

## Silicasulfuric Acid/ $\text{NaNO}_2$ as a New Reagent for Deprotection of *S,S*-Acetals under Solvent-free Conditions

Abdol R. Hajipour,<sup>†,\*,‡</sup> Amin Zarei,<sup>‡</sup> Leila Khazdooz,<sup>‡</sup> Seied Ali Pourmousavi,<sup>‡</sup> and Arnold E. Ruoho<sup>†</sup>

<sup>†</sup>Dept. of Pharmacology, University of Wisconsin, Medical School, 1300 University Avenue, Madison, WI 53706-1532, USA

\*E-mail: haji@cc.iut.ac.ir

<sup>‡</sup>Pharmaceutical Research Laboratory, College of Chemistry, Isfahan University of Technology, Isfahan 84156, IR Iran

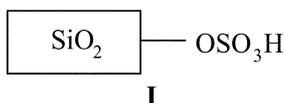
Received October 5, 2004

**Key Words :** Silicasulfuric acid, Dethioacetalization

Protection and deprotection of reactive functional groups are essential steps in the synthesis of polyfunctional compounds. Thioacetalization is well-known as a reaction that protects carbonyl groups of aldehydes and ketones.<sup>1</sup> Thioacetals are frequently encountered synthetic step for the preparation of many important organic compounds including natural products.<sup>2</sup> Their stability under acidic and basic conditions make them versatile carbonyl protecting groups.<sup>3,4</sup>

For this reason, the protection and deprotection of the carbonyl functional group remain crucial challenges to the organic chemists. Experience shows that the critical parameters are generally the stability and the cleavage of the protecting group rather than its introduction. Therefore regeneration of the parent carbonyl group from their masked form seems to be a useful synthetic process. There are several methods for the deprotection of thioacetals and thioketals.<sup>5,6</sup> The most of these methods are toxic to the environment, expensive and their preparations are difficult.<sup>5</sup>

In continuation of our studies on the application of solid acids we found that silica gel reacts with chlorosulfonic acid to give silicasulfuric acid (I). It is interesting to note that the reaction is straightforward, clean and does not need any further purification, because HCl gas is evolved from the reaction vessel immediately. We and others find that silica sulfuric acid (I) is an excellent candidate for sulfuric acid replacement in organic reactions without any limitations such as destruction of acid sensitive functional groups.<sup>7</sup>



In continuation of our ongoing program to develop environmentally benign methods under solvent-free conditions,<sup>8</sup> We wish here to report the use of silicasulfuric acid/ $\text{NaNO}_2$  as a convenient and efficient reagent for conversion of *S,S*-acetals to the corresponding parent carbonyl compounds (Scheme 1).

Initially the conversion of 4-methoxyphenyl-1,3-dithiolane to 4-methoxybenzaldehyde was carried out with supported silicasulfuric acid/ $\text{NaNO}_2$  on wet  $\text{SiO}_2$  (60% w/w) in various solvents and solvent-free conditions, the results are summarized in Table 1.

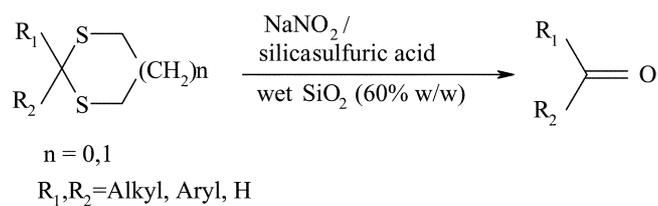
**Table 1.** Dethioacetalization of 4-methoxyphenyl-1,3-dithiolane in the presence of silicasulfuric acid/ $\text{NaNO}_2$  and wet  $\text{SiO}_2$  (60% w/w)

Solvent	Overall Yield (%) <sup>c</sup>	4-methoxybenzaldehyde (%)	4-methoxybenzoic acid (%)
Acetonitrile <sup>a</sup>	70	50	20
Dichloromethane <sup>a</sup>	60	45	15
Diethyl ether <sup>a</sup>	50	35	15
Solvent-free <sup>b</sup>	98	93	5

<sup>a</sup>was stirred at 0-5 °C for 2 hours. <sup>b</sup>was ground at room temperature for 2 min. <sup>c</sup>monitored by TLC and GC.

