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Xianzhu Zeng, Samir Zard. Modular Routes to 1,3-Dithian-2-ones and 1,2-Dithiolanes. *Organic Letters*, 2022, 24 (29), pp.5241-5244. 10.1021/acs.orglett.2c02214 . hal-04245547

HAL Id: hal-04245547

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Submitted on 17 Oct 2023

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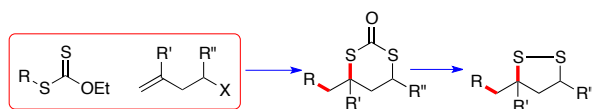
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Modular Routes to 1,3-Dithiane-2-ones and 1,2-Dithiolanes

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Supporting Information Placeholder



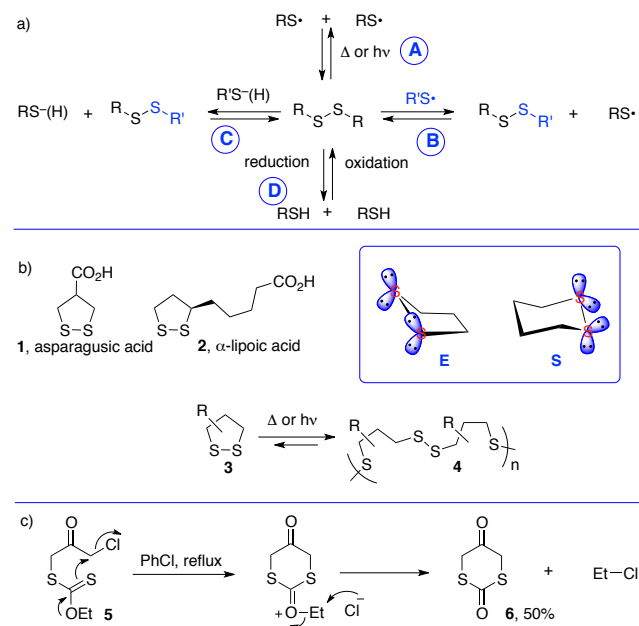
ABSTRACT: Convergent routes to 1,3-dithiane-2-ones based on the radical addition of xanthates to alkenes possessing a suitably located (latent) leaving group are described. These can be converted into 1,2-dithiolanes by base mediated hydrolysis and oxidation. A broad variety of functional groups can be introduced and the process is modular, uses inexpensive starting materials and reagents, and is atom economical, since both sulfur atoms of the xanthate end up in the products.

The sulfur-sulfur bond in disulfides is thermodynamically stable but kinetically labile in that it can be reversibly cleaved thermally, photochemically, by the action of thiyl radicals, or ionically by nucleophilic displacement with a thiol or a thiolate (Scheme 1a).¹ Redox combinations can also be used to switch between the thiol and the disulfide. These very useful features have been exploited by nature and by chemists to dynamically modify the structure of proteins and to produce adaptable materials that respond to various stimuli.² One everyday application is the modification of hairstyles by straightening or curling the hair strands through cleavage and reformation of the disulfide bonds in hair proteins.

The case of cyclic disulfides, especially 1,2-dithiolanes, is particularly interesting. This motif is present in asparagusic acid **1** and α -lipoic acid **2** (Scheme 1b). The former was isolated from asparagus, whereas the latter is present in essentially all organisms and is extensively used as an over-the-counter dietary supplement, as a drug against diabetic neuropathy, and in dermatology and cosmetics.³ Interestingly, in the rather flat 5-membered disulfide, the lone pairs on the adjacent sulfur atoms are partially eclipsed (structure **E** in the box), whereas they are staggered in the homologous 6-membered disulfide (structure **S** in the box). The eclipsed disposition increases the electronic repulsion and weakens the S—S bond. Calorimetric measurements indicate 1,2-dithiolanes to be 3.7 kcal/mol less stable than the corresponding 1,2-dithianes.^{4a} This translates into a 10³ fold faster thiolate-disulfide exchange for the former as compared to the latter.^{4b} The ring strain present in 1,2-dithiolanes **3** causes the equilibrium with the open-chain polymers **4** to favor the latter.⁵ Furthermore, it was found that this equilibrium can be established under mild thermal or photochemical conditions.^{5a,b} For instance, merely heating lipoic acid to 70 °C is sufficient to induce polymer formation^{5c,d} These observations have triggered numerous studies, especially from material scientists

