Chemoselective thioacetalization with odorless 2-(1,3-dithian-2-ylidene)-3-oxobutanoic acid as a 1,3-propanedithiol equivalent

Haifeng Yu, Dewen Dong, Yan Ouyang, and Qun Liu

Abstract: Odorless 2-(1,3-dithian-2-ylidene)-3-oxobutanoic acid (**1c**) was prepared and investigated in the thioacetalization of carbonyl compounds as a 1,3-propanedithiol equivalent. The results showed that the thioacetalization of various carbonyl compounds **2** with **1c** proceeded smoothly and afforded the corresponding dithioacetals **3** in high yields (up to 99%) in the presence of acetyl chloride at room or reflux temperatures. Moreover, the thioacetalization exhibited high chemoselectivity between aldehydes and ketones.

Key words: chemoselectivity, 2-(1,3-dithian-2-ylidene)-3-oxobutanoic acid, α-oxo ketene dithioacetal, 1,3-propanedithiol equivalent, thioacetalization.

Résumé : On a préparé l'acide inodore 2-(1,3-dithian-2-ylidène)-3-oxoburanoîque (**1c**) et on a évalué son utilité comme équivalent du propane-1,3-dithiol dans la thioacétalisation de composés carbonyles. Les résultats ont montré que la thioacétalisation des divers composés **2** à l'aide de **1c** en présence de chlorure d'acétyle, à la température ambiante, s'effectue sans problème et conduit aux dithioacétals **3** avec des rendements élevés (99 %). De plus, la thiacétalisation présente une chimiosélectivité élevée entre les aldéhydes et les cétones.

Mots clés : chimiosélectivité, acide 2-(1,3-dithian-2-ylidène)-3-oxoburanoîque, dithioacétal d'α-oxocétène, équivalent du propane-1,3-dithiol, thioacétalisation.

[Traduit par la Rédaction]

Introduction

Thioacetals play very important roles in organic synthesis since they are widely used as protecting groups for carbonyl compounds and applied as umpolung reagents in a diverse array of organic transformations (1, 2).

To date, there are many approaches developed for the synthesis of thioacetals from carbonyl compounds or *O*,*O*-acetals with thiols employing various acid catalysts such as protic acids, Lewis acids, and solid acids (3, 4). Unfortunately, the conventional methods suffer from the use of volatile, foul-smelling, low molecular weight thiols that can lead to serious safety and environment problems. To resolve these drawbacks, some attempts have been made to develop odorless substitutes for these obnoxious thiols. As a result, a range of odorless or faint smell thiols have been prepared by increasing the alkyl chain length of thiol or introducing a trialkylsilyl group into the benzene ring of benzyl mercaptan and benzenethiol (5). Alternatively, incorporation of 1,3-propanedithiol functions within linear or cross-linked copolymeric reagents have been realized and applied in organic synthetic chemistry (6). However, the multistep process of preparation, the high cost of catalysts, and the toxicity of some precursors limit the further utilization of such thiol reagents or their equivalents. From the green chemistry point of view, the development of practically odorless and less volatile substitutes for such thiols is still of great importance and necessity.

Recently, we developed a novel thioacetalization with nonthiolic odorless cyclic ketene dithioacetals, e.g., 2-(2-chloro-1-(1-chloroethenyl)-2-propenylidene)-1,3-dithiane (**1a**) and 3-(1,3-dithian-2-ylidene)pentane-2,4-dione (**1b**) (Fig. 1), as 1,3-propanedithiol equivalents (7). We demonstrated that the reaction of carbonyl compounds with **1a** is an acid-assisted, self-catalyzed thioacetalization running through the formation of the intermediate **1b** (7*a*). The thioacetalization of **1b**, achieved under mild acidic conditions with high chemoselectivity (7*b*), encouraged us to believe that a wide range of cyclic ketene dithioacetals might be used as dithiol equivalents. There are many reports, including some review articles, regarding synthesis and application of α-oxo ketene dithioacetals (8). The decomposition reaction of α-oxo ketene dithioacetals had a different course depending on the reagent structure (9). For example, 2-(1,3-dithian-2-ylidene)-3-oxobutanoic acid (**1c**) undergoes iododecarboxylation rather than iododeacylation after treatment with iodine in

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H. Yu, D. Dong,[1] Y. Ouyang, and Q. Liu.[2] Department of Chemistry, Northeast Normal University, Changchun, 130024, P.R. China.

