Simple, Mild and Efficient Thioacetalization and Transthioacetalization of Carbonyl Compounds and Deprotection of Thioacetals: Unique Role of Thiols in the Selectivity of Thioacetalization[1]

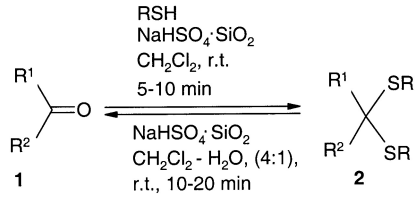
Biswanath Das,* Ravirala Ramu, Majjigapu Ravinder Reddy, Gurram Mahender

Organic Chemistry Division – I, Indian Institute of Chemical Technology, Hyderabad – 500 007, India
Fax +91(40)7160512; E-mail: biswanathdas@yahoo.com

Received 6 September 2004

Abstract: Silica supported sodium hydrogen sulfate ($NaHSO_4{\cdot}SiO_2$) has been employed for efficient thioacetalization and transthioacetalization of carbonyl compounds in CH_2Cl_2 at room temperature. Selectivity of thioacetalization was dependent on the thiols used for the conversion. The same catalyst was also found to be effective for deprotection of thioacetals in CH_2Cl_2–H_2O at room temperature.

Keywords: carbonyl compounds, thioacetalization, transthioacetalization, deprotection of thioacetals, $NaHSO_4{\cdot}SiO_2$, selectivity



Scheme 1

Thioacetalization is an important process for protection of carbonyl group and is frequently used in the synthesis of multifunctional organic molecules.[2] Thioacetals are quite stable towards different reagents under various reaction conditions.[2] They are also useful as acyl carbanion equivalents in organic synthesis.[3] The deprotection of thioacetals at the desired stage of synthesis to generate the parent carbonyl compounds is also highly required. In general, thioacetalization[4] and dethioacetalization[5] are carried out with various protic and Lewis acids. Despite their potential utilities many of the reported methods are associated with certain disadvantages such as treatment with strong acids, long reaction times, drastic reaction conditions, toxic reagents, expensive catalysts, multistep operations, disturbance to other functional groups and unwanted side reactions. Thus, still there is a need to develop novel and efficient methods for thioacetalization and dethioacetalization, though these conversions have been studied well.

In continuation of our work[6] on the application of silica-supported sodium hydrogen sulfate ($NaHSO_4{\cdot}SiO_2$) as a heterogeneous catalyst in organic synthesis we have recently observed that the catalyst can be employed efficiently for thioacetalization of carbonyl compounds as well as for deprotection of thioacetals (Scheme 1).

Several aromatic, heterocyclic, aliphatic and conjugated aldehydes were converted into thioacetals by treatment with thiols in CH_2Cl_2 in the presence of $NaHSO_4{\cdot}SiO_2$ at room temperature (Table 1). Various Ketones also underwent thioacetalization under such treatment. The reaction was carried out with thiols of different chain lengths. The method was general for aldehydes and ketones (aromatic and aliphatic) when EtSH was used for thioacetalization. The reaction was completed within 5–10 minutes to afford the products in excellent yields. Several functional groups such as hydroxyl, ether, halogen, nitro, amino and allyl groups remained intact. Electron-donating or electron-withdrawing groups did not affect the reaction. Thioacetalization was also carried out with long chain (C-10, C-12 and C-16) thiols. The important matter is that the selectivity of the reaction was highly dependent on the thiols used for the conversion. With long chain thiols, the conversion was equally efficient for the aromatic aldehydes as with EtSH to produce the corresponding thioacetals in very high yields within 10 minutes (Table 1). However, aliphatic aldehydes or ketones (aliphatic and aromatic) afforded no product with these long chain thiols under similar experimental conditions. When the reaction times were increased to 2 hours an aliphatic aldehyde formed the thioacetals with long chain thiols with the yields of 58–64%, while a ketone formed the thioacetals with long chain thiols in yields of 15–18% only. Thus with the proper choice of reacting thiols general thioacetalization as well as selective thioacetalization of carbonyl function of aromatic and aliphatic aldehydes and ketones can be achieved (Schemes 2 and 3). Previously the role of thiols on the selectivity of thioacetalization of carbonyl compounds has not been well studied.

