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Acid-Promoted Thioacetalization in Water using 2-(1,3-Dithian-2-ylidene)malonic Acid as an Odorless and Efficient Thioacetalization Reagent

Yan Ouyang^a, Dewen Dong^a, Yongjiu Liang^a, Yanyan Chai, ^a & Qun Liu^a ^a Department of Chemistry, Northeast Normal University, Changchun, China

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Acid-Promoted Thioacetalization in Water using 2-(1,3-Dithian-2-ylidene)malonic Acid as an Odorless and Efficient Thioacetalization Reagent

Yan Ouyang, Dewen Dong, Yongjiu Liang, Yanyan Chai, and Qun Liu

Department of Chemistry, Northeast Normal University, Changchun, China

Abstract: Thioacetalization using 2-(1,3-dithian-2-ylidene)malonic acid 1 as a non-thiolic, odorless 1,3-propanedithiol equivalent promoted by *p*-dodecylbenzenesulfonic acid in water has been achieved. A range of selected carbonyl compounds 2 was converted into the corresponding dithioacetals 3 in high yields. Moreover, the thioacetalization showed high chemoselectivity between aldehydes and ketones.

Keywords: chemoselectivity, 2-(1,3-dithian-2-ylidene)malonic acid, *p*-dodecylbenzenesulfonic acid, thioacetalization, water

INTRODUCTION

The use of water as a solvent in organic chemistry was rediscovered in the 1980s in Breslow's work, which showed that hydrophobic effect can strongly enhance the rates of some organic reactions.^[1] The organic reactions in water without the use of any organic solvent can also benefit from the fact that water is an easily available, cheap, safe, and environmentally benign solvent.^[2,3]

Recently, Iimura, and co-workers reported that thioacetalization can be conducted in aqueous media with surfactant-type Brønsted acid catalysts.^[4]

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Address correspondence to Dewen Dong, Department of Chemistry, Northeast Normal University, Changchun 130024, China. E-mail: dongdw663@nenu.edu.cn

Thioacetals have been extensively investigated as carbonyl protection groups and versatile intermediates in the synthesis of multifunctional complex molecules and natural products.^[5,6] Generally, thioacetals are prepared by the condensation of carbonyl compounds with thiols or dithiols employing various acidic catalysts.^[7,8] However, these thiols are flammable, harmful, and odorous reagents, which can lead to serious environmental and safety problems. Very recently, we have developed a novel thioacetalization reaction using nonthiolic, odorless cyclic ketene dithioacetals as 1,3-propanedithiol equivalents^[9] and found that *p*-dodecylbenzenesulfonic acid (DBSA), a surfactant-type Brønsted acid, can be used as an acid catalyst for the thioacetalization in water.^[10] With the aim of obtaining a more efficient and practical reagent for general application, we investigated the thioacetalization reaction of 2-(1,3-dithian-2-ylidene)malonic acid **1** with a range of selected carbonyl compounds **2** catalyzed by DBSA in water. In the present work, we report our findings.

RESULTS AND DISCUSSION

According to the reported procedure,^[11] diethyl 2-(1,3-dithian-2-ylidene)malonate was prepared from diethyl malonate, carbon disulfide, 1,3-dibromopropane and K_2CO_3 in nearly quantitative yield, which was then transformed into compound **1** via a hydrolysis process.^[12]

The reaction of **1** with benzaldehyde **2a** (1.0 equiv) was initially performed in the presence of 0.17 mol/L of DBSA-H₂O (Table 1, entry 1). After the mixture was heated to reflux and stirred for about 6 h, **2a** was consumed, as indicated by thin-layer chromatography (TLC). A white solid

			$ \qquad \qquad$	⟨S>		
	OH 1		2a		3а	
Entry	1 (mmol)	2a (mmol)	DBSA/H ₂ O (mol/L)	Time (h)	Yield ^a (%)	
1	5	5	0.17	6.0	89	
2	5	5	0.22	4.0	88	
3	5	5	0.28	2.5	89	
4	5	5	0.33	1.8	90	
5	5	5	0.39	1.2	91	
6	5	5	0.56	1.1	90	

Table 1. Reactions between 1 and benzaldehyde 2a

^aIsolated yields.

