

The First Nonthiolic, Odorless 1,3-Propanedithiol Equivalent and Its Application in Thioacetalization

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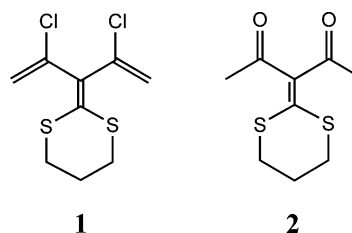
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Abstract: 2-[2-Chloro-1-(1-chlorovinyl)allylidene]-1,3-dithiane **1** was synthesized by the chlorination of 3-(1,3)-dithianylidenepentane-2,4-dione **2** using the Vilsmeier–Haack reagent in 99% yield. As a novel nonthiolic, odorless 1,3-propanedithiol equivalent, **1** was investigated in the thioacetalization reaction. Various types of aldehydes and ketones **3** were converted to the corresponding dithianes **4** in the presence of **1** in high yields (79–97%). Moreover, **1** exhibited obvious chemoselectivity between aldehyde and ketone in this thioacetalization reaction. A mechanism for this thioacetalization reaction is proposed.

Thioacetalization is well-known as a reaction that protects carbonyl groups of aldehydes and/or ketones.¹ Recently, extensive work has been focused on its applications, such as the unparalleled dithiane carbanion lynchpin strategy in natural and/or complex molecule synthesis,^{2–4} the new approach to titanium–alkylidene chemistry to form a C–C bond,⁵ and the dithiane-/trithiane-based photolabile scaffolds in molecular recognition.^{6,7} Unfortunately, most of the above work related to the thioacetalization reaction has involved the use of flammable, harmful, and obnoxious odor producing thiols or sulfides, which can lead to serious environmental and safety problems.^{1–7} To circumvent these problems, the development of odorless substitutes for these obnoxious thiols and sulfides is therefore of great merit.^{8–12} In our previous work, much effort has been devoted to the

synthesis and application of various ketene dithioacetals.^{13,14} As part of the further investigations, we report herein a novel ketene dithioacetal, 2-[2-chloro-1-(1-chlorovinyl)allylidene]-1,3-dithiane **1**, and its application in a thioacetalization reaction as a nonthiolic, odorless substitute for 1,3-propanedithiol.



Through the Vilsmeier–Haack reaction,¹⁵ compound **1** was synthesized from 3-(1,3)-dithian-2-ylidenepentane-2,4-dione **2** in 99% yield. It is worth noting that the odorless **1** could be stored in a desiccator for several months without any chemical change, namely, it is quite stable. Compound **2** was prepared from acetylacetone, carbon disulfide, and 1,3-dibromopropane in nearly quantitative yield following the procedure described in the literature.¹⁶

The thioacetalization reaction between **1** and selected aldehydes/ketones **3** was carried out via a simple procedure. The preparation of dithiane **4d** is described below as an example. Piperonal **3d** (2.0 mmol), compound **1** (2.2 mmol), and methanol (99%, 15 mL) were added to a flask equipped with a condenser. The mixture was heated at reflux and stirred under N₂. Once the aldehyde had been consumed, as indicated by TLC, the resulting mixture was worked up and separated via silica gel chromatography (eluent: petroleum ether) to afford **4d** in 97% yield (mp 86–87 °C). Various types of aromatic aldehydes with electron-donating and electron-withdrawing groups were converted to the corresponding dithianes **4** in the presence of **1**. Similarly, aliphatic aldehydes, cycloketones, and aromatic ketones also gave high yields of the corresponding dithianes **4**. The structures of the starting materials and the products, along with the reaction conditions and product yields, are given in Table 1.

From Table 1, **1** exhibited generality in the thioacetalization reaction since it worked very well with both aldehydes and ketones. It was noted, however, that the thioacetalization of aldehydes proceeded more easily with the shorter reaction time and higher yields than that of