When thioacetalization was carried out with ethane dithiol, aldehydes were protected within 3–3.5 hours to form the thioacetals in high yields (72–81%) while ketones like acetophenone and benzophenone did not afford the dithiolanes during this period under the similar experimental conditions (Scheme 4). Thus the differences in behavior of ethane thiol and ethane dithiol towards the thioacetalization of aldehydes and ketones (regarding times and selectivity) are noteworthy.

SYNTHESIS 2005, No. 2, pp 0250–0254
Advanced online publication: 24.11.2004
DOI: 10.1055/s-2004-834934; Art ID: P10504SS

Table 1 Thioacetalization and Transthioacetalization of Carbonyl Compounds Using $NaHSO_4{\cdot}SiO_2$[a]

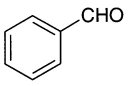
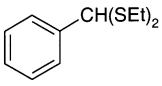
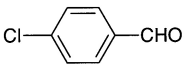
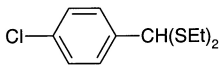
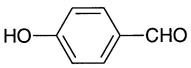
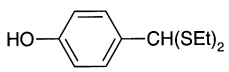
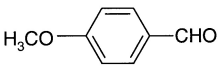
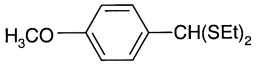
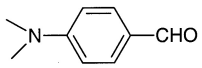
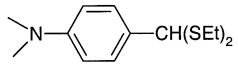
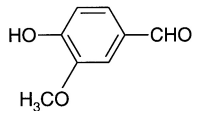
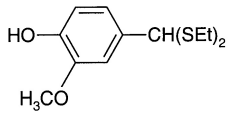
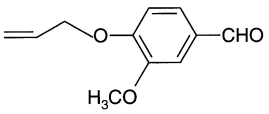
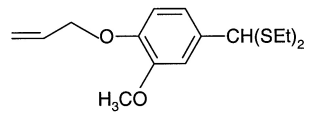
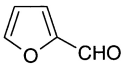
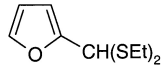
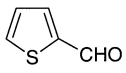
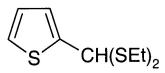
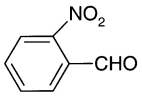
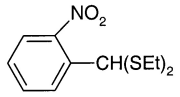
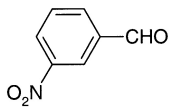
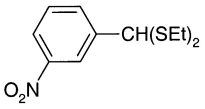
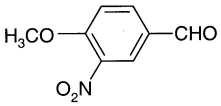
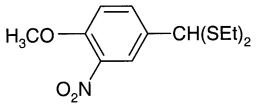
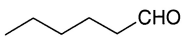
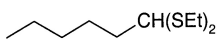
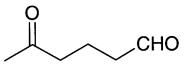
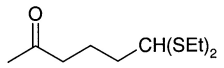
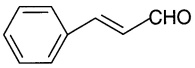
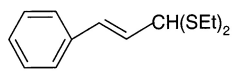
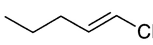
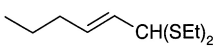
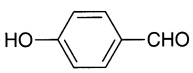
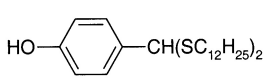
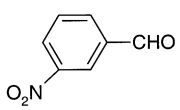
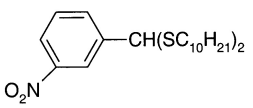
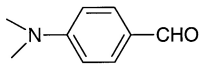
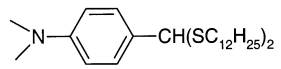
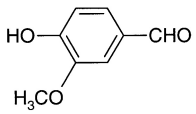
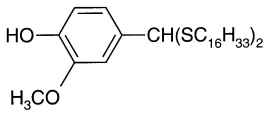
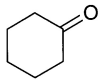
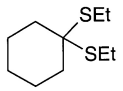
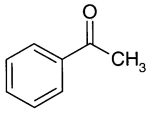
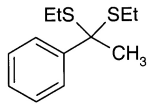
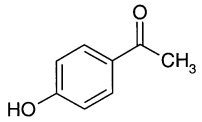
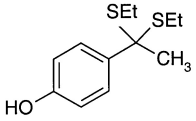
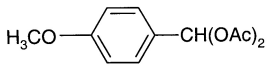
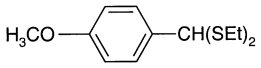
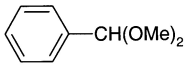
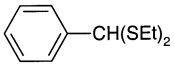
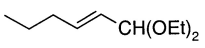
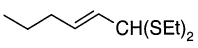
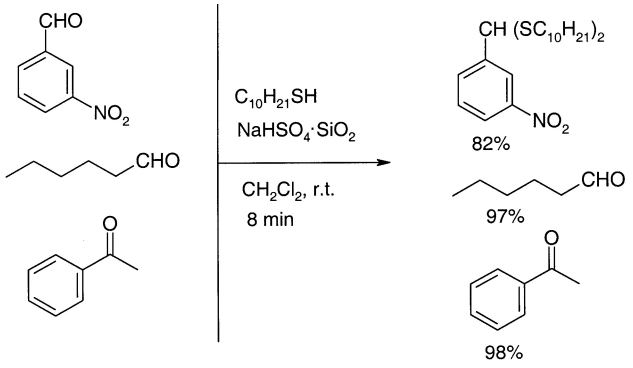
Entry	Substrate	Product **2**	Time (min)	Isolated yield (%)	Ref.
a			5	98	5i
b			5	96	5i
c			5	95	5i
d			5	97	5i
e			5	94	
f			5	93	5j
g			5	96	5j
h			8	92	5i
i			5	91	5i
j			5	94	5i
k			5	97	
l			5	90	5j
m			10	93	5i
n			10	91	5j
o			8	93	5j
p			10	95	5i
q			10	80	
r			10	78	
s			10	75	

