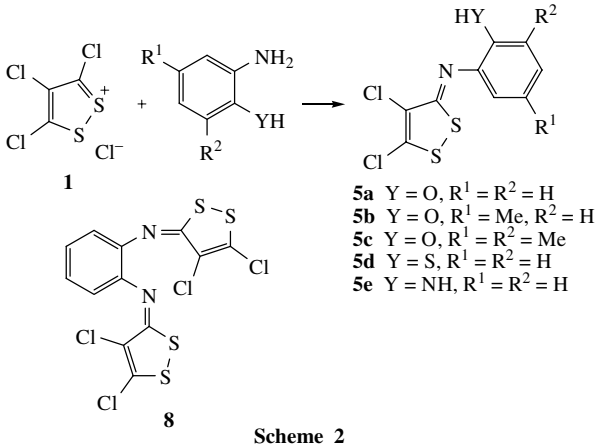
*Synthesis of 1,2-dithiolo[4,3-*b*][1,4]benzoxazines* **7**. A mixture of **6** (1 mmol) and a corresponding base (2 mmol) in acetonitrile or THF (25 ml) was refluxed for 2–24 h until the disappearance of **6**. Solvents were evaporated, and the residue was separated by column chromatography (Silica gel Merck 60).

New compounds were characterised by elemental analysis, ^{1}H and ^{13}C NMR, IR and mass spectra and some of them, by HMRS.

7a: yellow crystals, mp 217–219 °C. Found M$^+$, 346.9748; $C_{15}H_9NO_3S_3$ requires 346.9745. ^{1}H NMR ($CDCl_3$) δ: 6.92 (d, 1H, ArH, *J* 7.4 Hz), 7.07 (m, 3H, ArH), 7.62 (t, 2H, ArH, *J* 8.1 Hz), 7.72 (t, 1H, ArH, *J* 7.4 Hz), 8.12 (d, 2H, ArH, *J* 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 115.16, 125.83, 126.09, 128.00, 128.26, 129.54, 134.85 (7CH), 132.17, 139.05, 140.56, 142.56, 147.80, 167.47 (6*sp*^{2} tertiary C). IR (KBr, ν/cm^{-1}): 1584 (C=N). MS, *m*/*z* (%): 347 (M$^+$, 80), 206 (M – $PhSO_2$, 63), 162 (M – $PhSO_2$ – CS, 100).

7b: brown crystals, mp 206–207 °C. Found M$^+$, 360.9903; $C_{16}H_{11}NO_3S_3$ requires 360.9901. ^{1}H NMR ($CDCl_3$) δ: 2.26 (s, 3H, Me), 6.88 (m, 3H, ArH), 7.65 (m, 3H, ArH), 8.09 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 20.69 (Me), 114.73, 126.43, 128.23, 128.43, 129.51, 134.79 (6CH), 123.78, 131.83, 135.68, 139.10, 140.50, 140.79, 167.30 (7*sp*^{2} tertiary C). IR (KBr, ν/cm^{-1}): 1620, 1584 (C=N). MS, *m*/*z* (%): 361 (M$^+$, 90), 220 (M – $PhSO_2$, 68), 176 (M – $PhSO_2$ – CS, 100).

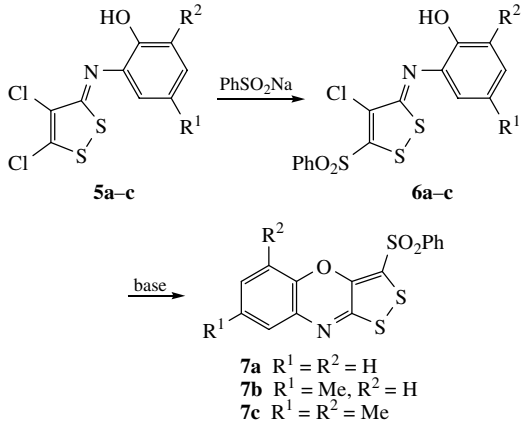
7c: orange crystals, mp 195–196 °C. ^{1}H NMR ($CDCl_3$) δ: 2.20 (s, 3H, Me), 2.30 (s, 3H, Me), 6.80 (m, 2H, ArH), 7.63 (m, 2H, ArH), 7.68 (m, 1H, ArH), 8.15 (m, 2H, ArH). ^{13}C NMR ($CDCl_3$) δ: 18.18, 20.85 (2Me), 122.58, 125.53, 128.17, 128.60, 132.02 (5CH), 127.51, 134.29, 134.62, 138.95, 138.76, 140.05, 140.37, 167.15 (8*sp*^{2} tertiary C). IR (KBr, ν/cm^{-1}): 1560 (C=N). MS, *m*/*z* (%): 375 (M$^+$, 100), 234 (M – $PhSO_2$, 67), 190 (M – $PhSO_2$, CS, 94).



