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# Preparation of Cyclic Disulfides from Bisthiocyanates

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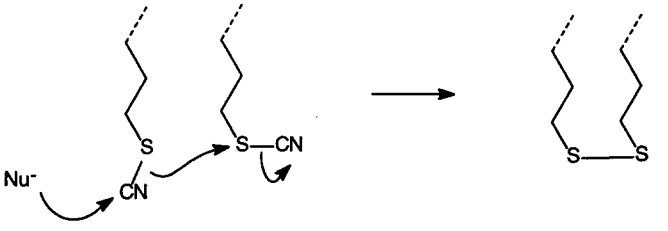
**Abstract:** A mild method for the preparation of disulfides from acyclic bisthiocyanates is presented. The method involves cleavage of thiocyanates with TBAF to form the cyclic disulfides in moderate to good yield. The method can also be applied to the synthesis of acyclic disulfides. Base-sensitive functionalities, such as esters, are unaffected by the reaction conditions.

Keywords: thiocyanates; disulfides; sulfur compounds.

The disulfide moiety occurs ubiquitously in proteins and is also found in a variety of small molecule natural products and pharmacologically active compounds.[1] In addition, cyclic and acyclic disulfides are useful intermediates in synthesis[2] and in the preparation of adsorbed monolayers.[3] Acyclic disulfides are typically prepared through oxidation of thiols.[4] Similarly, cyclic disulfides are typically prepared by the oxidative dimerisation of α,ω-dithiols (e.g. $I_2$, $NEt_3$;[5] $Br_2$;[6] $K_3Fe(CN)_6$;[7] $CCl_4$, $NEt_3$;[8] $H_2O_2$/KI/AcOH;[9] $Pb(OAc)_4$, S;[10] $KO_2$[11]) and may also be prepared by reacting α,ω-dihalogenated compounds with $Na_2S/S_8$.[12]

Thiocyanates have also been used in the preparation of disulfides. Thus, treatment of thiocyanates with base (e.g. NaOH or $NH_3$) has been shown to generate disulfides in moderate to good yield via the process shown diagrammatically in Scheme 1.[13] More recently, reaction of α,ω–bisthiocyanates with samarium diiodide[14] or tetrathiomolybdate[15] has been employed in the synthesis of cyclic disulfides. As part of a program directed towards the synthesis of functionalised cyclic disulfides for monolayer adsorption studies,[16] we required a simple route to disulfides from thiocyanates that would not affect base sensitive functionality (specifically esters) and which did not require specialist reagents or reaction conditions. Herein we report that tetrabutylammonium fluoride (TBAF) generates disulfides from the corresponding thiocyanates in moderate to good yield under mild conditions.




**Scheme 1**: Formation of disulfides from thiocyanates ($Nu^- = OH^-$, $NH_3$ etc.)[13]

Results are summarised in the Table. The starting bisthiocyanates were prepared by literature methods[17] and, after purification, were allowed to react with tetrabutylammonium fluoride in tetrahydrofuran in the quantities shown.


