

# An efficient procedure for protection of carbonyls catalyzed by sulfamic acid

Bo Wang<sup>a, c</sup>, Yanlong Gu<sup>a</sup>, Guoyong Song<sup>a</sup>, Tao Yang<sup>a</sup>,  
Liming Yang<sup>a, \*</sup>, Jishuan Suo<sup>b</sup>

<sup>a</sup> State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, China

<sup>b</sup> Chengdu Organic Chemicals Co. Ltd., Chinese Academy of Sciences, Chengdu 610041, China

<sup>c</sup> Graduate School of the Chinese Academy Sciences, Beijing 100039, China

Received 19 November 2004; received in revised form 2 February 2005; accepted 2 February 2005

## Abstract

Sulfamic acid ( $\text{H}_2\text{NSO}_3\text{H}$ ) has been used as an efficient and recyclable catalyst for acetalization and ketalization between carbonyl compounds and diols. This system is reasonably general and can be applied to converting several carbonyl compounds to the corresponding acetals and ketals using neopentyl glycol and other diols as protection reagents. The use of an inexpensive, green and stable catalyst, convenient reaction operation and high selectivity to desired products are the features contained in this reaction. Sulfamic acid can be reused five times in the reaction between benzaldehyde and neopentyl glycol without loss of activity.

© 2005 Elsevier B.V. All rights reserved.

**Keywords:** Sulfamic acid; Carbonyl compounds; Neopentyl glycol; Acetalization and ketalization; Green synthesis

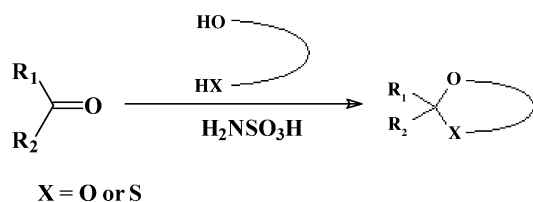
## 1. Introduction

The acetalization or ketalization reaction is a process that is widely used in organic synthesis to protect the carbonyl group of aldehydes and ketones [1,2]. The acetals are important reactants for synthesis of enantiomerically pure compounds, which were widely used as steroids, pharmaceuticals, and fragrances [3–13]. Previously, the catalysts used in the acetalization or ketalization reactions were generally protonic acids, Lewis acids, and a number of transitional metal complexes including Rh, Pd, and Pt [14–17]. Although good results were obtained, the separation of the product from the catalyst system after the reaction was still difficult and the noble metal catalysts used were quite expensive and usually unstable [18]. Therefore, the development of a catalytic sys-

tem that may be stable, easily separable, and reusable has long been awaited.

In the past 2 years, utilizations of a solid organic acid, sulfamic acid ( $\text{H}_2\text{NSO}_3\text{H}$ ), in catalytic and organic reactions as an alternative for conventional acidic materials have received much attention due to its unique characters (nonvolatile, non-hygroscopic, odorless, and white crystalline solid with outstanding stability) [19–23]. As a part of our ongoing studies on the use of sulfamic acid as a green catalyst in organic transformations, we recently reported the tetrahydropyranlation of hydroxy compounds [24], acetolysis of cyclic ethers [25], esterification of cyclic olefins with aliphatic acids under solvent-free conditions [26], the Beckmann rearrangement of ketoxime in dried  $\text{CH}_3\text{CN}$  [27] and transesterification of  $\beta$ -ketoesters in ionic liquid [28]. We further report here a practical procedure for protection of various carbonyl compounds by the formation of acetals or ketals in the presence of catalytic amount of sulfamic acid as depicted in Scheme 1.

\* Corresponding author. Fax: +86 931 8277088.  
E-mail address: [limy@lzb.ac.cn](mailto:limy@lzb.ac.cn) (L. Yang).



Scheme 1. Sulfamic acid catalyzed formation of acetals or ketals.

