Oxalic Acid-promoted Preparation of Dithioacetals from Carbonyl Compounds or Acetals

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This letter describes oxalic acid-promoted syntheses of dithioacetals from carbonyl compounds and thiols. Acetals are also converted into dithioacetals by the reaction with thiols under similar conditions.

Recently, we have reported that oxalic acid can promote the reaction between acetals and dithioacetals, and this reaction is useful as a method of converting dithioacetals to carbonyl compounds.[1] In the course of the study, we have found that the activation of some C–O bonds by oxalic acid can also be applied to the synthesis of dithioacetals.

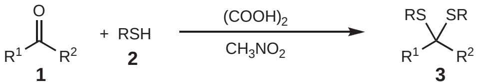
Dithioacetal is an important functional group not only as an acyl anion equivalent but also as a protected carbonyl compound.[2] The conversion of carbonyl compounds into dithioacetals can be accomplished by the reaction with thiols in the presence of some catalysts, such as $BF_3{\cdot}OEt_2$,[3] $InCl_3$,[4] $TiCl_4$,[5] $Sc(OTf)_3$,[6] $SOCl_2$–silica gel,[7] Nafion-H,[8] $ZrCl_4$,[9] heteropoly acids,[10] and $SnCl_2{\cdot}2H_2O$ under microwave irradiation.[11] Some of these methods, however, need strong acidic conditions, and some of the catalysts used in these methods are expensive or troublesome to prepare. We find that the corresponding transformation can be accomplished by using oxalic acid as a catalyst. As oxalic acid is not only an inexpensive and readily available compound but also a relatively weak acid, the reaction is expected to proceed with good chemoselectively. Experimental results are summarized in Table 1.[12]

Although a nucleophilic or radical conjugate addition of thiol to α,β-unsaturated carbonyl compound, such as cinnamaldehyde, occurs easily, the formation of dithioacetal proceeded without affecting the carbon–carbon double bond to give unsaturated dithioacetal (Entries 5, 6, and 11). The ester group was not affected under these conditions (Entry 9). The reaction with 1,3-propanedithiol (**2c**) proceeded more smoothly than other thiol such as 1-dodecanethiol (**2a**), which is useful as odorless thiol,[13] or thiophenol (**2b**) to give cyclic dithioacetal in excellent yield (Entries 11 and 12).

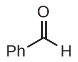
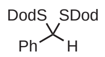
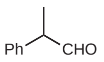
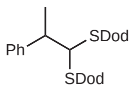
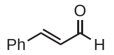
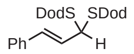
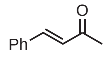
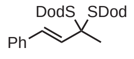
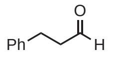
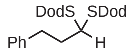
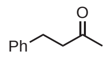
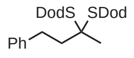
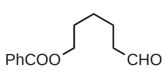
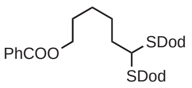
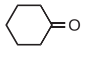
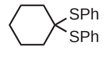
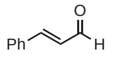
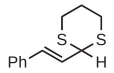
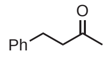
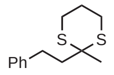
Acetals also reacted with thiols under similar conditions to produce dithioacetals. Some acid catalysts are effective to the conversion of acetals to dithioacetals. For example, BF_3–OEt_2,[14] tetrabutylammonium tribromide (TBATB),[15] and Nafion-H[16] are effective. The results of the oxalic acid-promoted conversion are summarized in Scheme 1. Interestingly, even when a large excess of acetal, such as **4** or **6**, was added, dithioacetal was obtained chemoselectively and monothioacetal was not obtained. This outcome suggests that the monothioacetal **12** is more reactive than acetal **6** under these conditions, and the equilibrium shown in Scheme 2 gives dithioacetal **7** exclusively.

When 4,4-dimethoxy-2-butanone (**8**) was treated with 2.4 equiv. of thiol in the presence of anhydrous $(COOH)_2$, 4,4-didodecylthio-2-butanone (**9**) was obtained at a yield of 69%. Methoxymethyl ether **10** gave **11** and **5** under the similar conditions. Such a result indicates that the present method is a useful one for a deprotecting acetal-type protecting group. Similarly, *p*-methoxybenzyl ether **13** can be converted into alcohol **11** and sulfide **14** under similar conditions (Scheme 3), and this was found to be useful as a method to remove the *p*-methoxybenzyl ether-type protecting group. Further study on this methodology is in progress.

