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Oxalic acid catalyzed reaction between dithioacetals and acetals. A simple and eco-friendly method for a conversion of a dithioacetal to a carbonyl compound

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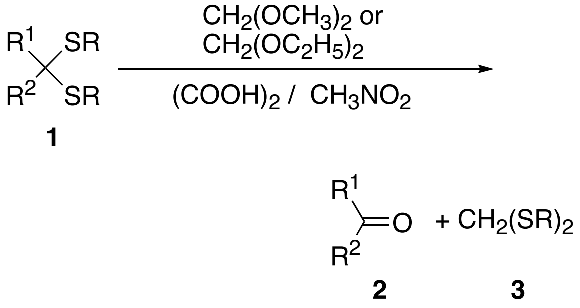
Abstract Oxalic acid catalyzes a reaction between dithioacetals and acetals. This reaction is useful in a new and eco-friendly method to convert dithioacetals to carbonyl compounds.

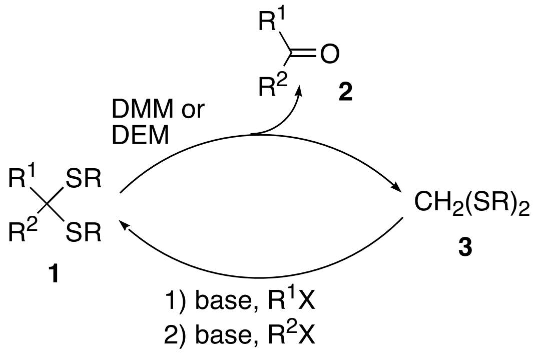
Dithioacetals are widely used as acyl anion equivalents in organic synthesis. For example, the metalation of 1,3-dithiane followed by substitution with an alkyl halide is a useful method for preparing a substituted 1,3-dithiane.[1] A double conjugate addition of 1,3-propanedithiol to ynone is also a useful method for preparing β-keto-1,3-dithianes.[2] The dithioacetal group is also used as a protecting group[3] for protecting the carbonyl group from undesired reactions. However, dithioacetal is a relatively stable functional group, and it is not easily converted into a carbonyl group. Heavy metal salts, such as $HgCl_2$ and HgO are often used as effective reagents for such conversions,[4] and the reaction usually proceeds under mild conditions. However, the toxicity of Hg(II) is a serious drawback to this method, and complicated procedures are required to dispose of the byproducts, which contain mercury compounds. However, most of other methods, using $AgClO_4$,[5] isoamyl nitrite,[6] Ph_3CClO_4,[7] $GaCl_3$,[8] Bi^{3+},[9] $FeCl_3$,[10] $NaHSO_4$,[11] HIO_3,[12] bromonium ion,[13] Cr^{6+},[14] or DMSO,[15] also have some shortcomings in terms of chemoselectivity, cost, and the toxicity of the reagent . For these reasons, Hg(II) salts are still widely used in these types of conversion. In this paper, we will report on a low cost and eco-friendly conversion method.

Although the hydrolysis of acetals proceeds easily under acidic conditions, dithioacetal hydrolysis does not proceed even in the presence of strong acids. However, we find that oxalic acid catalyses the hydrolysis of dithioacetals in the presence of acetals such as dimethoxymethane (DMM) or diethoxymethane (DEM) (Scheme 1).



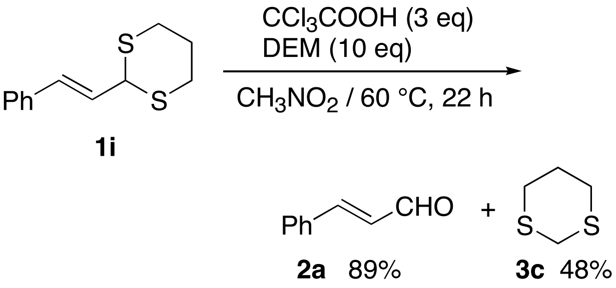
Scheme 1.