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was deposited from the reaction system when the resulting mixture was cooled down to ambient temperature, which was filtered and washed with water to afford a quite pure product characterized as 2-phenyl-1,3-dithiane 3a (89%). To optimize the conditions of the thioacetalization, the reactions of 1 and 2a were carried out in varied concentrations of DBSA in water (Table 1, entries 2-6). The reactions are significantly accelerated when increasing the concentration of DBSA, in particular at low concentrations. It appears that there might exist a critical micelle concentration for the thioacetalization. The highest reaction activity is attained when it proceeds in the presence of 0.39 mol/L of DBSA-H₂O at reflux, leading to the conversion of 2a into 3a in 91% yield within 1.2 h (Table 1, entry 5). The reaction mixture forms white turbid emulsions at the beginning and becomes clear when heated to temperatures higher than 80°C. The phenomena suggest that micelles would be formed in the reaction system and the reaction should take place on the interface or inside the micelles. Moreover, because of the hydrophobic nature of the micelles, the product would be expected to go inside the micelles and the by-product H₂O would be expelled out of the micelles, which might accelerate the reaction. It is worth noting that the thioacetalization proceeds much faster in water compared with that in organic solvent.^[9]All these results fully demonstrate that compound 1 is an efficient and practical thioacetalization reagent even in aqueous systems and that DBSA is an efficient catalyst for thioacetalization.

In the next studies, we investigated the thioacetalization of 1 with various types of selected aldehydes and ketones 2 under conditions identical to those described in entry 5, Table 1. Some of the results are summarized in Table 2. A range of aromatic aldehydes (Table 2, entries 1–6), heterocyclic aldehyde (Table 2, entry 7), aliphatic aldehyde (Table 2, entry 8), and ketones (Table 2, entries 9 and 10) could be converted into the corresponding dithianes **3** in the presence of DBSA under reflux conditions in water in high yields. In contrast, the reactions of aromatic ketones proceed with greater difficulty than that of the counterpart aldehyde based on the lower conversion, even with prolonged reaction times (Table 2, entries 11 and 12). This might be attributed to their reactivity differences based on steric and electronic effects.

The difference of the reactivity between aldehydes and ketones suggests that the thioacetalization can be used for the selective protection of different carbonyl groups. Some competitive reactions among aromatic aldehydes, aliphatic ketones, and aromatic ketones were then carried out. When aromatic aldehyde **2a**, aromatic ketone **2k**, and **1** with a 1:1:1 molar ratio were subjected to the identical conditions, thioacetal **3a** was obtained in 90% yield, and starting material **2k** was almost completely recovered (Table 2, entry 13). Similarly, the competitive reaction of aliphatic cyclic ketone **2j**, aromatic ketone **2k**, and **1** with a 1:1:1 molar ratio gave thioacetal **3j** in 93% yield along with intact starting material **2k** (Table 2, entry 14). The validity of the two reactions prompted us to examine the chemoselective

		$\langle S - \rangle + R^{1} \langle R^{2} \rangle$	≻o	$\frac{\text{DBSA}}{\text{H}_2\text{O}, \text{Reflux}}$	R^1 S R^2 S	\rangle
	OH	1	2		3	
Entry	Substrate 2	\mathbb{R}^1	\mathbb{R}^2	Product 3	Time (h)	Yield ^a (%)
1	2a	Ph	Н	3a	1.2	91
2	2b	3, 4-OCH ₂ OPh	Н	3b	1.0	98
3	2c	4-NMe ₂ Ph	Н	3c	2.0	93
4	2d	4-HOPh	Н	3d	2.0	94
5	2e	4-ClPh	Н	3e	2.1	92
6	2f	PhCH=CH	Н	3f	2.0	91
7	2g	2-thienyl	Н	3g	2.6	90
8	2h	n-C ₄ H ₉	Н	3h	2.0	90
9	2i	n-C ₄ H ₉	Me	3i	2.2	88
10	2ј	(CH ₂) ₅	(CH ₂) ₅	3ј	1.5	95
11	2k	Ph	Me	3k	8.0	67
12	21	4-ClPh	Me	31	8.0	42
13	2a + 2k			3 a	1.2	$90(98)^{b}$
14	2j + 2k			3h	1.5	93(97) ^b

Table 2. Thioacetalization reactions of selected aldehydes/ketones 2 with 2-(1,3-dithian-2-ylidene) malonic acid 1 in water

^aIsolated yields.

^bMolar ratio of 1: 2a(2j): 2k is 1: 1: 1, the data in brackets are recovery of 2k.

thioacetalization of the compound 2m with two different carbonyl groups on the same molecule. As shown in Scheme 1, the reaction between 2m and 1 with a 1:1 molar ratio proceeded within 2.5 h to afford product 3m in 92% yield. All the results reveal that the thioacetalization in water exhibits significantly high chemoselectivity among various carbonyl compounds in the presence of 1.



Scheme 1. Chemoselective thioacetalization of 2m with 1 in water.



Scheme 2. Proposed mechanism for the thioacetalization of 2 with 1 in water.

