Article

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Preparation of Nano Silica Supported Sodium Hydrogen Sulfate: As an Efficient Catalyst for the Trimethyl, Triethyl and *t*-Butyldimethyl Silylations of Aliphatic and Aromatic Alcohols in Solution and under Solvent-free Conditions

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Nano silica supported sodium hydrogen sulfate has been prepared by mixing $NaHSO_4$ with activated Nano silicagel. We wish to report a new method for the synthesis of trimethyl (TMS), triethyl (TES) and *t*-butyldimethyl silyl (TBS) ethers from benzylic, allylic, propargylic alcohols, phenols, naphtholes and some of phenolic drugs in the solution and under solvent-free conditions.

Keywords: Silyl ethers; Phenolic drugs; TMSCl; TESCl; TBSCl; Nano silica; $NaHSO_4$.

INTRODUCTION

Hexamethyldisilazane (HMDS) is considered as one of the most useful reagents for this protection due to its availability, cheapness and stability. Although HMDS has easy handling and requires no special precautions, the low silylating power is the main drawback to its application. A variety of catalysts have been reported to improve the silylating power of this reagent, such as zirconium sulphophenyl phosphonate,[1] K-10 montmorillonite,[2] $LiClO_4$,[3] chlorotrimethylsilane,[4] $ZrCl_4$,[5] silica chloride,[6] trichloroisocyanuric acid,[7] $Al(HSO_4)_3$,[8] 1,3-dibromo-5,5-diethylbarbituric acid,[9] $Fe(HSO_4)_3$,[10] and nitrogen ligand complexes of metal chlorides.[11] Although these procedures have been improved, most of them suffer from disadvantages such as long reaction times, forceful reaction conditions, low selectivity, tedious work-up and use of toxic or expensive reagents. Hence, introduction of new methods to circumvent these problems is still in demand.

Recently, the use of metal hydrogen sulfates in organic reactions has become the focus of research area.[12-16] In this paper, we investigated the applicability of nano silica instead of silica with Sodium hydrogen sulfate and use chlorosilane instead of HMDS in these reactions. We report an efficient method for the synthesis of silyl ethers of alcohols, phenols, naphtols and some of phenolic drugs with chlorosilanes in the presence of $NaHSO_4.SiO_2$ (nano)/Et_3N, both in solution and under solvent-free conditions (Scheme 1). Different types of alcohols and phenols were subjected to trimethyl, triethyl and *t*-butyldimethyl silylations using this method at room temperature and under completely heterogeneous reaction conditions (Tables 1-3).

Scheme 1 Preparation of silyl ethers with $NaHSO_4.SiO_2$ (nano)/Et_3N, in solution and under solvent-free condition

$$ROH + R'_3SiCl \xrightarrow{\text{A or B}} ROSiR'_3$$

A: $NaHSO_4.SiO_2$ (nano)/Et_3N/CH_3CN

B: $NaHSO_4.SiO_2$ (nano)/Et_3N/Solvent-Free

R': Me, Et, *t*-$BuMe_2$

EXPERIMENTAL

Synthesis of silyl ethers were carried out under dry argon to exclude oxygen and moisture from the reaction systems.

Materials: Chemicals were purchased from Fluka, Merk and Aldrich chemical companies. Different methods are used during multi-step synthesis to protect alcoholic hydroxyl groups such as trimethylsilylation, which is one of the most widely used methods for this purpose. All of trimethylsilyl ethers and some of triethylsilyl ethers and tert-butyldimethyl silyl ethers are known compounds, and were characterized by spectra analyses, comparisons with authentic samples (IR and NMR), and also by silica-gel polygram SILG/UV 254 plates.

Measurements: ^{1}H-NMR spectra were recorded on a Brucker 400 AC spectrometer in $CDCl_3$. The Infrared spectra were recorded on a Shimadzu FT IR-408 spectrophotometer.

