

Cyclization reactions of vicinal dianions with 1,2-dielectrophiles: synthesis and properties of the first 2,3-diiminothietanes†

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Reaction of dilithiated ethyl thioglycolate with bis(imidoyl chloride)s of oxalic acid afforded the first 2,3-diiminothietanes, which underwent ring expansion reactions upon treatment with ethyl thioglycolate or dimethyl acetylenedicarboxylate.

Four-membered ring lactams and lactones represent pharmacologically important compounds which, due to their ring strain, readily undergo ring-expansion or -opening reactions.¹ To the best of our knowledge, azetidine-2,3-diones represent the only known heterocycles which combine the biologically significant structural features of a four-membered ring and a 1,2-dione subunit.² Due to their high reactivity, oxetanes and thietanes containing a 1,2-dione subunit are unknown to date. However, a few examples of the corresponding heterocyclic 1,2-diimines have been reported.^{3,4} We envisaged that reaction of 1,2-dianions with oxalic acid dielectrophiles could provide a convenient synthesis of four-membered ring heterocycles containing a 1,2-dione or related subunit. Much to our surprise, until recently cyclization reactions of oxalic acid dielectrophiles with 1,1-, 1,2-, 1,3- or 1,4-dianions had not been reported.⁵ This is presumably due to the fact that these reactions can suffer from several drawbacks, such as overaddition of the nucleophile, expulsion of CO or decomposition. We have recently shown that bis(imidoyl chloride)s of oxalic acid [Cl₂C₂(NR)₂] represent useful C₂ building blocks in cyclization reactions with 1,3-dianions.⁶ Herein we report that bis(imidoyl chloride)s can be cyclized with 1,2-dianions equally successfully. To the best of our knowledge, these transformations represent the first examples of cyclization reactions of 1,2-dianions with 1,2-dielectrophiles to date.⁷

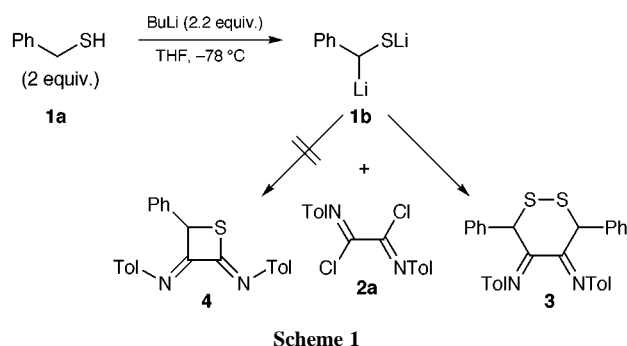
Our first aim was the preparation of 2,3-diiminothietanes by reaction of dilithiated thiols with bis(imidoyl chloride)s.^{4,8} Unfortunately, treatment of bis(imidoyl chloride) **2a** with the dianion of BnSH **1b**^{9a} gave a complex reaction mixture from which the cyclic disulfide **3** was isolated in low yield (Scheme 1). Formation of **3** can be explained by initial condensation of **2a** with 2 equiv. of **1b** and subsequent oxidative cyclization. The yield of **3** could be improved by the use of 2 rather than only

1 equiv. of the dianion. However, a change of the reaction conditions (slow addition of the dianion to **2a**) and of the work-up procedure (filtration under inert conditions rather than aqueous work-up) did not provide the desired product **4**. Similar disappointing results were obtained when the dianion of prop-2-enethiol was employed.

