

Communication

# Efficient and practical protocol for silylation of hydroxyl groups using reusable lithium perchlorate dispersed in silica gel under neutral condition

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## Abstract

A very efficient and mild procedure for the trimethylsilylation of a wide variety of alcohols, including primary, allylic, benzylic, secondary, hindered secondary, tertiary, and phenols with hexamethyldisilazane on the surface of silica gel dispersed with  $\text{LiClO}_4$  in room temperature at few minutes in excellent yields under neutral conditions is reported. This procedure also allows the excellent selectivity under LP-SiO<sub>2</sub> system for silylation of alcohols in the presence of amine and phenolic hydroxy groups.

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## 1. Introduction

Protection and deprotection of functional groups are indispensable in gradients of the synthesis of poly functional compounds, and several chemical conversions and multiple sequence syntheses often require protection of hydroxyl groups. The trimethylsilyl group is one of the most popular and widely used groups for protecting the hydroxyl function in synthetic organic chemistry and often is used in analytical chemistry to prepare silyl ethers as volatile derivatives of alcohols and phenols [1].

Several methods have been reported for this conversion, including the reaction of an alcohol with trimethylsilyl halides in the presence of a stoichiometric amount of a tertiary amine [2], with trimethylsilyl triflate and trimethylsilyl methallylsulfonates, which are more reactive than the chloride [3], allylsilanes in the presence of a catalytic amount of *p*-toluenesulfonic acid [3], iodine [4], trifluoromethanesulfonic acid [5],  $\text{Sc}(\text{OTf})_3$  [6], zinc chloride

[7], and tungstophosphoric acid [7c]. Hexamethyldisilazane (HMDS) is frequently used for the trimethylsilylation of hydroxyl groups. HMDS is an inexpensive and commercially available reagent. Its handling does not require special precautions, and the workup is not time-consuming, because the byproduct of the reaction is ammonia, which is simple to remove from the reaction medium. The low silylation power of HMDS is the main drawback to its application. Therefore, there are variety of catalysts for activating of this reagent, such as  $\text{I}_2$  [8],  $(\text{CH}_3)_3\text{SiCl}$  [9] and K-10 montmorillonite [10]. Recently, trimethylsilyl azide used as an efficient reagent for the silylation of hydroxyl group in neat conditions [11]. However, in most case a long reaction time, drastic reaction conditions, or tedious workup is needed. In addition, trimethylsilyl azide is expensive and toxic. The lack of a simple and general synthetic methodology for the silylation of hydroxyl group in alcohols and phenols under essentially neutral conditions, prompted us to develop an efficient, convenient, and practical procedure for the protection of hydroxyl groups at room temperature.

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## 2. Results and discussion

In recent years, the use of lithium perchlorate in diethyl ether (LPDE) as a medium has attracted attention due to the enhanced rate and selectivity to various organic transformations [12]. The LPDE provides a convenient medium to carry out reactions under neutral and easy work-up conditions. In continuation of our interest on the application of lithium perchlorate for various organic transformations [13], in this paper, we explore a very efficient, simple and practical method for the silylation of phenols and alcohols under neutral conditions. By using different reaction conditions for the silylation of an alcohol with HMDS, we found out that lithium perchlorate dispersed on silica gel (chromatography grade) in  $\text{CH}_2\text{Cl}_2$  in ratio of LP-SiO<sub>2</sub> (1:2 ratio, 1.0 g), HMDS (6 mmol), and ROH (10 mmol) at room temperature, is the best reaction conditions. Interestingly, reactions catalyzed by  $\text{LiClO}_4$  alone in the absence of silica in  $\text{CH}_2\text{Cl}_2$  or on the silica surface without  $\text{LiClO}_4$  are not complete and the yields are very low. On the other hand, in the case of solid alcohols, when the reaction is carried out under neat conditions, the mixture becomes extremely viscous and difficult to stir. Therefore, the reaction with silica gel and under solvent-free condition was not complete after long reaction time. Lithium perchlorate dispersed on silica gel in  $\text{CH}_2\text{Cl}_2$  (in the case of simple alcohols petroleum ether can be used) was used for the silylation of hydroxyl function for a variety of alcohols and phenols with simple and highly efficient reaction conditions. The results are summarized in Tables 1 and 2. Primary, secondary, tertiary, allylic, benzylic, hindered, acid sensitive alcohols and phenols can be converted to the cor-

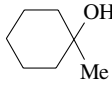
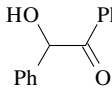
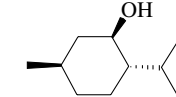
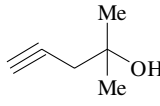
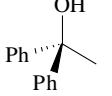
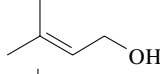
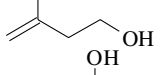
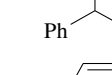
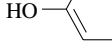
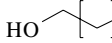

