

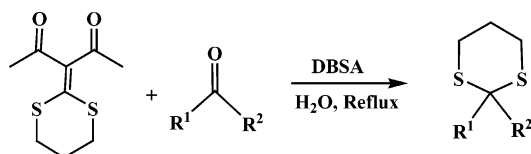
Chemoselective Thioacetalization in Water: 3-(1,3-Dithian-2-ylidene)pentane-2,4-dione as an Odorless, Efficient, and Practical Thioacetalization Reagent

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A chemoselective thioacetalization utilizing 3-(1,3-dithian-2-ylidene)pentane-2,4-dione as a novel nonthiolic, odorless 1,3-propanedithiol equivalent catalyzed by *p*-dodecylbenzenesulfonic acid in water has been developed.

Over the past decade, organic reactions in water without the use of organic solvents have attracted a great deal of attention since water is an easily available, economical, and safe solvent, especially in relation to recent environmental concerns.^{1,2} It has been demonstrated that a variety of organic reactions, including dehydration, can be realized in the presence of surfactant-type Lewis or Bronsted acid catalysts in water.³ Recently, Kobayashi reported that thioacetalization can be conducted in aqueous media with surfactant-type Bronsted acid catalysts.⁴ Thioacetals have been widely used as carbonyl protecting groups and intermediates in the conversion of a carbonyl function to a hydrocarbon derivative to form a C–C bond.^{5,6} Generally, thioacetals are prepared by the condensation of carbonyl compounds and low molecular weight thiols, such as 1,2-ethanedithiol and 1,3-propanedithiol, in the presence of various types of acidic catalysts.^{7,8} Unfortunately, these thiols are

TABLE 1. Reaction between **1** and **2a** in Aqueous Media

entry	1 , mmol	2a , mmol	H ₂ O, mL	DBSA, mmol	time, h	yield, ^a %
1	2	2	12.0	1.0	8.0	98
2	2	2	6.0	1.0	4.3	98
3	2	2	4.0	1.0	3.0	98
4	2	2	3.0	1.0	2.2	97
5	2	2	3.0	1.6	0.9	98
6	2	2	3.0	3.0	0.8	95

^a Isolated yields for **3a**.

flammable, harmful, and odorous reagents, which can lead to serious environmental and safety problems. Recently, we have developed a novel thioacetalization procedure using nonthiolic, odorless 2-(2-chloro-1-(1-chloroethenyl)-2-propenylidene)-1,3-dithiane, or 3-(1,3-dithian-2-ylidene)pentane-2,4-dione as 1,3-propanedithiol equivalents.⁹ It should be noted that this protocol involves the use of methanol, a highly volatile and harmful organic solvent. In our ongoing research program to circumvent the above drawback in thioacetalization, we found that *p*-dodecyl benzenesulfonic acid (DBSA), a surfactant-type Bronsted acid, can be used as an acid catalyst for the cleavage of ketene dithioacetals to form odorless thio-containing intermediates. The results prompted us to explore the feasibility of the thioacetalization in aqueous media. In the present work, we describe our preliminary results on a novel thioacetalization in water using DBSA as the catalyst and 3-(1,3-dithian-2-ylidene)pentane-2,4-dione **1** as a 1,3-propanedithiol equivalent.

The initial studies were performed on the reaction between piperonal **2a** and **1** with various feed ratios of DBSA in water with stirring at reflux. To our delight, all the reactions of **2a** proceeded in water affording dithioacetal **3a** in excellent yields and some of the results are summarized in Table 1. It was observed that the

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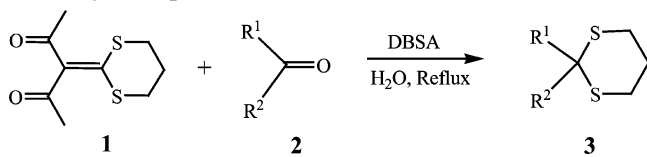
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amount of the surfactant DBSA has a great effect on the rate of thioacetalization. The reactions are significantly speeded up by increasing the feed ratio of DBSA–H₂O, in particular at low ratio values. It appears that there might exist a critical ratio for the thioacetalization, in other words there is nearly no change on the rate of the reaction beyond this ratio. The highest catalytic activity is attained when the reaction proceeds in the presence of a 1:100 molar ratio of DBSA–H₂O at reflux, leading to the conversion of **2a** into **3a** in 98% yield within 1 h (entry 5). It is noteworthy that in all the cases the reaction mixture forms white turbid emulsions at the beginning. However, when heated to 80 °C, the mixtures become clear. This phenomena suggests that micelles are formed in the reaction system and the reaction should take place on the interface or inside of the micelles. Moreover, due to the hydrophobic nature of the micelles the product would be expected to go inside the micelles and the byproduct H₂O would be expelled out of the micelles, which might accelerate the reaction. In fact, the thioacetalization proceeds much faster in water than in organic solvent.^{9b} In addition, the protocol is associated with very simple separation processes. In the above cases, the product is a solid and deposits from the reaction system once formed. The pure product is obtained in excellent yield after the solid is filtered and washed with water. All the above 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.

To test the general applicability of this protocol, we next investigated the thioacetalization of **1** with various types of selected aldehydes and ketones **2** using optimized conditions. The reactions were refluxed in the presence of DBSA–H₂O (1:100 by molar ratio) with a 5:5:4 feed molar ratio of **1**:**2**:DBSA, respectively. A selection of the results are listed in Table 2. It is clear that all the aromatic aldehydes with electron-donating or electron-withdrawing groups could be converted into the corresponding dithianes **3** in the presence of DBSA in excellent yields. Similarly, aliphatic aldehydes and ketones also gave high yields of the corresponding dithianes **3**. In contrast, the product yields in the cases of aromatic ketones **2p–2s** were very low even with prolonged reaction times. Apparently, the thioacetalization of aromatic ketones proceeds with greater difficulty than that of the counterpart aldehyde, which is attributed to their reactivity differences based on steric and electronic effects. Nonetheless, all the results demonstrate the scope and generality of the thioacetalization with respect to a variety of aldehydes and aliphatic ketones using **1** as the 1,3-propanedithiol equivalent in aqueous media. It is worth mentioning that in all the cases nearly no free 1,3-propanedithiol is generated during the reaction since only a very faint odor of thiol can be detected during both the reaction and the workup processes.