Table 1. Synthesis of dithioacetals from carbonyl compounds

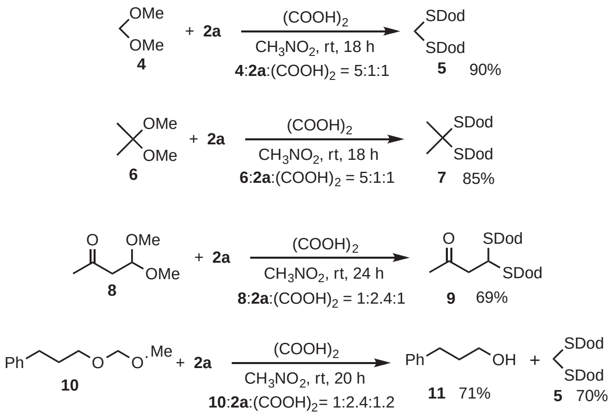


2a: 1-dodecanethiol (DodSH)
2b: thiophenol (PhSH)
2c: 1,3-propanedithiol

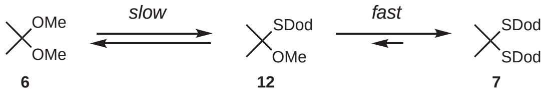
Entry	Substrate (**1**)	Thiol (**2**)	Dithioacetal (**3**)	Conditions	Yield/%[a]
1		2a		rt, 48 h	85
2				60 °C, 7 h	86
3		2a		rt, 72 h	90
4				60 °C, 2 h	69
5		2a		rt, 2 h	98
6		2a		rt, 16 h	84
7		2a		rt, 18 h	78
8		2a		rt, 18 h	75
9		2a		rt, 16 h	91
10		2b		rt, 48 h	76
11		2c		rt, 2 h	95
12		2c		rt, 3 h	98

[a]Isolated yield. Dod: dodecyl.

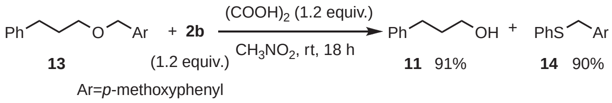
Other carboxylic acids such as trichloroacetic acid, which has similar acidity to oxalic acid, is as effective as oxalic acid for the conversion of carbonyl compounds to dithioacetals. Catalytic amount of (1*R*)-10-camphorsulfonic acid is also effec-



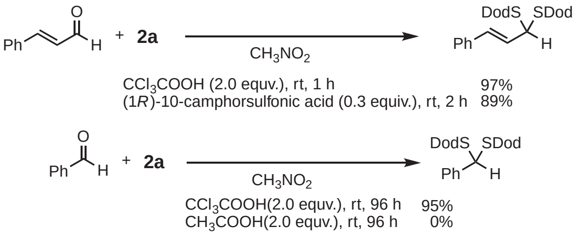
Scheme 1.



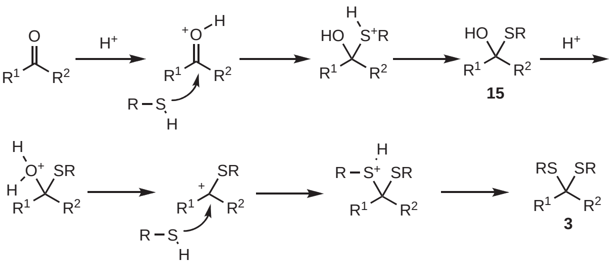
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

tive. However, acetic acid is not effective. Results are summarized in Scheme 4.

These results suggest that not only oxalic acid, but also some Brønsted acids are effective. The plausible mechanism of this reaction is shown in Scheme 5. Brønsted acid protonates the carbonyl oxygen, and nucleophilic attack of thiol to the carbonyl carbon gives **15**. And the following acid-catalyzed replacement of hydroxy group by alkylthio group gives dithioacetal.

In conclusion, oxalic acid and some carboxylic acids, such as trichloroacetic acid, effectively promote the conversion of carbonyl compounds and acetals to dithioacetals. The merits of using oxalic acid are as follows. Oxalic acid is readily available, and after the reaction, it can be removed easily by aqueous workup.[12]

References and Notes

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12 Typical procedures are as follows. The general procedures for the dithioacetalization of carbonyl compound **1** are as follows. A nitromethane (5 mL) solution of **1** (5.0 mmol), $(COOH)_2$ (12 mmol), and thiol (12 mmol for **2a** or **2b**, whereas 6.0 mmol for **2c**) was stirred under the conditions shown in Table 1. The mixture was poured into water and extracted using ethyl acetate. After the usual workup, the crude mixture was purified by column chromatography on silica gel. The reactions of acetals (**4**, **6**, **8**, and **10**) and *p*-methoxybenzyl ether (**13**) were also accomplished using procedures similar to those described above.

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