When a dithioacetal such as 3,3-bis(dodecylthio)-1-phenyl-1-propene (**1a**) is stirred with oxalic acid, DMM, and nitromethane at 60°C, we can obtain cinnamaldehyde (**2a**) and bis(dodecylthio)methane (**3a**) in excellent yield. The dithioacetals of not only aldehydes, but also ketones, react with DMM or DEM to give carbonyl compounds under similar conditions. Results supporting this find are summarized in Table 1. The dithioacetals, which have no polar functional group, are insoluble to nitromethane. Low solubility often causes a prolonged reaction time. In many cases in our study, the transformation of acyclic dithioacetal proceeded in excellent yield. However, when DMM was used, the corresponding reaction of cyclic dithioacetals, such as the 1,3-dithiane derivatives **1i** or **1j**, produced a lower yield, and the additional use of DMM and oxalic acid was not effective. In these cases, yields can be improved using DEM instead of DMM. For example, although the DMM mediated reaction of **1i** gave **2a** in 67% yield, the corresponding DEM mediated reaction gave **2a** in 90% yield. The deprotection of 1,3-dithiolane derivative **1k** also proceeded in **% yield. Although large excesses of DMM or DEM were present in the reaction mixture, we did not obtain a monothioacetal such as (dodecylthio)methyl methyl ether, although we did obtain bis(dodecylthio)methane (**3a**) in excellent yield. However, the corresponding reaction of bis(phenylthio)acetal **1h** gave only small amount of bis(phenylthio)methane (**2b**), and monothioacetal $PhCH_2OC_2H5$ was obtained in 78% yield. The reasons of these unexpected results are under investigation. 1.3-Dithiane (**3b)** was obtained only in poor yield, probably because it has relatively low boiling point, and a considerable amount of **3b** was lost from the reaction mixture during the course of purification with other compounds with a low boiling point. The recovered **3a** can be used as a new acyl cation equivalent. This means that the recycling of dithioacetal, shown in Scheme 2, is possible. Some dithioacetals like **1** are often prepared from **3a** using stepwise alkylation.



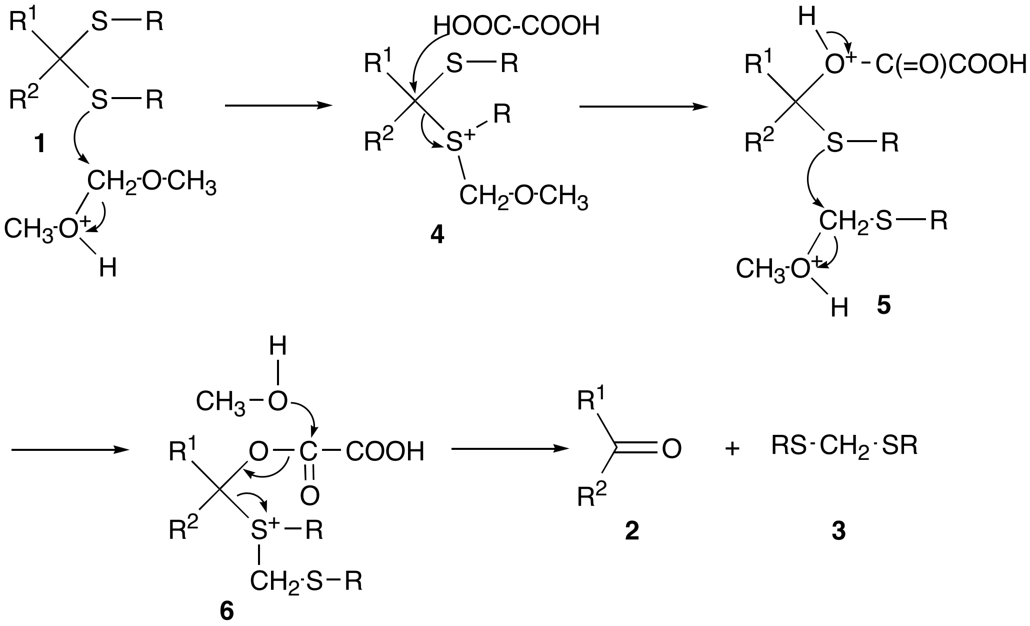
Scheme 2.

