Solid silica-based sulfonic acid as an efficient and recoverable interphase catalyst for selective tetrahydropyranylation of alcohols and phenols

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Abstract

Various types of alcohols and phenols are converted to the corresponding tetrahydropyranyl (THP) ether using a catalytic amount of solid silica-based sulfonic acid. The catalyst shows high thermal stability (up to 300 °C) and can be recovered and reused for at least eight reaction cycles without loss of reactivity.
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1. Introduction

The protection of hydroxyl function in alcohols is a common and versatile event in many syntheses of reasonable complexity and tetrahydropyranylation is one of the most frequently used method for this purpose [1]. THP groups are also the protecting group of choice in peptide, nucleotide, carbohydrate and steroid chemistry [2]. This transformation has been generally achieved using both protonic as well as Lewis acid catalyst. Consequently, a variety of reagents have been introduced for tetrahydropyranyl protection of alcohols such as *p*-toluene sulfonic acid (PTSA) [3], bis[trimethylsilyl]sulfate [4], $(CH_3)_3SiI$ [5], $CuCl_2$ [6], DDQ [7], $Ru(CH_3)_3(triphos)](OTf)_2$ [8], I_2 [9], $AlCl_3 \cdot 6H_2O$ [10], $In(OTf)_3$ [11], $ZrCl_4$ [12], $K_5CoW_{12}O_{40} \cdot 3H_2O$ [13], ionic liquids [14], $Bu_4N^+Br_3^-$ [15], and LiOTf [16]. A number of solid catalysts including K-10 clay [17], alumina impregnated with $ZnCl_2$ [18], silica chloride [19], and Ps-$AlCl_3$ [20] have also been developed for this purpose. Although,

these methods are quite useful in many synthetic transformations, many of them are associated with several drawbacks, which including long reaction time and harsh refluxing condition. Moreover the vast majority of these protocols call for expensive, moisture-sensitive, and unrecoverable catalysts. While the polymer-supported catalyst have been widely used in research and in process chemistry due to its easy recovery, but their use is also restricted because of easy damage of the organic backbone (thermal or chemical) [21]. One way to overcome this problem of the traditional polymer-supported catalysts is to change the expensive organic polymer chain to silica chain having a covalently anchored organic spacer to create organic–inorganic hybrid (interphase) catalysts [22]. In this type of solids, the reactive centers are highly mobile similar to homogeneous catalysts and at the same time it has the advantage of recyclability like the heterogeneous catalysts. Based on this idea, several types of sulfonic acid-functionalized silica has been synthesized and applied as an alternative to traditional sulfonic resins in catalyzing chemical transformations [23]. However, to the best of our knowledge there is no report on the use of these catalysts in tetrahydropyranylation of alcohols and phenols.

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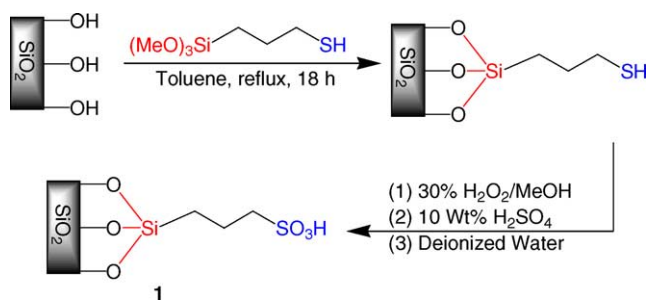
Scheme 1.

In this work, we wish to explore a new mild and efficient method for tetrahydropyranylation of a variety of alcohols and phenols using dihydro-4*H*-pyran (DHP) in the presence of a catalytic amount of solid silica-based sulfonic acid at room temperature. The preparation procedure of the catalyst **1** is outlined in Scheme 1 according to the known literature procedure with slight modification (see Section 2) [24].

Quantitative determination of the organic functional group covalently anchored onto the surface in catalyst **1** was performed with thermogravimetric analysis (TGA), acid–base titration and ion-exchange pH analysis. Typically a loading at ca. 0.35 mmol/g is obtained. When the washed sulfonated product **1** was placed in an aqueous NaCl solution, the solution pH dropped virtually instantaneously to pH ≈ 2, as ion exchange occurred between protons and sodium ions (proton exchange capacity: 0.33 mmol/g of sulfonic acid **1** which is in good agreement with the result obtained from TGA and titration, Fig. 1). This result also shows that more than 94% of the surface-bound thiol groups are converted to the corresponding sulfonic acid group.

