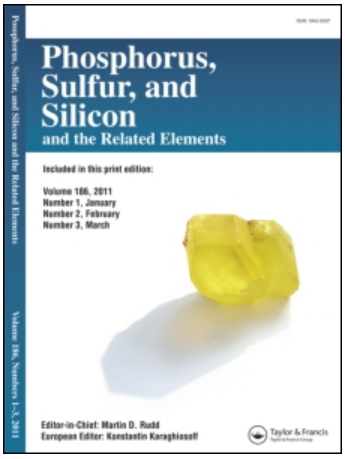

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A Mild, Simple, Efficient, and Selective Protection of Hydroxyl Groups Using Silica-Supported Sodium Hydrogen Sulfate as a Heterogeneous Catalyst

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A Mild, Simple, Efficient, and Selective Protection of Hydroxyl Groups Using Silica-Supported Sodium Hydrogen Sulfate as a Heterogeneous Catalyst

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A mild, simple, novel, and highly efficient method for the rapid protection of various primary, secondary, tertiary aliphatic alcohols, aromatic alcohols, and oximes using hexamethyldisilazane (HMDS) in the presence of silica-supported sodium hydrogen sulfate ($NaHSO_4$-SiO_2), as an active, inexpensive, nontoxic, heterogeneous, and readily available catalyst under ambient conditions is described. Timethylsilyl ethers were prepared in high to excellent yields, with short reaction times under mild and almost neutral reaction conditions at room temperature.

Keywords Alcohol; heterogeneous catalyst; hexamethyldisilazane; $NaHSO_4$-SiO_2; oxime; silylation

INTRODUCTION

Organic synthesis involving less environmentally unfriendly processes and under solvent-free conditions have been investigated worldwide due to stringent environment and economic regulations.[1] Toxic, homogeneous, corrosive liquid acid catalysts, such as H_2SO_4, HF, HBr, HCl, CF_3COOH, and complexes of BF_3, are frequently used in organic synthesis.[2] However, processes involving solid heterogonous catalysts are inherently associated with problems such as high toxicity, corrosive and polluting reagents, catalyst waste, difficulty in separation and recovery.[2] Replacement of these conventional acids by solid heterogeneous catalyst is desirable to achieve effective and catalyst

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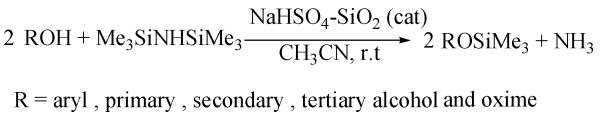
handling, product purification and to decrease waste production. [3] Considering the facts that most of the organic reagents involved in fine chemical synthesis are sensitive to harsh conditions, it is desirable to choose catalysts, which can catalyze organic transformations under mild conditions.[3]

The preparation of silyl ethers can be carried out by treatment of alcohols with silyl chlorides or silyl triflates in the presence of an organic base.[4–13] However, these methods have frequently suffered from drawbacks such as lack of reactivity or the difficulty in removal of amine salts.[6] 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) is a stable, commercially available, and inexpensive reagent for trimethylsilylation of hydrogen-labile substrates, giving NH_3 as the only by-product.[4–6] Even though the handling of this reagent is easy, the low silylation power of HMDS is the main drawback to its application; therefore, there are a variety of catalysts for activating of this reagent, such as $(CH_3)_3SiCl$,[14] zirconium sulfophenyl phosphonate,[15] $ZnCl_2$,[16] Envirocat EPZGO,[17] tungstophosphoric acid,[18] K-10 Montmorillionite,[19] iodine,[20] lithium perchlorate,[21] cupric sulfate pentahydrate, [22] H–β Zeolite,[23] $MgBr_2$,[24] lithium perchlorate suported on silica gel,[25] $Al(HSO_4)_3$,[26] $Al(OTF)_3$,[27] magnesium triflate,[28] copper triflate,[29] silica sulfate,[30] silica chloride,[31] and SiO_2-$HClO_4$.[32]