As shown in Table 1, in comparison to conventional methods the yield of the reaction under solvent-free conditions are higher and reaction time is shorter. When we treated 4-methoxyphenyl-1,3-dithiolane in the presence of supported silicasulfuric acid/ $\text{NaNO}_2$  on wet  $\text{SiO}_2$  (60% w/w) in acetonitrile at 0-5 °C for 2 hours the yield of 4-methoxybenzaldehyde was 50% and 20% of 4-methoxybenzoic acid due to over oxidation of producing 4-methoxybenzaldehyde was also obtained. When we examined-methoxyphenyl-1,3-dithiolane in the presence of supported silicasulfuric acid/ $\text{NaNO}_2$  on wet  $\text{SiO}_2$  (60% w/w) in other solvent such as Dichloromethane and diethyl ether at 0-5 °C for 2 hours the over all yield was 60 and the yield of 4-methoxybenzaldehyde was low and 15% of 4-methoxybenzoic acid due to over oxidation of producing 4-methoxybenzaldehyde was also obtained in each case. The noteworthy of this procedure under solvent-free condition in comparison with reaction in solvent is the higher over all yields of product and low further oxidation. A variety of *S,S*-acetals were treated with silicasulfuric acid/ $\text{NaNO}_2$  and wet  $\text{SiO}_2$  (60% w/w) under solvent-free conditions. A bright-red color is obtained immediately may be due to formation of thionitrite, which then is converted to the parent carbonyl compound (Table 2).<sup>9</sup>

The deprotection of a variety of *S,S*-acetals including aromatic diacetal containing electron-withdrawing and electron-donating substituents, and  $\alpha,\beta$ -unsaturated diacetal and aliphatic *S,S*-acetals was examined with this reagent under solid-state conditions at room temperature (Scheme 1, Table 2). The results are summarized in Table 2. In each case



Scheme 1

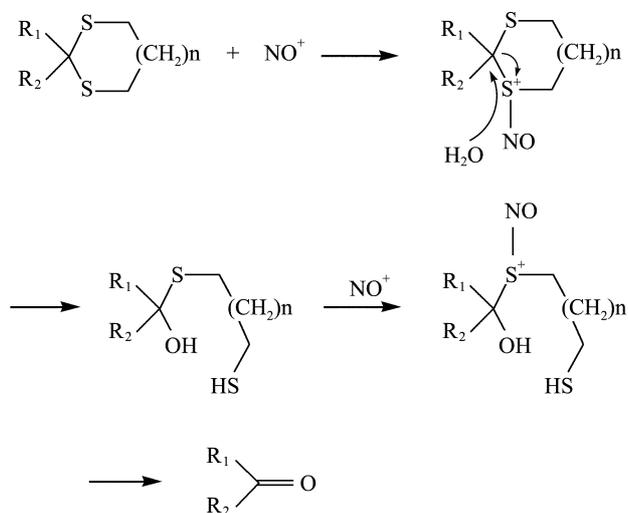
**Table 2.** Deprotection of various *S,S*-acetals in the presence of silicasulfuric acid/ $\text{NaNO}_2$  and wet  $\text{SiO}_2$  (60% w/w) under solvent-free conditions at room temperature<sup>a,b</sup>

Entry	Substrate	product	Time (min)	Yield (%)
1			2	82 <sup>c</sup>
2			3	88 <sup>c</sup>
3			2	87 <sup>c</sup>
4			3	88 <sup>c</sup>
5			3	90 <sup>c</sup>
6			2	84 <sup>c</sup>
7			2	86 <sup>c</sup>
8			2	82 <sup>c</sup>
9			2	85 <sup>c</sup>
10			3	80 <sup>c</sup>
11			2	85 <sup>c</sup>
12			3	90 <sup>c</sup>
13			3	92 <sup>c</sup>
14			3	90 <sup>c</sup>

Table 2. Continued

Entry	Substrate	product	Time (min)	Yield (%)
15			2	85 <sup>c</sup>
16			2	85 <sup>c</sup>
17			4	91
18			4	90
19			4	90
20			4	88
21			3	87
22			3	92
23			3	90
24			4	88
25			4	85
26			4	87
27			4	90
28			4	90

<sup>a</sup>The yields refer to the isolated products after purification. <sup>b</sup>All of the products were characterized by physical data and their spectral (IR, <sup>1</sup>H-NMR, TLC and GC). <sup>c</sup>5-10% of corresponding acid was obtained.



Scheme 2

the corresponding carbonyl compounds were obtained in good to excellent yields and short reaction time. Using *aromatic S,S*-acetals with -withdrawing and electron-donating substituents or  $\alpha,\beta$ -unsaturated *S,S*-acetals did not effect the yield of product or reaction time. This method also is suitable for deprotection of aliphatic *S,S*-acetals in good to excellent yields. The products were purified by column chromatography and the purity of the products was determined by GC and IR, NMR analysis. Moreover, this procedure is highly chemoselective, providing selective.

The possible mechanism of the reaction is outlined in Scheme 2. Initially a red solution was obtained which may be due to the formation of sulfonitrile complex. Then this complex was hydrolysis to the corresponding carbonyl compounds as shown in Scheme 2.

In conclusion we have developed a simple, mild, inexpensive, environmentally safe method for deprotection of *S,S*-acetals. High yields and short reaction times are noteworthy feature of the reported method.

