Chemoselective Thioacetalization Using 3-(1,3-Dithian-2-ylidene)pentane-2,4-dione as an Odorless and Efficient Propane-1,3-dithiol Equivalent under Solvent-Free Conditions

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Abstract: As a non-thiolic, odorless propane-1,3-dithiol equivalent, 3-(1,3-dithian-2-ylidene)pentane-2,4-dione has been investigated in acid-promoted thioacetalization under solvent-free conditions. A range of selected aldehydes and aliphatic ketones have been converted into the corresponding dithioacetals in high yields. The relatively slow reaction rate of aromatic ketones allowed chemoselective protection of aromatic aldehydes or aliphatic ketones, in contrast to aromatic ketones.

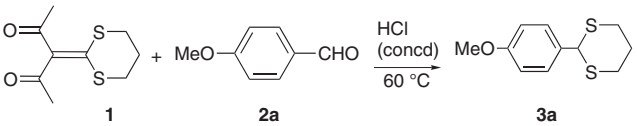
Key words: chemoselectivity, concentrated hydrochloric acid, solvent-free reaction, thioacetalization, α-oxo ketene *S*,*S*-acetals

In recent years, the development of solvent-free organic synthetic methods has become an important and popular research area to eliminate the use of volatile organic solvents in organic synthesis, with the objectives to make syntheses simpler, save energy, prevent solvent waste, hazards, and toxicity, and especially in the context of current environmental concern or 'green chemistry'.[1,2] Extensive work has revealed that a range of organic reactions, of solids, liquids, and gases, can be realized in the presence of various catalysts under solvent-free conditions.[3–5] Recently, some research groups have achieved solvent-free thioacetalization with various catalysts.[6–8] Thioacetalization has become a very useful tool in protecting carbonyl groups as thioacetals as well as transforming carbonyl functions into hydrocarbon derivatives to form C–C bonds in organic chemistry.[9,10]

Unfortunately, conventional thioacetalization suffers from the use of volatile, foul-smelling, low-molecular-weight thiols that can lead to serious safety and environmental problems.[11,12] To resolve these drawbacks, some attempts have been made to develop odorless substitutes for these obnoxious thiols. Accordingly, a range of odorless or faint-smelling thiols have been prepared by increasing the alkyl chain lengths of the thiol or introducing trialkylsilyl groups onto the benzene ring of benzyl mercaptan and benzenethiol.[13] Alternatively, incorporation of propane-1,3-dithiol functions within linear or cross-linked copolymeric reagents have been realized and applied in organic synthetic chemistry.[14] 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.

Very recently, we achieved novel thioacetalization[15] and thia-Michael addition[16] with non-thiolic, odorless α-oxo ketene *S*,*S*-acetals and their derivatives as thiol equivalents. In the present work, we describe our preliminary results in an acid-promoted thioacetalization using 3-(1,3-dithian-2-ylidene)pentane-2,4-dione (**1**) as a propane-1,3-dithiol equivalent under solvent-free conditions.

Table 1 Solvent-Free Thioacetalization Reaction between 3-(1,3-Dithian-2-ylidene)pentane-2,4-dione and 4-Methoxybenzaldehyde[a]



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

Entry	Concn of HCl (mM)	Time (min)	Yield[b] (%)
1	5.0	40	93
2	7.5	25	94
3	10	15	97
4	15	15	96
5	20	15	97

[a] Reagents and conditions: **1** (10 mmol), **2** (10 mmol), HCl, 60 °C.
[b] Isolated yields of **3a**.