General procedure for the preparation of silyl ethers in CH_3CN: To a mixture of the substrate (1 mmol), triethylamine (1 mmol) and $NaHSO_4.SiO_2$ (nano) (0.03 mmol) in CH_3CN (5 mL), chlorosilane (1 mmol) was added dropwise within 10 min with stirring at room temperature. After completion of the reaction, (TLC or GC), water was added (10 mL) and the organic layer was separated, dried ($MgSO_4$) and filtered. Evaporation of the solvent

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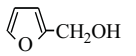
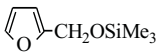
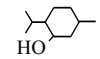
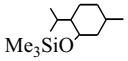
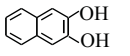
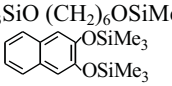
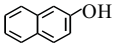
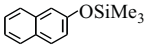
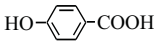
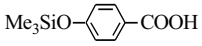
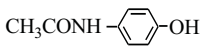
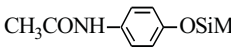
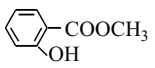
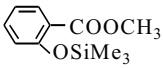
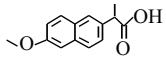
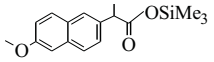
Table 1. Trimethylsilylation of aliphatic and aromatic alcohols in solution and under solvent-free conditions[a]

Entry	Substrate	Product	Silylation in CH_3CN		Solvent-free silylation	
			Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	$C_6H_5CH_2OH$	$C_6H_5CH_2OSiMe_3$	Fast	90	Fast	95
2	4-$BrC_6H_4CH_2OH$	4-$BrC_6H_4CH_2OSiMe_3$	12	85	6	80
3	4-$MeOC_6H_4CH_2OH$	4-$MeOC_6H_4CH_2OSiMe_3$	4	80	1	95
4	4-$NO_2C_6H_4CH_2OH$	4-$NO_2C_6H_4CH_2OSiMe_3$	Fast	90	Fast	95
5	C_6H_5OH	$C_6H_5OSiMe_3$	Fast	90	Fast	95
6	4-$NH_2C_6H_4OH$	4-$NH_2C_6H_4OSiMe_3$	10	90	10	90
7	4-$NO_2C_6H_4OH$	4-$NO_2C_6H_4OSiMe_3$	Fast	95	Fast	95
8	4-ClC_6H_4OH	4-$ClC_6H_4OSiMe_3$	7	90	7	90
9	$CH{\equiv}CCH_2OH$	$CH{\equiv}CCH_2OSiMe_3$	3	85	5	85
10	$CH_2{=}CHCH_2OH$	$CH_2{=}CHCH_2OSiMe_3$	8	90	3	95
11			5	80	1	80
12	CH_3OH	CH_3OSiMe_3	9	85	3	85
13	$C_6H_{11}OH$	$C_6H_{11}OSiMe_3$	5	80	5	85
14	$C_2H_5CH(OH)CH_3$	$C_2H_5CH(OSiMe_3)CH_3$	3	80	3	80
15	$(CH_3)_3COH$	$(CH_3)_3COSiMe_3$	3	98	2	98
16			Fast	90	Fast	90
17	HO $(CH_2)_6OH$	Me_3SiO $(CH_2)_6OSiMe_3$	10	80	5	80
18			5	85	5	85
19			5	80	5	90
20			15	90	9	90
21			Fast	80	Fast	80
22			1	98	1	98
23			1	95	1	95

[a] Product were characterized by their physical constant, IR, NMR and Mass spectroscopy. [b] Isolated yield.

gave under reduced pressure afforded the silylated compounds in high purity. Further purification was proceeded by vacuum distillation or recrystallization to afford the pure silyl ethers in good high yields.

General procedure for the preparation of silyl ethers under solvent-free conditions: Further purification was proceeded by vacuum distillation or recrystallization to afford pure silyl ether. A mixture of the substrate (1 mmol), triethylamine (1 mmol) and $NaHSO_4.SiO_2$ (nano) (0.03 mmol), chlorosilane (1 mmol) was stirred at room temperature. The progress of the reaction was monitored by TLC. Water (10 mL) was added and the mixture was extracted with diethyl ether (3 × 7 mL). The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave almost pure product(s).

Synthesis of silica nanoparticals: Ammonia solution 25% (750 μL, 10 mmol) and water (1.98 mL) were added into a 250 mL round bottom flask containing absolute methanol (100 mL). The solution is stirred for 10 min at room temperature. While stirring of the solution, tetraethoxysilane, TEOS (10.41 g, 500 mmol) was added dropwise. The final solution is stirred continuously for three days at ambient temperature. The particle size was examined under scanning electron microscopy (Fig. 1).

