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Autoxidation of [2-(1,3-Dithianyl)]lithium: A Cautionary Note

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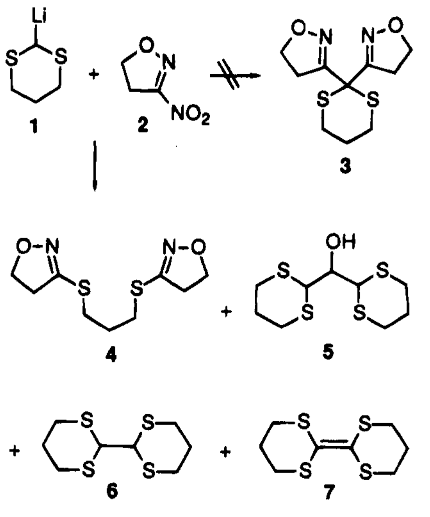
In connection with a study[1] on the synthesis of 4,5-dihydroisoxazole-3-carboxaldehyde derivatives, we examined the displacement reaction of [2-(1,3-dithianyl)]-lithium (**1**)[2] and 4,5-dihydro-3-nitroisoxazole (**2**) (Scheme 1). The initial data suggested formation of dithiane **3** as a reaction product but the ^{13}C-NMR spectrum lacked a signal attributable to the C-2 ring carbon atom. Mass spectral data were also inconsistent with **3** as the correct structure, indicating the bis(thioimidate) **4**. Thorough characterization has confirmed structure **4** as the displacement reaction product. In these reactions, the bis(thioimidate) **4** was obtained in varying yield up to 82%, accompanied by bis[2-(1,3-dithianyl)]methanol (**5**), 2-[2-(1,3-dithianyl)]-1,3-dithiane (**6**), and a trace of **7**. Here we present a mechanistic explanation of these results and a cautionary note on the use of **1** as a nucleophile.

Repetition of the displacement reaction using oxygen-free argon to degas the THF solution of 1,3-dithiane prior to preparation of **1** significantly altered the product ratio. Both alcohol **5** (half as much; 20% yield based on **2** as limiting reagent) and bis(thioimidate) **4** (8% yield) were obtained in substantially reduced quantity, linking these two products to an oxygen-induced decomposition reaction of **1**. Here the bis(dithiane) **6** was obtained in 22% yield and the alkene **7** in 6% yield. The bis(dithiane) **6** was presumably formed by initial electron transfer from **1** to **2** and coupling of the resulting dithianyl radical with more **1**. Similar electron transfer has been documented from **1** to aromatic nitro compounds resulting in the formation of **6**.[3] Several unexplored possibilities exist for the formation of **7**.

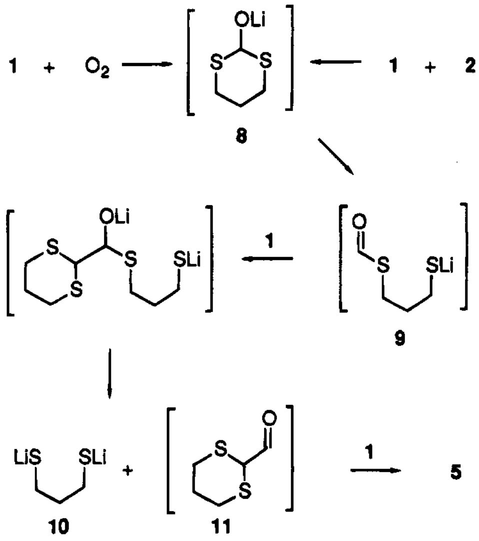
We next examined the effect of oxygen on THF solutions of **1** in the absence of **2**. Preparation of **1** under an argon atmosphere followed by simple quenching resulted in the formation of variable amounts of alcohol **5**. However, when special precautions to avoid air were employed, no detectable **5** was obtained after quenching. An experiment was run simultaneously where air was first avoided in the preparation of **1** and, subsequently, a dose of air was added prior to quenching. In this latter experiment, alcohol **5** was obtained in 6% yield (based on **1** as limiting reagent). Thus, air clearly leads to decomposition of **1** affording **5**.