The initial studies were performed on the reaction between 4-methoxybenzaldehyde (**2a**) and **1** at various concentrations of aqueous hydrogen chloride in a very simple procedure. To our delight, all the reactions of **2a** proceeded smoothly, affording dithioacetal **3a** in excellent yields (some of the results are summarized in Table 1). Obviously, the amount of hydrogen chloride has a great effect on the rate of the thioacetalization reactions. The reactions were significantly accelerated by higher feed ratios of hydrogen chloride/**1**. The highest reaction rate was attained with a feed ratio hydrogen chloride/**1** of 1:1 (Table 1, entry 3), as indicated by the high yield of **3a** and short reaction time. In all the cases, the thioacetalization proceeded much faster under solvent-free conditions than in organic

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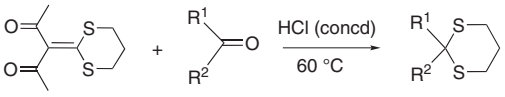
solvent or water,[15] and the reaction mixture formed a white solid when cooled to ambient temperature. It is noteworthy that the solid is almost pure product after being washed with water for several times; this provides a very simple separation process. All the above results fully demonstrated that compound **1** is an efficient and practical thioacetalization reagent even under solvent-free conditions and that concentrated aqueous hydrogen chloride can efficiently promote the thioacetalization.

In the next studies, we turned our attention to the thioacetalization of **1** with various selected aldehydes and ketones **2** under the conditions described in Table 1, entry 3. The results are summarized in Table 2. It is clear that most of the aromatic aldehydes (Table 2, entries 1–8) and the acyclic aliphatic aldehyde (entry 10) and ketone (entry 11) can be converted into the corresponding dithianes **3** within one hour in very high yields under solvent-free conditions. However, under identical conditions, the reaction with aromatic aldehydes with strong electron-withdrawing groups, such as the nitro group, proceeds with some difficulty (Table 2, entry 9). Similarly, the cyclic aliphatic ketones (Table 2, entries 12–14) need slightly longer reaction times for complete conversion, whereas the reactions with aromatic ketones (entries 15–18) proceed at sluggish rates and in much lower conversion. The thioacetalization of aromatic ketones appears to be much more difficult to achieve than that of its aldehyde counterparts, a reactivity difference that can be attributed to steric and electronic effects. All the results confirm the general value of **1** as key reagent for the thioacetalization of a variety of aldehydes and aliphatic ketones under solvent-free conditions. It is worth mentioning that only a very faint thiol smell was apparent during both reaction and workup processes, and this agrees with practically no release of propane-1,3-dithiol.

Table 2 Solvent-free Thioacetalization of Selected Carbonyl Compounds with 3-(1,3-Dithian-2-ylidene)pentane-2,4-dione

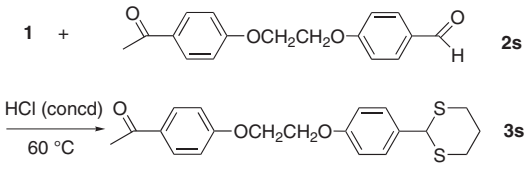


1 **2** **3**

Entry	Substrate **2**	R^1	R^2	Product **3**	Time (min)	Yield[a] (%)
1	**2a**	PMP	H	**3a**	15	97
2	**2b**	Ph	H	**3b**	25	95
3	**2c**	Tol	H	**3c**	25	93
4	**2d**	1,3-benzodioxol-5-yl	H	**3d**	25	96
5	**2e**	4-$Me_2NC_6H_4$	H	**3e**	60	91
6	**2f**	4-HOC_6H_4	H	**3f**	20	95
7	**2g**	4-ClC_6H_4	H	**3g**	20	90
8	**2h**	2-thienyl	H	**3h**	35	96
9	**2i**	4-$O_2NC_6H_4$	H	**3i**	110	58
10	**2j**	Bu	H	**3j**	30	91
11	**2k**	Bu	Me	**3k**	55	88
12	**2l**	$(CH_2)_4$		**3l**	80	92
13	**2m**	$(CH_2)_5$		**3m**	60	98
14	**2n**	$(CH_2)_6$		**3n**	90	91
15	**2o**	Ph	Me	**3o**	480	28
16	**2p**	4-ClC_6H_4	Me	**3p**	480	39
17	**2q**	4-HOC_6H_4	Me	**3q**	480	25
18	**2r**	4-$O_2NC_6H_4$	Me	**3r**	480	46
19	**2b** + **2o**			**3b**	30	94
20	**2m** + **2o**			**3m**	60	95