seeking to take advantage of these remarkable properties.⁶ However, most of the work has revolved around commercially available lipoic and asparagusic acids and simple derivatives thereof, namely esters and amides. Comparatively little effort has been devoted to establishing generally applicable routes to such disulfides or their 1,3-dithiol precursors.

Scheme 1. Aspects of Disulfide and 1,3-Dithiane-2-one Chemistry



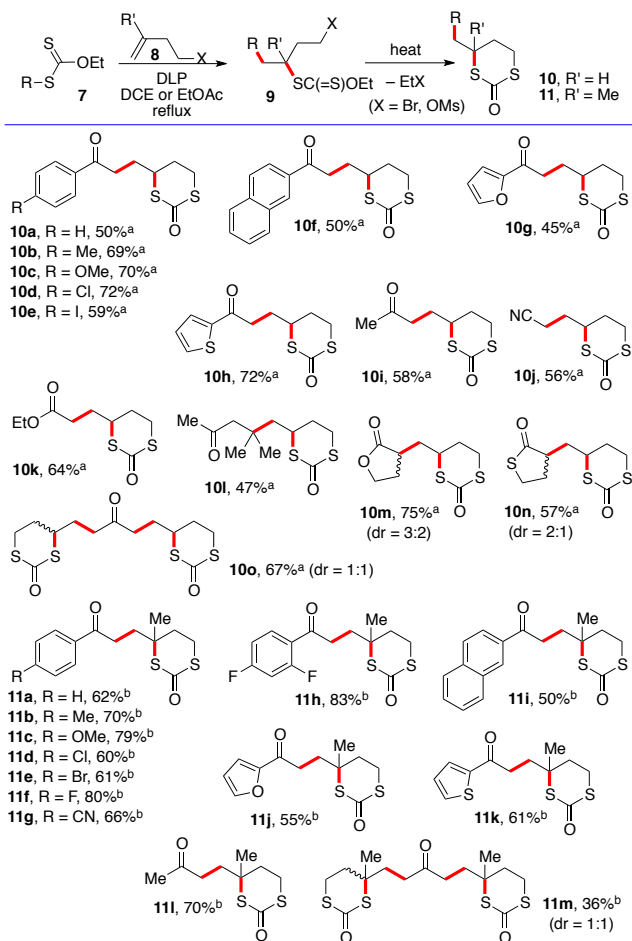
Broadly speaking, there are two main routes to these compounds. The first starts from 1,3-diols, which are converted into sulfonates or halides and substituted with a suitable sulfur nucleophile.⁷ Treatment of 1,3 diols or their esters with thiourea under strongly

acidic conditions (HI or HBr) has also been reported.⁸ The second involves Michael addition of hydrogen sulfide or, more conveniently, a synthetic equivalent to unsaturated ketones and esters followed by reduction of the oxygen function to the alcohol, conversion into a leaving group and substitution with a sulfur nucleophile.⁹ These approaches are relatively lengthy for accessing such rather simple structures and suffer from various limitations which have discouraged material scientists from going beyond lipoic acid and its derived esters and amides. Herein, we describe practical, modular routes to 1,3-dithiols protected as 1,3-dithian-2-ones. These are easily saponified into 1,3-dithiols and then oxidized to the corresponding 1,2-dithiolanes.

