4,5-Dichloro-1,2-dithiole-3-thione in the synthesis of benzimidazole, benzoxazole and benzothiazole derivatives of 1,3-dithioles

Vladimir A. Ogurtsov,[a] Oleg A. Rakitin,*[a] Charles W. Rees*[b] and Alexey A. Smolentsev[a]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 135 5328; e-mail: orakitin@ioc.ac.ru*

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

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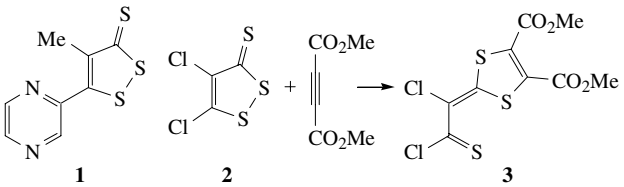
4,5-Dichloro-1,2-dithiole-3-thione 2 undergoes a 1,3-dipolar cycloaddition with DMAD to give stable aliphatic thioacyl chloride 3, which is highly reactive towards nucleophiles such as *o*-substituted amines to give benzimidazole, benzoxazole and benzothiazole derivatives of 1,3-dithioles 9.

There is considerable current interest in the use and mode of action of 1,2-dithiole-3-thiones as cancer chemopreventive agents. 4-Methyl-5-pyrazinyl-1,2-dithiole-3-thione, Oltipraz **1**, is currently in phase 2 clinical trials as a protective agent against environmentally induced hepatocellular carcinoma.[1] We wished to extend the range of dithiolethiones available for testing, for example by displacement of chlorine in 5-chloro-1,2-dithiole-3-thiones or related compounds readily available from dithioles.

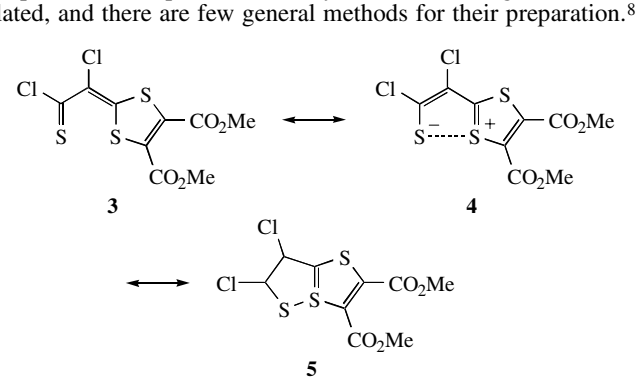
One of the most interesting properties of 1,2-dithiole-3-thiones is their ability to cycloadd to alkynes as 1,3-dipoles.[2–4] The first cycloaddition was accomplished by heterocyclic ring opening to give 1,3-dithiols (*e.g.*, **3** in Scheme 1), which sometimes add a second alkyne in a Diels–Alder reaction to give 1,4-dihydrothiopyran.[5,6]



1 **2** **3**

Scheme 1

An attractive starting material could be 4,5-dichloro-1,2-dithiole-3-thione **2**, which is readily prepared from 3,4,5-trichloro-1,2-dithiolium chloride,[7] and in which the 5-chlorine is activated towards nucleophilic displacement. However if **2**, reacted, as in Scheme 1, with DMAD, for example, it would generate dimethyl 2-(1,2-dichloro-2-thioxoethylidene)-1,3-dithiole-4,5-dicarboxylate **3**, which is expected to be more reactive towards nucleophiles. Indeed, **2** reacted with DMAD in xylene at room temperature to give a virtually quantitative yield of 1:1 adduct **3** with the desired thioacyl group, as a stable deeply red solid (mp 144–145 °C), which was characterised by chemical analysis and spectroscopy.[†] Whilst aromatic and heteroaromatic thioacyl chlorides are reasonably stable, their aliphatic counterparts are usually not stable enough to be isolated, and there are few general methods for their preparation.[8]



3 **4** **5**

Scheme 2

The crystallinity and striking stability of **3** may result from an interaction between thiocarbonyl and heterocyclic sulfur atoms, as in **4** or in canonic form **5** (Scheme 2), which would presumably reduce the electrophilicity of the thioacyl group.

Thioacyl chloride **3** reacted rapidly (1–5 min) with benzylamine, *m*-toluidine, morpholine, phenol and thiophenol in acetone at room temperature to give the corresponding thioamides and thiono and dithio esters **6**, mostly in very good yields (Scheme 3).

The treatment of morpholino compound **6c** with a large excess of morpholine as a solvent for 10 h at room temperature gave 4-{2-[4,5-bis(morpholin-4-ylcarbonyl)-1,3-dithiol-2-

[†] *Synthesis of thioacyl chloride* **3**. A mixture of 4,5-dichloro-1,2-dithiole-3-thione **2** (2 mmol) and DMAD (6 mmol) was stirred at room temperature in xylene (15 ml) for 10 h. Solvents were evaporated and the crystalline compound was washed with hexane and dried. Yield of **2** is quantitative.