2. Experimental

2.1. General remarks

Chemicals were either prepared in our laboratories or purchased from Merck, Fluka and Aldrich Chemical companies. All yields refer to isolated products unless otherwise stated. The products were characterized by comparison of their physical data with those of known samples or by their spectral data. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500 MHz spectrometer in $CDCl_3$ as the solvent and TMS as internal standard. Gas liquid chromatography (GLC) was carried out on a Varian Star CP-3800 gas chromatograph, using nitrogen as carrier gas and capillary CP-SIL-8-CB (25 m, 0.25 mm, 0.25 μm). All of the products are known and the isolated products gave satisfactory IR and NMR spectra.

2.2. Preparation of 3-mercaptopropylsilica (MPS)

Mesoporous amorphous silica gel (average pore diameter 60 Å) was activated by refluxing in concentrated hydrochloric acid (6 M) for 24 h and then washed thoroughly with the deionized water and dried before undergoing chemical surface modification. Refluxing the activated silica gel (10 g) with 3-mercaptopropyltrimethoxysilane (MPTMS, 5 mmol) in dry toluene for 18 h. The solid materials were filtered off and washed with hot toluene for 12 h in a continuous extraction apparatus (Soxhlet) and then dried in oven at 110 °C overnight to give the surface-bound thiol (MPS) group.

2.3. Preparation of solid silica-based sulfonic acid **1**

The thiol groups of the modified silica (MPS, 5 g) were oxidize with a 30% H_2O_2 solution (50 ml) and concentrated
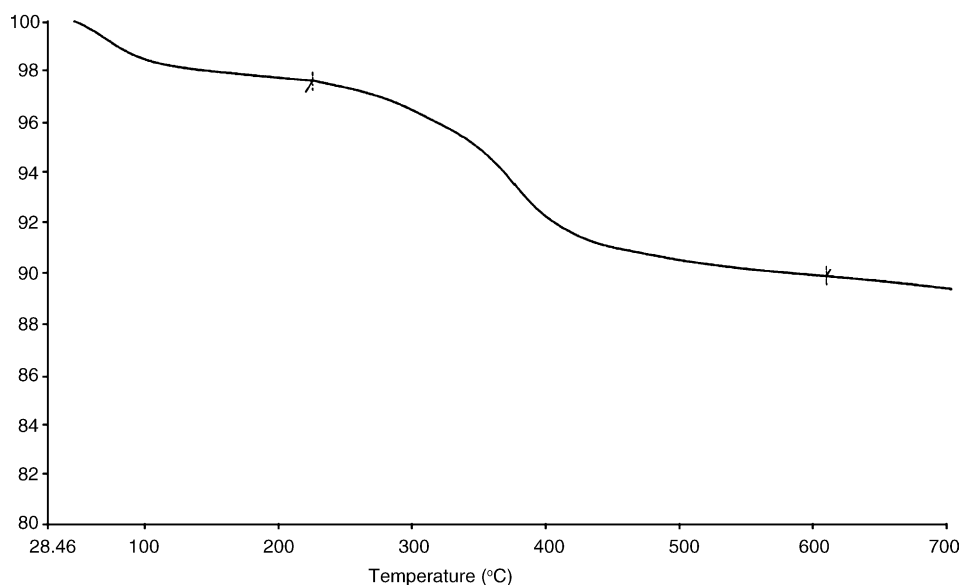

Fig. 1. TGA diagram for a sample of silica-based sulfonic acid under nitrogen stream.

H_2SO_4 (two drops) in methanol (15 ml) for 12 h at room temperature and the solid was filtered off and washed three times with deionized water (50 ml). In order to ensure that all the sulfonic acid groups were protonated, the solid was suspended in 10 wt.% H_2SO_4 solution (30 ml) for 4 h. The solid was then filtered off and washed thoroughly with deionized water and dried at 120 °C overnight.

