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A novel and highly efficient method for the silylation of alcohols with hexamethyldisilazane (HMDS) catalyzed by recyclable sulfonic acid-functionalized ordered nanoporous silica

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Abstract—Silylation of alcohols with hexamethyldisilazane (HMDS) in dichloromethane provides the corresponding silyl ethers in almost quantitative yields at room temperature using 1–3 mol % of sulfonic acid-functionalized silica. Additionally, the catalyst displays a high activity and thermal stability (up to 240 °C) and it can be easily recovered and reused for at least 20 reaction cycles without loss of reactivity.

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The role of silyl groups has already been recognized, of late, as an important part of organic chemistry from both analytical and synthetic point of views, especially as protecting groups in many syntheses of reasonable complexity.[1] Silyl ethers have a general stability for most non-acidic reagents and a high solubility in non-polar solvents. Silyl ethers, are commonly obtained by reaction of the parent alcohols with silyl halides or silyl triflates in the presence of stoichiometric amounts of a base such as imidazole,[2] 4-(*N*,*N*-dimethylamino)pyridine,[3] *N*,*N*-diisopropylethylamine,[4] Li_2S[5] and occasionally with a non-ionic super base catalyst.[6] However, these base-catalyzed silylation methods have serious disadvantages since careful extraction and filtration are required to remove ammonium salts derived from the reaction of by-product acids and co-bases during the silylation reaction.

On the other hand, hexamethyldisilazane (HMDS) is an inexpensive, commercially available, and stable compound that can be used for the preparation of trimethylsilyl ethers from hydroxy compounds. Its handling does not require special precautions, and the workup is not time-consuming, because the by-product of the reaction is ammonia, which is easily removed from the reaction medium. However, the main drawback of HMDS is its poor silylating power which needs forceful conditions and long reaction times in many instances.[7] Therefore, a variety of catalysts have been developed for activation of this reagent, such as $(CH_3)_3SiCl$,[8] sulfonic acids,[9] $ZnCl_2$,[10] K-10 montmorilonite,[11] $LiClO_4$,[12] tungstophosphoric acid ($H_3PW_{12}O_{40}$),[13] and special types of catalysts having the general formula X–NH–Y, in which at least one of X and Y is an electron-withdrawing group containing a CO, SO_2, or P=O moiety directly linked to the nitrogen atom and the other may be hydrogen, or X and Y together represent an electron-withdrawing group forming a cyclic system with the nitrogen atom.[7] Recently, iodine has also been used as an effective catalyst for the activation of HMDS in silylation reactions.[14a] In addition, a combination of hexamethyldisilazane and a catalytic amount of $[PdCl(\eta^3\text{-}C_3H_5)]_2$–$PPh_3$ was found to be effective for the trimethylsilylation of alcohols.[14b] Although these procedures provide an improvement, in many instances, long reaction times, drastic reaction conditions, or tedious workups are needed. Many of these reagents are moisture sensitive or expensive and cannot be reused. Hence, there is much room for the development of new protocols to circumvent these problems.

Increasing awareness of the environmental costs of traditional acid-catalyzed chemical transformations has created an opportunity for new solid acid-based

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Keywords: Solid acids; Protecting groups; Green chemistry; Solid sulphonic acid; Hexamethyldisilazane; Catalysts.

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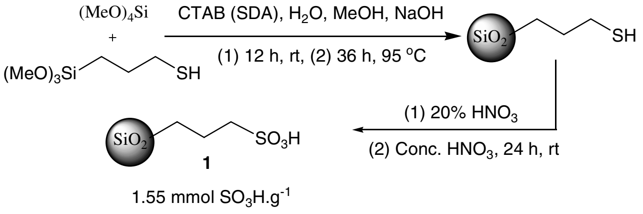
approaches for many important laboratory and industrial reactions.[15–19] Solid acids offer simpler and more environmentally benign alternatives than do their homogeneous counterparts. However, to maintain an economic viability, a suitable heterogeneous system must not only minimize the production of waste, but should also exhibit a high stability, activities, and selectivities comparable or superior to the existing homogeneous routes. Polymer-supported catalysts have been widely used in research and in process chemistry due to an easy recovery. However, their use is restricted because of easy damage to the organic backbone (thermal or chemical).[20] One way to overcome this problem of traditional polymer supported catalysts is to change the expensive organic polymer chain to a silica chain having a covalently anchored organic spacer to create organic–inorganic hybrid (interphase) catalysts.[21] In this type of solid, the reactive centers are highly mobile being similar to homogeneous catalysts and at the same time they have the advantage of recyclability of the heterogeneous catalysts. Based on this idea, several types of sulfonic acid functionalized silica have been synthesized and applied as alternatives to traditional sulfonic resins in catalyzing chemical transformations.[22] Among the different types of silica-based sulfonic acids, Stein and co-workers prepared a novel sulfonic functionalized ordered microporous silicate, which shows a high loading, a high stability, and yet a uniform nanostructure.[22j] We found that this solid sulfonic acid efficiently catalyzes the selective deprotection of alcoholic TBDMS ethers in the presence of phenolic TBDMS ethers.[23] However, to the best of our knowledge, there is no report on the use of this catalyst for the trimethylsilylation of alcohols.