General procedure for the preparation of **9**. A mixture of **3** (0.7 mmol), the corresponding *o*-substituted aniline (0.7 mmol) and *N*-ethyldiisopropylamine (3.5 mmol) were refluxed for 48 h in a mixture of xylene and THF (3:1, 20 ml). Solvents were evaporated, and the residue was separated by column chromatography (Merck 60 Silica gel). Yields are given in Scheme 6.

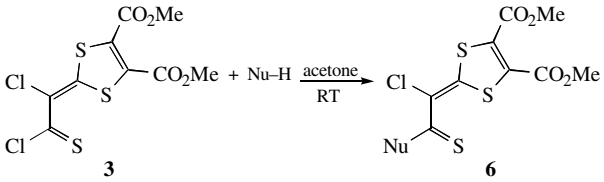
All new compounds were fully characterised by elemental analysis, ^{1}H and ^{13}C NMR, IR and mass spectra and HMRS (for compound **3**).

3: deep red crystals, mp 144–145 °C. ^{1}H NMR [$(CD_3)_2CO$] δ: 3.93 (s, 3H, Me), 3.95 (s, 3H, Me). ^{13}C NMR ($CDCl_3$) δ: 180.17 [C(S)Cl], 159.50 and 158.85 (C=O), 162.27, 134.61, 133.87 and 118.23 (4sp^2 tertiary C), 55.82 (2Me). IR, ν/cm^{-1}: 2950 (CH), 1740 and 1720 (C=O), 1250 (C=S). MS, *m*/*z* (%): 348 (M$^+$ + 4, 5), 346 (M$^+$ + 2, 18), 344 (M$^+$, 22), 311 (M – Cl + 2, 100), 309 (M – Cl, 41), 274 (M – 2Cl, 25). Found M+, 343.8811; $C_9H_6Cl_2O_4S_3$ requires 343.8805. Found (%): C, 31.6; H, 1.7. Calc. for $C_9H_6Cl_2O_4S_3$ (%): C, 31.3; H, 1.7.

9a: brown crystals, mp 160–161 °C. ^{1}H NMR ($CDCl_3$), δ: 3.83 (s, 3H, Me), 3.89 (s, 3H, Me), 6.36 (m, 1H, Ar), 6.86 (m, 2H, Ar), 7.08 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 160.68 and 159.83 (C=O), 144.60, 143.16, 136.56, 131.03, 128,16, 123.98 and 107.79 (7sp^2 tertiary C), 128.94, 128.44, 117.61 and 116.90 (4C–H), 53.69 (2Me). IR, ν/cm^{-1}: 2950 (CH), 1730 (C=O). MS, *m*/*z* (%): 384 (M$^+$ + 2, 40), 382 (M$^+$, 100), 274 (20), 208 (27), 164 (26). Found (%): C, 47.3; H, 2.7; N, 7.6. Calc. for $C_{15}H_{11}ClN_2O_4S_2$ (%): C, 47.1; H, 2.9; N, 7.3.

9b: orange crystals, mp 176–178 °C. ^{1}H NMR [$(CD_3)_2CO$] δ: 3.92 (s, 3H, Me), 3.94 (s, 3H, Me), 7.34 (m, 2H, Ar), 7.56 (m, 1H, Ar), 7.76 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 159.88 and 158.34 (C=O), 149.89, 143.93, 142.41, 135.82, 130.20, 130.00 and 98.69 (7sp^2 tertiary C), 125.12, 124.92, 120.70 and 110.70 (4C–H), 53.65 (2Me). IR, ν/cm^{-1}: 2930 (CH), 1730 (C=O). MS, *m*/*z* (%): 385 (M$^+$ + 2, 55), 383 (M$^+$, 100), 209 (20), 146 (22). Found (%): C, 47.1; H, 2.7; N, 3.6. Calc. for $C_{15}H_{10}ClNO_5S_2$ (%): C, 46.9; H, 2.6; N, 3.7.

9c: yellow crystals, mp 170–172 °C. ^{1}H NMR ($CDCl_3$) δ: 3.92 (s, 3H, Me), 3.95 (s, 3H, Me), 7.37 (m, 1H, Ar), 7.50 (m, 1H, Ar), 7.87 (d, 1H, Ar, *J* 7.8 Hz), 8.04 (d, 1H, Ar, *J* 7.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 163.30 and 160.36 (C=O), 159.62, 154.46, 139.79, 136.34, 134.57, 128.86 and 105.20 (7sp^2 tertiary C), 126.49, 124.86, 122.63 and 121.55 (4C–H), 53.57 (2Me). IR, ν/cm^{-1}: 2950 (CH), 1750 and 1730 (C=O). MS, *m*/*z* (%): 401 (M$^+$ + 2, 50), 399 (M$^+$, 100), 257 (32), 225 (23), 146 (30). Found (%): C, 45.3; H, 2.6; N, 3.2. Calc. for $C_{15}H_{10}ClNO_4S_3$ (%): C, 45.0; H, 2.5; N, 3.5.