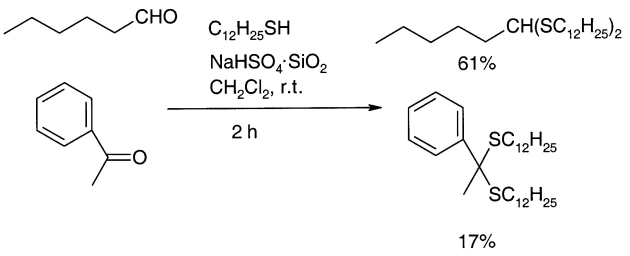
Table 1 Thioacetalization and Transthioacetalization of Carbonyl Compounds Using $NaHSO_4{\cdot}SiO_2$[a] (continued)

Entry	Substrate	Product **2**	Time (min)	Isolated yield (%)	Ref.
t			10	75	
u			10	90	5i
v			10	82	5f
w			10	78	5f
x			10	92	5i
y			5	95	5i
z			10	93	5i

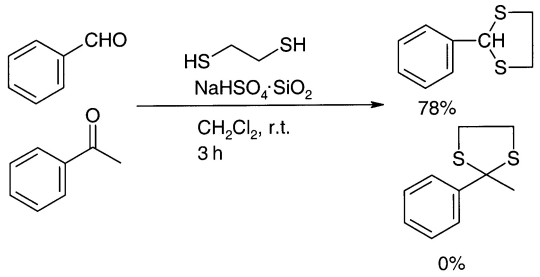
[a] Products were characterized from their spectral (IR, ^1H NMR and MS) data.



Scheme 2

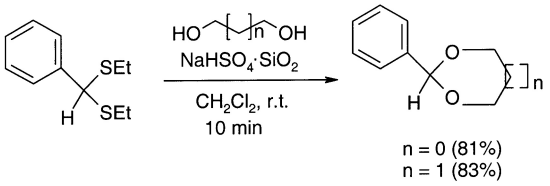


Scheme 3



Scheme 4

The present method is also suitable for transthioacetalization of carbonyl compounds. Different *S*,*S*-acetals have been prepared from the corresponding *O*,*O*-acetals in very high yields within a short period of time (5–10 min) (Table 1). However, *S*,*S*-acetals on treatment with ethane-1,2-diol or propane-1,3-diol in the presence of $NaHSO_4{\cdot}SiO_2$ in CH_2Cl_2 afforded *O*,*O*-acetals at room temperature (Scheme 5).