## 2. Experimental

### 2.1. Materials and reagents

All solvents and chemicals used were commercially available and used without further purification. Butanone, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, 4-nitrobenzaldehyde, 4-hydroxybenzaldehyde, hexanal, neopentyl glycol, 2,3-butandiol, 1,3-propanediol and 2-pyridinecarboxaldehyde were purchased from Aldrich. Diisobutylketone, piperonal, vanillin, benzyl methyl ketone, crotonaldehyde were bought from Acros Organics. 2-Furaldehyde, benzaldehyde, sulfamic acid, ethylene glycol, acetophenone, cinnamaldehyde, 1,2-propanediol, cyclohexanone, cyclopentanone, 2-mercaptoethanol and pentaerythritol were obtained from Shanghai Chemicals Co. Toluene was distilled over sodium-benzophenone prior to use.

### 2.2. Acetalization or ketalization of carbonyl compounds with diols

All the reactions (Scheme 1) were performed in a 25 mL round-bottom flask equipped with a magnetic stirrer and a distillation condenser. For a typical experiment, 0.29 g sulfamic acid (3 mmol) and benzaldehyde (20 mmol) were put into 15 mL toluene, and 24 mmol neopentyl glycol were successively charged into the reactor. Then the content was stirred for 4 h at 110 °C. After the desired reaction time, the reaction mixture was cooled to room temperature (15 °C). The solid sulfamic acid was separated by filtration, and could be reused

for the next run after simple treatments including washing with toluene (1 mL  $\times$  2) and drying under air.

### 2.3. Qualitative and quantitative analysis

The qualitative analysis of liquid reaction mixture was carried out on a Hewlett-Packard 6890/5793 GC/MS system equipped with a HP 5MS column (30 m) with helium as carrier gas. The column temperature was raised from 80 to 260 °C at a heating rate of 10 °C min<sup>-1</sup>.

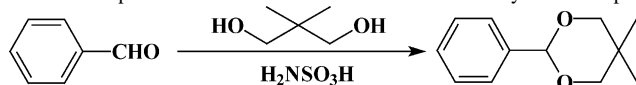
The quantitative analysis of the extract solution was carried out on a temperature-programmed Hewlett-Packard GC-5790 apparatus equipped with a  $\phi 3 \times 3000$  mm PTFE column. The concentration of reactant and product was directly given by the system of GC chemstation according to the area of each chromatograph peak.

## 3. Results and discussion

### 3.1. Optimization of reaction conditions

Initially, neopentyl glycol has been used to react with benzaldehyde over sulfamic acid catalyst in toluene solution, and the results are listed in Table 1. When equivalent amount of benzaldehyde and neopentyl glycol was used, the conversion of benzaldehyde was unsatisfactory (entry 1). For the improvement of benzaldehyde conversion, slightly excess alcohol must be used. When the ratio of neopentyl glycol to benzaldehyde increased from 1.0 to 1.2, conversion of benzaldehyde correspondingly increased from 77% to 97% (entry 2). When the reaction time was shortened to 3 h or 10 mmol% sulfamic acid dosage was used, the conversions were only 84% and 87%, respectively (entries 3 and 5). The subsequent condition optimization experiments revealed that both the 4 h reaction time and 15 mmol% catalyst dosage were necessary to complete the reaction. Further prolongation of reaction time and increase in the catalyst dosage seems to be ineffective for the improvement of the acetalization

Table 1  
Conditions optimization of the reaction between benzaldehyde and neopentyl glycol over sulfamic acid<sup>a</sup>



Entry	Benzaldehyde/neopentyl glycol (M/M)	Amount of sulfamic acid (%)	Reaction time (h)	Reaction temperature (°C)	Concentration (%)	Selectivity (%)
1	1:1	15	4	110	77	~100
2	1:1.2	15	4	110	97	~100
3	1:1.2	10	4	110	84	~100
4	1:1.2	20	4	110	97	~100
5	1:1.2	15	3	110	87	~100
6	1:1.2	15	5	110	98	~100
7	1:1.2	15	4	80	68	~100
8	1:1.2	15	4	50	42	~100

<sup>a</sup> Reaction conditions: benzaldehyde, 2.12 g (20 mmol); toluene, 15 mL.

reaction (entries 4 and 6). When the reaction was conducted at 80 or 50 °C, the benzaldehyde cannot be completely consumed and the conversions were only 68% and 42%, respectively (entries 7 and 8). Thus, the optimized conditions should be 1.2 for the ratio of neopentyl glycol to benzaldehyde, 15 mmol% sulfamic acid, 4 h for the reaction time and 110 °C for the reaction temperature. It should be pointed out here, the selectivity to the desired acetalization product was close to 100% in any condition as shown in Table 1, indicating the specific activity of sulfamic acid for the acetalization reaction.