However, in most of these cases, a long reaction time, drastic reaction conditions, accompanied with side reactions, such as etherification, oxidation, elimination, problem of corrosives, pollution or tedious work-up have been observed. In addition, many of these reagents are moisture sensitive or expensive. The lack of a facile and effective synthetic methodology in many of these reports for the silylation of hydroxyl groups prompted us to develop a convenient and practical procedure for the protection of hydroxyl groups in the presence of silica-supported sodium hydrogen sulfate as catalyst at room temperature. In the present research for functional group transformation, we wish to describe a new protocol for the mild and rapid trimethylsilylation of a wide variety of hydroxyl groups using HMDS, and a catalytic amount of silica-supported sodium hydrogen sulfate at room temperature. Silica-supported sodium hydrogen sulfate is an active catalyst, inexpensive, readily available, nontoxic, safe, easy to handle, environmentally benign with fewer disposal problems (Scheme 1).

RESULTS AND DISCUSSION

To optimize the reaction conditions, initially, we converted benzyl alcohol (1mmol) to its corresponding benzylsilylether with the amount of



SCHEME 1

silica-supported sodium hydrogen sulfate as catalyst and HMDS (0.7 mmol) in the presence of various solvents and also solvent-free conditions at room temperature (Table I).

The results in Table I show that amongst these solvents, acetonitrile was the solvent of choice in terms of time. Thus, we prepared a range of silylethers under the optimized reaction conditions: hydroxyl compound (1 eq), HMDS (0.7 eq), $NaHSO_4$-SiO_2 (0.28 eq), and acetonitrile (2 mL) (Table II).

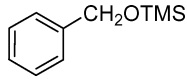
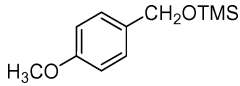
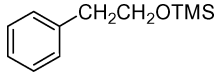
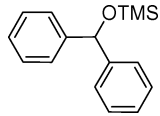
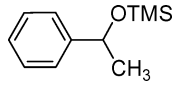
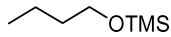
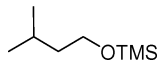
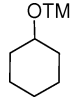
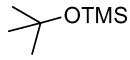
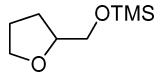
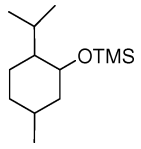
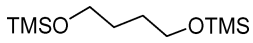
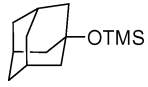
A wide range of various alcohols and oximes underwent silylation by this procedure to provide the corresponding TMS ethers in good to excellent isolated yields (Table II, Entries 1–16). Benzylic alcohols and primary alcohols generally are protected faster than secondary and tertiary alcohols. Trimethylsilylation of aldoxime and ketoxime also produce the corresponding trimethylsilylated compounds at these conditions (Table II, Entries 17–19), whereas thiophenol, 1,3-propane ditiol (Table II, Entries 20, 21), aniline and phthalimide (Table II, Entries 22, 23) were intact under the reaction conditions. Generally, in all cases, the reaction of benzyl, primary, secondary, tertiary alcohols, and oximes were completed within less than 47 min, accompanied by evolution of NH_3 gas from the reaction mixture. Inspection of the data in Table II clearly shows that different types of hindered secondary and

TABLE I Silylation of Benzyl Alcohols with HMDS in the Presence of Solid $NaHSO_4$-SiO_2 as Catalyst Under Solvent and Solvent-Free Condition at Room Temperature

Entry	Solvent[a]	Molar ratio Substrate/HMDS/Catalyst	Time (min)	GC Yield (%)
1	Dichloromethane	1/0.7/0.28	10	100
2	Chloroform	1/0.7/0.28	7	100
3	Ethyl acetate	1/0.7/0.28	7	100
4	n-Hexane	1/0.7/0.28	10	100
5	Solvent-Free	1/0.7/0.28	45	100
6	Diethyl ether	1/0.7/0.28	10	100
7	Acetonitrile	1/0.7/0.28	2	100

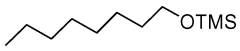
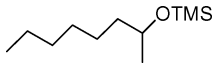
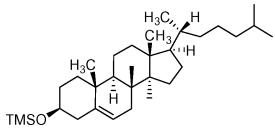
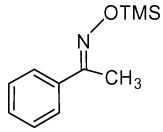
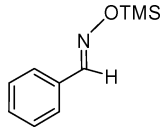
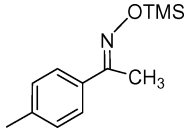
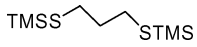
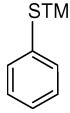
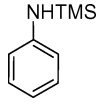
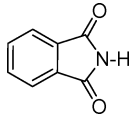
[a] The amount of solvent was chosen to 2 mL.