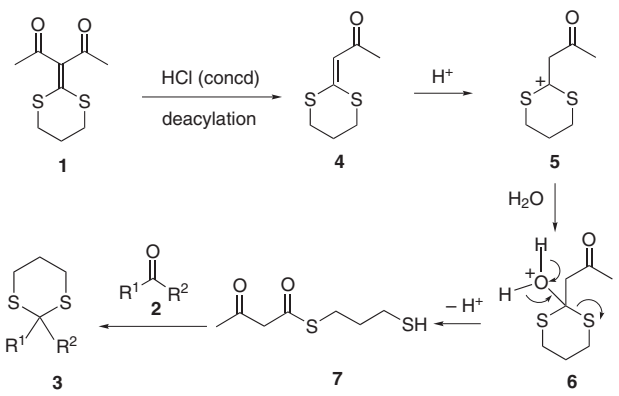
[a] Isolated yields after purification by chromatography (silica gel).

To exploit the different thioacetalization rates of aldehydes and aliphatic ketones versus aromatic ketones for selective protections, we carried out competitive reactions under the above conditions. The reaction of **2b**/**2o**/**1** (1:1:1) performed at 60 °C (Table 2, entry 19) afforded thioacetal **3b** in 94% yield, while ketone **2o** was almost completely recovered (98%), and no **3o** was detected. Similar results were obtained in the case of **2m**/**2o**/**1** (1:1:1) (Table 2, entry 20), where **2m** was converted into thioacetal **3m** in 95% yield while **2o** remained unchanged. Compound **2s**, with two different carbonyl groups in the same molecule, was synthesized for the same test. As shown in Scheme 1, the reaction between **2s** and **1** (1:1 molar ratio) proceeded within 25 min to afford product **3s** in 94% yield. The reported thioacetalization procedure thus shows high chemoselectivity, providing selective protection of an aromatic aldehyde or an aliphatic ketone in the presence of an aromatic ketone.



Scheme 1 Chemoselective thioacetalization of a dicarbonyl compound with 3-(1,3-dithian-2-ylidene)pentane-2,4-dione

On the basis of these results combined with those from our previous studies,[15] the thioacetalization reaction between **1** and **2** has been assumed to proceed by acid-catalyzed trans-thioacetalization, as shown in Scheme 2. The reaction commences with acid-promoted deacylation of compound **1**, affording ketene dithioacetal **4**. Addition of a proton to the C=C bond of ketene dithioacetal **4** converts it into a carbocation **5**, which is stabilized by the electron-donating bis(alkylsulfanyl) groups. Attack of water on carbocation **5** transforms it into oxocation **6**, which forms intermediate **7** by a deprotonation and decyclization process. Finally, intermediate **7** reacts with carbonyl compound **2** to yield the corresponding dithiane **3**.



Scheme 2 Proposed mechanism for the solvent-free thioacetalization

In conclusion, odorless 3-(1,3-dithian-2-ylidene)pentane-2,4-dione **1** has been investigated as a propane-1,3-dithiol equivalent in thioacetalization under solvent-free conditions. In a reaction promoted by concentrated hydrochloric acid, a wide range of aldehydes and aliphatic ketones has been converted into the corresponding dithianes **3** in high yields. The relatively slow reaction rate of aromatic ketones allows chemoselective protection of an aromatic aldehyde or an aliphatic ketone in the presence of an aromatic ketone. The mild conditions, simple procedure, and high yields provide a convenient and clean protocol for the synthesis of thioacetals and the protection of carbonyl compounds in high chemoselectivity.