### 3.2. Sulfamic acid catalyzed reactions between various carbonyl compounds and neopentyl glycol


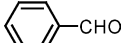
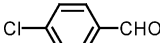

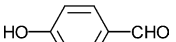
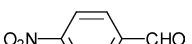
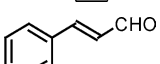
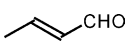
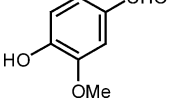
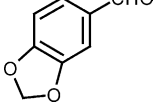
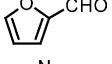
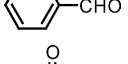
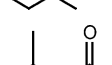
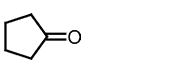


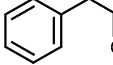
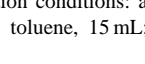
Various carbonyl compounds have been used as substrates to react with neopentyl glycol over sulfamic acid catalyst. The results in Table 2 clearly demonstrate that the method of protecting carbonyls using neopentyl glycol as protect reagent is efficient, with almost quantitative conversion and exclusive selectivity in most cases. The molar ratio of aldehyde or ketone to neopentyl glycol is 1:1.2. Hexanal reacted with neopentyl glycol in 99% conversion and 100% selectivity (Table 2, entry 1). Aromatic aldehydes, such as *p*-chlorobenzaldehyde, *p*-methoxybenzaldehyde, *p*-nitrobenzaldehyde, *p*-hydroxybenzaldehyde could also be acetalized to afford the corresponding 1,3-dioxolanes with 96%, 92%, 91% and 99% conversions respectively in the same conditions (entries 3–6). Cinnamaldehyde and crotonaldehyde were converted to the corresponding products without any damage of the double bond (entries 7 and 8). The ketalization reactions were also examined over the H<sub>2</sub>NSO<sub>3</sub>H system. The linear chain ketones such as butanone and diisobutyl ketone can also be converted to the corresponding ketals in moderate yields (entries 13 and 14). Cyclohexanone and cyclopentanone are also worked well, but the reactivity of cyclopentanone seems to be slightly lower than that of cyclohexanone (entries 15 and 16). When acetophenone and benzyl methyl ketone were used as substrates, the ketalization products were obtained in conversions of 84% and 70%, respectively (entries 17 and 18).

Protection of carbonyls with neopentyl glycol is also a useful tool for the heterocyclic compounds. 2-Furaldehyde and 2-pyridinecarboxaldehyde were consequently used as substrates in our system and the results are listed in Table 2. These two aldehydes have been successfully acetalized, and conversions of the two aromatic aldehydes were 96% and 81%, respectively (entries 11 and 12), further expanding the generality of this catalytic system to heterocyclic aromatic aldehydes.

In our system, many acid-labile substrates such as 4-methoxybenzaldehyde, cinnamaldehyde, crotonaldehyde, vanillin and piperonal all worked well (entries 4, 7–10). Especially, the reaction of nitrogen-containing substrates, for example, 2-pyridinecarboxaldehyde, which has been consid-

Table 2

Sulfamic acid catalyzed reaction between carbonyl compounds and neopentyl glycol<sup>a</sup>

Entry	Carbonyl compounds	Reaction time (h)	Concentration <sup>b</sup> (%)
1		4	99
2		4	97
3		4	96
4		4	92
5		4	91
6		4	99
7		4	95
8		4	85
9		4	97
10		4	99
11		6	96
12		10	81
13		8	89
14		8	68
15		6	89
16		6	96
17		8	84
18		8	70

<sup>a</sup> Reaction conditions: aldehyde or ketone, 20 mmol; neopentyl glycol, 24 mmol; toluene, 15 mL; sulfamic acid, 3 mmol; reaction temperature, 110 °C.