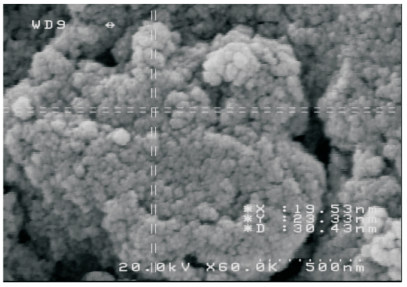
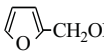
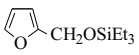
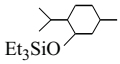
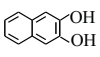
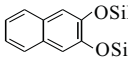
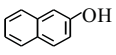
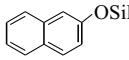
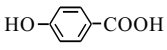
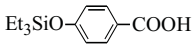
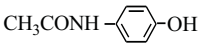
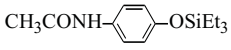
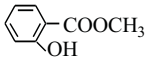
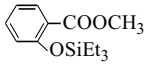
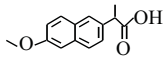
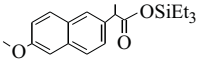


Fig. 1. The SEM image of silica nanoparticles.

Table 2. Triethylsilylation of aliphatic and aromatic alcohols in solution and under solvent-free conditions[a]

Entry	Substrate	Product	Silylation in CH_3CN		Solvent-free silylation	
			Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	$C_6H_5CH_2OH$	$C_6H_5CH_2OSiEt_3$	Fast	90	Fast	95
2	4-$BrC_6H_4CH_2OH$	4-$BrC_6H_4CH_2OSi\ Et_3$	7	85	7	85
3	4-$MeOC_6H_4CH_2OH$	4-$MeOC_6H_4CH_2OSi\ Et_3$	13	85	Fast	95
4	4-$NO_2C_6H_4CH_2OH$	4-$NO_2C_6H_4CH_2OSi\ Et_3$	Fast	95	Fast	95
5	C_6H_5OH	$C_6H_5OSi\ Et_3$	Fast	90	Fast	95
6	4-$NH_2C_6H_4OH$	4-$NH_2C_6H_4OSi\ Et_3$	15	90	13	90
7	4-$NO_2C_6H_4OH$	4-$NO_2C_6H_4OSi\ Et_3$	Fast	95	Fast	95
8	4-ClC_6H_4OH	4-$ClC_6H_4OSi\ Et_3$	7	90	Fast	95
9	$CH{\equiv}CCH_2OH$	$CH{\equiv}CCH_2OSi\ Et_3$	Fast	95	Fast	95
10	$CH_2{=}CHCH_2OH$	$CH_2{=}CHCH_2OSi\ Et_3$	5	95	Fast	95
11			1	90	Fast	80
12	CH_3OH	$CH_3OSi\ Et_3$	5	95	Fast	95
13	$C_6H_{11}OH$	$C_6H_{11}OSi\ Et_3$	2	90	2	90
14	$C_2H_5CH(OH)CH_3$	$C_2H_5CH(OSi\ Et_3)CH_3$	Fast	85	Fast	90
15	$(CH_3)_3COH$	$(CH_3)_3COSi\ Et_3$	Fast	90	Fast	95
16			Fast	90	Fast	90
17	HO $(CH_2)_6OH$	$Et_3SiO\ (CH_2)_6OSi\ Et_3$	Fast	90	Fast	90
18			Fast	80	Fast	80
19			Fast	85	Fast	85
20			20	90	5	95
21			1	80	Fast	80
22			1	95	Fast	98
23			1	95	1	95

[a] Product were characterized by their physical constant, IR, NMR and Mass spectroscopy. [b] Isolated yield.

Procedure for the preparation of sodium hydrogen sulfate onto silica nanoparticles: The silica nanoparticles suspension are precipitated with n-hexane and extracted through centrifugation (twice at 6000 rpm). Silica (1.016 g) was suspended in H_2O (5 mL) and the sodium hydrogen sulfate chloride (1.2 g, 0.01 mmol) was then added. The mixture was stirred for 1 day at ambient temperature. After drying of residue under vacuum at 110-115 °C, the Sodium hydrogen sulfate supported on silica nanoparticles was prepared.