Surprisingly, 1,3-dithian-2-ones have been seldom reported in the open literature. A search in REAXYS returned fewer than 10 such derivatives, essentially all prepared by reaction of 1,3-dithiols with carbonyl diimidazole. We accidentally discovered one such compound, **6**, initially as a side-product while examining the radical additions of xanthate **5** to various alkenes, and later confirmed its formation by heating this substance alone in refluxing chlorobenzene (Scheme 1c).^{10b} We have now found that this observation could be translated into a general synthesis of 1,3-dithian-2-ones.

Our route is outlined in Scheme 2. The radical addition of xanthate **7** to alkene **8** possessing a leaving group X (X = Br, OMs) in the homoallylic position gives rise to adduct **9**.¹¹ It is not necessary to isolate this intermediate; further heating of the reaction mixture completes the cyclization to afford dithianone **10** with concomitant loss of EtX. Fortunately, this second step does not interfere with the radical addition which is taking place concomitantly. The reactions were conducted in refluxing 1,2-dichloroethane (DCE) or ethyl acetate. Incidentally, it is fortunate in this respect that the formation of dithianedione **6** from xanthate **5** is sufficiently sluggish in these lower boiling solvents to allow the radical additions leading to α -chloroketones to proceed without premature destruction of the starting xanthate.^{10b}

Scheme 2. Examples of 1,3-Dithian-2-ones

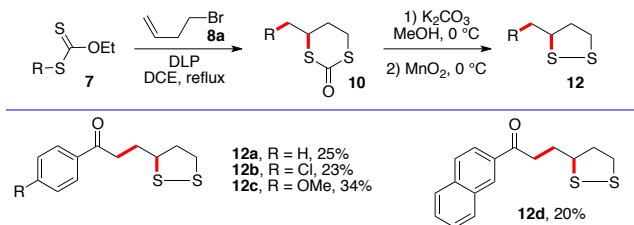


^a Solvent: DCE; **8**, X = Br, R' = H; ^b solvent: EtOAc; **8**, X = OMs, R' = Me

The examples of 1,3-dithian-2-ones **10a-o** and **11a-m** displayed in Scheme 2 were prepared starting with two alkenes, 1-bromo-3-butene **8** (X = H, R' = H) and 1-mesyloxy-3-methyl-3-butene **8** (X = OMs, R' = Me), respectively. The additions were initiated with dilauroyl peroxide (DLP) and 2 equivalents of alkene **8** were used. This one-pot synthesis of 1,3-dithian-2-ones allows the attachment of various functional groups, including ketones, nitriles, esters, lactones, thiolactones, nitriles, and tolerates the presence of aromatic bromides and iodides. This functionality can be subsequently exploited in myriad ionic and organometallic reactions to expand the diversity of the structures. Compounds **10o** and **11m** arise from a double radical addition and correspond to masked tetrathiol, which would be useful for making crosslinked polymers (cf. **4** in Scheme 2), strong chelators for the recovery of (heavy) metals, or multipronged anchors for the modification of metallic surfaces.

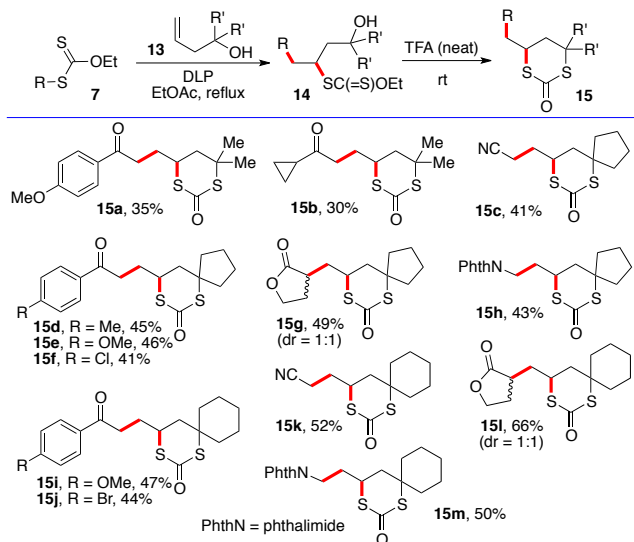
The formation of 1,3-dithian-2-ones **10** and their conversion into the corresponding 1,2-dithiolanes **12** could also be accomplished in a one-pot procedure (Scheme 3). Thus, upon completion of the cyclization leading to dithianones **10**, the cyclic dithiocarbonate is cleaved with potassium carbonate in cold methanol and the resulting dithiol (not shown) oxidized with manganese dioxide into 1,2-dithiolanes **12a-d**. The overall (unoptimized) yield of dithiolanes **12a-d** is modest, possibly because of competing formation of polydisulfide polymer (cf. **4** in Scheme 1b).