[1]Corresponding author (e-mail: dongdw663@nenu.edu.cn).
[2]Corresponding author (e-mail: liuqun@nenu.edu.cn).

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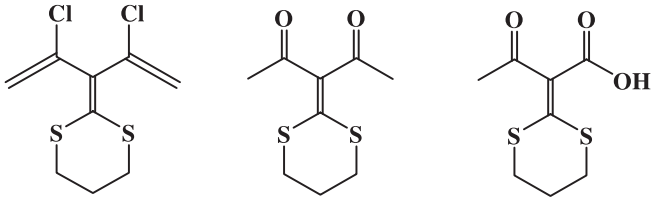
Fig. 1. Odorless cyclic ketene dithioacetals.



EtOH–H_2O, affording the same intermediate obtainable with **1b** (9*a*). With the aim of obtaining efficient and practical reagents for general application, we investigated the thioacetalization reaction of a range of selected carbonyl compounds **2** with **1c**.

Results and discussion

According to the literature, we prepared ethyl 2-(1,3-dithian-2-ylidene)-3-oxobutanoate (10) from ethyl 3-oxobutanoate, carbon disulfide, 1,3-dibromopropane, and K_2CO_3 in nearly quantitative yield (99%), then we converted it into the 2-(1,3-dithian-2-ylidene)-3-oxobutanoic acid (**1c**) via a hydrolysis process (9*a*, 11). It is worth noting that **1c** is an odorless solid, stable under ambient atmosphere, which is associated with some advantages such as a simple synthetic procedure, mild conditions, high yield, and commercial starting materials without a foul smell.

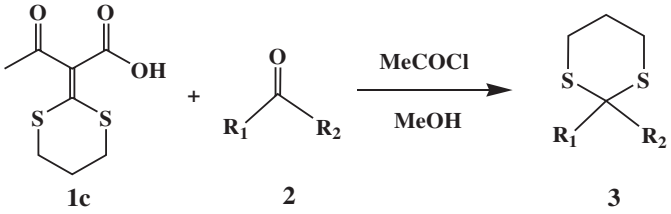
Since our previous experience has revealed that it is a convenient way to achieve the thioacetalization of a range of aldehydes and ketones in the presence of a mixture of acetyl chloride and methanol (7*b*), in the present work the same mixture was adopted for studying the thioacetalization of various carbonyl compounds **2** with **1c** (Scheme 1).

The thioacetalization of piperonal (**2a**) with **1c**, initially carried out under reflux, showed that the reaction was completed within 30 min affording the corresponding dithioacetal **3a** in 89.3% yield. Significantly, this reaction proceeded much faster in comparison to the reaction reported in our previous work (7). So, we repeated the reaction at room temperature. To our delight, **2a** was transformed into **3a** in 92.7% yield within 2 h. It is worth mentioning that only a very faint smell of thiol was perceived during both the reaction and work-up process, in agreement with practically no release of 1,3-propanedithiol.

We next investigated the thioacetalization of aromatic, aliphatic, and heterocyclic aldehydes and ketones (**2a**–**2w**) with **1c** in the presence of acetyl chloride in methanol at both room and reflux temperatures. With a constant feed molar ratio of acetyl chloride : **1c** : **2** of 3:2:2, all the reactions proceeded smoothly under mild acidic conditions. Table 1 summarizes some reaction data. The results confirm the general value of **1c** as a key reagent for the thioacetalization reaction.

A range of aromatic and aliphatic aldehydes and aliphatic ketones (**2a**–**2p**) were rapidly converted into their corresponding dithioacetals (**3a**–**3p**) in very high yields at both room and reflux temperatures. The reflux condition allowed a shorter reaction time, nevertheless, some thermosensitive substrates could benefit from the use of room temperature. In the cases of entries 23 and 24 in Table 1, the yield was increased by 25% when the reaction of thermo- and acid-sensitive furan-2-carbaldehyde (**2l**) proceeded at room temperature rather than at reflux. Generally, it is difficult to cleanly realize the thioacetalization of **2l** with the use of conventional acid catalysts (12). Several research groups reported high-yield thioacetalizations of **2l** by using thionyl chloride treated silica gel (12), trimethylsilyl chloride (13), and lithium tetrafluoroborate (14) as the catalyst, respectively. Our thioacetalization of **2l** can be considered a useful alternative procedure.