2-(4-Methoxyphenyl)-1,3-dithiane (3a): Typical Procedure

Compound **1** (10 mmol), benzaldehyde **2a** (10 mmol), and concd aq HCl (10 mmol) were added to a flask in a water bath. The mixture was heated to 60 °C under stirring and monitored by TLC every 5 min. After the reaction was completed, within 15 min as indicated by TLC, the reaction mixture was cooled down to r.t. and neutralized with 10% aq $NaHCO_3$ (10 mL). The solid product was collected by filtration and washed with H_2O (3 × 30 mL). Further purification was carried out by flash column chromatography (silica gel, PE–EtOAc, 75:1); this gave **3a** as a white solid; yield: 97%. [In the case of liquid products **3j**–**3l**, the resulting mixture was neutralized with 10% aq $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with H_2O (3 × 30 mL) and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave almost pure product. Further purification was carried out by flash column chromatography (silica gel, PE–EtOAc, 75:1)]. Dithioacetals **3a**–**r** prepared in the present work are known compounds and were identified by their ^{1}H NMR and IR spectroscopy data and by elemental analyses; the data for these compounds were in good agreement with that appearing in the literature.

4-[2-(4-Acetylphenoxy)ethoxy]benzaldehyde (2s)

Compound **2s** was prepared by a literature procedure.[15c]

White solid; yield: 96%; mp 104–106 °C.

IR (KBr): 1673, 1600, 1570, 1247, 1162 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.57 (s, 3 H), 4.43 (s, 4 H), 6.98–7.02 (dd, *J* = 9.0, 8.5 Hz, 4 H), 7.85–7.97 (dd, *J* = 9.0, 8.5 Hz, 4 H), 9.90 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): 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.

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.90; H, 5.64.

1-(4-{2-[4-(1,3-Dithian-2-yl)phenoxy]ethoxy}phenyl)ethanone (3s)

Compound **3s** was prepared from **2s** by the method described above for the synthesis of **3a**.

White solid; yield: 94%; mp 160–162 °C.

IR (KBr) 3446, 2934, 1675, 1601, 1508, 1245, 1175 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90–1.93 (m, 1 H), 2.16–2.19 (m, 1 H), 2.57 (s, 3 H), 2.89–2.92 (m, 2 H), 3.03–3.08 (m, 2 H), 4.34–4.38 (dd, *J* = 5.0, 5.0 Hz, 4 H), 5.14 (s, 1 H), 6.90–6.99 (dd, *J* = 8.5, 8.5 Hz, 4 H), 7.40–7.42 (d, *J* = 8.5 Hz, 2 H), 7.94–7.96 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): 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.

Anal. Calcd for $C_{20}H_{22}O_3S_2$: C, 64.14; H, 5.92. Found: C, 64.19; H, 5.58.