<sup>b</sup> The corresponding selectivities were all ca. 100%.

ered being very difficult over protonic acids or Lewis acids catalysts, because the acidic catalyst is readily trapped by nitrogen atom, can also be performed in the sulfamic acid system. These results indicated the usefulness of sulfamic acid as catalyst for the title reactions.

### 3.3. Sulfamic acid catalyzed reaction between carbonyl compounds and different protection reagents

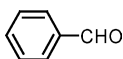
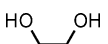
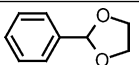
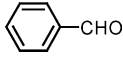
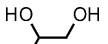
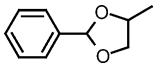
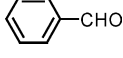
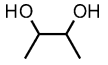
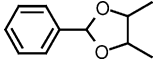
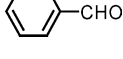
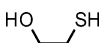
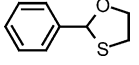
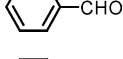
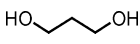
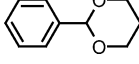
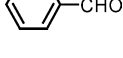
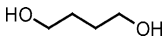
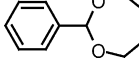
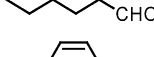
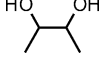
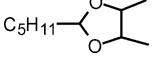
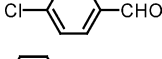
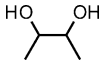
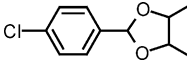

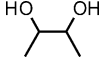
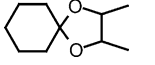
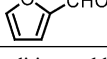
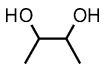
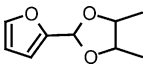
Table 3 shows the results of sulfamic acid catalyzed acetalizations between benzaldehyde and different protection reagents, including ethylene glycol, 1,2-propanediol, 2,3-butandiol, 1,3-propanediol, 1,4-butandiol and 2-mercaptoethanol. Under identical conditions, the conversions of benzaldehyde were increased as follows: 1,4-butandiol < 2-mercaptoethanol < ethylene glycol < 1,3-propanediol < 1,2-propanediol < 2,3-butandiol < neopentyl glycol. It should be pointed out here that selectivities to desired products are all close to 100% over the sulfamic acid catalyst. In consequent investigations, another diol, 2,3-butandiol, has been used as protection reagent of a variety of carbonyl compounds and the results are listed in Table 3. Conversions of 4-chlorobenzaldehyde, hexanal, cyclohexanone and 2-furaldehyde are all more than 90% after certain periods. These good results may profit from the hindrance of two methyl groups in 2,3-butandiol molecule.

### 3.4. Sulfamic acid catalyzed condensation of carbonyls and pentaerythritol

Like the acetalization or ketalization of carbonyl compounds, the reactions of carbonyl compounds with pentaerythritol to form the diacetals or diketals are also commonly used in the protection of carbonyls [29]. Many conventional acidic catalysts including mineral acid [30], solid acid or *p*-toluene sulfonic acid [31–33] are all examined; however, they suffered from disadvantages such as corrosion of equipment, the difficulty of catalyst separation from product and low activity. Here, sulfamic acid has subsequently been used as catalyst to evaluate the reactivity of carbonyl compounds with pentaerythritol.

Under our optimized conditions, the conversion of benzaldehyde was only 26% even at prolonged reaction time (Table 4, entry 1). In this reaction, the by-product, water, was formed in twofold amount of product; immediate removal of water should be helpful for the improvement of benzaldehyde conversion. Thus, this reaction was conducted at a round bottom flask equipped with a water separator under reflux conditions. Here, toluene was used as water-carrying reagent. The content was stirred vigorously for 4 h. GC analysis indicated that the conversion of substrate could be efficiently improved, and dibenzal-pentaerythritol was obtained in 84% benzaldehyde conversion and 96% selectivity (Table 4, entry 2). Under the same conditions, similar reactions of cyclohexanone

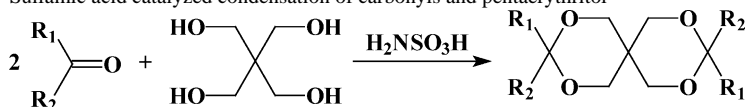
Table 3  
Sulfamic acid catalyzed reaction between carbonyl compounds and different protection reagents<sup>a</sup>

Entry	Carbonyl compounds	Protection reagents	Products	Reaction time (h)	Concentration <sup>b</sup> (%)
1				10	43
2				10	78
3				10	90
4				10	30
5				10	75
6				10	23
7				6	94
8				8	92
9				8	97
10				8	91

<sup>a</sup> Reaction conditions: aldehyde or ketone, 20 mmol; diol, 24 mmol; toluene, 15 mL; sulfamic acid, 3 mmol; reaction temperature, 110 °C.