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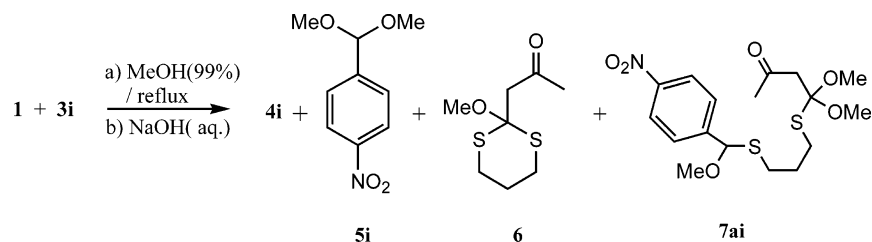
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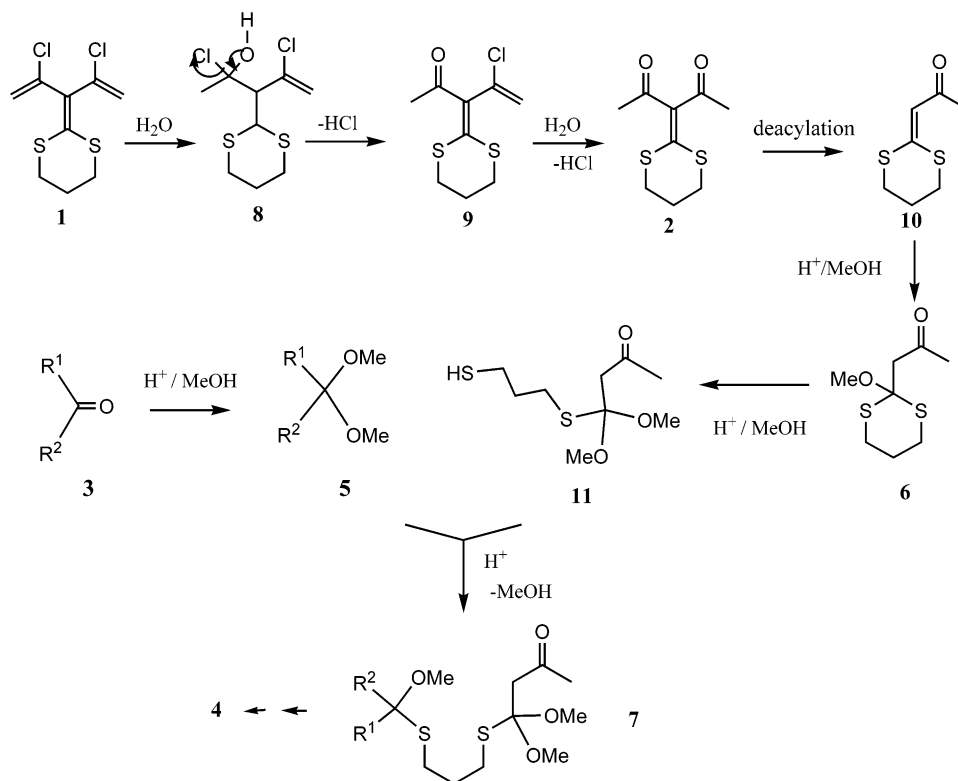
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SCHEME 1. Intermediates Obtained in the Thioacetalization Reaction



SCHEME 2. Proposed Mechanism for the Thioacetalization Reaction



ketones, compare **3a** with **3n** and **3i** with **3q**. The fact that aldehydes appear to be more reactive than ketones in this thioacetalization reaction is attributed to steric effects. For further comparison, two more thioacetalization reactions were carried out using **3a/3n/1** (mole ratio 1:1:1) and **3i/3q/1** (mole ratio 1:1:1). Products **4a** and **4i** were obtained in 81% (reaction time: 150 min) and 91% yield (reaction time: 110 min), respectively, and no production arising from reaction with the ketone was detected. This indicates that **1**, as a thioacetalization reagent, is chemoselective for aldehydes over ketones.

In an attempt to optimize the reaction conditions, the thioacetalization reaction with **1** was carried out in dried, absolute solvents, including MeOH, EtOH, THF, CH₂Cl₂, *t*-BuOH, and *i*-PrOH. Unfortunately, there was no evidence that the thioacetalization reaction had taken place at either room or reflux temperature. It appears that the small amount of water present in the solvent plays an important role in the reaction.

