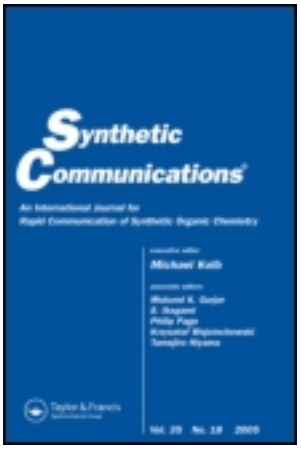

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Chemoselective and Odorless Transthioacetalization of Acetals Using α-Oxo-Ketene Dithioacetals as Thiol Equivalents

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CHEMOSELECTIVE AND ODORLESS TRANSTHIOACETALIZATION OF ACETALS USING α-OXO-KETENE DITHIOACETALS AS THIOL EQUIVALENTS

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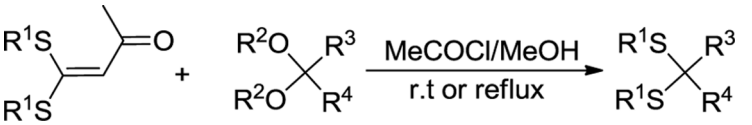
GRAPHICAL ABSTRACT



Abstract *Using α-oxo-ketene dithioacetals **1a** as odorless thiol equivlents, an efficient and odorless transthioacetalization of acetals **2** has been developed. In the presence of MeCOCl in MeOH, the cleavage of **1a** commences to generate thiols at both room and reflux temperatures, and the generated thiols then react with acetals **2** to give correspecting thioacetals **3** in good yield. This transthioacetalization is characterized by mild reaction conditions, simple procedure, good yields, and perfect chemoselectivity. It is noteworthy that only a very faint odor of thiols can be perceived during both the reaction and workup.*

Keywords Acetals; chemoselectivity; odorless thiols equivalents; α-oxo-ketene dithioacetals; transthioacetalization reaction

INTRODUCTION

A switchover of one protective group to another is often required on the basis of their stability under the reaction conditions in subsequent steps.[1] Thioacetals and acetals are two useful protecting groups of carbonyl compounds in the synthesis of multifunctional complex molecules.[2] However, thioacetals are more important than the corresponding acetals because they are more stable to a variety of reagents, including acidic ones,[2] and are considered as acyl carbanion equivalents in C-C bond-forming reactions.[3] Thus, transthioacetalization of acetals is a synthetically useful transformation in organic synthesis. Unfortunately, the transformation usually suffers from the use of harmful, odorous thiols, which can lead to serious safety and environment problems.[4] From the green chemistry point of view, an efficient and odorless transthioacetalization of acetals involving an environmentally

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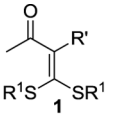


1a R' = H; **1b** R' = $COCH_3$; **1c** R' = COOH; **1d** R' = $COOCH_3$;
1e R' = $CONH_2$; **1f** R' = $CONH(2\text{-}CH_3C_6H_4)$

Figure 1. α-Oxo-ketene dithioacetals **1.**

friendly reagent is of great importance. To the best of our knowledge, no research on odorless transthioacetalization of acetals has been reported in the literature. Recently, we initiated an investigation of α-oxo-ketene dithioacetals as odorless thiol equivalents to develop an environmentally responsible chemistry, and it was found that α-oxo-ketene dithioacetals **1a–f** (Figure 1) could be used in thioacetalization,[5] thia-Michael additions,[6] synthesis of substituted dihydro-1,4-dithiins/1,4-dithiepins,[7] and thiolysis of oxiranes [8] as nonthiolic and odorless thiol equivalents. In our ongoing research to expand the applications of α-oxo-ketene dithioacetals as odorless thiol equivalents in organic synthesis, we investigated the transthioacetalization of acetals **2** using **1a**, which showed great reaction activity than **1b–f** in our previous works, as odorless thiol equivalents. Herein, we report our findings.