The catalyst is prepared from a mixture consisting of (3-mercaptopropyl) trimethoxysilane (MPTS), tetramethoxysilane (TMOS), and cetyl trimethoxy ammonium bromide, (CTAB), as a template or structure directing agent (SDA). Extracted mercaptopropyl-MCM-41 was oxidized to the corresponding sulfonic acid derivative using HNO_3 as the oxidant (Scheme 1).[22j]

The organic composition of the solid sulfonic acid was quantitatively determined by thermogravimetric analysis (TGA) and ion exchange pH analysis.[24] Typically a loading of ca. 1.55 mmol/g was obtained.

In continuation of our studies on the catalytic properties of solid catalysts,[23,25] herein we disclose for the first time the use of a trace amount (1–3 mol %) of solid sulfonic acid **1** as a recyclable catalyst for highly efficient O-trimethylsilylation of a wide variety of alcohols and phenols using readily available hexamethyldisilazane HMDS (Scheme 2).



Scheme 1.

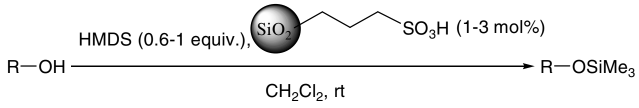
The feasibility of the reaction was initially examined with benzyl alcohol and hexamethyldisilazane. In this regard, we found that, when a mixture of benzyl alcohol (1 mmol), hexamethyldisilazane (0.6 mmol), and a small amount of solid sulfonic acid **1** (19 mg, 3 mol % of SO_3H groups), in dichloromethane was stirred for 55 min the corresponding silyl ether was obtained in a 99% GC yield (Table 1, entry 1).

This result led us to apply nearly similar reaction conditions for the silylation of other types of alcohols. Representative examples for the synthesis of various alcoholic TMS ethers are collected in Table 1. Thus primary alcohols (Table 1, entries 1–9 and 16) were readily transformed into the corresponding silyl ethers in high yields. This method is also efficient for the silylation of secondary alcohols (Table 1, entries 10–12 and 17–23). Phenol, $4\text{-}BrC_6H_4OH$, and 2-naphthol were also silylated in an efficient manner in excellent yields (Table 1, entries 13–15). In the case of tertiary alcohols, the yield of TMS ethers was rather lower and longer reaction times were required than for less sterically hindered substrates (Table 1, entries 24–26). It should be noted that, in the case of hindered tertiary alcohols, no elimination by-products were observed at all.

To show the effect of solid sulfonic acid **1**, the reaction of HMDS and benzyl alcohol was examined in the absence of the catalyst. However, this reaction remained incomplete and only 20% of the desired product was obtained after 2 h.

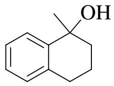
To demonstrate that the protection of alcohols catalyzed by **1** is really a heterogeneous process, the silylation of benzyl alcohol was carried out in dichloromethane in which the catalyst was filtered off at 50% conversion and the resulting clear solution stirred for an additional 2 h in the absence of the solid. No significant increase in the yield occurs after removal of the catalyst, thus indicating the solution does not contain any catalytically active species that could have leached from the solid to solution.

After performing one reaction under the conditions described in Table 1, the catalyst was recovered by filtration, washed with an aliquot of fresh MeOH and CH_2Cl_2, and then reused for a consecutive run under the same reaction conditions. Thus, after the first run, which gave the corresponding trimethylsilyl ether from benzyl alcohol in 100% conversion, after recovery, the catalyst was subjected to a second silylation reaction from which it also gave the silyl ether in 100% conversion; the average chemical yield for 20 consecutive runs



Scheme 2.