Grayshan *et al.*[4] have previously noted the formation of **5** as a byproduct[5] in the reaction of **1** with a series of oxiranes. Bulman-Page *et al.*[6] noted the formation of **5** from **1** in THF solution and made the unlikely proposal that **1** reacted with THF to produce **5**. Apparently no mechanistic rationale for the formation of **5** has previously been presented.

Scheme 1



Scheme 2



A likely scenario for the formation of **4** and **5** is presented in Scheme 2. Reaction of **1** with oxygen would be expected to produce a hydroperoxide anion and subsequently the alcoholate **8**.[7] Apparently there is also oxygen transfer from the nitro group of **2** leading to formation of **8** since we were unable to suppress formation of **5** by excluding air if **2** were present. Ring-opening of **8** (a relatively strong base) to thioester **9** (a weaker base) would be anticipated, and reaction of **9** with excess **1** would also be anticipated. Ultimately, ring-opening of **8** could result in extrusion of the original C-2 carbon atom and concomitant formation of dilithium 1,3-propanedithiolate (**10**). Reaction of **10** with **2**, then, is the hypothesized source of **4**. The extruded carbon atom of **8** would be present in aldehyde **11**, the logical precursor to alcohol **5**.

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(1) Wade, P. A.; D'Ambrosio, S.; Price, D. T. *J. Org. Chem.*, manuscript submitted.

(2) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

(3) Bartoli, G.; Dalpozzo, R.; Grossi, L.; Todesco, P. E. *Tetrahedron* **1986**, *42*, 2563.

(4) Grayshan, R.; Keal, C. A.; Sackville, M. A. *J. Chem. Res. (M)* **1986**, 2501.

(5) An unidentified side product was noted in the sequential reaction of 1 with ethyl 2-(diethylphosphono)acrylate and benzaldehyde. However, based on a tentative identification, this side product does not appear to be related to autoxidation of 1: Kleschick, W. A.; Heathcock, C. H. *J. Org. Chem.* **1978**, *43*, 1256.

(6) Bulman-Page, P. C.; Chadwick, D. J.; Van Niel, M. B. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1987**, *C43*, 803.

(7) For an example of oxygen-induced carbanion hydroxylation and references to the older literature, see: Hartwig, W.; Born, L. *J. Org. Chem.* **1987**, *52*, 4352.

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It was confirmed that dithiolate **10** would react as hypothesized with **2**. A solution of **10** was first prepared by reaction of 1,3-propanedithiol and butyllithium in THF. Subsequently, **2** was allowed to react with this solution at −45 to −35 °C, affording the bis(thioimidate) **4** in 88% yield.

Of particular significance is the observation that **2** preferentially underwent nucleophilic attack by **10**, the decomposition product, rather than by **1** itself. Thus, when **1** is to be employed as a nucleophile, scrupulous avoidance of air is recommended to avoid the possible presence of dilithium 1,3-propanedithiolate (**10**). Tetrahydrofuran which is distilled from sodium−benzophenone ketyl and stored under argon is adequate for use. A good grade of inert gas, low (<50 ppm) in oxygen, and a commercially available oxygen scrubber should be used to sustain an inert atmosphere during the preparation of **1** and its subsequent use. The THF solution of 1,3-dithiane should be briefly degassed with an oxygen-free argon stream prior to introduction of butyllithium.

