

SO₃H-functionalized silica for acetalization of carbonyl compounds with methanol and tetrahydropyranylation of alcohols

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Abstract—Sulfonic acid group-functionalized amorphous silica acts as a highly effective and reusable catalyst for acetalization of various carbonyl compounds with methanol and tetrahydropyranylation of alcohols.

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Acetalization is one of the most useful protecting methods for carbonyl compounds. Dimethylacetals are popular protecting groups and are generally synthesized using *p*-toluenesulfonic acid (PTSA), triflic acid, and pyridinium salts.¹ These homogeneous catalysts present limitations due to the use of toxic and corrosive reagents, the tedious work-up procedure, and the necessity of neutralization of the strong acid media producing undesired wastes. Various heterogeneous catalysts (clays,² sulfonic resins,³ and zeolites⁴) have been employed for the dimethylacetal formation with trialkyl orthoformate. However, very few solid catalysts (Ce-exchanged clay⁵ and siliceous mesoporous silica⁶) can catalyze the acetalization with methanol. Protection of alcohols as tetrahydropyranyl (THP) ethers is also useful in organic synthesis, and generally protic and Lewis acids are used as homogeneous catalysts for this reaction.^{1a,7} From the environmental and economical standpoints, various solid catalysts such as clays,⁸ sulfonic resins,⁹ and zeolites¹⁰ were also reported. However, some of these procedures suffer due to a high catalyst to substrate ratio, a long reaction time and formation of side products.

Sulfonic acid-functionalized silica¹¹ can be an alternative to commercially available sulfonic resin, which suffer from low surface area and thermal stability. Although the catalytic applications of the resins for organic synthesis have been well established¹² relatively few examples have been reported on the use of sulfonic acid mesoporous silica for organic reactions.¹¹ As a part of an ongoing research on heterogeneous catalysis of the functionalized silica for clean synthesis,¹³ we present herein the sulfonic acid-functionalized amorphous silica (SO₃H–SiO₂) as a highly effective and reusable catalyst for acetalization of aldehydes and ketones with methanol and tetrahydropyranylation of alcohols.

Solvents and reagents were obtained from commercial sources and were used without further purification. SH-functionalized amorphous silica was prepared by sol–gel method. To the solution of ethanol (20 mL) with deionized water (15 mL), 44.8 mmol of tetraethylorthosilicate (Si(OEt)₄) and 3.55 mmol of 3-mercaptopropyltriethoxysilane were added, and the mixture was stirred at reflux temperature for 2 h. The wet gel was filtered and washed with ethanol, followed by drying in vacuo at 25 °C. The SH groups were converted into the sulfonic acid groups by an oxidation in a mixture of aqueous H₂O₂ (31%, 5 mL) and CH₃CN (30 mL) for 6 h at a reflux temperature. After filtration and washing with water and ethanol, the sample was then acidified in 0.1 M H₂SO₄ solution for 1 h, followed by washing with water until neutral pH, and by drying at 100 °C for 6 h. N₂ adsorption experiment confirmed a high surface area

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(632 m²/g) of the catalyst. Sulfur content of the sample, obtained by conventional elemental analysis, was 0.97 mmol g⁻¹ (C/S = 3.78). The number of H⁺ site of SO₃H–SiO₂ determined by acid-base titration^{11f} was 0.83 ± 0.05 meq g⁻¹. This value corresponds to about 86% of the sulfur content, indicating that most of the sulfur species on the sample are in the form of the sulfonic acid groups. Amorphous silica (Cab-O-Sil, 200 m² g⁻¹) was used for a comparison.

First, we show the acetalization of carbonyl compounds with methanol. When a solution of hydrocinnamaldehyde (2.5 mmol) in methanol (5 mL) is treated in the presence of a catalytic amount of SO₃H–SiO₂

(0.5 mol%, 13 mg) at room temperature in air for 20 h, a complete conversion of the aldehyde was attained. The acetal could be isolated with 79% yield after a simple filtration and washing of the catalyst with CH₂Cl₂, followed by evaporation of the solvent. No measurable by-products were observed by TLC, GC, and ¹H NMR analyses. A possible contribution of homogeneous catalysis was excluded as the following experiment. When the SO₃H–SiO₂ was removed at an early stage of the reaction (*t* = 30 min, 38% yield), the reaction did not proceed further, confirming that the heterogeneous catalysis of SO₃H–SiO₂. The amorphous silica did not catalyze the acetalization of hydrocinnamaldehyde after 24 h. As summarized in Table 1, SO₃H–SiO₂ was

Table 1. SO₃H–SiO₂ catalyzed acetalization of carbonyl compounds with methanol^a

Entry	Substrate	Time (h)	Product	Conv. (%) ^b	Yield (%) ^c
1		6		100	(85)
2 ^d		60		91	90
3 ^e		6		92	89
4		10		96	93 (75)
5		3		97	91 (88)
6		20		100	97 (79)
7		10		99	94
8		20		92	92
9		3		87	82
10		1		97	90
			R = H R = Cl		
11		3, 3 ^f , 3 ^g		90, 88 ^f , 90 ^g	90, 88 ^f , 87 ^g
12		1		93	87
13		12		91	91
			R=H R=But ^t		

^a Substrate (2.5 mmol), methanol (5 mL), catalyst (0.5 mol%) at 25 °C.

^b Conversions of carbonyl compounds determined by GC using *n*-dodecane (0.2 mmol) as an internal standard.

^c Yields determined by GC using internal standard method. Isolated yields are in parentheses.

^d 1-Butanal (50 mmol), methanol (50 mL), catalyst (0.01 mol%) at 25 °C.