Scheme 5

Deprotection of thioacetals was also carried out using $NaHSO_4 \cdot SiO_2$ at room temperature. Various thioacetals were converted into their parent carbonyl compounds (Table 2) by employing the catalyst in CH_2Cl_2–H_2O (4:1) within 10–20 minutes. The yields of the carbonyl compounds were excellent. Deprotection could also be carried out in MeOH but time required was longer (2–3 h).

The catalyst, $NaHSO_4 \cdot SiO_2$ works under heterogeneous conditions. The catalytic activity of the reagent has not yet been explored widely. In recent years heterocyclic catalysts are of increasing attention because of economic and environmental considerations. The present catalyst can be easily prepared[7] from the readily available ingredients, $NaHSO_4$ and silica gel (finer than 200 mesh). It can be easily handled and removed from the reaction mixture by filtration. The catalyst should be properly activated before use. The experimental procedures for both thioacetalization and deacetalization using this catalyst are very simple. In absence of the catalyst or only with $NaHSO_4$ or silica gel the protection of carbonyl compounds with thiols as well as deprotection of thioacetals under the present experimental conditions could not be achieved.

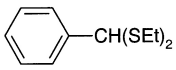
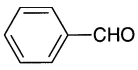
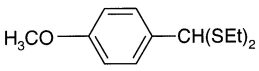
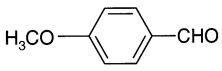
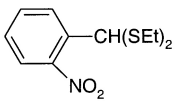
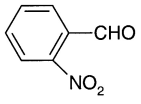
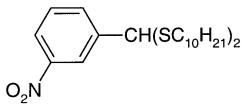
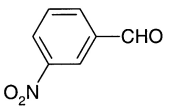
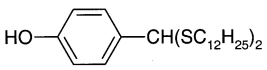
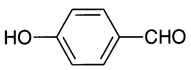
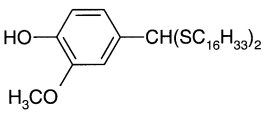
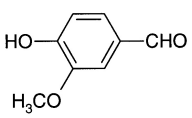
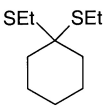
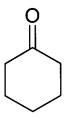
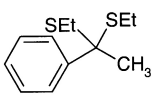
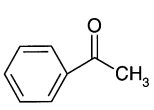
In conclusion, we have developed a very simple and efficient method for thioacetalization of carbonyl compounds and deprotection of thioacetals using the same catalyst ($NaHSO_4 \cdot SiO_2$) in different solvent systems. The method is associated with mild experimental conditions, utilization of an inexpensive and non-toxic catalyst, short reaction times and excellent yields. The unique feature of the present thioacetalization is its selectivity depending on the nature of the reacting thiols. Transthioacetalization can also be achieved following the similar process. We feel that the developed method will find important applications in organic synthesis.

Melting points were measured on a Buchi 510 instrument and are uncorrected. The ^1H NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200 MHz spectrometer using TMS as an internal standard and EI–MS on a VG Micromass 7070H (70eV) instrument. Column Chromatography was carried out with silica gel 100–200 mesh and TLC with silica gel GF_{254}.

Thioacetalization and Transthioacetalization; General Procedure

To a stirred mixture of a carbonyl compound (1 mmol) or an acetal (1 mmol) and alkyl thiol (2.2 mmol) or ethane dithiol (1.2 mmol) in CH_2Cl_2 (10 mL), activated $NaHSO_4 \cdot SiO_2$ (200 mg) was added at r.t. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and the filtrate was concentrated. The residue was subjected to column chromatography over silica gel and the column was eluted with EtOAc–hexane (1:4)

Table 2 Deprotection of Thioacetals Using $NaHSO_4 \cdot SiO_2$[a]

Entry	Substrate	Product	Time (min)	Isolated yield (%)
a			10	96
b			15	93
c			10	90
d			15	85
e			20	83
f			20	80
g			15	78
h			20	76

[a] Products were characterized by comparison of their spectral (IR, ^1H NMR and MS) data with those of authentic samples.

to afford pure thioacetal. The spectral and analytical data of the unknown compound are given below.