TABLE II Silylation of Alcohols and Oximes with HMDS in the Presence of $NaHSO_4$-SiO_2 as Catalyst (0.28 mmol, 0.05 g) in Acetonitrile Under Ambient Conditions

Entry	Product	Ratio Substrate/HMDS	Time (min)	Yield (%)[a]
1		1/0.7	2	93–97[b]
2		1/0.7	2	97
3		1/0.7	4	95
4		1/0.7	17	96
5		1/0.7	16	94
6		1/0.7	10	85
7		1/0.7	10	87
8		1/0.7	43	98
9		1/0.7	45	88
10		1/0.7	15	91
11		1/0.7	45	97
12		1/1.3	12	87
13		1/0.7	47	97

(Continued on next page)

TABLE II Silylation of Alcohols and Oximes with HMDS in the Presence of $NaHSO_4$-SiO_2 as Catalyst (0.28 mmol, 0.05 g) in Acetonitrile Under Ambient Conditions *(Continued)*

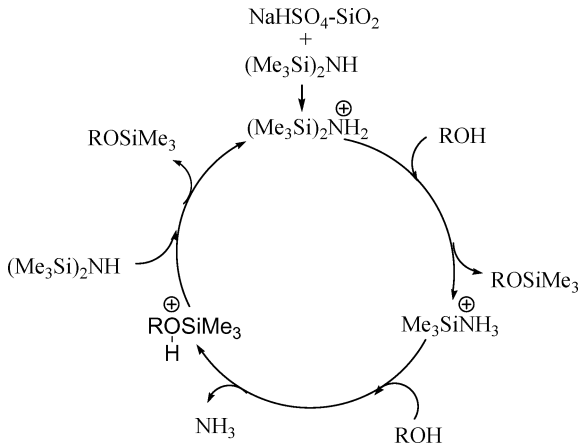
Entry	Product	Ratio Substrate/HMDS	Time (min)	Yield (%)[a]
14		1/0.7	10	93
15		1/0.7	40	94
16		1/0.7	45	97
17		1/0.7	11	92
18		1/0.7	10	95
19		1/0.7	10	89
20		1/1.3	45	—
21		1/0.7	45	—
22		1/0.7	45	—
23		1/0.7	45	—

[a]Yields refer to pure isolated products. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.[14–32b] Yields after three time recovery of catalyst.

tertiary alcohols were successfully converted to the corresponding silyl ethers under the same experimental conditions (Table II).

We also investigated selective silylation of different binary mixture of alcohols (Table III). This method was shown to be highly selective for primary alcohols such as benzyl alcohols and 1-octanol compare to secondary and tertiary alcohols (Table III, Entries 1–5). The primary alcohols were completely converted to the corresponding silylether, while the secondary alcohols were converted to the corresponding silylated product with 1–17% yield. Excellent selectivity was also observed for the conversion of primary and secondary alcohols in the presence of tertiary alcohols such as adamantanol (Table III, Entries 4–6).