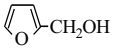
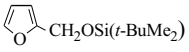
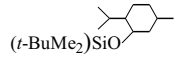
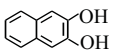
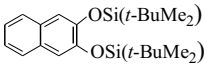
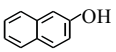
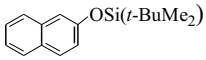
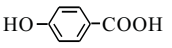
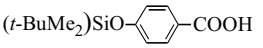
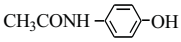
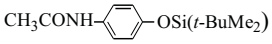
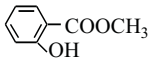
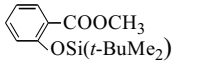
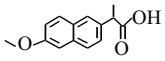
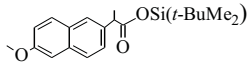
RESULTS AND DISCUSSION

At first $NaHSO_4.SiO_2$ (nano) is prepared by addition of silica nanoparticles to a solution of $NaHSO_4$ and water at room temperature. This reagent is stable and can be stored for several months without losing its activity. Next, the catalytic applicability of $NaHSO_4.SiO_2$ (nano) is examined for the protection of benzylic, allylic, propargylic alcohols, naphtholes and some of phenolic drugs in the presence of Et_3N in CH_3CN at room temperature. Reactions were completed after 1-100 min.

The SEM image of silica nanoparticles was obtained and compared with the SEM images of Nano silica supported sodium hydrogen sulfate. Comparing the SEM image of silica nanoparticles with Nano silica supported sodium hydrogen sulfate showed that the mean size of silica nanoparticles is smaller than Nano silica supported sodium hydrogen sulfate (Figure 2).

The protection of a wide range of alcohols such as primary, secondary, and hindered tertiary alcohols proceed efficiently with high yields (Tables 1-3 entries 13-15).

Table 3. Tert-butyldimethylsilylation of aliphatic and aromatic alcohols in solution and under solvent-free conditions[a]

Entry	Substrate	Product	Silylation in CH_3CN		Solvent-free silylation	
			Time (min)	Yield (%)[b]	Time (min)	Yield (%)[b]
1	$C_6H_5CH_2OH$	$C_6H_5CH_2OSi(t\text{-}BuMe_2)$	10	85	6	85
2	$4\text{-}BrC_6H_4CH_2OH$	$4\text{-}BrC_6H_4CH_2OSi(t\text{-}BuMe_2)$	13	80	10	80
3	$4\text{-}MeOC_6H_4CH_2OH$	$4\text{-}MeOC_6H_4CH_2OSi(t\text{-}BuMe_2)$	15	80	Fast	95
4	$4\text{-}NO_2C_6H_4CH_2OH$	$4\text{-}NO_2C_6H_4CH_2OSi(t\text{-}BuMe_2)$	5	80	5	90
5	C_6H_5OH	$C_6H_5OSi(t\text{-}BuMe_2)$	5	90	Fast	90
6	$4\text{-}NH_2C_6H_4OH$	$4\text{-}NH_2C_6H_4OSi(t\text{-}BuMe_2)$	6	90	6	95
7	$4\text{-}NO_2C_6H_4OH$	$4\text{-}NO_2C_6H_4OSi(t\text{-}BuMe_2)$	Fast	90	Fast	90
8	$4\text{-}ClC_6H_4OH$	$4\text{-}ClC_6H_4OSi(t\text{-}BuMe_2)$	10	85	10	95
9	$CH{\equiv}CCH_2OH$	$CH{\equiv}CCH_2OSi(t\text{-}BuMe_2)$	1	90	Fast	90
10	$CH_2{=}CHCH_2OH$	$CH_2{=}CHCH_2OSi(t\text{-}BuMe_2)$	5	95	Fast	95
11			15	85	1	90
12	CH_3OH	$CH_3OSi(t\text{-}BuMe_2)$	1	95	Fast	95
13	$C_6H_{11}OH$	$C_6H_{11}OSi(t\text{-}BuMe_2)$	10	85	Fast	90
14	$C_2H_5CH(OH)CH_3$	$C_2H_5CH(OSi(t\text{-}BuMe_2))CH_3$	5	95	Fast	95
15	$(CH_3)_3COH$	$(CH_3)_3COSi(t\text{-}BuMe_2)$	5	90	1	90
16			10	80	Fast	85
17	HO $(CH_2)_6OH$	$(t\text{-}BuMe_2)SiO$ $(CH_2)_6OSi(t\text{-}BuMe_2)$	10	80	Fast	90
18			5	90	Fast	95
19			5	95	Fast	95
20			1	80	Fast	90
21			1	80	Fast	80
22			5	95	1	95
23			3	90	1	95

[a] Product were characterized by their physical constant, IR, NMR and Mass spectroscopy. [b] Isolated yield.

Nano-SiO_2 particles have extremely high surface activity and porous structure. Hence, we expect that nano-SiO_2 can be used as an inorganic carrier to prepare this reagent. As shown in Tables, different type of alcohols, phenols and naphtholes, is efficiently converted to their corresponding TMS, TES and TBS ethers, with excellent yields under the selected conditions.