4-*N*,*N*-Dimethylbenzaldehyde Diethylthioacetal (2e)
Light yellow oil.

^{1}H NMR: δ = 7.30 (d, *J* = 8.0 Hz, 2 H), 6.68 (d, *J* = 8.0 Hz, 2 H), 4.86 (s, 1 H), 2.98 (s, 6 H), 2.62–2.43 (m, 4 H), 1.16 (t, *J* = 7.0 Hz, 6 H).

EIMS: *m*/*z* = 255 [M$^+$], 240, 194, 179, 120.

Anal. Calcd for $C_{13}H_{21}NS_2$: C, 61.18; H, 8.24; N, 5.49. Found: C, 61.32; H, 8.17; N, 5.33.

3-Nitrobenzaldehyde Diethylthioacetal (2k)
Light yellow oil.

^{1}H NMR : δ = 8.28 (br d, *J* = 1.5 Hz, 1 H), 8.12 (br dd, *J* = 8.0, 1.5 Hz, 1 H), 7.80 (br dd, *J* = 8.0, 1.5 Hz, 1 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 4.92 (s, 1 H), 2.58–2.46 (m, 4 H), 1.22 (t, *J* = 7.0 Hz, 6 H).

EIMS: *m*/*z* = 257 [M$^+$], 196, 168, 121.

Anal. Calcd for $C_{11}H_{15}NO_2S_2$: C, 51.36; H, 7.55; N, 5.45. Found: C, 51.55; H, 7.72; N, 5.38.

4-Hydroxybenzaldehyde Didodecylthioacetal (2q)
Mp 141–143 °C.

^{1}H NMR: δ = 7.22 (d, *J* = 8.0 Hz, 2 H), 6.70 (d, *J* = 8.0 Hz, 2 H), 5.28 (br s, 1 H), 4.76 (s, 1 H), 2.60–2.38 (m, 4 H), 1.58–1.42 (m, 4 H), 1.38–1.04 (m, 36 H), 0.82 (t, *J* = 7.0 Hz, 6 H).

EIMS: *m*/*z* = 508 [M$^+$], 307, 201, 139.

Anal. Calcd for $C_{31}H_{56}OS_2$: C, 73.23; H, 11.02. Found: C, 73.43; H, 11.18.

3-Nitrobenzaldehyde Didecylthioacetal (2r)
Mp 105–107 °C.

^{1}H NMR: δ = 8.22 (br d, *J* = 1.5 Hz, 1 H), 8.01 (br dd, *J* = 8.0, 1.5 Hz, 1 H), 7.78 (br dd, *J* = 8.0, 1.5 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 4.82 (s, 1 H), 2.62–2.38 (m, 4 H), 1.60–1.42 (m, 4 H), 1.38–1.14 (m, 28 H), 0.84 (t, *J* = 7.0 Hz, 6 H).

EIMS: *m*/*z* = 481 [M$^+$], 308, 168, 140.

Anal. Calcd for $C_{27}H_{47}NO_2S_2$: C, 67.36; H, 9.77; N, 2.91. Found : C, 67.52; H, 9.61; N, 2.83.

4-*N*,*N*-Dimethylbenzaldehyde Didodecylthioacetal (2s)
Mp 113–115 °C.

^{1}H NMR: δ = 7.28 (d, *J* = 8.0 Hz, 2 H); 6.64 (d, *J* = 8.0 Hz, 2 H), 4.78 (s, 1 H), 2.96 (s, 6 H), 2.62–2.36 (m, 4 H), 1.55–1.40 (m, 4 H), 1.35–1.02 (m, 36 H), 0.81 (t, *J* = 7.0 Hz, 6 H).

