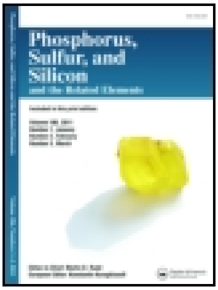

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Silica Sulfuric Acid as a Reusable Catalyst for Efficient and Simple Silylation of Hydroxyl Groups Using Hexamethyldisilazane (HMDS)

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To cite this article: Hossein Ghafuri, Bagher Eftekhari-Sis & Mohammed M. Hashemi (2007) Silica Sulfuric Acid as a Reusable Catalyst for Efficient and Simple Silylation of Hydroxyl Groups Using Hexamethyldisilazane (HMDS), Phosphorus, Sulfur, and Silicon and the Related Elements, 182:7, 1645-1651, DOI: 10.1080/10426500701289781

To link to this article: http://dx.doi.org/10.1080/10426500701289781

Phosphorus, Sulfur, and Silicon, 182:1645–1651, 2007

ISSN: 1042-6507 print / 1563-5325 online
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Silica Sulfuric Acid as a Reusable Catalyst for Efficient and Simple Silylation of Hydroxyl Groups Using Hexamethyldisilazane (HMDS)

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At room temperature, alcohols and phenols are efficiently protected with hexamethyldisilazane (HMDS) in the presence of silica sulfuric acid in good to excellent yields. The catalyst can be recycled for subsequent reactions without any appreciable loss of efficiency.

Keywords Hexamethyldisilazane; hydroxyl group; protection; silica sulfuric acid; silylation

INTRODUCTION

Protection of the hydroxyl functional group is an important process in multi-step synthesis. One of the popular methods for this purpose is to convert hydroxyl group to their corresponding silylethers. Several silylating agents such as chlorotrimethylsilane, hexamethyldisilazane (HMDS) and N,O-bis (trimethylsilyl) acetamide, and so on. have been developed and become available on the commercial scale.[1,2] For trimethylsilyl ethers, the most common preparative method is the chlorotrimethylsilane/pyridine system. However, it is accompanied by the formation of voluminous pyridine salts as a by-product and requires a careful filtration of the salt before isolating the silylated compounds. The product yields are not so high in most cases. HMDS is a stable, cheap, commercially available compound that can be used for the preparation of trimethylsilylethers from hydroxyl compounds, giving ammonia as the only by-product. Even though the handling of this reagent is easy, its main draw-back is its poor silylating ability;

Received November 20, 2006; accepted December 26, 2006.

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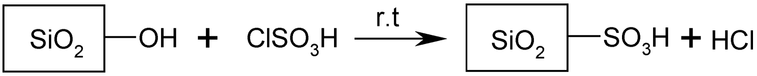
forceful conditions and long reaction times are required.[3] Various catalysts have been reported for the activation of HMDS in silylation reactions.[4–16] However, in most cases a long reaction time, drastic reaction conditions, or tedious work-up is needed. In addition, many of these reagents are moisture sensitive or expensive. The lack of a facial and general synthetic methodology for the silylation of hydroxyl groups prompted us to develop an efficient, convenient, and practical procedure for the protection of hydroxyl groups under solvent-free conditions and at room temperature.

Recently, silica sulfuric acid has emerged as a powerful solid acidic catalyst in synthetic methodology.[17–24] Silica sulfuric acid could easily be prepared by the reaction of silica gel and chlorosulfonic acid (Scheme 1).[25]



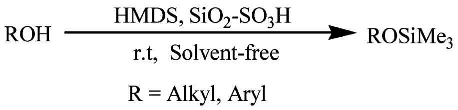
$$\boxed{SiO_2}-OH + ClSO_3H \xrightarrow{r.t} \boxed{SiO_2}-SO_3H + HCl$$

SCHEME 1

As part of our research on chemical transformations,[26–31] in this article we report a simple and environmentally benign methodology for the silylation of hydroxyl groups under solvent-free conditions and at room temperature using silica sulfuric acid as the catalyst.

RESULTS AND DISCUSSION

Various alcohols and phenols were subjected to silylation with HMDS using silica sulfuric acid as catalyst at room temperature under solvent-free conditions. The overall reaction is shown in Scheme 2.



$$ROH \xrightarrow[\text{r.t, Solvent-free}]{\text{HMDS, }SiO_2\text{-}SO_3H} ROSiMe_3$$

$$R = \text{Alkyl, Aryl}$$

SCHEME 2

We started to study the trimethylsilylation catalyzed by silica sulfuric acid by examining the conditions required for the reaction involving 2-chlorobenzyl alcohol (3 mmol) and HMDS (2.5 mmol) to give the corresponding silylether. The results are summarized in Table I. Entries 1–7 show the effect of various solvents on the time of the reaction and yield of the product. Although acetonitrile, dichloromethane, acetone, and solvent-free conditions afforded the product in high yields, we chose solvent-free conditions for economical and environmental acceptability.