Experimental Section

Reaction of [2-(1,3-Dithianyl)]lithium (1) with 4,5-Dihydro-3-nitroisoxazole (2). Run A: Oxygen Free. A solution of **1** in THF was prepared by first adding 1,3-dithiane (0.58 g, 4.8 mmol) to freshly distilled THF (10 mL) and bubbling a slow stream of oxygen-scrubbed[8] argon through the solution for 20 min. The solution was cooled to −40 °C (dry ice−acetone). A 2.5 M solution of butyllithium in hexanes (2 mL, 4.8 mmol of BuLi) was added dropwise and the solution stirred for 2 h at −20 to −40 °C. The solution was cooled to −60 °C, and **2** (0.12 g, 1.1 mmol) was added. Stirring at −45 to −35 °C was allowed for 2 h and then water (5 mL) was cautiously added. Volatiles were removed at reduced pressure, and the residue was taken up in CH_2Cl_2. The solution was washed with brine (three 30-mL portions), dried over anhydrous Na_2SO_4, filtered, and concentrated at reduced pressure. The crude product was purified by preparative TLC (hexanes−EtOAc, 75:25) to give **4** (11 mg, 8% yield based on starting **2**) from the most polar fraction: mp 47−47.5 °C; ^{1}H-NMR ($CDCl_3$) δ 4.36 (t, 4H, J = 9.6 Hz), 3.16 (t, 4H, J = 7.1 Hz), 3.03 (t, 4H, J = 9.6 Hz), 2.21 (quint, 2H, J = 7.1 Hz); ^{13}C-NMR ($CDCl_3$) δ 155.3, 68.6, 39.4, 30.1, 28.2; HRMS (FAB) calcd for $C_9H_{15}N_2O_2S_2$ (M + H$^+$) 247.0575, found 247.0575. Anal. Calcd for $C_9H_{14}N_2O_2S_2$: C, 43.88; H, 5.73; N, 11.37. Found: C, 43.59; H, 5.72; N, 11.12.

Alcohol **5** (29 mg, 20% yield) was obtained from the second most polar fraction: mp 104−105 °C (lit.[4] 108−110 °C); ^{1}H-NMR matches the literature; ^{13}C-NMR ($CDCl_3$) δ 75.4, 47.5, 27.9, 27.2, 25.5; HRMS (EI) calcd for $C_9H_{16}OS_4$ (M$^+$) 268.0084, found 268.0082.

Bis(dithiane) **6** (28 mg, 22% yield) was obtained from the third most polar fraction: ^{1}H-NMR and ^{13}C-NMR matched the literature.[9]

Alkene **7** (7 mg, 6% yield) was obtained from the fourth most polar fraction: ^{1}H-NMR matched the literature;[10] HRMS (FAB) calcd for $C_8H_{13}S_4$ (M + H$^+$) 236.9900, found 236.9890.

Run B: Not Oxygen Free. In early work, the above reaction was duplicated several times using an argon atmosphere with no special precautions to exclude oxygen. More **4** and **5** were obtained in all cases. In one run **4** (97 mg, 82% yield) and **5** (53 mg) were obtained while significant quantities of **6** and **7** were absent.

Autoxidation of [2-(1,3-Dithianyl)]lithium (1). Run A: Oxygen Free. The above procedure (run A) was duplicated but addition of **2** was omitted. The crude products contained no detectable alcohol **5**. Run B was performed simultaneously.

Run B: Added Oxygen. Run A was repeated except that air (30 mL) was added to the atmosphere above the prepared solution of **1**. Workup afforded 41 mg (6% yield based on **1** as the limiting reagent) of alcohol **5**.

Reaction of Dilithium 1,3-Propanedithiolate (10) with 4,5-Dihydro-3-nitroisoxazole (2). A solution of 1,3-propanedithiol (0.13 mL, 1.3 mmol) in THF (5 mL) was cooled under oxygen-scrubbed[8] argon to −78 °C, and a 2.5 M solution of butyllithium in hexanes (1 mL, 2.5 mmol of BuLi) was cautiously added. The resulting solution was stirred for 90 min at −40 to −20 °C, was cooled to −60 °C, and was treated with **2** (0.29 g, 2.5 mmol). The solution was stirred at −45 to −35 °C for 2 h. Workup and purification as in the reaction of **1** with **2** gave bis(thioimidate) **4** (0.27g, 88% yield) identical with the previous sample.

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[8] Argon was passed through an Oxiclear Gas Purifier (Model DGP-250-R1).

[9] Thiem, J.; Wessel, H.-P. *Liebigs Ann. Chem.* **1983**, 2173.

[10] Stahl, I. *Chem. Ber.* **1985**, *118*, 4857.