On the basis of these experimental results together with our previous studies,^[9,10] a mechanism for the thioacetalization reaction in water is proposed as shown in Scheme 2. Compound 1 undergoes decarboxylation catalyzed by DBSA to give ketene dithiolacetal 4, which is followed by the addition of a proton to its carbon–carbon double bond, and the ketene dithiolacetal 4 is converted into a carbocation 5, which is stabilized by the electron-donating bis(alkylthio) groups. With the attack of H₂O, the carbocation 5 is transformed to an oxocation 6, which leads to the formation of the intermediate 7 through a deprotonation and decyclization process. Finally, intermediate 7 reacts with carbonyl compound 2 to yield the corresponding dithiane 3.

CONCLUSIONS

In summary, odorless 2-(1,3-dithian-2-ylidene)malonic acid **1** has been investigated as a 1,3-propanedithiol equivalent in thioacetalization promoted by DBSA in water. In the presence of **1**, a range of carbonyl compounds **2**, aldehydes, and aliphatic ketones has been converted into corresponding dithioacetals **3** in high yields. The relatively slow reaction rate of aromatic ketones allows chemoselective protection of an aromatic aldehyde or an aliphatic ketone from an aromatic ketone. Associated with mild conditions and simple procedure, the reported procedure provides a convenient and clean protocol for the protection of various carbonyl compounds with high chemoselectivity.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. ¹H NMR spectra were recorded at

 25° C on a 500-MHz spectrometer in CDCl₃ and TMS as internal standard. IR spectra (KBr) were recorded on a FTIR spectrophotometer in the range of 400-4000 cm⁻¹.

General Procedure for Dithioacetals 3

To a 50-mL single-necked flask equipped with a condenser, **1** (5.0 mmol), **2a** (5.0 mmol), H₂O (9.0 mL), and DBSA (3.5 mmol) were added. The mixture formed white turbid emulsions immediately. When heated to reflux, the mixture became clear as observed by naked eyes. After stirring at reflux temperature for about 1.2 h, the reaction was complete as indicated by TLC and was then allowed to cool down to ambient temperature. The white solid was collected by filtration and washed with aqueous NaHCO₃ (10%, 25 mL \times 3) and water (25 mL \times 3) to give dithioacetal **3a** (yield: 91%).

In the cases of liquid products **3h** and **3j**, the resulting mixture was neutralized with aqueous NaHCO₃ (10%, 10 mL) and extracted with diethyl ether (3 × 20 mL). The extracts was washed with H₂O (3 × 30 mL) and dried over Na₂SO₄. Evaporation of the solvent gave almost pure product. Further purification was carried out over flash silica-gel chromatography (eluent: petroleum ether–ethyl acetate = 75: 1, v/v).

Data

2m: white solid; yield: 96%; mp: $104-106^{\circ}$ C. ¹H NMR (CDCl₃, 500 MHz) δ 2.57 (s, 3H), 4.43 (s, 4H), 6.98–7.02 (dd, J = 9.0, 8.5 Hz, 4H), 7.85-7.97 (dd, J = 9.0, 8.5 Hz, 4H), 9.90 (s, 1H). ¹³C NMR (CDCl₃, 125 MHz) δ 26.7, 66.6, 66.8, 114.5, 115.1, 130.6, 130.9, 131.0, 132.3, 162.5, 163.7, 191.1, 197.1. IR (KBr, cm⁻¹) 1673, 1600, 1570, 1247, 1162. Anal. calcd. for C₁₇H₁₆O₄: C, 71.82; H, 5.67; found: C, 71.90; H, 5.64.

3m: white solid; yield: 94%; mp: $160-162^{\circ}$ C. ¹H NMR (CDCl₃, 500 MHz) δ 1.90-1.93 (m, 1H), 2.16 (m, 1H), 2.57 (s, 3H), 2.89-2.92 (m, 2H), 3.03-3.08 (m, 2H), 4.34-4.38 (dd, J = 5.0, 5.0 Hz, 4H), 5.14 (s, 1H), 6.90-6.99 (dd, J = 8.5, 8.5 Hz, 4H), 7.40-7.42 (d, J = 8.5 Hz, 2H), 7.94-7.96 (d, J = 8.5 Hz, 2H). ¹³C NMR (CDCl₃, 125 MHz) δ 25.3, 26.7, 32.4, 50.9, 66.5, 66.8, 114.5, 115.0, 129.3, 130.9, 132.2, 158.7, 162.7, 197.1.IR (KBr, cm⁻¹) 3446, 2934, 1675, 1601, 1508, 1245, 1175. Anal. calcd. for C₂₀H₂₂O₃S₂: C, 64.14; H, 5.92; found: C, 64.19; H, 5.58.

Dithioacetals 3a-1 prepared in the present work are known compounds and identified by NMR, IR spectroscopy, and elemental analyses; the data for these compounds are in good agreement with those in literatures (Ref. 9a and 10).

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