^e 1-Butanal (50 mmol), methanol (50 mL), catalyst (0.01 mol%) at a reflux temperature.

^f Second cycle.

^g Third cycle.

applicable for the acetalization of a wide variety of aldehydes and some ketones. Using a small amount of the catalyst under mild and simple reaction conditions (at room temperature in air), aromatic aldehydes, a conjugated aldehyde, aliphatic aldehydes, and cyclic ketones underwent smooth transformation to the corresponding acetal in good yield. A linear ketone, 2-octanone, did not react at all (result not shown). After the first run for the acetalization of *p*-chlorobenzaldehyde, reusability of the $\text{SO}_3\text{H-SiO}_2$ was tested. The catalyst can be easily separated from the reaction mixture by a simple centrifugation, followed by washing with CH_2Cl_2 and by drying in vacuo at 298 K. The recovered $\text{SO}_3\text{H-SiO}_2$ catalyzed the reaction at least three times keeping good yields without any reactivation-treatment. An acid-sensitive 2-furancarboxaldehyde was converted to the corresponding dimethylacetal with 82% yield. The double bond in *d*-citroneral did not undergo isomerization during acetal formation. These results indicate that the reaction conditions are mild and not sufficiently acidic to cause side-reactions. It was reported that linear aldehydes were less reactive with Ce-exchanged clay⁵ and siliceous mesoporous silica⁶ at room temperature, resulting in low yields (below 34%). In contrast, $\text{SO}_3\text{H-SiO}_2$ catalyzed the acetalization of aliphatic aldehydes, including linear aldehydes, with good yields at room temperature (entries 1,2,4,5,6, and 8). Another advantage of $\text{SO}_3\text{H-SiO}_2$ is its high turnover numbers. Using a very small amount of the catalyst (0.01 mol%), the acetal yield for 1-butanal was 90% after 60 h, which corresponds to turnover numbers of 9000. To the best of our knowledge, this is the highest turnover numbers for the heterogeneously catalyzed acetalization of carbonyl compounds by methanol. At a reflux temperature, 1-butanal was converted to the acetal with 89% yield after 6 h, corresponding to the turnover frequencies of 1483 h^{-1} .

$\text{SO}_3\text{H-SiO}_2$ was also shown to be effective for the tetrahydropyranylation of various alcohols by 3,4-dihydro-2*H*-pyran (DHP) at room temperature (Table 2). For example, cyclohexanol was completely converted after 0.5 h by $\text{SO}_3\text{H-SiO}_2$ (0.5 mol%), and the THP ether was isolated with 88% yield after a simple filtration and washing of the catalyst with CH_2Cl_2 , followed by an evaporation. Note that the amorphous silica did not catalyze the reaction. The filtrate after the reaction for 5 min showed no catalytic activity, confirming the heterogeneous catalysis of the $\text{SO}_3\text{H-SiO}_2$. As shown in Table 2, primary, secondary, benzylic, allylic and acetylenic alcohols were converted to the corresponding THP ethers with good yields. The low acid strength of the catalyst and mild reaction conditions have not affected double or triple bonds during the reaction of allylic and acetylenic alcohols. The double bond in *d*-citronerol did not undergo isomerization during the reaction. For the syntheses of THP ether from allyl alcohol, $\text{SO}_3\text{H-SiO}_2$ was reused without any reactivation-treatment at least 4 times. The reaction of 1-hexanol (125 mmol) and 3,4-dihydro-2*H*-pyran (150 mmol) proceeded in the presence of only 0.01 mol% of $\text{SO}_3\text{H-SiO}_2$ in the solvent-free condition, and 82% yield and turnover numbers of 8200 were attained after 12 h. In

Table 2. $\text{SO}_3\text{H-SiO}_2$ catalyzed tetrahydropyranylation of alcohols^a

Entry	Substrate	Time (h)	Yield (%) ^b
1	1-Hexanol	1	93 (80)
2	1-Hexanol ^c	12	82
3	2-Octanol	1	91 (86)
4	Cyclohexanol	0.5	92 (88)
5	<i>p</i> -Methyl benzyl alcohol	0.5	92 (89)
6	Allyl alcohol	1	95, 94 ^d , 96 ^e , 95 ^f , 99 ^g
7	Propargyl alcohol	1	(78)
8	<i>d</i> -Citronerol	3	(87)
9	2-Hydroxyethyl acrylate	1	(82)
10	Benzhydrol	6	(81)

^a Alcohol (2.5 mmol), DHP (3 mmol), CH_2Cl_2 (5 mL), catalyst (0.5 mol%) at 25 °C.

^b Yields determined by GC using *n*-dodecane (0.5 mmol) as an internal standard. Isolated yields are in parentheses.

^c 1-Hexanol (125 mmol), DHP (150 mmol), catalyst (0.01 mol%) at 25 °C.

^d Second cycle.

^e Third cycle.

^f Fourth cycle.

^g Fifth cycle.

addition, $\text{SO}_3\text{H-SiO}_2$ can catalyze the deprotection of a THP ether. By stirring a mixture of the THP ether of 1-hexanol (2 mmol) in methanol (5 mL) with $\text{SO}_3\text{H-SiO}_2$ (0.5 mol%) at room temperature for 2 h, the THP ether was completely converted into 1-hexanol with 91% yield.

In conclusion, the present communication demonstrates that the sulfonic acid group-functionalized silica acts as a highly effective and reusable catalyst for acetalization of various carbonyl compounds with methanol and tetrahydropyranylation of alcohols. These methods do not require strict anhydrous condition, use of dehydrated reagents, nor catalyst pre-treatment. The high turnover numbers and applicability of the catalyst coupled with its environmentally friendly nature should make these methods particularly attractive.

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