<sup>b</sup> The corresponding selectivities were all ca. 100%.

Table 4  
Sulfamic acid catalyzed condensation of carbonyls and pentaerythritol<sup>a</sup>



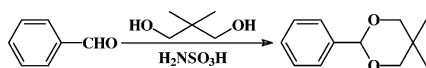
Entry	Carbonyl compounds	Reaction time (h)	Concentration (%)	Selectivity (%)
1		18	26	94
2		4	84	96
3		4	87	99
4		4	88	97

<sup>a</sup> Reaction conditions: aldehyde or ketone, 20 mmol; pentaerythritol, 12 mmol; toluene, 15 ml; sulfamic acid, 3 mmol; reaction temperature, 110 °C.

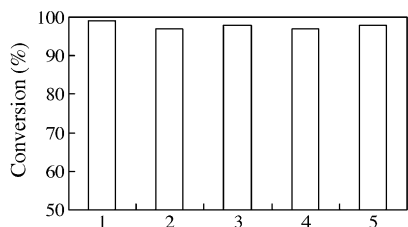
and hexanal with pentaerythritol occurred with comparative results (entries 3 and 4).

### 3.5. Recovery and reuse of sulfamic acid

One of special properties of sulfamic acid is immiscibility with non-polar organic compounds or solvents. Thus, recovery of catalyst is very convenient in sulfamic acid catalyzed reactions when a non-polar solvent was used as a medium. In the present acetalization and ketalization reactions, sulfamic acid seems to be a heterogeneous acid catalyst because it is insoluble in the reaction medium, toluene. After reaction, by cooling the reaction mixture to room temperature (15 °C), sulfamic acid catalyst was recovered by filtration. To rule out the possibility of catalyst leaching, the activity of the recovered catalyst in each reaction was investigated carefully. The experimental results revealed that sulfamic acid could be recycled in 99.9%. Therefore, loss resulting from catalyst leaching is negligible. In the condensation of benzaldehyde with neopentyl glycol, H<sub>2</sub>NSO<sub>3</sub>H could be reused for five times without visible loss of activity (Fig. 1).



(a)



(b)

Fig. 1. Recycling of sulfamic acid in the reaction between benzaldehyde and neopentyl glycol. (a) Reaction conditions: benzaldehyde, 20 mmol; neopentyl glycol, 24 mmol; toluene, 15 mL; sulfamic acid, 3 mmol; reaction temperature, 110 °C. (b) The corresponding selectivities were all ca. 100%.

## 4. Conclusion

Sulfamic acid has been used as an efficient and recyclable catalyst for acetalization and ketalization between carbonyl compounds and diols. After optimizing reaction conditions, various aldehydes and ketones were successfully converted to corresponding acetals and ketals using neopentyl glycol and 2,3-butandiol as protection reagents. Inexpensive, corrosive and stable catalyst, convenient operation and high selectivity to desired product are the features contained in the H<sub>2</sub>NSO<sub>3</sub>H system. Sulfamic acid showed a higher catalytic activity perfectly maintained after four recyclings. The simple procedures as well as easy recovery and reuse of this novel catalytic system are expected to contribute to the development of more benign acetalization and ketalization reactions.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [10.1016/j.molcata.2005.02.006](https://doi.org/10.1016/j.molcata.2005.02.006).