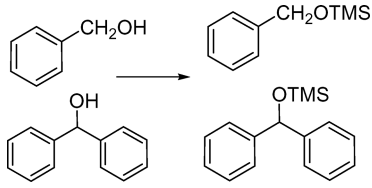
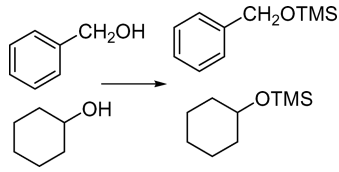
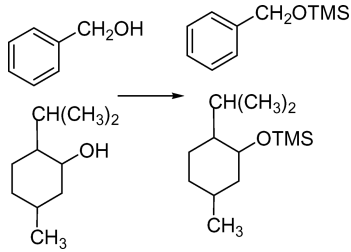
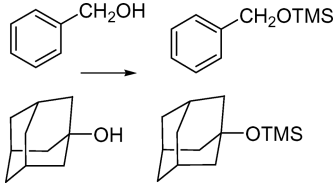
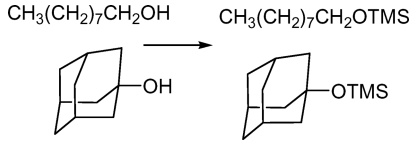
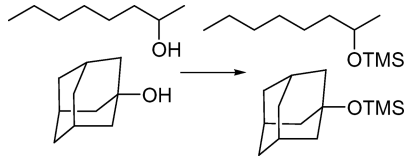
The proposed mechanism of the silica-supported sodium hydrogen sulfate catalyzed silylation of hydroxyl groups is shown in Scheme 2.



SCHEME 2

The reusability of the catalysts is one of the most important benefits and makes them useful for commercial applications. Thus, the recovery and reusability of $NaHSO_4$-SiO_2 was investigated. The recyclability amount of the catalyst in the reaction of benzyl alcohol and HMDS using $NaHSO_4$-SiO_2 was checked (Table II, Entry 1). After the reaction was complete, the catalyst was filtered out and can be reused after washing with ethyl acetate and drying at 100°C. The recovered catalyst was obtained in excellent yield and it was used in the mentioned reaction for three times. It showed the same activity such as fresh catalyst without any loss of its activity and converted benzyl alcohol to the desired TMS ether in excellent yields (93–97%).

TABLE III Selective Silylation of Different Binary Mixture of Alcohols

Entry	Substrate→Product Binary mixture	Molar Ratio Sub 1/Sub 2 /HMDS/Catalyst	Time (min)	GC Yield (%)
1		1/1/0.7/0.28	10	100 1
2		1/1/0.7/0.28	10	100 17
3		1/1/0.7/0.28	10	100 13
4		1/1/0.7/0.28	10	100 2
5		1/1/0.7/0.28	10	100 4
6		1/1/0.7/0.28	10	100 6

EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. $NaHSO_4$-SiO_2 was prepared according to the reported procedure.[33] All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (IR,^{1}H NMR spectra). The NMR spectra were recorded on a Bruker Avance DPX 300 and 500 MHz instrument. The spectra were measured in $CDCl_3$ relative to TMS (0.00 ppm). GC analysis was run with Shimadzu GC-14A. IR spectra were recorded on a JASCO FT-IR 460plus spectrophotometer. TLC was performed on Silica-gel polygram SIL G/UV 254 plates.

General Procedure for Trimethylsilylation of Hydroxyl Compounds Using $NaHSO_4$-SiO_2 as Catalyst

To a stirred solution of alcohols or oximes (1 mmol), HMDS (0.7 mmol), and acetonitrile as solvent (2 ml), $NaHSO_4$-SiO_2 (0.28 mmol, 0.05 g) was added at room temperature and the mixture was stirred at appropriate time (Table II). The reaction was followed by TLC (n-hexane–EtOAc, 9:1). After completion reaction, the catalyst was filtered and separated catalyst was washing with ethyl acetate and drying at 100°C. Silica gel (2 g) was added to the filtrate solution and the solvent was evaporated at reduced pressure. The resulting solid material was purified by a short column chromatography using n-hexane (2×10 mL) as eluent. Evaporation of the solvent under reduced pressure gave pure product(s) in high to excellent yield (Table II).

The desired pure product(s) was characterized by comparison of their physical data with those of known compounds.[14–32]

CONCLUSION

In conclusion, an efficient method for the protection of alcohol and oximes using HMDS under mild and ambient conditions is described. Simple work-up procedure, including filtering the mixture through a short pad of silica gel column, followed by evaporation of the solvent and reusability of catalyst, is another advantage of this method.

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