Scheme 3. Synthesis of 1,2-Dithiolanes



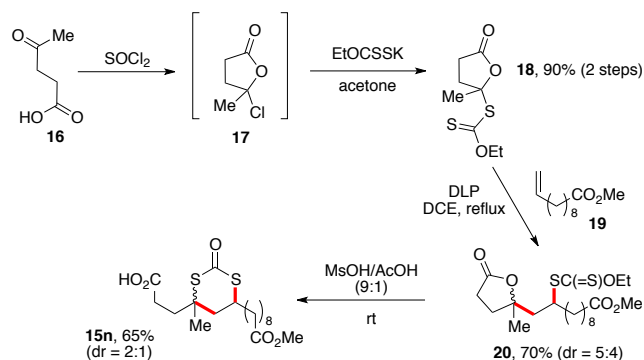
A complementary route to 1,3-dithian-2-ones of general structure **15** is presented in Scheme 4. It consists in the radical addition of xanthates **7** to tertiary homoallylic alcohols **13** followed by treatment of the resulting adducts **14** with trifluoroacetic acid (TFA). This is also a one-pot process that does not require the isolation of the intermediate radical adducts. The yields of 1,3-dithian-2-ones **15a-m** are moderate and correspond to the two steps combined.

Scheme 4. A Second Route to 1,3-Dithian-2-ones



We explored briefly a third route to 1,3-dithian-2-ones **15**, in which all the components needed to construct the sulfur heterocycle are located in the starting xanthate. It is illustrated by the conversion of adduct **20** into dithianone **15n** (Scheme 5). A 9:1 mixture of methanesulfonic acid (MsOH) and acetic acid had to be used instead of TFA. The xanthate precursor **18** is derived from levulinic acid **16** via intermediate chloride **17**, which is used directly without purification.¹² Interestingly, *all the carbon atoms in the main chain of dithianone 15n are derived from the biomass*. Levulinic acid **16** is obtained from lignocellulosic waste¹³ and methyl 10-undecenoate **19** is a thermolysis product from the castor oil plant (*Ricinus communis*), a sturdy shrub that can grow in non-arable lands and does not therefore interfere with the production of food.¹⁴

Scheme 5. An Example of a Third Approach to 1,3-Dithian-2-ones



In summary, we have developed practical routes to 1,3-dithian-2-ones and 1,2-dithiolanes. The corresponding 1,3 could also be produced in principle, if so desired. Such derivatives have numerous applications. 1,2-Dithiolanes related to lipoic acid for example have been used to make adhesive polymers,¹⁵ structurally dynamic and photocurable adaptable hydrogels,¹⁶ polymers with antifouling properties,¹⁷ additives for lubricants,¹⁸ and polymers for the removal of pollutants.¹⁹ Hopefully, the present, easy access to a broad variety of these important organosulfur compounds will assist in expanding the application scope.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and copies of ¹H and ¹³C NMR for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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ACKNOWLEDGMENTS

We thank the China Scholarship Council (CSC) for a scholarship to X. Z., Dr Béatrice Quiclet-Sire and Xuan Chen for preliminary experiments, and Mrs Sophie Bourcier and Mr Vincent Jactel for HRMS measurements (all at Ecole Polytechnique).

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