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Dianions of 3-oxodithioic acids: preparation and conversion to 3*H*-1,2-dithiole-3-thiones

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Abstract

Reaction of ketones with CS_2 and 2 equivalents of KH in THF–*N*,*N*′-dimethylpropyleneurea solution produces the dianions of 3-oxodithioic acids. These dianions are converted in good yield to 3*H*-1,2-dithiole-3-thiones by the sequential action of hexamethyldisilathiane and an oxidizing agent such as hexachloroethane.

Keywords: dithioles; sulfur compounds; sulfur heterocycles; thioacids.

The dithiolethiones (3*H*-1,2-dithiole-3-thiones, **1**) continue to be of interest as potent chemoprotective agents against a variety of animal models of cancer.[1] One representative of this class of heterocyclic sulfur compounds (Oltipraz, **1**, R^1 = pyrazinyl, R^2 = methyl) is currently undergoing human trials in an area of China which has a high incidence of liver cancer.[2] Unfortunately, finding a general and high-yielding method for synthesis of the dithiolethione ring system remains a challenging problem. In this connection, some time ago we published a method for dithiolethione synthesis in which the 3-oxodithioic acids **2** resulting from condensation of CS_2 with ketones were converted to dithiolethiones by the action of NCS and hexamethyldisilathiane (HMDT) in the presence of a catalytic amount of imidazole.[3] We presented evidence that this novel cyclization proceeded via oxidative dimerization of the 3-oxodithioic acids to tetrathianes **3**, which were then converted to dithiolethiones by reaction with HMDT.[3] However, in a number of cases the yields of dithiolethiones obtained were low, in part because isolation of the corresponding 3-oxodithioic acids was accompanied by severe decomposition and losses.[4] In a continuing effort to improve the yields obtained by this sequence, we have investigated the formation and reactions of dianions **4** of the 3-oxodithioic acids. This work has now led to an improved synthesis of dithiolethiones **1** by a route which does not appear to involve the intermediacy of tetrathianes **3** and which is the subject of this communication.

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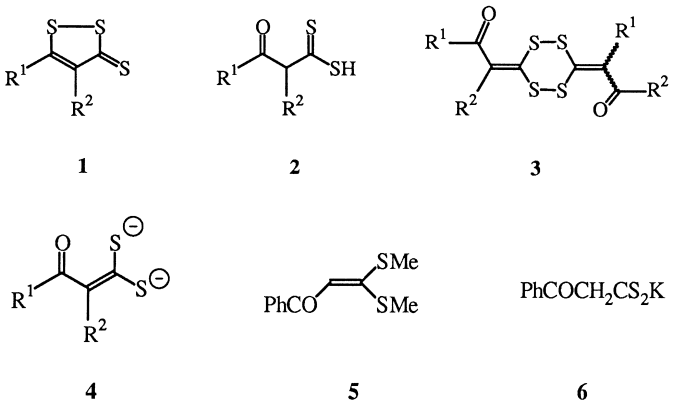
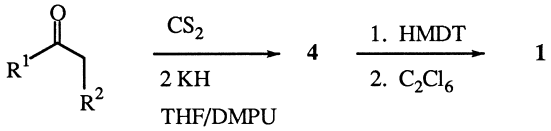


In a model experiment, reaction of acetophenone with CS_2 in the presence of 2 equivalents of KH led to the evolution of 2 equivalents of hydrogen as measured gasometrically. Addition of excess methyl iodide then produced ketenedithioacetal **5** in 99% chromatographic yield *without any additional gas evolution*. This experiment is clearly consistent only with the formation of dianion **4** prior to addition of the electrophile. In order to obtain complete conversion to dianion **4** in a THF solution it was found necessary to use a dipolar aprotic cosolvent, either HMPA or *N*,*N*′-dimethylpropyleneurea (DMPU). This is most likely due to the low solubility of monopotassium salts such as **6** which hinders further reaction with an insoluble base like KH. The need for a dipolar aprotic solvent to achieve complete conversion to the dianion **4** is likely *not* due to the weak acidity of the first formed monoanion. Sulfur acids in general show a greater acidity than their oxygen analogues, and the pKa_2 of acetoacetic acid (in water) is reported to be 14.1.[5]

Initial attempts to oxidize the dianions **4** to tetrathianes, which could then be converted to dithiolethiones with HMDT, gave results no better than those obtained previously.[3] However, yields improved dramatically when the dianion **4** was *first* treated with HMDT and then with oxidant. The most generally satisfactory oxidant was found to be hexachloroethane, although yields using bromine or iodine were similar or only slightly lower. The overall transformation is shown by Eq. (1) and the results obtained with a range of ketone substrates are given in Table 1.[6] In general, the yields ranged from good to essentially quantitative, with aralkyl ketones (entries 1–4) tending to give higher yields than dialkyl ketones (entries 6–10). In all cases the yields were superior to those obtained by the previously published two-step procedure involving isolation and oxidative cyclization of the free 3-oxodithioic acid **2**.[3]



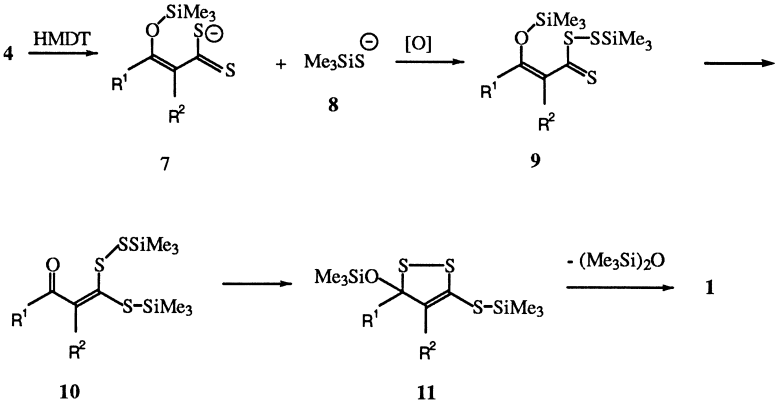
(1)