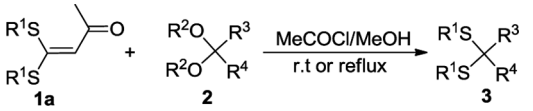
RESULTS AND DISCUSSION

α-Oxo-ketene dithioacetals **1a**, odorless solids that are perfectly stable in open air, were prepared in good yields via an acid-promoted deacylation process of α-oxo-ketene dithioacetals **1b**, which was synthesized from acetyl acetone, carbon disulfide, and bromoethane/benzyl chloride in the presence of K_2CO_3 in nearly quantitative yields.[5h,5i,6a]

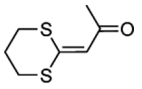
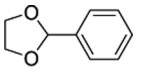
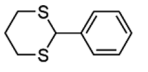
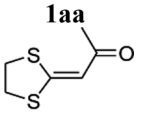
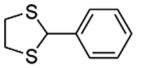
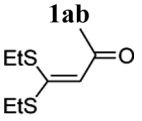
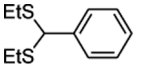
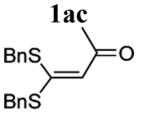
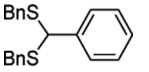
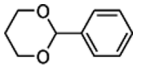
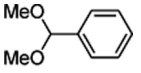
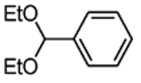
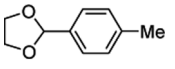
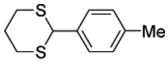
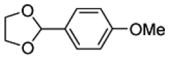
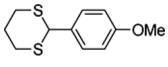
According to our previous thioacetalization reaction of aldehydes/ketones using **1a** as thiol equivalents,[5h,5i] we initially studied the reaction of 2-phenyl-1,3-dioxolane **2a** (1 mmol) with 1-(1,3-dithian-2-ylidene)propan-2-one **1aa** (1 mmol) in the presence of acetyl chloride (1.5 mmol) in MeOH (2 mL) at room temperature. The reaction was completed within 3 h, affording 2-phenyl-1,3-dithiane **3a** in 95% isolated yield. Encouraged by this result, we repeated the reaction under reflux and found that **3a** could be obtained in 94% isolated yield within 0.5 h. It is noteworthy that only a very faint odor of thiols can be perceived during both the reaction and workup.

We next investigated the transthioacetalization of various acetals **2** with **1a** under these optimized conditions to examine the scope of this procedure. With a constant feed molar ratio of acetyl chloride–**1a**–**2** of 3:2:2, all the reactions proceeded smoothly, and the results are summarized in Table 1. Compounds **1a** could be used as diversified odorless thiol equivalents such as propane-1,3-dithiol, ethane-1,2-dithiol, ethanethiol, and benzyl mercaptan (Table 2, entries 1–4) in the reaction. It is noteworthy that **1aa**, 4,4-bis(ethylthio)but-3-en-2-one **1ac**, and 4,4-bis(benzylthio)but-3-en-2-one **1ad** as thiol equivalents showed much better reaction activity than 1-(1,3-dithiolan-2-ylidene)-propan-2-one **1ab**. Both cyclic acetals (**2a**, 2-phenyl-1,3-dioxane **2b**) and dialkyl acetals (1-(dimethoxymethyl) benzene **2c**, 1-(diethoxymethyl) benzene **2d**)

Table 1. Transthioacetalization of acetals **2** using **1a** as thiol equivalents[a]

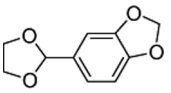
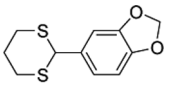
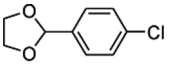
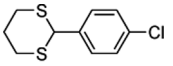
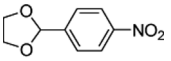
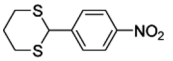
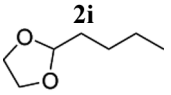
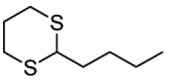
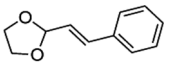
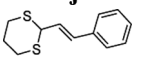
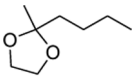
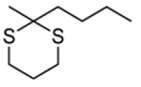
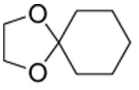
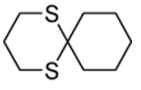
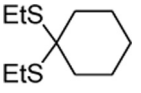
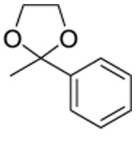
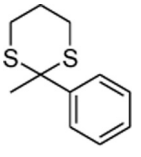