Scheme 2

found to depend significantly on the solvent. With *o*-aminophenol and its derivatives, the best yields of **5a–c** (84–87%)† were achieved in THF at room temperature. With *o*-aminothiophenol and *o*-phenylenediamine, dichloromethane was better, but the yields of **5d** and **5e** were much lower, 49 and 16%, respectively, the major product in the diamine reaction being bis(adduct) **8** (52%) (Scheme 2).

As noted above, the cyclisation of monochloro-1,2-dithiole-3-thione **3a** was unsuccessful; treatment with sodium hydride in THF led to complete decomposition, although **3a** was stable to prolonged refluxing in acetonitrile. This suggests that a nucleophilic attack by hydride may occur preferentially at sulfur with heterocyclic ring opening rather than displacement of the 4-chlorine atom in **3a**. If so, this problem might be overcome by increasing the reactivity of the chlorine atom, and this was achieved by first displacing the 5-Cl in **5a–c** with sodium benzenesulfinate by increasing the reactivity of the leaving group to give the more powerful electron withdrawing 5-phenylsulfonyl series **6a–c**. Treatment of compounds **6** with a base (NaH or Hünig's base in THF or K_2CO_3 in MeCN) led to a new tricyclic system, 1,2-dithiolo[4,3-*b*][1,4]benzoxazine **7**, with similar yields under all the reaction conditions (39–45%) (Scheme 3).† Its synthesis was extended to a few more heterocyclic fused oxazinodithioles: imines **5b**,**c** gave derivatives **7b**,**c** in 27 and 35% yields, respectively.



Scheme 3

The structure of **7a** was fully supported by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry and was proved by X-ray crystallography (Figure 1).‡ In the tricyclic system, the six-membered rings are almost planar while the five-membered ring is characterised by the envelope conformation with the deviation of the S(2) atom by 0.158(1) Å.

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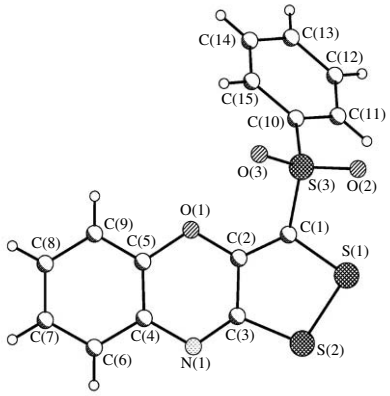

Figure 1 The general view of **7a**. Selected bond lengths (Å): S(1)–C(1) 1.752(2), S(1)–S(2) 2.0972(8), S(2)–C(3) 1.757(2), O(1)–C(2) 1.366(2), O(1)–C(5) 1.410(3), N(1)–C(3) 1.303(3), N(1)–C(4) 1.416(3), C(1)–C(2) 1.363(3), C(2)–C(3) 1.458(3); selected bond angles (°): C(1)–S(1)–S(2) 93.97(8), C(3)–S(2)–S(1) 96.37(8), C(2)–O(1)–C(5) 116.2(2), C(3)–N(1)–C(4) 114.6(2).

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‡ X-ray diffraction analysis: at 120 K crystals of **7a** ($C_{15}H_9NO_3S_3$) are monoclinic, space group $P2_1/c$, a = 14.631(2), b = 7.3479(8) and c = = 14.052(2) Å, β = 109.137(2)°, V = 1427.2(3) Å^3, Z = 4, (Z' = 1), M = 347.41, d_{calc} = 1.617 g cm^{-3}, μ(MoKα) = 5.30 cm^{-1}, F(000) = 712. Intensities of 7464 reflections were measured with a Smart 1000 CCD diffractometer at 120 K [λ(MoKα) = 0.71072 Å, $2\theta < 57°$], and 3391 independent reflections (R_{int} = 0.0456) were used in the further refinement. The structure was solved by a direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic–isotropic approximation. The hydrogen atoms were located from the Fourier density synthesis. The refinement converged to wR_2 = 0.1203 and GOF = 1.090 for all independent reflections [R_1 = 0.0480 was calculated against F for 2993 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.

Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). These data can be obtained free of charge *via* www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk). Any request to the CCDC for data should quote the full literature citation and CCDC reference number 262517. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2005.