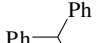

Table 1  
Silylation of alcohols and phenols with HMDS

$$\text{ROH} \xrightarrow[\text{CH}_2\text{Cl}_2, \text{ r.t.}]{\text{HMDS}(0.6 \text{ eq.}), \text{LiClO}_4\text{-SiO}_2} \text{ROSiMe}_3$$

Entry	ROH	Yield (%) <sup>a</sup>	Time (min)
1	1-Hexanol	96	5
2	Cyclohexanol	96	5
3	<i>tert</i> -Butanol	96	5
4	Allyl alcohol	95	5
5	Benzyl alcohol	98	5
6	4-Chlorobenzyl alcohol	97	5
7	4-Methoxy benzyl alcohol	92	5
8	Cinnamyl alcohol	95	5
9	1-Octanol	96	5
10	2-Octanol	94	5
11	Propargylic alcohol	96	5
12	2-Propanol	96	5
13	Furfuryl alcohol	96	5
14	Cetyl alcohol	95	5
15	Isoamyl alcohol	96	5
16	1-Naphtol	90	120
17	2-Naphtol	84	120
18	Phenol	90	120
19	4-Methyl phenol	90	120
20	4-Chloro phenol	84	120

<sup>a</sup> Isolated yields.

Table 2  
Silylation of *sec.*, *tert.*, and acid-sensitive alcohol

Entry	ROH	Yield (%) <sup>a</sup>	Time (min)
1		94	20
2		97	20
3		96	30
4		97	15
5		88	40
6		97	15
7		96	15
8		89	30
9		96 <sup>b</sup>	6
10		96 <sup>c</sup>	40 <sup>d</sup>
11		95 <sup>c</sup>	40 <sup>d</sup>
12		95 <sup>c</sup>	40 <sup>d</sup>
13		87	50

<sup>a</sup> Isolated yield.

<sup>b,c</sup> 1.5 equiv. HMDS was used.

<sup>d</sup> The yield of bis(trimethylsilyl) ether.

responding ethers under these conditions. The reactions are very fast and even bulky and acid-sensitive alcohols, which required long reaction time (few days) by other conventional reported methods, are found to give high yields in few minutes at room temperature. In the case of simple alcohols, silylation occurs quantitatively in a few minutes (Table 1). Due to the mild and neutral reaction conditions, no isomerization of double or triple bond and elimination product were observed. The LP-SiO<sub>2</sub> can also be used as a catalyst for phenol derivatives. In general phenols give lower yield and have longer reaction time in comparison with alcohols.

We also explored the chemoselectivity of LP-SiO<sub>2</sub> system. Table 3 clearly shows that in the presence of an amine, and phenol the reaction with alcohol is completely selective and the corresponding silylated alcohol is the

Table 3  
Selective *O*-trimethylsilylation of alcohol in the presence of amine, and phenolic hydroxyl


sole product. Also, in the presence of an amino group, only phenol reacts with HMDS to form the corresponding silylated product. In the case of diol and dihydroxy phenol (Table 2, entries 9–12), only bis(silylated) diol is formed. Although the mechanism of this reaction is not clear, silica gel has an important role and its presence was found to be essential for the high efficiency of the reaction.

In summary  $\text{LiClO}_4\text{-SiO}_2$  is found to be superior, efficient and novel catalyst for the silylation of various hydroxy substrates with HMDS under mild and neutral conditions. This procedure provides a novel, efficient and general methodology for the preparation of trimethylsilyl ether in high yields. In addition,  $\text{LP-SiO}_2$  is cheap, stable, easy to handle and non-toxic with very simple work-up procedure, which consists of filtration and removal of solvent. The  $\text{LP-SiO}_2$  can be re-used several times after activation. Furthermore, HMDS exhibit excellent selectivity under  $\text{LP-SiO}_2$  system for silylation of alcohols in the presence of amine, acid and phenol. Further investigation to broaden the scope and synthetic applications of  $\text{LP-SiO}_2$  under solvent-free conditions is under way in our laboratory.

### 3. General procedure for the silylation reaction

To a stirred solution of alcohols (10 mmol) and  $\text{LP-SiO}_2$  [14] (1.0 g) in  $\text{CH}_2\text{Cl}_2$  or petroleum ether (10 mL), HMDS (6 mmol) was added and stirred at room temperature under an argon atmosphere for the specified time (Tables 1 and 2). When the reaction was complete (TLC or GC analysis),  $\text{CH}_2\text{Cl}_2$  or petroleum ether was added (10 mL), and  $\text{LP-SiO}_2$  was removed by filtration. The solvent was evaporated and the trimethylsilyl ether was isolated almost as a pure crude product. Further purification was carried out by short column chromatography on silica gel eluting with ethyl acetate/petroleum ether, if necessary. All compounds are known and were characterized on the basis of their spectroscopic data (IR and NMR) and by comparison with those reported in the literature [8,11,13].

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