### Experimental Section

**General.** Products were characterized by comparison with authentic samples (IR,  $^1\text{H-NMR}$  spectrum, CHN analysis, melting point and TLC analysis) with those obtained by literature method<sup>5</sup> and using alternative method of synthesis. All mps. were taken on a Gallenkamp melting apparatus and are uncorrected.  $^1\text{H NMR}$  spectra were recorded on a Varian 250 NMR Spectrometer operating at 250 MHz. The spectra were measured in  $\text{CCl}_4$  and  $\text{CDCl}_3$  relative to TMS (0.00 ppm). IR spectra were recorded on a Shimadzu 435 IR

spectrophotometer. Spectra of solids were performed using KBr pellets. Silicasulfuric acid was prepared according to reported method.<sup>7</sup>

**Dethioacetalization of *p*-chlorophenyl-1,3-dithiolane by using silicasulfuric acid/ $\text{NaNO}_2$  and wet  $\text{SiO}_2$  (60% w/w), a typical procedure.** In a mortar a mixture of *p*-chlorophenyl-1,3-dithiolane (0.21 g, 1 mmol), silicasulfuric acid (0.55 g, 2 mmol),<sup>7</sup>  $\text{NaNO}_2$  (0.14 g, 2 mmol) and wet  $\text{SiO}_2$  (60% w/w) (0.5 g) was ground with a pestle for 3 min. The progress of the reaction was followed by TLC/GC. The product was isolated by ether ( $2 \times 15$  mL) and washed with saturated  $\text{NaHCO}_3$  (10 mL). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and the solvent removed under reduced pressure. The residue was purified through a short column of silica gel (cyclohexane/ $\text{EtOAc}$ , 3 : 1) to obtain a pure product of *p*-chlorobenzaldehyde (0.12 g, 88%; mp: 45-47 °C).

**Acknowledgment.** We gratefully acknowledge the funding support received for this project from the Isfahan University of Technology (IUT), IR Iran. Further financial support from Center of Excellence in Chemistry Research (IUT) is gratefully acknowledged.

### References

- Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981.
- Kunz, H.; Waldmann, H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 6, pp 677-681.
- Corey, E. J.; Seebach, D. *J. Org. Chem.* **1966**, 31, 4097.
- Mori, Y.; Kohchi, Y.; Suzuki, M. *J. Org. Chem.* **1991**, 56, 631.
- Hajipour, A. R.; Khoee, S.; Ruoho, A. E. *Org. Prep. Proced. Int.* **2003**, 35, 527-581.
- Kamal, A.; Reddy, P. S. M. M.; Reddy, R. *Tetrahedron Lett.* **2003**, 44, 2857.
- (a) Hajipour, A. R.; Mirjalili, B. F.; Zarei, A.; Khazdooz, L.; Ruoho, A. E. *Tetrahedron Lett.* **2004**, 45, 6607. (b) Zolfigol, M. A. *Tetrahedron* **2001**, 57, 9509. (c) Zolfigol, M. A.; Mohammadpoor-Baltork, I.; Mirjalili, B. F.; Bamoniri, A. *Synlett* **2003**, 1877. (d) Mirjalili, B. F.; Zolfigol, M. A.; Zarei, A.; Bamoniri, A.; Zarei, A. *Bull. Korean Chem. Soc.* **2003**, 24, 400. (e) Shirini, F.; Zolfigol, M. A.; Mohammadi, K. *Bull. Korean Chem. Soc.* **2004**, 25, 325. (f) Pore, M.; Desai, U. D.; Mane, R. B.; Wadgaonkar, P. P. *Synth. Commun.* **2004**, 34, 2135.
- (a) Hajipour, A. R.; Islami, F. *Ind. J. Chem.* **1999**, 38B, 461. (b) Hajipour, A. R.; Hantehzadeh, M. *J. Org. Chem.* **1999**, 64, 8475. (c) Hajipour, A. R.; Arbabian, M.; Ruoho, A. E. *J. Org. Chem.* **2002**, 67, 8622. (d) Hajipour, A. R.; Ruoho, A. E. *Org. Prep. Proced. Int.* **2002**, 34, 647. (e) Hajipour, A. R.; Baltork, I. M.; Nikbaghat, K.; Imanzadeh, Gh. *Synth. Commun.* **1999**, 29, 1697. (f) Hajipour, A. R.; Mazloumi, G. *Synth. Commun.* **2002**, 32, 23. (g) Hajipour, A. R.; Ruoho, A. E. *J. Chem. Research (S)* **2002**, 547. (h) Hajipour, A. R.; Adibi, H.; Ruoho, A. E. *J. Org. Chem.* **2003**, 68, 4553. (i) Hajipour, A. R.; Bageri, H.; Ruoho, A. E. *Bull. Korean Chem. Soc.* **2004**, 25, 1238. (j) Hajipour, A. R. Malakutikhah, M. *Org. Prep. Proced. Int.* **2004**, 364, 647. (k) Hajipour, A. R.; Ruoho, A. E. *Sul. Lett.* **2002**, 25, 151.
- Fuji, K.; Ichikawa, K.; Fujita, E. *Tetrahedron Lett.* **1978**, 19, 3561.