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References

(1) Tanaka, K. *Solvent-Free Organic Synthesis*; Wiley-VCH: Weinheim, **2003**.
(2) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford: London, **1998**.
(3) (a) Rothenberg, G.; Dowine, A. P.; Raston, C. L.; Scott, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 8701. (b) Bolm, C.; Palazzi, C.; Francio, G.; Leitner, W. *Chem. Commun.* **2002**, 1588. (c) Clark, J. H. *Green Chem.* **1999**, 1.
(4) (a) Metzger, J. O. *Angew. Chem. Int. Ed.* **1998**, *37*, 2975. (b) Varma, R. S. *Green Chem.* **1999**, 43.
(5) (a) Toda, F.; Yagi, M.; Kiyoshige, K. *J. Chem Soc., Chem. Commun.* **1988**, 958. (b) Toda, F.; Tanaka, K.; Hamai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3207. (c) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025. (d) Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun.* **2001**, 2159.
(6) (a) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58. (b) Firouzabadi, H.; Karimi, B.; Eslami, S. *Tetrahedron Lett.* **1999**, *40*, 4055. (c) Firouzabadi, H.; Iranpoor, N.; Kamal, A. *Synthesis* **2002**, 59.
(7) (a) Deka, N.; Sarma, J. C. *Chem. Lett.* **2001**, 794. (b) Kazahaya, K.; Tsuji, S.; Sato, T. *Synlett* **2004**, 1640. (c) Aoyama, T.; Takido, T.; Kodomari, M. *Synlett* **2004**, 2307.
(8) (a) Anand, R. V.; Saravanan, P.; Singh, V. K. *Synlett* **1999**, 415. (b) Siddhartha, G.; Jagat, C. B.; Nabin, C. B. *Synlett* **2004**, 1592.
(9) (a) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, **1994**. (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, **1999**.
(10) (a) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097. (b) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239. (c) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (d) Smith, A. B. III; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35. (e) Breit, B. *Angew. Chem. Int. Ed.* **1998**, *37*, 453. (f) Smith, A. B. III; Pitram, S. M.; Gaunt, M. J.; Kozmin, S. A. *J. Am. Chem. Soc.* **2002**, *124*, 14516.
(11) (a) Ku, B.; Oh, D. Y. *Synth. Commun.* **1989**, *19*, 433. (b) Page, P. C. B.; Prodger, J. C.; Westwood, D. *Tetrahedron* **1993**, *49*, 10355. (c) Kumar, P.; Reddy, R. S.; Singh, A. P.; Pandey, B. *Synthesis* **1993**, 67. (d) Anand, R. V.; Saravanan, P.; Singh, V. K. *Synlett* **1999**, 415. (e) Tietze, L. F.; Weigand, B.; Wulff, C. *Synthesis* **2000**, 69.
(12) (a) Garlaschelli, L.; Vidari, G. *Tetrahedron Lett.* **1990**, *31*, 5815. (b) Patney, H. K. *Tetrahedron Lett.* **1991**, *32*, 2259. (c) Saraswathy, V. G.; Sankararaman, S. *J. Org. Chem.* **1994**, *59*, 4665. (d) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527. (e) Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2002**, *43*, 1347. (f) Kamal, A.; Chouhan, G. *Tetrahedron Lett.* **2003**, *44*, 3337.
(13) (a) Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T. *Tetrahedron Lett.* **2001**, *42*, 9207. (b) Nishide, K.; Miyamoto, T.; Kumar, K.; Ohsugi, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 8569. (c) Nishide, K.; Ohsugi, S.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 5177. (d) Miyazaki, T.; Han-ya, Y.; Tokuyama, H.; Fukuyama, T. *Synlett* **2004**, 477.
(14) (a) Bertini, V.; Lucchesini, F.; Pocci, M.; De Munno, A. *Tetrahedron Lett.* **1998**, *39*, 9263. (b) Bertini, V.; Lucchesini, F.; Pocci, M.; De Munno, A. *J. Org. Chem.* **2000**, *65*, 4839. (c) Bertini, V.; Pocci, M.; Lucchesini, F.; Alfei, S.; De Munno, A. *Synlett* **2003**, 864.
(15) (a) Liu, Q.; Che, G.; Yu, H.; Liu, Y.; Zhang, J.; Zhang, Q.; Dong, D. *J. Org. Chem.* **2003**, *68*, 9148. (b) Yu, H.; Liu, Q.; Yin, Y.; Fang, Q.; Zhang, J.; Dong, D. *Synlett* **2004**, 999. (c) Dong, D.; Ouyang, Y.; Yu, H.; Liu, Q.; Liu, J.; Wang, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4535.
(16) (a) Yu, H.; Dong, D.; Ouyang, Y.; Liu, Q.; Wang, Y. *Lett. Org. Chem.* **2005**, *2*, 755. (b) Dong, D.; Yu, H.; Ouyang, Y.; Liu, Q.; Bi, X.; Lu, Y. *Synlett* **2006**, 283.