1a **2** **3**

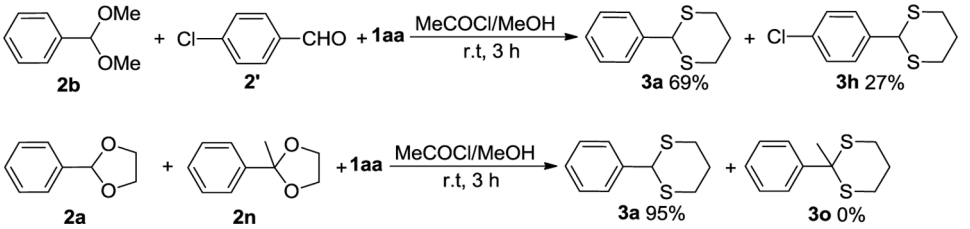
Entry	1a	2	Temp. (°C)	Time (h)	3	Yield (%)[b]	References
1		 **2a**	25 Reflux	3 0.5	 **3a**	95 94	5a–c, 9
2	**1aa** 	**2a**	25 Refux	10 3	 **3b**	56 90	5d
3	**1ab** 	**2a**	25 Reflux	3 0.5	 **3c**	87 90	5 h
4	**1ac** 	**2a**	25 Reflux	3 0.5	 **3d**	91 94	5 h
5	**1ad** **1aa**		25 Reflux	3 0.5	**3a**	94 92	5a–c, 9
6	**1aa**	**2b** 	25 Reflux	2 0.4	**3a**	94 96	5a–c, 9
7	**1aa**	**2c** 	25 Reflux	2 0.4	**3a**	95 96	5a–c, 9
8	**1aa**	**2d** 	25 Reflux	2.5 0.5	 **3e**	92 93	5a–c, 10
9	**1aa**	**2e**  **2f**	25 Reflux	2.5 0.5	 **3f**	94 95	5a–c, 11

(*Continued*)

Table 1. Continued

Entry	1a	2	Temp. (°C)	Time (h)	3	Yield (%)[b]	References
10	**1aa**		25 Reflux	3 0.5		97 96	5a–c, 12
		2g			**3g**		
11	**1aa**		25 Reflux	2.5 0.5		95 96	10, 12
		2h			**3h**		
12	**1aa**		25 Reflux	3 0.5		92 94	5a–c, 13
		2i			**3i**		
13	**1aa**		25 Reflux	3 0.5		88 89	5a–c,
		2j			**3j**		
14	**1aa**		25 Reflux	3 0.5		83 80	5a–c, 13
		2k			**3k**		
15	**1aa**		25 Reflux	4 1		89 87	10
		21			**31**		
16	**1aa**		25 Reflux	4 0.6		95 94	10, 13
		2m			**3m**		
17	**1ac**		25 Reflux	4 0.6		92 91	5 h
					**3n** 		
18	**1aa**		Reflux	5		91	9b, 13
		2n			**3o**		

[a]Conditions: **1a** (1 mmol), **2** (1 mmol), MeCOCl (1.5 mmol), MeOH (2 mL).
[b]Isolated yield.