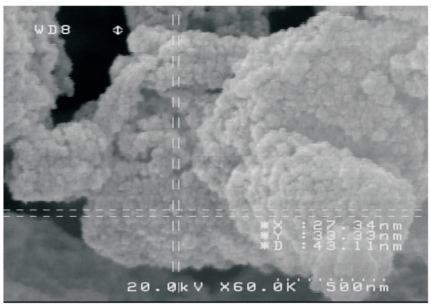


Fig. 2. The SEM image of sodium hydrogen sulfate supported on silica nanoparticles.

To improve our new method for functional group transformation, we have introduced ferric hydrogen sulafte as a new reagent system for the silylation of hydroxyl groups with HMDS.[10] Even though the activity of HMDS has been increased drastically in the presence of this reagent, the method suffers from limitations. With $Fe(HSO_4)$/HMDS, trimethylsilylation of alcohols and phenols in solution and under solvent-free conditions were performed at reflux and 90-100 ^oC, respectively.

In order to overcome these limitations, we conducted

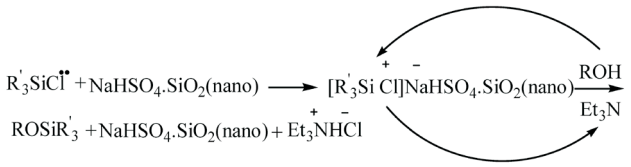
Table 4. Comparison of some of the results obtained by the present method (1) (Trimethylsilylation) with some of those reported by $Fe(HSO_4)_3$/HMDS (2)[10]

Entry	R1	(t/min)		(Yield %)	
		Silylation in CH_3CN		Solvent-free silylation	
		(1)	(2)	(1)	(2)
1	$C_6H_5CH_2OH$	(fast)(90)	(102)(70)	(fast)(95)	(15)(90)
2	4-$NO_2C_6H_4CH_2OH$	(fast)(90)	(24)(85)	(fast)(95)	(17)(90)
3	Menthol	(fast)(90)	(72)(70)	(fast)(90)	(42)(88)

the silylation reactions in the presence of $NaHSO_4.SiO_2$ (nano)/Et_3N with chlorosilanes instead of silazanes. In this way, not only trimethylsilylether but also other hindered silyl ethers such as triethylsilyl and *t*-butyldimethylsilyl ethers are synthesized. Since the reaction time and the yield of the products were not changed considerably by omitting the solvent, the need for the solvent is avoided and the work-up procedure became easier.

The mechanism of transformations is unclear and it seems that the Et_3N acts as a base and polarize the O-H bond in ROH, then chlorosilane reacts with $NaHSO_4.SiO_2$ (nano) as a Lewis acid to produce the silylating agent. A rapid reaction with ROH and the concomitant release of the corresponding silyl ether is a feature of this mechanism that is shown in Scheme 2. In order to show the efficiency of this method Table 4 compares some of the results with some those reported in the literature.

Scheme 2 The mechanism of preparation of silyl ethers with $NaHSO_4.SiO_2$ (nano) reagent



CONCLUSION

In conclusion, we demonstrated a mild and efficient method for the preparation of silyl ethers using nano silica supported sodium hydrogen sulfate. Excellent yields of the products, relatively short reaction times, simple and convenient procedure, mild and solvent-free reaction conditions are among the other advantages of the present method.

ACKNOWLEDGEMENTS

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17. Triethylsiloxy naphtalene, FT-IR (KBr) (ν_{max}; cm^{-1}) 3057,

2956, 1629, 1467, 1270, 1071, 874. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.83 (q, *J* = 7.9 Hz, 6 H, 3 CH_2), 1.03 (t, *J* = 7.6 Hz, 9 H, 3 CH_3), 7.18 (s, 2 H, Ar), 7.30 (q, *J* = 3.2 Hz, 2 H, Ar), 7.63 (q, *J* = 3.2 Hz, 2 H, Ar) ppm. Tert-butyldimethyl-siloxy phenyl amine, FT-IR (KBr) (ν_{max}; cm^{-1}) 3341, 3283, 2981, 1510, 1474, 1255, 1092, 902, 825. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.68 (s, 6 H, 2 CH_3), 0.89 (s, 9 H, 3 CH_3), 3.85 (s, 2 H, NH_2), 7.26 (d, *J* = 15.43, 2 H, ph), 7.45 (d, *J* = 15.43, 2 H, ph) ppm.