TABLE I Reaction of 2-Chlorobenzyl Alcohol (3 mmol) and HMDS (0.25 mmol) under Different Conditions

Entry	Solvent	Catalyst amount (g)	Time (min)	Yield (%)
1	THF	0.25	2	86
2	CH_2Cl_2	0.25	2	92
3	Acetone	0.25	2	90
4	CH_3CN	0.25	2	94
5	EtOAc	0.25	2	90
6	Solvent-free	0.25	5	92, 88, 80[a]
7	Solvent-free	0.20	5	75
8	Solvent-free	0.12	5	60
9	Solvent-free	0	80	10

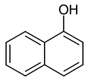
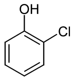
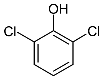
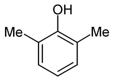
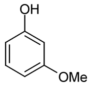
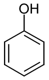
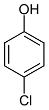
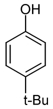
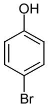
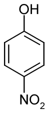
[a] Recovered catalyst was used for three times.

Entry 6 describes the yields of three consecutive reactions leading to 2-chlorobenzyl trimethylsilyl ether. In these experiments the product was isolated by filtration, the solid residues washed with dichloromethane, and the remaining catalyst reloaded with fresh reagents for further runs. No significant decrease in the yield was observed demonstrating that silica sulfuric acid can be reused as a catalyst in trimethylsilylation of alcohols and phenols. The optimum amount of catalyst (0.25 g) was determined from experiments corresponding to entries 6–8. Entry 9 shows the effect of silica sulfuric acid in the reaction. The best reaction conditions require the presence of small amounts of silica sulfuric acid (0.25 g) and 2.5 mmol of HMDS with respect to the alcohols (3 mmol) at room temperature under solvent-free conditions (Entry 6).

In order to understand the scope and limitations of this silica sulfuric acid catalyzed procedure for the protection of hydroxyl groups, various phenols and alcohols were treated with HMDS under solvent-free conditions. The results are shown in Table II and Table III. Primary, secondary, allylic and benzylic, sterically hindered, and acid-sensitive alcohols, as well as phenols can be converted to the corresponding trimethylsilyl ethers under these conditions. The reactions are very fast; even with bulky and acid-sensitive alcohols to give high yields in few minutes at room temperature.

In conclusion, $SiO_2—SO_3H$ is found to be an efficient and simple catalyst for the silylation of various hydroxyl substrates with HMDS under very mild conditions. The present procedure provides a novel, efficient and general methodology for the preparation of trimethylsilylethers in high yields. In addition, SiO_2-SO_3H is cheap, stable, easy to handle and nontoxic. The work-up process is very simple, consisting of merely filtration and removal of solvent. Furthermore, $SiO_2—SO_3H$ can be reused

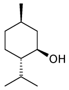
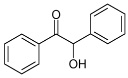
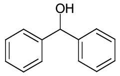
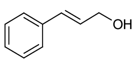
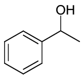
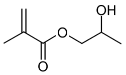
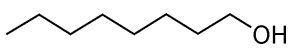
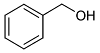
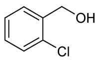
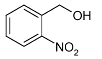
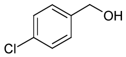
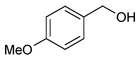
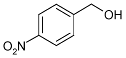
TABLE II Silylation of Various Phenols with HMDS

Entry	Phenol	Time (min)	Yield (%)[a]
1		5	86
2		5	92
3		5	89
4		5	90
5		5	94
6		5	90
7		5	94
8		5	90
9		5	93
10		100	45[b]

[a] All yields refer to isolated products characterized by spectroscopic data (IR and NMR); and [b] When the reaction was carried out in CH_2Cl_2 the product was obtained in 80% yield within 15 min.

several times. After the reaction is complete, CH_2Cl_2 or petroleum ether is added under stirring, and SiO_2—SO_3H is precipitated and separated by filtration. This simple work up also allows facile recovery of the reaction products.

TABLE III Silylation of Various Alcohols with HMDS

Entry	Alcohol	Time (min)	Yield (%)^a
1		10	76
2		15	82
3		10	85
4		15	53
5		15	89
6		10	75
7		5	90
8		10	93
9		5	92
10		7	85
11		5	93
12		5	92
13		5	90

^{a}All yields refer to isolated products characterized by spectroscopic data (IR and NMR).

EXPERIMENTAL

NMR spectra were recorded on a Bruker ACF 500. IR spectra were measured using a Perkin Elmer 781 spectrometer. Column chromatography was performed on silica gel, Merck grade 60. CH_2Cl_2 was distilled before use. Chemicals were purchased from Fluka or Merck. All of the products are known and were identified by comparison of their spectral data with those of authentic samples. The progress of reaction was monitored by thin-layer chromatography (TLC) on silica gel.

General Procedure for the Preparation of Trimethylsilylethers of Alcohols and Phenols Using HMDS Catalyzed with Silica Sulfuric Acid

To a mixture of alcohols or phenols (3 mmol) and 0.25 g of SiO_2-SO_3H, HMDS (2.5 mmol) was added and stirred at room temperature for the specified time (Tables II and III). When the reaction was complete as monitored by TLC, CH_2Cl_2 or petroleum ether were added, and SiO_2-SO_3H was removed by filtration. The solvent was evaporated and silylether was isolated as an almost pure product. Further purification was carried out by short-column chromatography on silica gel using ethyl acetate/petroleum ether as the eluent, if necessary. All compounds are known and were characterized on the basis of their spectroscopic data (IR, NMR) and by comparison with those reported in the literature.

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