While certain details remain obscure, we believe that the transformation of dianion **4** to dithiolethione **1** proceeds by the sequence of steps shown in Scheme 1. Direct confirmation of the first step in this scheme was possible using pinacolone as the ketone, since the corresponding dianion **4**, $R^1 = t$-Bu, $R^2 = H$, was soluble enough in THF–DMPU to allow NMR spectra to be

Table 1
Conversion of ketones to 3*H*-1,2-dithiolethiones by Eq. (1)[a]

entry	R^1	R^2	Yield (%)[b]
1	Ph	H	99
2	Ph	Me	91
3	Ph	SMe	90
4	4-MeOPh	H	88
5	*t*-Bu	H	91
6	$-(CH_2)_3-$		73
7	$-(CH_2)_4-$		77
8	Me	H	76
9	Me	Me	60[c]
10	Et	Me	72

[a]See note 6 for reaction conditions.
[b]Determined by HPLC using the internal standard method.
[c]An additional 11% of the isomeric dithiolethione R^1 = Et, R^2 = H, was formed.



Scheme 1.

taken and the course of the reaction with HMDT to be observed directly. The dianion **4** from pinacolone showed the expected two singlets in its ^{1}H NMR spectrum at δ 1.0 (9H, *t*-Bu) and 7.0 (1H, vinyl hydrogen). When 1 equivalent of HMDT was added to the dianion solution, the vinyl hydrogen resonance shifted to δ 6.1 and two new resonances appeared in the spectrum at δ 0.20 (9H) and 0.05 (9H). We attribute these to the TMS groups of enol ether **7** and thiolate **8**, respectively, since authentic thiolate **8** (generated from HMDT, KH, and water) gave a peak at δ 0.05 in this solvent mixture. Furthermore, the same set of peaks minus the one at δ 0.05 was generated when the dianion was quenched with 1 equivalent of TMS chloride in place of HMDT.[8] Addition of hexachloroethane or iodine to the dianion plus HMDT mixture brought about a rapid conversion to dithiolethione **1**, $R^1 = t$-Bu, $R^2 = H$, without any evidence for the formation of tetrathiane **3** either by NMR or, in a separate experiment, by HPLC. In the absence of evidence for any intermediates, we believe that the further transformation of the mixture of **7** and **8** into dithiolethione **1** upon addition of oxidant is most simply rationalized as proceeding via the intermediacy of the mixed disulfide **9**. Formation of the disulfide bond in **9** probably involves initial attack of the oxidizing agent on the more nucleophilic thiolate **8** to form a sulfenylating

species such as Me_3SiSCl, which then reacts with **7** to form **9**. We propose that **9** is then converted to dithiolethione **1** by migration of a TMS group from oxygen to sulfur giving the bis-*S*-silylated intermediate **10**, whose ring-closure by addition of an Si–S bond across the carbonyl group leads to intermediate **11**. Elimination of the elements of hexamethyldisiloxane from **11** then gives the dithiolethione **1**.

In conclusion, we have developed a simple one-pot procedure for conversion in good yield of ketones to dithiolethiones via the intermediacy of the dianions **4** derived from 3-oxodithioic acids. The further synthetic utility of dianions **4** is under investigation and will be reported in due course.

Acknowledgements

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6. **CAUTION**: Because of the noxious odor and probable toxicity of HMDT and because flammable hydrogen gas is evolved, this procedure should be conducted only in a well-ventilated fume hood. Representative procedure: To a well-stirred suspension of KH (2.06 g, 51.3 mmol) in dry THF (50 mL) and dry DMPU (25 mL) was added under an atmosphere of dry argon a solution of 4′-methoxyacetophenone (3.75 g, 25 mmol) in dry THF (7 mL) at a rate sufficient to maintain rapid evolution of hydrogen. The enolate suspension was stirred for an additional 15 min after gas evolution had ceased, then a solution of carbon disulfide (2.09 g, 27.5 mmol) in dry THF (12 mL) plus dry DMPU (6 mL) was added at a rate such that hydrogen was continually evolved. The resulting red solution was stirred for 10 min and HMDT (6.69 g, 37.5 mmol) was then added. After stirring an additional 20 min, the mixture was cooled to 0°C, treated with a solution of hexachloroethane (5.92 g, 25 mmol) in dry THF (15 mL), and stirred for 30 min more. MeOH (10 mL) was added cautiously to destroy any unreacted hydride and the mixture allowed to stand for 15 min. THF was removed in vacuo and the crude dithiolethione was precipitated with an excess of water. TLC (silica gel, 10% ethyl acetate in hexane) of this material showed only minor amounts of impurities. Recrystallization of the dried product from CCl_4 gave 5-(4-methoxyphenyl)-3*H*-1,2-dithiole-3-thione (5.06 g, 84%) **1**, R^1 = 4-MeOPh, R^2 = H, as a crystalline orange solid, mp 107.5–109°C (lit.[7] mp 109°C).
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8. We cannot rule out an alternative structure for silylated monoanion **7** in which the TMS group resides on sulfur rather than oxygen. Indeed, these two forms of the silylated monoanion may well be in equilibrium with each other via *O* to *S* silyl group migration. However, the well-known affinity of silicon for oxygen, as well as the fact that the alternative *S*-silylated monoanion would be the conjugate base of a weaker acid, argues in favor of the *O*-silylated structure **7**. The exact position of the TMS group is not crucial to the proposed mechanism, since either the *O*-silylated or the *S*-silylated monoanion may serve as a precursor to **10**.