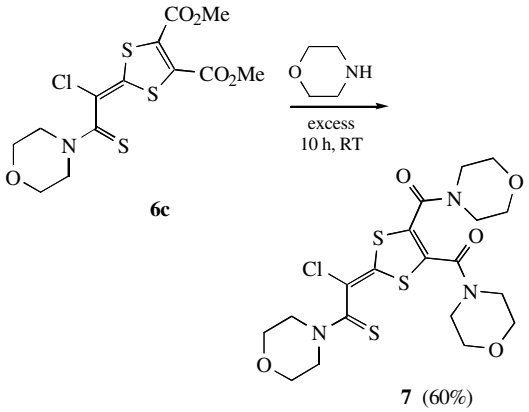


3 **6**

a Nu = $PhCH_2NH$ (87%)
b Nu = 3-MeC_6H_4NH (82%)
c Nu = morpholinyl (60%)
d Nu = PhO (89%)
e Nu = PhS (91%)

Scheme 3

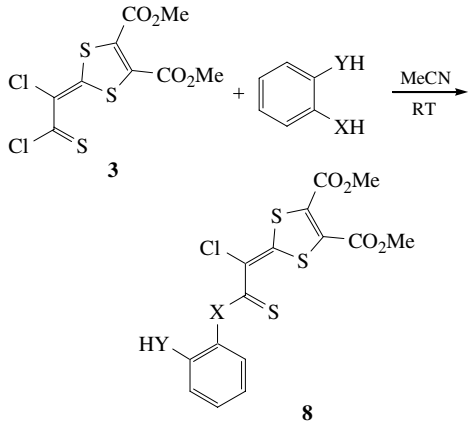
ylidene]-2-chloroethanethioyl}morpholine **7** (60%) with the intact 4-chlorine atom (Scheme 4). This chlorine atom was inert to intramolecular displacement with the bis-nucleophiles *o*-phenylenediamine, *o*-aminophenol and *o*-aminothiophenol.



7 (60%)

Scheme 4

When **3** was treated with 2 equiv. of *o*-phenylenediamine or *o*-aminophenol in acetonitrile at room temperature for 20 h, thioamides **8a** and **8b** were formed. With *o*-aminothiophenol the chlorine was displaced by more nucleophilic sulfur to give dithio ester **8c**; the potassium salt of *o*-aminophenol similarly gave thiono ester **8d** (all in high yields, Scheme 5).

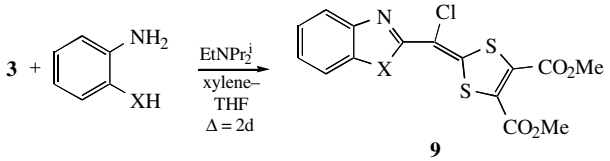


8

a X = Y = NH (79%)
b X = NH, Y = O (76%)
c X = S, Y = NH (80%)
d X = O, Y = NH (83%)

Scheme 5

Under more vigorous conditions on heating in a 3:1 mixture of xylene and THF at 100 °C for 2 days with *N*-ethyldiisopropylamine as a base, the second nucleophilic centre cyclised at the thiocarbonyl group with the elimination of H_2S rather than the displacement of chlorine to give dimethyl 2-[1*H*-benzimidazol-2-yl(chloro)methylene]-1,3-dithiole-4,5-dicarboxylate **9a**, dimethyl 2-[1,3-benzoxazol-2-yl(chloro)methylene]-1,3-dithiole-4,5-dicarboxylate **9b** (from **8b** and **8d**) and dimethyl 2-[1,3-benzothiazol-2-yl(chloro)methylene]-1,3-dithiole-4,5-dicarboxylate **9c** in good yields (Scheme 6).†

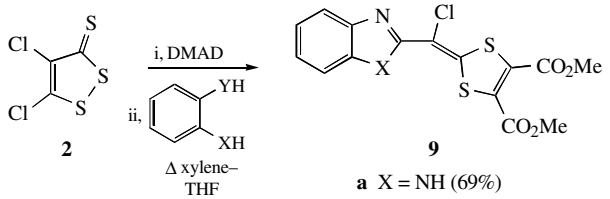


9

a X = NH (71%)
b X = O (69%)
c X = S (72%)

Scheme 6

This new synthesis of these heterocycles can be performed in one pot using 4,5-dichloro-1,2-dithiole-3-thione **2** in a 3:1 mixture of xylene and THF by adding DMAD at room temperature and then heating with the corresponding *o*-substituted aniline without the isolation of thioacyl chloride (Scheme 7).



9

a X = NH (69%)
b X = O (68%)
c X = S (71%)

Scheme 7

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