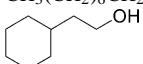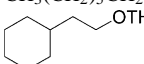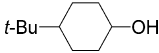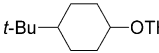### 2.4. General procedure for tetrahydropyranylation of alcohols
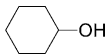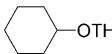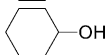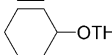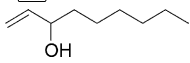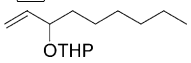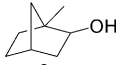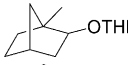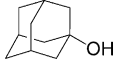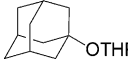
To a solution of alcohol (4 mmol) and DHP (4.8 mmol) in $CHCl_3$ (10 mL) the catalyst **1** (2 mol%, 0.244 g) was added. The reaction was stirred at room temperature for indicated time in Table 1 and during which the progress of the reaction monitored by TLC. After completion of the reaction, the reaction mixture was filtered off into a vessel containing dry Na_2CO_3. The catalyst was rinsed twice with small vol-

ume of $CHCl_3$ (2 × 15 ml), ethanol (10 ml), and ether (15 ml) and reused. Evaporation of the solvent in vacuo furnished the corresponding THP ether in good to excellent isolated yields (Table 1).

3. Results and discussion

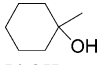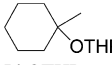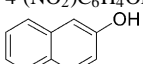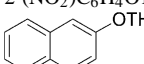To test the activity of **1** as a heterogeneous catalyst, we selected the tetrahydropyranylation of benzyl alcohol (1 equiv.) using DHP (1.2 equiv.) in $CHCl_3$ as a model reaction in the presence of the catalyst (2 mol%, 0.061 g). The reaction was almost completed within 15 min. After filtration of the reaction mixture, the catalyst was rinsed twice with small volume of $CHCl_3$ (2 × 15 ml), ethanol (10 ml), and ether (15 ml) and reused. Evaporation of the solvent in vacuo furnished the corresponding THP ether in 92% isolated yields (Table 1, entry 1), the purity of which was analyzed by GC to be more than 99% without any further purification.

Table 1
Efficient tetrahydropyranylation of alcohols and phenols in the presence of solid silica-based sulfonic acids

Entry	Substrate	Product	Time (min)	Yield (%)[a,b]
1	$PhCH_2OH$	$PhCH_2OTHP$	15	92
2	$2\text{-}(Me)C_6H_4CH_2OH$	$2\text{-}(Me)C_6H_4CH_2OTHP$	30	86
3	$4\text{-}(MeO)C_6H_4CH_2OH$	$4\text{-}(MeO)C_6H_4CH_2OTHP$	35	85
4	$4\text{-}(i\text{-}Pr)C_6H_4CH_2OH$	$4\text{-}(i\text{-}pr)C_6H_4CH_2OTHP$	35	89
5	$2,6\text{-}(Cl)C_6H_3CH_2OH$	$2,6\text{-}(Cl)C_6H_3CH_2OTHP$	50	93
6	$PhCH(OH)CH_3$	$PhCH(OTHP)CH_3$	55	94
7	$PhCH(OH)Ph$	$PhCH(OTHP)Ph$	100	96[c]
8	$PhCH_2CH_2CH_2OH$	$PhCH_2CH_2CH_2OTHP$	25	88
9	$PhCH_2CH_2OH$	$PhCH_2CH_2OTHP$	25	94
10	$CH_3(CH_2)_6CH_2OH$	$CH_3(CH_2)_5CH_2OTHP$	30	93
11	OH	OTHP	40	99[d]
12	*t*-Bu— OH	*t*-Bu— OTHP	35	93
13	OH	OTHP	40	85
14	OH	OTHP	15	40[e]
15	OH	OTHP	35	92
16	OH	OTHP	45	95[c]
17	OH	OTHP	45	93
18	OH	OTHP	85	95
19	$PhOH$	$PhOTHP$	40	89
20	$4\text{-}(Br)C_6H_4OH$	$4\text{-}(Br)C_6H_4OTHP$	45	94
21	$4\text{-}(NO_2)C_6H_4OH$	$2\text{-}(NO_2)C_6H_4OTHP$	45	91
22	OH	OTHP	50	94

[a] Yields refer to isolated pure product unless otherwise stated.

[b] All products gave satisfactory IR spectra.

[c] 1.5 equiv. DHP was used.

[d] GC yield.

