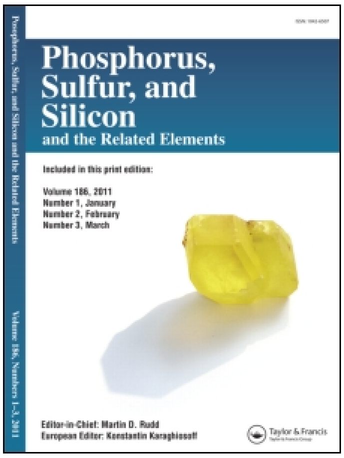

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A Mild and Efficient Method for Chemoselective Silylation of Alcohols Using Hexamethyldisilazane in the Presence of Silica Chloride

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A MILD AND EFFICIENT METHOD FOR CHEMOSELECTIVE SILYLATION OF ALCOHOLS USING HEXAMETHYLDISILAZANE IN THE PRESENCE OF SILICA CHLORIDE

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Reaction of alcohols with hexamethyldisilazane in the presence of silica chloride provides efficiently the corresponding trimethylsilyl ethers. This system discriminates absolutely amines and thiols from alcohols.

Keywords: Alcohol; chemoselective; hexamethyldisilazane; silica chloride; silyl ether

The utility of trimethylsilylation in organic synthesis is well recognized,[1–3] and the introduction of new reagents and the modification of existing ones is a continuous challenge. A large number of reagents and methods have been developed for the introduction of the trimethylsilyl group e.g. hexamethyldisiloxane,[4] allylsilanes,[5,6] chlorotrimethylsilane/lithium disulfide[7] and N-trimethyl-2-oxazolidinone[8] are examples.

One of the reported reagents for silylation is hexamethyldisilazane (HMDS)[9,10] which is a cheap and commercially available reagent. Its handling does not need special precaution, silylation using this reagnt is nearly neutral and the work-up of the reaction mixture is not time consuming. However, the main drawback of this reagent is its poor silylating power, which needs forceful conditions and long reaction times in many instances. Several methods have been developed to catalyze silylation with HMDS using for example $(Me)_3SiCl$,[11] sulfonic acids,[12]

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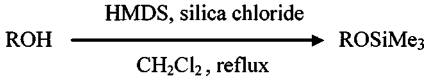
zirconium sulfophenyl phosphonate,[13] K-10 montmorilonite,[14] and nitrogen ligand complexes of methalchlorides.[15] Even though the activity of HMDS has been increased drastically, usually low selectivity, forceful conditions, and long reaction times have been observed in many of these reports.

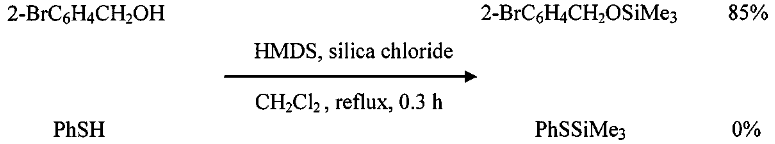
In continuation of our studies on the applications of silica chloride,[16–18] herein, we report a new protocol for the mild, efficient and chemoselective trimethylsilylation of alcohols using HMDS in the presence of silica chloride (Scheme 1). All reactions are performed in refluxing CH_2Cl_2 and under compeletly heterogeneous conditions in good to high yields (Table I).



$$\mathrm{ROH}\xrightarrow[\mathrm{CH_2Cl_2,\ reflux}]{\text{HMDS, silica chloride}}\mathrm{ROSiMe_3}$$

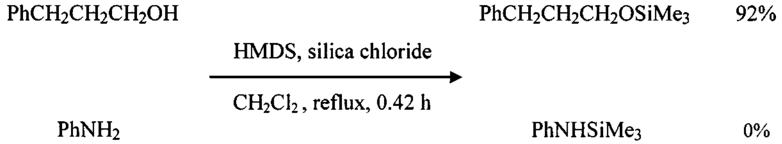
SCHEME 1

Phenols are silylated slower than alcohols with this method and the reaction is incomplete in most cases (Table I, entries 14–17). Amines and thiols did not undergo silylation with HMDS in the presence of silica chloride (Table I, entries 18–21). Thus, this methodology is suitable for the chemoselective silylation of alcohols in the presence of amines and thiols. The absolute chemoselectivity of this method is demonstrated by the silylation of 2-bromobenzyl alcohol and 3-phenyl-1-propanol in the presence of thiophenol or aniline (Schemes 2 and 3).



$$\begin{array}{c}\mathrm{2\text{-}BrC_6H_4CH_2OH}\\ \\ \mathrm{PhSH}\end{array}\xrightarrow[\mathrm{CH_2Cl_2,\ reflux,\ 0.3\ h}]{\text{HMDS, silica chloride}}\begin{array}{cc}\mathrm{2\text{-}BrC_6H_4CH_2OSiMe_3} & 85\%\\ \\ \mathrm{PhSSiMe_3} & 0\%\end{array}$$

SCHEME 2



$$\begin{array}{c}\mathrm{PhCH_2CH_2CH_2OH}\\ \\ \mathrm{PhNH_2}\end{array}\xrightarrow[\mathrm{CH_2Cl_2,\ reflux,\ 0.42\ h}]{\text{HMDS, silica chloride}}\begin{array}{cc}\mathrm{PhCH_2CH_2CH_2OSiMe_3} & 92\%\\ \\ \mathrm{PhNHSiMe_3} & 0\%\end{array}$$

SCHEME 3

TABLE I Silylation of Alcohols Using Hexamethyl-disilazane in the Presence of Silica Chloride

Entry	Substrate	Time (h)	Yileld%^{a,b}
1	2-Bromobenzyl alcohol	0.3	85
2	2-Chlorobenzyl alcohol	0.6	90
3	4-Chlorobenzyl alcohol	0.5	92
4	4-Methoxybenzyl alcohol	0.5	80
5	2-Methylbenzyl alcohol	0.6	90
6	1-Phenyl ethanol	2.5	87
7	Benzhydrol	5	90
8	1-Phenyl-2-propanol	0.7	95
9	3-Phenyl-1-propanol	0.42	92
10	Cyclohexanol	0.2	89
11	Cinnamyl alcohol	0.3	70
12	Benzoin	3.3	70
13	Furoin	1.8	80
14	Phenol	1	80
15	1-Naphthol	4	65
16	2-Naphthol	6.25	60
17	4′-Hydroxyacetophenone	5	50
18	Thiophenol	3.5	0^{c}
19	Toluene-2-thiol	3	0^{c}
20	Aniline	4	0^{c}
21	N-Methylaniline	4	0^{c}

[a] Isolated yields.

[b] Products were identified spectroscopically and also by the conversion of silyl ether to their corresponding alcohols.

[c] The starting material was recovered intact.

In conclusion, we have demonstrated a method for silylation of alcohols which has advantages in terms of yield, heterogeneous nature, chemoselectivity, low cost, availability of the reagents, and ease of work-up.

EXPERIMENTAL SECTION

General Procedure for Silylation of Alcohols

To a mixture of the substrate (1 mmol) and silica chloride (0.05 g) in CH_2Cl_2 (3 mL), HMDS (1 mmol) was added dropwise within 2 min with stirring under reflux condition. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure. To the resulting mixture, CCl_4 (10 mL) was added and filtered through a silica gel pad. The filter cake was washed with CCl_4(20 mL) and the filtrates were combined and evaporated to afford silylated compounds in high purity. Further purification proceeded by bulb to bulb distillation under reduced pressure which afforded the desired silyl ether in good to high yields.

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