## References

- [1] T.W. Greene, *Protective Groups in Organic Synthesis*, Wiley/Interscience, New York, 1981, p. 2.
- [2] F.A.J. Meskens, *Synthesis* (1981) 501.
- [3] W.S. Johnson, C.A. Harbert, R.D. Stipanovic, *J. Am. Chem. Soc.* 90 (1968) 5279.
- [4] W.S. Johnson, C.A. Harbert, B.E. Ratcliffe, R.D. Stipanovic, *J. Am. Chem. Soc.* 98 (1976) 6188.
- [5] P.A. Bartlett, W.S. Johnson, J.D. Elliott, *J. Am. Chem. Soc.* 105 (1983) 2088.
- [6] A. Mori, H. Yamamoto, *J. Org. Chem.* 50 (1985) 5444.
- [7] K. Narasaka, M. Inoue, T. Yamada, J. Sugimori, N. Iwasawa, *Chem. Lett.* (1987) 2409.
- [8] D.M. Clode, *Chem. Rev.* 79 (1979) 491.
- [9] K.A.M. Walker, US Patent 4,150,153 (1979).
- [10] K. Bruns, J. Conrad, A. Steigel, *Tetrahedron* 35 (1979) 2523.
- [11] K. Narasaka, M. Inoue, T. Yamada, J. Sugimori, N. Iwasawa, *Chem. Lett.* (1987) 2049.

- [12] D. Li, F. Shi, J. Peng, S. Guo, Y. Deng, *J. Org. Chem.* 69 (2004) 3582.
- [13] H.H. Wu, F. Yang, P. Cui, J. Tang, M.Y. He, *Tetrahedron Lett.* 45 (2004) 4963.
- [14] J. Ott, G.M. Ramos Tombo, B. Schmid, L.M. Venanzi, G. Wang, T.R. Ward, *Tetrahedron Lett.* 30 (1989) 6156.
- [15] Z. Zhu, J.H. Espenson, *Organometallics* 16 (1997) 3658.
- [16] B.H. Lipschutz, D. Pollart, J. Monforte, H. Kotsuki, *Tetrahedron Lett.* 26 (1985) 705.
- [17] R.V. Hoffman, *Tetrahedron Lett.* (1974) 2415.
- [18] M. Cataldo, E. Nieddu, R. Gavagnin, F. Pinna, G. Strukul, *J. Mol. Catal.* 142 (1999) 305.
- [19] T.S. Jin, G. Sun, Y.W. Li, T.S. Li, *Green Chem.* 4 (2002) 255.
- [20] T.S. Jin, G. Sun, Y.W. Li, T.S. Li, *J. Chem. Res., Synop.* 1 (2003) 30.
- [21] J.T. Li, J.F. Han, J.H. Yang, T.S. Li, *Ultrason. Sonochem.* 10 (2003) 119.
- [22] R. Nagarajan, C.J. Magesh, P.T. Perumal, *Synthesis* (2004) 69.
- [23] P.R. Singh, D.U. Singh, S.D. Samant, *Synlett* (2004) 1909.
- [24] B. Wang, L.M. Yang, J.S. Suo, *Synth. Commun.* 33 (2003) 3929.
- [25] B. Wang, Y. Gu, W. Gong, Y. Kang, L. Yang, J. Suo, *Tetrahedron Lett.* 45 (2004) 6599.
- [26] B. Wang, Y. Gu, L. Yang, J. Suo, *Catal. Lett.* 96 (1/2) (2004) 71.
- [27] B. Wang, Y.L. Gu, C. Luo, T. Yang, L.M. Yang, J.S. Suo, *Tetrahedron Lett.* 45 (2004) 3369.
- [28] B. Wang, L.M. Yang, J.S. Suo, *Tetrahedron Lett.* 44 (2003) 5037.
- [29] (a) Y. Peng, G. Song, X. Qian, *Synth. Commun.* 31 (2001) 3735; (b) T. Jin, H. Wang, K. Wang, T. Li, *Synth. Commun.* 34 (2004) 2993.
- [30] S.F. Marrian, *Chem. Rev.* 43 (1948) 149.
- [31] Z.H. Zhang, T.S. Li, T.S. Jin, *J. Chem. Res. (S)* (1998) 640.
- [32] E. ConradW, B.D. Gesner, L.A. Levasseur, *J. Org. Chem.* 26 (1961) 3571.
- [33] S. Mager, M. Hom, I. Gro su, et al., *Monatsch Chem.* 120 (1989) 735.