The reactivity difference between aldehydes and ketones suggests that the thioacetalization might be used for the selective protection of different carbonyl groups. Some competitive reactions among aromatic aldehydes, aliphatic ketones, and aromatic ketones were then car-

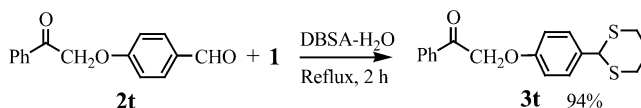
TABLE 2. DBSA-Catalyzed Thioacetalization of Various Carbonyl Compounds **2** with **1** in Water



entry	substrate 2	R ¹	R ²	product 3	time, h	yield, ^a %
1	2a	3,4-O ₂ CH ₂ Ph	H	3a	0.9	98
2	2b	Ph	H	3b	1.3	89
3	2c	4-MePh	H	3c	1.4	93
4	2d	4-MeOPh	H	3d	1.5	96
5	2e	4-(Me) ₂ NPh	H	3e	2.1	97
6	2f	4-HOPh	H	3f	2.0	94
7	2g	2-HOPh	H	3g	1.6	95
8	2h	2-thiophen	H	3h	2.8	90
9	2i	PhCH=CH	H	3i	2.0	93
10	2j	4-ClPh	H	3j	2.5	88
11	2k	4-O ₂ NPh	H	3k	2.7	72
12	2l	<i>n</i> -C ₄ H ₉	H	3l	2.0	90
13	2m	<i>n</i> -C ₄ H ₉	Me	3m	2.2	89
14	2n	-(CH ₂) ₅ -		3n	1.5	96
15	2o	-(CH ₂) ₆ -		3o	2.5	81
16	2p	Ph	Me	3p	8.0	69
17	2q	4-ClPh	Me	3q	8.0	39
18	2r	4-HOPh	Me	3r	8.0	25
19	2s	4-O ₂ NPh	Me	3s	8.0	66
20 ^b	2b + 2p			3b	1.5	91
21 ^b	2n + 2p			3n	2.0	90

^a Isolated yields for **3**, in the cases of entries 1–10, products were obtained by washing with water while the others were obtained by silica gel chromatography. ^b The molar ratio of **1**:aldehyde:ketone is 1:1:1

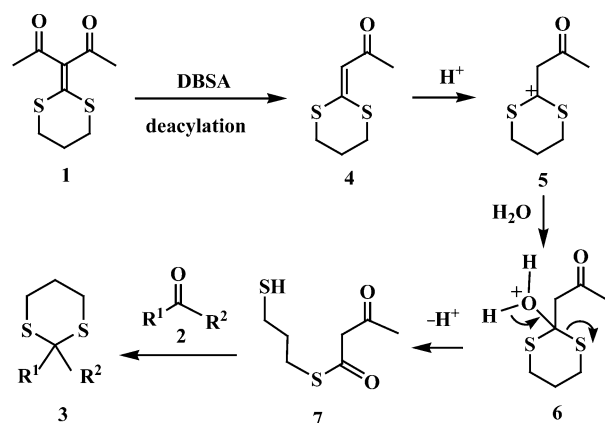
SCHEME 1. DBSA-Catalyzed Thioacetalization of Carbonyl Compounds **2t** with **1** in Water



ried out under the above conditions. In one representative case, the reaction of **2b/2p/1** with a 1:1:1 molar ratio was performed under the above conditions (entry 20). Subsequently, thioacetal **3b** was obtained in 91% yield, while starting material **2p** was almost completely recovered (98%) and **3p** was not detected. In another case, compound **2t** with two different carbonyl groups on the same molecule was synthesized to further validate the concept. As shown in Scheme 1, the reaction between **2t** and **1** with a 1:1 molar ratio proceeded within 2 h to afford product **3t** in 94% yield. All the results reveal that the thioacetalization in water exhibits significantly high chemoselectivity among various carbonyl compounds in the presence of **1**.

On the basis of the above experimental results together with our previous work,⁹ a mechanism for the thioacetalization reaction in aqueous media is proposed as shown in Scheme 2. On the interface of the micelles, **1** undergoes deacylation catalyzed by DBSA to give ketene dithiolacetal **4**. This 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** that is stabilized by the electron-donating bis(alkylthio) groups. With the attack of H₂O, the carbocation **5** is transformed

SCHEME 2. A Proposed Mechanism for the Thioacetalization of Carbonyl Compound 2 with 1 in Water



to an oxygen cation **6**, which leads to the formation of the intermediate **7** through a deprotonation and decylation process. Finally, intermediate **7** reacts with carbonyl compound **2** to yield the corresponding dithiane **3**.

In conclusion, we describe a novel thioacetalization reaction in water in the presence of DBSA. The results demonstrate that 3-(1,3-dithian-2-ylidene)pentane-2,4-dione **1** is an efficient and practical thioacetalization reagent in aqueous media. Associated with mild conditions, simple procedure, high yield, and environmentally benign reagents, this novel thioacetalization provides a convenient protocol for the synthesis of thioacetals and the protection of carbonyl compounds with high chemoselectivity.

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Supporting Information Available: Experimental details for the thioacetalization of **1** with selected carbonyl compounds **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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