Scheme 1. Thioacetalization of carbonyl compounds **2** with **1c**.



In contrast with **2a**–**2p**, the aromatic ketones **2q**–**2u** could not be thioacetalized at room temperature, but they gave their corresponding dithioacetals in high yields after prolonged reflux. The aromatic sterically hindered benzophenone (Table 1, entry 37) was the slowest to react with an excess of **1c** (feed molar ratio of acetyl chloride : **1c** : **2** = 3:4:2).

To exploit the differences in the thioacetalization rate of aldehydes and aliphatic ketones and aromatic ketones, for the selective protections we carried out some competitive reactions under the above reaction conditions (Table 1, entries 38 and 39). The reaction of **2b**–**2q**–**1c** with a 1:1:1 molar ratio performed at reflux temperature (Table 1, entry 38) afforded the thioacetal **3b** in 92.4% yield, while the ketone **2q** was almost completely recovered (97.2%), **3q** not even being detectable. Similar results were obtained in the case of **2p**–**2q**–**1c** with a 1:1:1 molar ratio (Table 1, entry 39), where **2p** was converted into thioacetal **3p** in 91.2% yield, while **2q** remained intact. The reported thioacetalization procedure thus showed a high chemoselectivity, providing selective protection of an aromatic aldehyde or an aliphatic ketone in the presence of an aromatic ketone.

The mechanism of the thioacetalization reaction was investigated with the help of a supporting reaction. The mixture of **1c** (1.0 mmol), **2a** (1.0 mmol), and acetyl chloride (1.5 mmol) in methanol (10 mL) was stirred at room temperature and interrupted after 50 min by neutralizing with 10% aq. $NaHCO_3$. With this procedure, decarboxylated product 1-(1,3-dithian-2-ylidene)propan-2-one (**4**) and dithioacetal **3a** were obtained in 79.3% and 14.6% yields, respectively, while unreacted **2a** (81.3%) was recovered. Compound **4** was also obtained in our previous work and assumed to be an intermediate (7*a*, 7*b*). These results indicate that **1c** undergoes decarboxylation much more easily than deacylation under the acidic conditions applied. The novelty of the reagent **1c** is in the fact that the thioacetalization of aldehydes and aliphatic ketones could proceed at room temperature with high yields. On the basis of the previously mentioned experimental results together with our previous work (7), a mechanism for the thioacetalization reaction of various carbonyl compounds with **1c** in methanol is proposed in

Table 1. Thioacetalization of carbonyl compounds **2** with **1c**.