Table 1. Synthesis of trimethylsilyl ethers using nanoporous solid silica sulfonic acid (1–3 mol %) in dichloromethane at room temperature

Entry	Substrate	HMDS (mmol)	Cat. (mol %)	Time (min)	Yield[a,b] (%)
1	$PhCH_2OH$	0.6	2 (3)	80 (55)	100 (99)
2	$PhCH_2CH_2OH$	0.6	3	40	100
3	$PhCH_2CH_2CH_2OH$	0.6	3	70	98
4	$2\text{-}NO_2C_6H_4CH_2OH$	1	1	360	90
5	$2\text{-}MeC_6H_4CH_2OH$	0.7	3	70	98
6	$4\text{-}MeC_6H_4CH_2OH$	0.6	3	80	97
7	$4\text{-}ClC_6H_4CH_2OH$	0.6	3	75	95
8	$2\text{-}ClC_6H_4CH_2OH$	0.6	3	70	93
9	$2,4\text{-}(Cl)_2C_6H_3CH_2OH$	0.6	2	55	99
10	$PhCH(OH)CH_2CH_3$	0.8	3	40	99
11	PhCH(OH)Ph	0.6	3	60	98
12	1-Biphenyl-4-yl-ethanol	0.6	3	90	95
13	PhOH	1	1	120	90
14	$4\text{-}BrC_6H_4OH$	1	1	100	98
15	2-Naphthol	1	1	420	80
16	1-Heptanol	0.6	2	40	99
17	2-Heptanol	0.6	3	60	97
18	Cyclooctanol	0.6	3	35	98
19	Cyclohexanol	0.6	3	60	92
20	2-Methylcyclohexanol	0.6	3	60	90
21	4-*tert*-Butyl-cyclohexanol	0.7	1	90	92
22	2-*tert*-Butyl-5-methyl-cyclohexanol	1	3	60	100
23	2-Adamantanol	0.6	3	80	99
24	1-Adamantanol	0.7	3	240	85
				330	90
25	$(Ph)_3COH$	1	3	24 h	81
26		1	3	60	20
				270	35
				24 h	90

[a] GC Yields.

[b] All products gave satisfactory FT-IR spectra.

was 98.8%, which clearly demonstrates the practical recyclability of this catalyst (Fig. 1). This reusability demonstrates the high stability and turnover of solid silica based sulfonic acid **1** under the conditions employed. It should be noted that, the recyclability test was stopped after 20 runs.

A typical procedure for the protection of alcohols as the corresponding silyl ethers is as follows: To a solution of alcohol (1 mmol) and hexamethyldisilazane (0.6 mmol) in dichloromethane (3 mL), catalyst **1** (19 mg, 1–3 mol %) was added. The mixture was stirred at room temperature for the period of time indicated in Table 1. Reaction progress was monitored by TLC. After completion of the reaction, the product was isolated by filtration. Evaporation of the solvent under reduced pressure gave the corresponding silyl ether in good to excellent yields (Table 1).

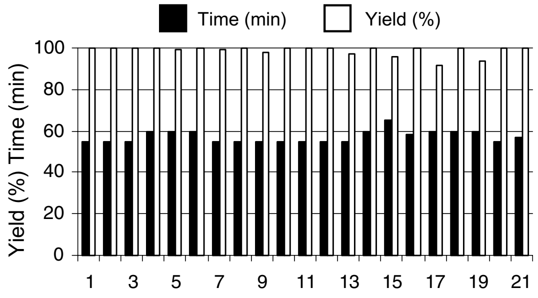


Figure 1. Recyclability of sulfonic acid **1** catalyst for the trimethylsilylation of benzyl alcohol.

In conclusion, sulfonic acid functionalized nanoporous silica **1**, which can be prepared simply from commercially available and relatively cheap starting materials, is an efficient, thermally stable (up to 240 °C), and recoverable catalyst for the silylation of alcohols in dichloromethane at an ambient temperature. The present procedure provides a novel, efficient, and recyclable methodology for the preparation of trimethylsilyl ethers in a high yield with an easy workup procedure. Additionally, by this method, bulky secondary, tertiary, and phenolic hydroxyl functional groups were protected in good to excellent yields. To the best of our knowledge, this protocol is the first example of silylation of alcohols using supported sulfonic acid in which the catalyst can be recovered and reused over several reaction cycles without considerable loss of reactivity. We are currently exploring further applications of this solid sulfonic acid for other types of functional group transformations in our laboratories.

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Supplementary data

The TGA diagram and the detailed experimental procedure for the preparation of solid sulfonic acid **1** are available online with this paper. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.030.

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