[e] The reaction was carried out in the presence of the catalyst **1** until the conversion was 40% and at that point the solid was filtered off and the liquid phase was allowed to react.
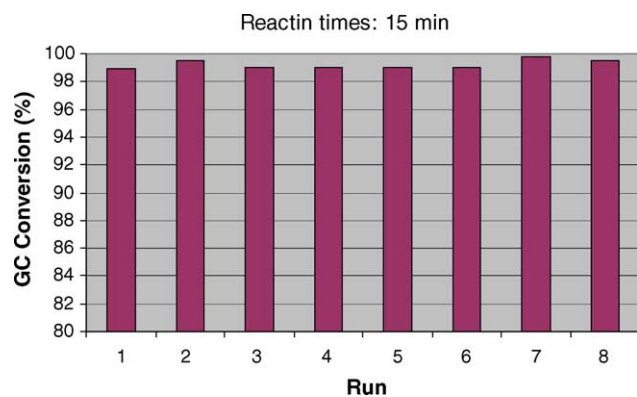
Fig. 2. Recyclability of solid silica-based sulfonic acid for the tetrahydropyranylation of benzyl alcohol.

Inspection of the data in Table 1 shows that the present protocol is quite general as a wide range of structurally diverse alcohols such as primary, secondary, hindered secondary, tertiary, benzylic, allylic, and phenolic underwent tetrahydropyranylation in good to excellent yields under mild reaction conditions. It is noteworthy that in the case of both allylic and tertiary alcohols no elimination product or isomerization of C=C bonds was detected (Table 1, entries 15 and 18).

To rule out the contribution of homogeneous catalysis in the results shown in Table 1, the reaction of cyclohexanol was carried out in the presence of the catalyst **1** until the conversion was 40% (15 min) and at that point the solid was filtered off. The liquid phase was allowed to react, but no further conversion was observed (Table 1, entry 14). However, one of the important points regarding the heterogeneous catalysts is their deactivation and reusability. To test this, a series of eight consecutive runs were carried out with same catalyst **1** sample, without noticeable decrease in the activity (>99%, Fig. 2).

This reusability demonstrates the high stability and turn over of solid silica-based sulfonic acid under operating condition. After using the catalyst **1**, the solid was simply filtered off, washed with CHCl$_3$, EtOH, and ether and reused.

In conclusion, this work shows that silica-based sulfonic acid, which can be prepared by simple operation from commercially available and relative cheap starting materials, efficiently catalyzes the tetrahydropyranylation of a variety of alcohols and phenols. The catalyst shows high thermal stability (up to 300 °C). It also could be recovered and reused for at least eight reaction cycles without noticeable loss of reactivity. Mild reaction condition, simplicity of the procedure, general applicability for primary through tertiary alcohols, offer improvement over many existing methods. Work on other applications of the catalyst **1** to other types of functional group transformations is ongoing in our laboratories.

3.1. 2-(4-Isopropylbenzyloxy)-tetrahydropyran

^{1}H NMR (500 MHz, CDCl$_3$, 25 °C, TMS): $\delta = 7.42$–7.45 (d, $J = 7.4$ Hz, 2H), 7.34–7.36 (d, $J = 7.4$ Hz, 2H), 4.76–4.81 (m, 1H), 4.70–4.73 (m, 2H), 3.45–4.20 (m, 2H), 2.85–2.90 (septet, $J = 7.1$ Hz, 1H), 1.52–1.97 (m, 6H), 1.27–1.29 (d, $J = 7.1$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C, TMS): $\delta = 147.11$, 136.10, 127.32, 127.12, 126.59, 126, 40, 86.47, 72.47, 63.78, 34.45, 32.17, 24.85, 24.40, 28.84, 20.11.

3.2. 2-(2,6-Dichlorobenzyloxy)-tetrahydropyran

^{1}H NMR (500 MHz, CDCl$_3$, 25 °C, TMS): $\delta = 8.13$ (s, 1H), 7.20–7.22 (d, $J = 8.5$ Hz), 7.12–7.16 (*pseudo*-t, $J = 8.5$ Hz), 1.98 (s, 6H); ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C, TMS): $\delta = 137.89$, 132.69, 130.43, 129.68, 125.50, 122.46, 85.41, 72.47, 63.70, 33.45, 33.47, 25.27, 25.38, 27.44, 20.38.

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