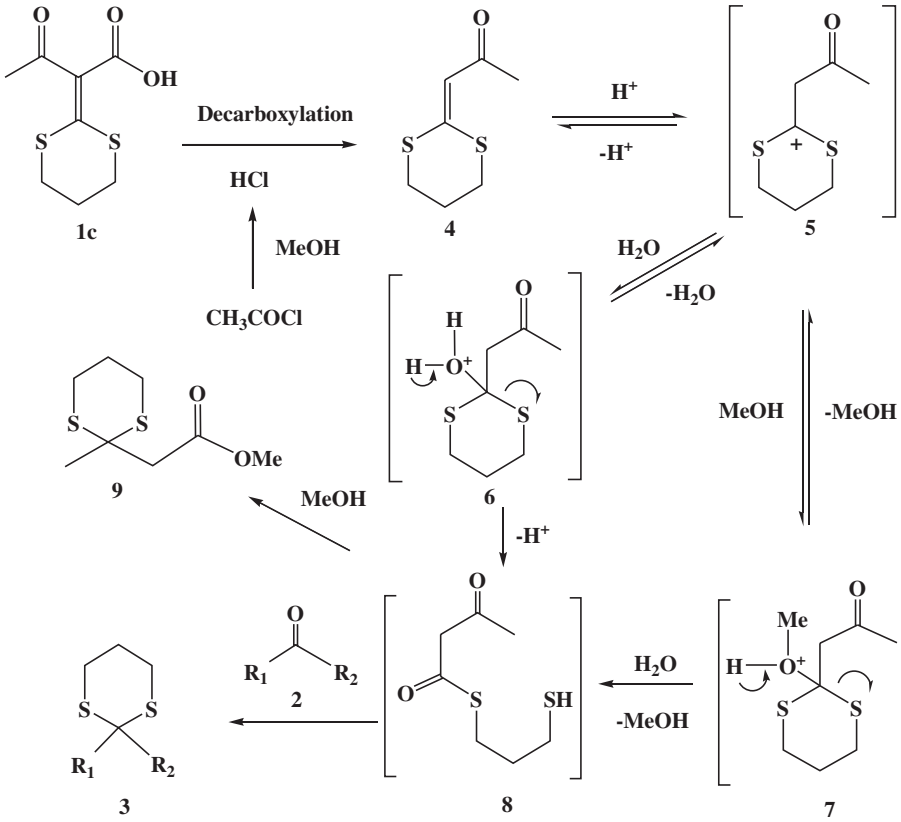
Entry	Substrate **2**	R_1	R_2	Product **3**	Temp.[a]	Time (min)	Yield[b] (%)	Reference
1	**2a**	3,4-O_2CH_2Ph	H	**3a**	A	25	89.3	4*c*, 7
2	**2a**	3,4-O_2CH_2Ph	H	**3a**	B	120	92.7	
3	**2b**	Ph	H	**3b**	A	25	91.8	3*a*, 3*c*, 7
4	**2b**	Ph	H	**3b**	B	120	92.5	
5	**2c**	4-MePh	H	**3c**	A	30	96.5	7, 14
6	**2c**	4-MePh	H	**3c**	B	120	96.2	
7	**2d**	4-MeOPh	H	**3d**	A	30	92.3	4*e*, 7
8	**2d**	4-MeOPh	H	**3d**	B	120	94.1	
9	**2e**	4-HOPh	H	**3e**	A	25	88.9	3*a*, 3*c*, 7
10	**2e**	4-HOPh	H	**3e**	B	120	91.2	
11	**2f**	4-ClPh	H	**3f**	A	25	88.9	4*c*, 4*i*, 14
12	**2f**	4-ClPh	H	**3f**	B	120	98.5	
13	**2g**	4-FPh	H	**3g**	A	30	96.5	7
14	**2g**	4-FPh	H	**3g**	B	120	97.2	
15	**2h**	$PhCH_2$	H	**3h**	A	40	91.2	4*f*, 7
16	**2h**	$PhCH_2$	H	**3h**	B	180	91.7	
17	**2i**	4-NO_2Ph	H	**3i**	A	60	97.4	4*f*, 7
18	**2i**	4-NO_2Ph	H	**3i**	B	180	96.9	
19	**2j**	PhCHCH	H	**3j**	A	50	82.5	4*f*, 7, 12
20	**2j**	PhCHCH	H	**3j**	B	180	87.7	
21	**2k**	*n*-C_4H_9	H	**3k**	A	30	89.7	[3]
22	**2k**	*n*-C_4H_9	H	**3k**	B	130	91.5	
23	**2l**	2-Furyl	H	**3l**	A	25	61.4	12–14
24	**2l**	2-Furyl	H	**3l**	B	120	87.2	
25	**2m**	2-Thiophen	H	**3m**	A	25	99.1	4*i*, 7
26	**2m**	2-Thiophen	H	**3m**	B	120	99.3	
27	**2n**	*n*-C_4H_9	Me	**3n**	A	45	90.5	14
28	**2n**	*n*-C_4H_9	Me	**3n**	B	300	92.1	
29	**2o**	$(CH_2)_4$		**3o**	A	50	90.7	7, 14
30	**2o**	$(CH_2)_4$		**3o**	B	360	91.5	
31	**2p**	$(CH_2)_5$		**3p**	A	45	93.4	4*h*, 7, 14
32	**2p**	$(CH_2)_5$		**3p**	B	300	94.7	
33	**2q**	Ph	Me	**3q**	A	240	96.9	3*c*, 4*f*, 7
34	**2r**	4-H_2NPh	Me	**3r**	A	300	90.2	7
35	**2s**	4-NO_2Ph	Me	**3s**	A	300	93.3	7
36	**2t**	4-ClPh	Me	**3t**	A	240	95.8	7
37	**2u**	Ph	Ph	**3u**	A	480	94.2[c]	3*c*, 4*c*
38	**2b+2q**			**3b**	A	25	92.4 (97.2)[d]	
39	**2p+2q**			**3p**	A	45	91.2 (91.8)[d]	