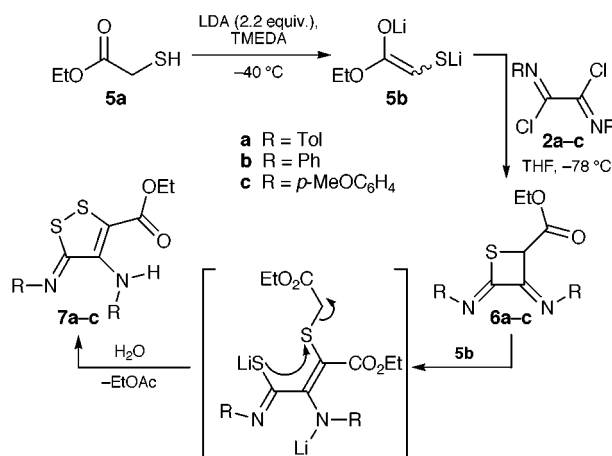
Much to our satisfaction, reaction of bis(imidoyl chloride) **2a** with the dianion of ethyl thioglycolate **5b**^{9b} afforded the 2,3-diiminothietane **6a** in 30% yield (Scheme 2).[‡] Thietane **6a** could be readily isolated by chromatography as it represented the only Et₂O-soluble product formed in the reaction. In contrast, reaction of **5b** with oxalyl chloride or diethyl oxalate gave polymeric material under a variety of conditions. In contrast to the open-chained derivative Me(PhHN)C=CH-CO₂Et, thietane **6a** adopted a 3-iminopropionate- rather than a 3-aminocrotonate structure, presumably for electronic reasons. Variable temperature ¹H NMR (CDCl₃) showed that 2,3-diiminothietane **6a** represented a structurally mobile compound due to *E/Z* isomerization of the imino group at C-3.[§]

Interestingly, treatment of bis(imidoyl chloride)s **2b,c** with the dianion **5b** resulted in formation of the 1,2-dithioles **7b** and **7c** in 41 and 40% yields, respectively (Scheme 2).¹⁰ The formation of the dithioles **7** can be explained by initial cyclization to give the 2,3-diiminothietanes **6**, subsequent ring opening, addition of a second equivalent of the dianion, cyclization and expulsion of EtOAc.

In order to elucidate the mechanism of the conversion of 2,3-diiminothietanes **6** into the bisthioles **7**, cycloaddition reactions of **6a** were studied. When a toluene solution of thietane **6a** and dimethyl acetylenedicarboxylate (DMAD) was stirred at 80 °C for 12 h, the yellow coloured thioimino ether **9** was isolated in 64% yield (Scheme 3). The formation of cycloadduct **9** can be explained by initial ring-opening of thietane **6a** to give the 1,4-zwitterionic intermediate **8** and subsequent regioselective cyclization of the latter with DMAD.[¶] Bisthiole **7a** was isolated in 58% yield when a toluene

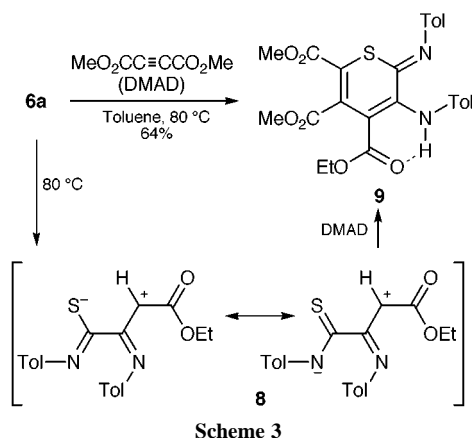


Scheme 1



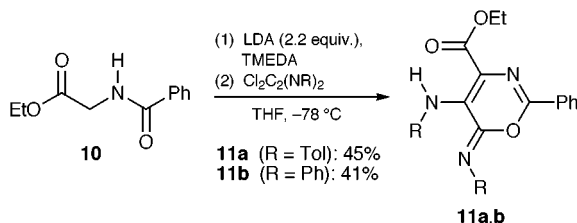
Scheme 2

† Dedicated to Professor A. Zeeck on the occasion of his 60th birthday.



solution of **6a** and of ethyl thioglycolate **5a** was stirred for 12 h at 80 °C. This experiment suggested that intermediate **8** was not only involved in the formation of the cycloadduct **9** but also in the conversion of the 2,3-diiminothietanes **6a–c** into the bisthioles **7a–c**.