Selecting the appropriate solvent is very important in this transformation. So far in our studies, we have found nitromethane to be the most effective. Other solvents such as DMF, THF, $CHCl_3$, CH_2Cl_2, and acetonitrile, are not as effective as nitromethane. Concerning the acid catalyst, some carboxylic acids are also effective to a certain extent. Trichloroacetic acid is especially effective as an oxalic acid. When three equivalents of trichloroacetic acid and DME (10 eq) were used instead of oxalic acid, the deprotection of dithioacetal **1i** proceeded in excellent yield (Scheme 3). However, it is often difficult to remove trichloroacetic acid from a reaction mixture without treatment using a base such as an aqueous solution of $NaHCO_3$, whereas oxalic acid can be removed very easily by aqueous workup without the addition of a base.



Scheme 3.

In this reaction, we convert an acetal into a corresponding dithioacetal. On the other hand, we did not observe transacetalization, and an acetal of **2** was not obtained. The methoxy group or ethoxy group of an acetal may be converted into an ester of oxalic acid. The plausible mechanism in our experiment was as follows (Scheme 4). Initially, a protonation of acetal occurred, and a nucleophilic attack of the sulfur atom to the methylene carbon caused a substitution that gave a sulfonium ion (**4**). The following nucleophilic attack of oxalic acid, caused the elimination of monothioacetal. The nucleophilic attack of the remaining sulfur atom of the substrate to a protonated monothioacetal (**5**) gave a sulfonium ion (**6**). The following elimination of dithioacetal (**3**) gave a carbonyl compound (**2**).



Scheme 4.

The general procedure we used was as follows. We added a powdered oxalic acid (6.0 mmol) to a mixture of nitromethane (5 ml), dimethoxymethane (or diethoxymethane) (20 mmol), and dithioacetal (**1**) (2.0 mmol). The mixture was stirred at 60ºC. After the reaction finished, the reaction mixture was poured into water. After usual workup, we purified the mixture using column chromatography on a silica gel to give carbonyl compound (**2**) and dithioacetal (**3**).

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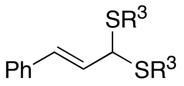
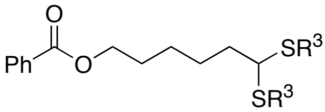
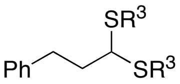
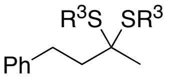
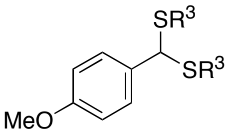
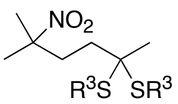
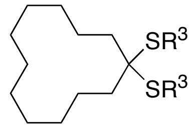
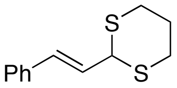
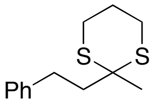
Table 1. Conversion of dithioacetals to carbonyl compounds.

Entry	Dithioacetals (**1**)[a]		Acetal (eq)	Conditions	Product yield (%)[b]			
					2		**3**	
1		(**1a**)	DMM (5)	60 °C, 14 h	**2a**	95	**3a**	96
2		(**1b**)	DMM (5)	60 °C, 14 h	**2b**	94	**3a**	97
3		(**1c**)	DMM (10)	60 °C, 25 h	**2c**	85	**3a**	96
4		(**1d**)	DMM (10)	60 °C, 28h	**2d**	92	**3a**	97
5			DEM (10)	60 °C, 32 h	**2d**	85	**3a**	92
6		(**1e**)	DMM (10)	60 °C, 6 h	**2e**	90	**3a**	–[c]
7			DEM (10)	60 °C, 5 h	**2e**	92	**3a**	–[c]
8		(**1f**)	DMM (10)	60 °C, 12 h	**2f**	95	**3a**	94
9		(**1g**)	DMM (10)	60 °C, 10 h	**2g**	88	**3a**	85
10		(**1h**)	DMM (5)	60 °C, 25 h	**2a**	67(26)[d]	**3b**	0
11			DEM (10)	60 °C, 26 h	**2a**	90	**3b**	8
12		(**1i**)	DMM (5)	60 °C, 22 h	**2d**	73(21)[d]	**3b**	18
13			DEM (10)	60 °C, 15 h	**2d**	87	**3b**	–[c]

[a] R^3= n-$C_{12}H_{25}$. [b] Isolated yield. [c] Not determined. [d] Yield of recovered dithioacetal(**1**) is in parentheses.