[a]Reflux temperature (A), room temperature (B).
[b]Yields after silica gel chromatography.
[c]Obtained with a feed molar ratio of acetyl chloride : **1c** : **2** of 3:4:2.
[d]Recovery of the intact compound **2q**.

Scheme 2. The reaction process starts with the generation of HCl from the esterification between acetyl chloride and methanol, which catalyzes the decarboxylation of **1c** to give **4**. Through the addition of a proton to the carbon–carbon double bond, **4** is converted into the carbocation **5**, stablized by the electron-donating effect of two sulfur atoms, then into **6** or **7** with H_2O or methanol, respectively, and finally by cleavage of the ring into **8**, which reacts with the carbonyl compound **2** to give the corresponding dithioacetal **3**. An indirect evidence of the formation of **8** is the production of the dithiane **9** (7*b*), obtained in the present work most likely from the inter- or intra-molecular transformation of **8**.

[3] Spectral properties of 2-butyl-1,3-dithiane (**3k**): IR (KBr, cm^{-1}): 2954, 2929, 2899, 1421, 1378, 1275, 1181, 908. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 (3H, t, *J* = 7.0 Hz), 1.29–1.36 (2H, m), 1.45–151 (2H, m), 1.72–1.84 (2H, m), 1.86–1.89 (1H, m), 2.10–2.13 (1H, m), 2.80–2.91 (4H, m), 4.04 (1H, t, *J* = 7.0 Hz). ^{13}C NMR (500 MHz, $CDCl_3$) δ: 14.15, 22.60, 26.30, 29.00, 30.77 (2C), 35.41, 47.90.

Scheme 2. Proposed mechanism for the thioacetalization of carbonyl compounds **2** with **1c**.



In summary, odorless 2-(1,3-dithian-2-ylidene)-3-oxobutanoic acid (**1c**) has been investigated as a 1,3-propanedithiol equivalent in thioacetalization. In the presence of **1c**, a wide range of carbonyl compounds, aldehydes, and ketones have been converted into the corresponding dithioacetals **3** in high yields. The thioacetalization reaction is characterized by a simple procedure, mild conditions, high yields, and high chemoselectivity towards aldehydes and aliphatic ketones with respect to aromatic ketones.

Experimental

All reagents were purchased from commercial sources. The products were purified by column chromatography over silica gel. ^{1}H NMR spectra were recorded at 25 °C on a Varian INOVA500 (500 MHz) spectrometer in $CDCl_3$ and with TMS as the internal standard. IR spectra (KBr) were recorded on a Magna-560 FT IR spectrophotometer. Elemental analyses were measured on a PE-2400 analyzer (PerkinElmer).

General procedure for thioacetalization of aldehydes and ketones 2 with 1c

Preparation of **3a** as a typical procedure: the mixture of **1c** (218 mg, 1 mmol), **2a** (150 mg, 1 mmol), and CH_3COCl (0.11 mL, 1.5 mmol) in MeOH (10 mL) was stirred under reflux. As monitored by TLC, compound **1c** was consumed within 10 min; whereas aldehyde **2a** disappeared after 25 min. The reaction mixture, allowed to cool to room temperature, was neutralized with 10% aq. $NaHCO_3$ and extracted with diethyl ether (3 × 10 mL). The combined organic extracts were dried over anhydr. $MgSO_4$, filtered, and concentrated under reduced pressure to yield the crude product. The purification by silica gel chromatography (eluent: petroleum ether – EtOAC, 75:1) gave the dithioacetal **3a** in 89.3% yield.

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