EIMS: *m*/*z* = 520 [M$^+$], 319, 201, 168.

Anal. Calcd for $C_{33}H_{61}NS_2$: C, 74.02; H, 11.40; N, 2.62. Found: C, 75.24; H, 11.29; N, 2.56.

4-Hydroxy-3-methoxybenzaldehyde Dihexadecylthioacetal (2t)
Mp 186–188 °C.

^{1}H NMR: δ = 6.98 (m, *J* = 1.5 Hz, 1 H), 6.82–6.75 (m, 2 H), 5.48 (s, 1 H), 4.72 (s, 1 H), 3.91 (s, 3 H), 2.54–2.40 (m, 4 H), 1.57–1.46 (m, 4 H), 1.38–1.19 (m, 52 H), 0.86 (t, *J* = 7.0 Hz, 6 H).

EIMS: *m*/*z* = 650 [M$^+$], 635, 378, 257, 224, 123.

Anal. Calcd for $C_{40}H_{74}O_2S_2$: C, 73.85; H, 11.39. Found: C, 73.72; H, 11.46.

Deprotection of Thioacetals; General Procedure
Thioacetal (1 mmol) and $NaHSO_4{\cdot}SiO_2$ (200 mg) were taken in CH_2Cl_2–H_2O (4:1, 10 mL). The mixture was stirred at r.t. After completion of the reaction the mixture was filtered. The concentrated filtrate was purified by column chromatography over silica gel using EtOAc–hexane (1:4) as eluent to produce the corresponding parent carbonyl compound.

Acknowledgment

The authors thank UGC, New Delhi for financial assistance.

References

(1) Part 39 in the series 'Studies on novel synthetic methodologies'; IICT Communication No. 041106.
(2) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, **1991**, 178–207. (b) Kocienski, P. J. *Protecting Groups*; Thieme: Stuttgart, **1994**, 156–170.
(3) (a) Corey, E. J.; Seebach, D. *Angew Chem. Int. Ed. Engl.* **1965**, *4*, 1075. (b) Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, *31*, 4097.
(4) (a) Colvin, E. W.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Chem. Commun.* **1971**, 858. (b) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553. (c) Ho, T. L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791. (d) Dishi, T.; Kamemoto, K.; Ban, Y. *Tetrahedron Lett.* **1972**, *13*, 1085. (e) Ellision, R. A.; Lukenbach, E. R.; Chiu, C. W. *Tetrahedron Lett.* **1975**, 499. (f) Schmittel, M.; Levis, M. *Synlett* **1996**, 315. (g) Hirano, A.; Ukawar, K.; Yakabe, S.; Clark, J. H.; Morimoto, T. *Synthesis* **1997**, 858.
(5) (a) Dijerassi, C.; Gorman, M. *J. Am. Chem. Soc.* **1953**, *75*, 3704. (b) Fieser, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 1945. (c) Olah, G. A.; Narang, S. C.; Meider, D.; Salem, G. F. *Synthesis* **1981**, 282. (d) Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 169. (e) Page, P. C. B.; Prodger, J. C.; Westwood, D. *Tetrahedron* **1993**, *49*, 10355. (f) Tateiwa, J.; Horiuchi, H.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 4039. (g) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Synthesis* **1999**, 58. (h) Yadav, J. S.; Reddy, B. V. S.; Pandey, S. K. *Synlett* **2001**, 238. (i) Kamal, A.; Choudhan, G. *Tetrahedron Lett.* **2003**, *44*, 3337. (j) Yadav, J. S.; Reddy, B. V. S.; Kondaji, G. *Chem. Lett.* **2003**, *32*, 672.
(6) (a) Mahender, G.; Ramu, R.; Ramesh, C.; Das, B. *Chem. Lett.* **2003**, *32*, 734. (b) Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. *Adv. Synth. Catal.* **2003**, 557. (c) Ramesh, C.; Ravindranath, N.; Das, B. *J. Org. Chem.* **2003**, *68*, 7101.
(7) Breton, G. W. *J. Org. Chem.* **1997**, *62*, 8952.