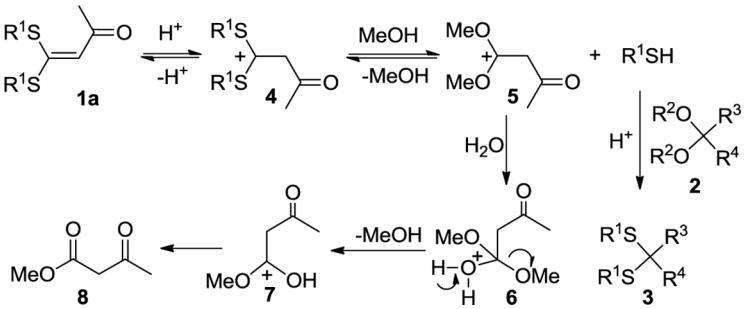


Scheme 1. Chemoselective protection reaction.

efficiently underwent transthioacetalization reaction with **1aa** to afford **3a** in good yields (Table 2, entries 1, 5–7). The aryl acetals **2e–i** derived from various types of substituted aromatic aldehydes with electron-donating and electron-withdrawing groups, the aliphatic acetals **2j–k**, and the aliphatic ketals **2l** and **m** derived from cyclic and open-chain aliphatic ketones were cleanly and rapidly converted to the corresponding thioacetals in excellent yields at both room and reflux temperature (Table 2, entries 8–17). Compared with **2a–m**, the aryl ketal **2n** could not be transthioacetalized at room temperature but could give its corresponding thioacetal **3o** in 91% yield after prolonged reflux (Table 2, entries 18).

To show the high chemoselectivity of the method, several competitive reactions were carried out under these reaction conditions (Scheme 1). In one case, the reaction of **2b**/4-chlorobenzaldehyde **2′**/**1aa** with a 1:1:1 molar ratio was performed at room temperature for 3 h. Subsequently, thioacetal **3a** was obtained in 69% yield, whereas thioacetal **3 h** was only produced in 27% yield. In another case of **2a/2n/1aa** with a 1:1:1 molar ratio, **2a** was converted into thioacetal **3a** in 95% yield, but **3o** was not detected in the reaction. Thus, it could be concluded that the reported transthioacetalization procedure showed high chemoselectivity, providing selective protection of an acetal in the presence of an aromatic aldehyde or a ketal.

On the basis of these results and some of our previous work,[5,6] a mechanism for transthioacetalization of acetals **2** using **1a** as odorless thiol equivalents is proposed as described in (Scheme 2) The reaction commences from the generation of HCl from the esterification between acetyl chloride and MeOH. Then addition of a proton to the carbon–carbon double bond of **1a** takes place to form a carbocation **4**, which is stablized by the adjacent electron-donating bis(alkylthio) groups. With



Scheme 2. Proposed mechanism for the thioacetalization of acetals **2** with **1a**.

the attacks by methanol, the carbocation **4** is transformed into the intermediate **5,** which was further attacked by H_2O to lead to the formation of methyl acetyl acetate **8** through the intermediate **7**. The in situ–generated thiols during the process undergo the thioacetalization reaction with acetals **2** to give the corresponding thioacetals **3**.

In conclusion, we have developed a chemoselective and odorless transthioacetalization of acetals **2** using α-oxo-ketene dithioacetals **1a** as thiol equivalents. This transthioacetalization is characterized by mild reaction conditions, simple and odorless procedure, good yields, and perfect chemoselectivity.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on Varian 400-MHz and 100-MHz instruments, respectively, and tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra (KBr) were recorded on a Magna-560 FTIR spectrophotometer. Elemental analyses were measured on a PE-24 analyzer (Perkin–Elmer).

Preparation of **3a**, as a typical procedure, was as follows: The mixture of **1aa** (0.174 g, 1 mmol), **2a** (0.15 g, 1 mmol), and CH_3COCl (0.11 mL, 1.5 mmol) in MeOH (2 mL) was stirred at room temperature. As monitored by thin-layer chromatography (TLC), **2a** disappeared after 3 h. The reaction mixture was then neutralized with 10% aqueous $NaHCO_3$ and extracted with diethyl ether (3×10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product. The purification was carried out over silica-gel chromatography (eluent: petroleum ether–EtOAC = 75:1) to give dithioacetal **3a** in 95% yield.

This procedure was followed by all the reactions listed in Table 1. All the dithioacetals **3** listed in Table 1 are known compounds, and their spectroscopic data (^{1}H NMR and IR) and elemental analyses are in good agreement with those in the literature.

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