*PII:* S0040-4039(99)01333-7

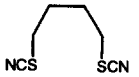
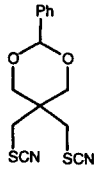
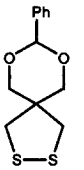
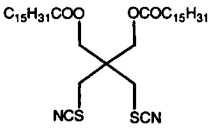
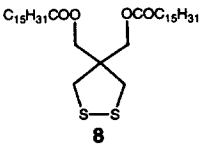
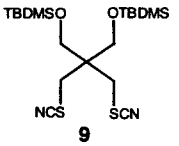
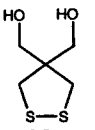
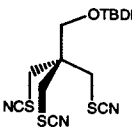
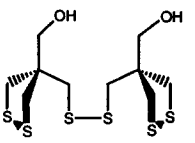
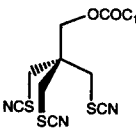
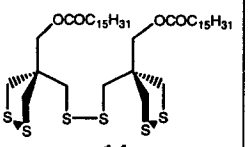
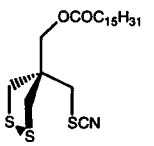
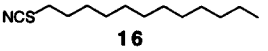
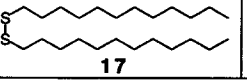
| ENTRY | BISTHIOCYANATE | Eq. TBAF | PRODUCT | YIELD |
|---|---|---|---|---|
| 1 |  **1** | 2 |  **2** | 36% |
| 2 |  **3** | 2 |  **4** | 66% |
| 3 |  **5** | 2 |  **6** | 74% |
| 4 |  **7** | 2 |  **8** | 37% |
| 5 |  **9** | 3 |  **10** | 31% |
| 6 |  **11** | 1.5 |  **12** | 36% |
| 7 |  **13** | 2.0 |  **14**<br>  **15** | 40%<br>31% |
| 8 |  **16** | 2.0 |  **17** | 100% |

**Table**: Preparation of disulfides from bisthiocyanates by treatment with TBAF

5-Membered (entries 3, 4, 5), 6-membered (entry 1) and 7-membered (entry 2) cyclic disulfides were all formed under the reaction conditions in moderate to good yields. Esters (entries 4 and 7) and ketals (entry 3) were unaffected by the mild experimental procedure however, as expected, silyl ethers were cleaved (entries 5 and 6). Acyclic disulfides can also be formed under these reaction conditions (entries 6, 7, 8) allowing the formation of the sulfur-rich species shown in entries 6 and 7. While such disulfide bridged dithians have been proposed previously as the products from *in situ* oxidation of the corresponding thiols[18] this report constitutes the first successful synthesis of such compounds.

The mechanism for this reaction presumably involves fluoride acting as nucleophile via the process shown in Scheme 1. There are, to the best of our knowledge, no reports of fluoride attack at the carbon of organic thiocyanates in the literature, and therefore we examined the use of an alternative source of fluoride for this transformation. Treatment of the bisthiocyanate (**7**) with KF/18-crown-6 in THF under anhydrous conditions also furnishes the corresponding disulfide (**8**) (in 60% yield) further supporting the proposed mechanism. While we could not detect FCN in the conversion of dodecyl thiocyanate to dodecyl disulfide (entry 8) with continual monitoring of the reaction by $^{19}$F-n.m.r., this material is known to be unstable and to polymerise rapidly,[19] and it may be that the formation of a stable FCN polymer or oligomer provides the driving force for the reaction.

Further studies on this reaction are underway, and the properties of monolayers formed from adsorption of the product disulfides on gold surfaces will be reported in due course.

**General Experimental procedure:** A solution of tetrabutylammonium fluoride (4.9ml, 1M THF solution, Aldrich) was added to a solution of the bisthiocyanate (2.4 mmol) in dry THF (7ml). The solution was stirred overnight at room temperature, evaporated to dryness and the residue chromatographed on silica. $^{1}$H-n.m.r., $^{13}$C-n.m.r., mass spectra and microanalyses were obtained for all new compounds.[20]