The influence of the heteroatoms of the 1,2-dianion on the regiochemistry of cyclization was next studied. No cyclization could be induced in the reaction of bis(imidoyl chloride) **2a** with the dianion of ethyl lactate, presumably due to the lower nucleophilicity of the oxygen relative to the sulfur atom. In contrast, reaction of **2a,b** with the dianion of ethyl hippurate **10**¹¹ afforded the 6-imino-6*H*-1,3-oxazines **11a,b** by regioselective cyclization *via* the carbon and the oxygen atom of the dianion (Scheme 4). The regioselectivity of this reaction, which was carried out under kinetic conditions, can be explained by the higher electron density at the oxygen rather than at the nitrogen atom of the dianion or, alternatively, by initial formation of a four-membered ring and subsequent ring expansion. Similar to bisthioles **7a–c**, oxazines **11a,b** represent masked 1,2,3,4-tetracarbonyl systems containing strong intramolecular hydrogen bonds (N–H⋯O).



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Notes and references

‡ **Preparation of 6a**: A THF solution of LDA (2.5 equiv.) was prepared by addition of BuLi (9.4 ml, 1.6 M solution in hexane) to a THF solution (15 ml) of diisopropylamine (2.1 ml) at 0 °C. To this solution TMEDA (2.3 ml) and ethyl thioglycolate (0.54 ml) were added at –40 °C. The deep yellow solution was stirred at 0 °C for 2 h and subsequently transferred to a THF solution (80 ml) of **2a** (1.8 g) at –78 °C. The temperature was allowed to rise to ambient and the mixture was stirred for 2 h at 20 °C. The solvent was removed *in vacuo* and the residue was purified by chromatography (silica gel, Et₂O–light petroleum = 1:10 → 1:3) to give 634 mg (30%) of a yellow solid, mp 110 °C (decomp.); δ_{H} (CDCl₃, 200 MHz) 0.98 (t, *J* 7, 3 H, CH₂CH₃), 2.32, 2.34 (s, 6 H, Tol-CH₃), 4.94 (m, 2 H, CH₂CH₃), 5.33 (s, 1 H, CHCO₂Et), 6.95–7.25 (m, 8 H, Tol); δ_{C} (CDCl₃, 50 MHz) 13.62 (CH₂CH₃), 21.01, 21.18 (Tol-CH₃), 54.47 (CH, CHCO₂Et), 62.21 (CH₂CH₃), 121.44, 122.37, 129.75, 129.99 (CH, Tol), 136.66, 137.34 (C, Tol-C to CH₃), 142.95, 143.25 (C, Tol-C to N), 157.00 (C, CHCNTol),

158.99 (C, SCNTol), 167.39 (C, CO₂Et); ν_{max} (KBr)/cm^{–1} 2980 (w), 1738 (s), 1655 (m), 1641 (m), 1505 (s), 1268 (s), 1235 (m), 1125 (m), 1030 (m), 823 (m); *m/z* (CI, H₂O) 353 (M⁺ + 1), 236 (M⁺ + 1 – TolN≡C), 203 (M⁺ + 1 – TolN=C=S) (Calc. for C₂₀H₂₀N₂O₂S: C, 68.16; H, 5.72; N, 7.94. Found: C, 68.51; H, 5.79; N, 8.07%).

§ From 90 to 60 °C the ¹H NMR spectra exhibited only one set of signals. By cooling, broadening of the signals and coalescence (60 °C) were observed giving rise to two signals each for the CH, CH₂ and CH₃ group with the integration ratio 1:5. Singlets were detected for the CH groups and multiplets were detected for the CH₂ groups, both for the major and the minor component. The free energy of activation of this process (ΔG^\ddagger = 74.0 kJ mol^{–1}) lies in the range of typical activation barriers for *E/Z* isomerizations of imines.



¶ To the best of our knowledge, open-chained 1,4-zwitterions related to **8** have not been reported so far. In contrast, 1,3-zwitterions have been previously discussed as intermediates in the chemistry of thietanes, see refs. 4(a) and 8(c). The mass spectrum of **6a** exhibited characteristic fragment peaks (loss of electroneutral TolN=C=S) which independently supported the existence of intermediate **8**. Cleavage of the carbon–sulfur bond of a 2-iminothietane has been observed during the thermal rearrangement of the latter to an α,β-unsaturated thioamide, see ref. 8(b).

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