To investigate the mechanism of this thioacetalization reaction, several supporting experiments were carried out. In one experiment, a mixture of **1** (2.2 mmol) and **3i** (2.0 mmol) in methanol (99%, 20 mL) was stirred at room temperature for 20 min; the final pH value of the reaction

TABLE 1. Thioacetalization of Selected Aldehydes/Ketones **3** with Compound **1**

entry	R ¹	R ²	time (min)	yield ^a (%)
3a, 4a	Ph	H	150	95
3b, 4b	2-Furyl	H	145	96
3c, 4c	PhCH=CH	H	160	95
3d, 4d	3,4-O ₂ CH ₂ C ₆ H ₃	H	160	97
3e, 4e	4-MeOC ₆ H ₄	H	160	92
3f, 4f	4-CHOC ₆ H ₄	H	160	85
3g, 4g	4-FC ₆ H ₄	H	120	92
3h, 4h	4-Me ₂ NC ₆ H ₄	H	120	91
3i, 4i	4-NO ₂ C ₆ H ₄	H	120	93
3j, 4j	2-CHOC ₆ H ₄	H	150	79
3k, 4k	4-HOC ₆ H ₄	H	150	79
3l, 4l	<i>n</i> -C ₆ H ₁₃	H	120	81
3m, 4m	-(CH ₂) ₆ -		350	91
3n, 4n	Ph	Me	300	91
3o, 4o	Ph	Ph	300	90
3p, 4p	4-NH ₂ C ₆ H ₄	Me	350	86
3q, 4q	4-NO ₂ C ₆ H ₄	Me	400	85

^a Isolated yields after column chromatography on silica gel.

mixture was approximately 3.5. Dimethylacetal **5i** (structure see Scheme 1) and ketene dithioacetal **2** were obtained in 97% and 10% yields, respectively, with 90% of **1** remaining in the system. This indicates that the thioacetalization reaction does not occur at room temperature. Obviously, **5i** is the acetalized product of **3i**, and **2** has resulted from the hydrolysis of **1**. In another experiment, a mixture of **1** (2.2 mmol) and **3i** (2.0 mmol) in methanol (99%, 20 mL) was heated at reflux for 70 min. The pH of the reaction mixture fell to 2.5 prior to being quenched with aqueous NaOH. Consequently, dimethylacetal **5i**, dithio ortho ester **6**, monothioacetal **7ai**, and dithiane **4i**, as shown in Scheme 1, were obtained from the resulting reaction mixture in 14%, 9%, 11%, and 45% yields, respectively. Obviously, the temperature plays another important role in the thioacetalization reaction and the change of pH indicates that the reaction proceeds with the release of acid. The experiment suggests that **6**, as an intermediate of the thioacetalization reaction, might result from **2** and the dithiane **4** would be potentially formed via a trans-thioacetalization between **6** and the acetal **5**.

On the basis of the above experimental results, a mechanism for this thioacetalization reaction is proposed as shown in Scheme 2. With the strong nucleophilicity from the electron-donating alkylthio groups,¹⁷ **1** is easily hydrolyzed by water from the solvent and subsequently releases HCl to form **2**. With the released HCl as catalyst, **2** then undergoes deacylation. The solvent, methanol, then can add to the deacylated product **10** to give **6**. This can further react with methanol to give **11**, which can then add to intermediate **5** to generate the mixed acetal **7**. Further reaction of **7** will then lead to the dithiane **4**.

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Although it was not separated from the reaction system, **10** was prepared by the deacylation of **2** using HCl as the catalyst. Both compounds **2** and **10** were applied to the above thioacetalization reaction. Replacing **1** with compounds **2** and **10** in the above thioacetalization reaction and under similar conditions as described in Table 1 unfortunately proved unsuccessful. However, **4a** was obtained from experiments with **3a** /**1**/ **2** (mole ratio: 2:1:1) and **3a** /**1**/ **10** (mole ratio: 2:1:1) in 75% and 77% yields, respectively. The experiments reveal that both compounds **2** and **10** could act as suitable thioacetalization reagents only when the appropriate catalyst is used. Therefore, the reaction between **1** and aldehyde/ketone is actually an acid-assisted, self-catalyzed trans-thioacetalization reaction.

In summary, a novel ketene dithioacetal, compound **1**, as a nonthiolic, odorless, stable thioacetalization reagent has been developed. Various types of aldehydes and ketones have been converted to the corresponding dithianes in the presence of this reagent in high yield (79–97%). Meanwhile, the thioacetalization reaction with its associated mild reaction conditions, high yields, and chemoselectivity between aldehydes and ketones has been demonstrated as an acid-assisted, self-catalyzed trans-thioacetalization reaction. Further investigations on the applications of this novel thioacetalization reagent are in progress.

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Supporting Information Available: Experimental details and analytical data for **1**, its thioacetalization products **4**, and the synthetic intermediates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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