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**References and Notes**

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20 Spectroscopic data for compounds prepared in this work:
**2**, $^1$H-n.m.r. (200MHz, $CDCl_3$) 1.97 (m, 2H), 2.83 (m, 2H), m.p. <40° (lit.[21] 32-3°);
**4**, $^1$H-n.m.r. (200MHz, $CDCl_3$) 1.79 (2H, m), 2.00 (m, 4H), 2.83 (m, 4H); b.p. 115-125°/20mmHg (Kügelrohr), (lit. 57-60°/5mm)[22];
**6**, $^1$H-n.m.r. (400MHz, $CDCl_3$) 2.70 (2H, s), 3.48 (2H, s), 3.88 and 4.12 (2H each, AB q), 5.50 (1H, s), 7.36-7.49 (5H, m); $^{13}$C-n.m.r. (100MHz, $CDCl_3$) 43.4, 48.1, 50.9, 74.6, 102.7, 126.7, 129.1, 129.9, 138.3; *m/z* 254 ($M^+$); (Found $M^+$, 254.0439. $C_{12}H_{14}O_2S_2$ requires 254.0435);
**8**, $^1$H-n.m.r. (200MHz, $CDCl_3$) 0.88 (6H, m), 1.25 (48H, m), 1.60 (4H, m), 2.34 (4H, m), 2.99 (4H, s), 4.11 (4H, s); $^{13}$C-n.m.r. (100MHz, $CDCl_3$) 14.8, 23.4, 25.6, 29.8, 30.0, 30.1, 30.2, 30.3, 30.36, 30.40, 32.6, 34.8, 45.3, 55.0, 65.6, 174.0; $\upsilon_{max}$ 1731 $cm^{-1}$; *m/z* 642 ($M^+$); (Found $M^+$, 642.4744. $C_{12}H_{14}O_2S_2$ requires 642.4716);
**10**, m.p. 129° (Lit. 129-130°)[23] $^1$H-n.m.r. (200MHz, $d_6$-DMSO) 2.85 (4H, br s), 3.60 (4H, d, *J* 6Hz), 4.40 (2H, t, *J* 6Hz); $^{13}$C-n.m.r. (50MHz, $CDCl_3$+ $d_6$-DMSO) 43.2, 57.3, 63.4; *m/z* 166 ($M^+$); Found C, 36.5; H, 6.1%. $C_7H_{10}O_2S_2$ requires C, 36.1; H, 6.0%;
**12**, $^1$H-n.m.r. (400MHz, $CDCl_3$ + $d_6$-DMSO) 3.05 (8H, AB q), 3.18 (4H, s), 3.61 (4H, d, *J* 5.3Hz), 4.71 (2H, t, *J* 5.3); $^{13}$C-n.m.r. (50MHz, $d_6$-acetone) 44.8, 45.7, 57.1, 63.8; *m/z* 362 ($M^+$); (Found $M^+$, 361.9631. $C_{10}H_{18}O_2S_6$ requires 361.9602);
**14**, $^1$H-n.m.r. (200MHz, $CDCl_3$) 0.88 (6H, m), 1.25 (48H, m), 1.62 (4H, m), 2.34 (4H, t, *J* 8Hz), 3.00 and 3.10 (4H each, AB q), 3.18 (4H, s), 4.17 (4H, s);$^{13}$C-n.m.r. (50MHz, $CDCl_3$) 14.1, 22.7, 24.9, 29.2, 29.27, 29.34, 29.5, 29.7, 31.9, 34.2, 45.9, 55.4, 66.1, 173.2; $\upsilon_{max}$ 1736$cm^{-1}$, *m/z* 418 ($(M/2)^+$); Found C, 60.4; H, 9.2%. $C_{42}H_{78}O_4S_6$ requires C, 60.1; H, 9.4%.
**15**, $^1$H-n.m.r. (200MHz, $CDCl_3$) 0.88 (3H, m), 1.25 (24H, m), 1.62 (2H, m), 2.35 (2H, t, *J* 7Hz), 3.07 (4H, s), 3.31 (2H, s), 4.21 (2H, s);$^{13}$C-n.m.r. (50MHz, $CDCl_3$) 14.1, 22.7, 24.7, 29.1, 29.2, 29.3, 29.4, 29.7, 31.9, 34.0, 39.8, 45.9, 55.2, 65.7, 111.9, 173.1; *m/z* 445 ($M^+$); Found C, 59.6; H, 9.0%. $C_{22}H_{39}NO_2S_3$ requires C, 59.3; H, 8.8%.
**16**, $^1$H-n.m.r. (200MHz, $CDCl_3$) 0.88 (6H, m), 1.26 (36H, m), 1.67 (4H, m), 2.68 (4H, m).

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