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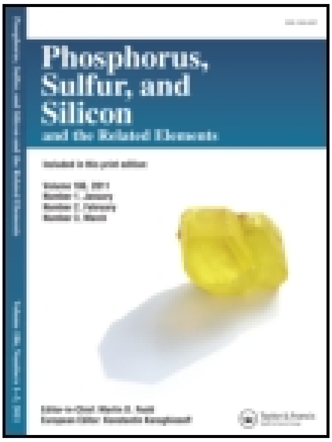

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Trimethylsilyl Protection of Alcohols Over Phosphorus Pentoxide Supported on Silica Gel

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TRIMETHYLSILYL PROTECTION OF ALCOHOLS OVER PHOSPHORUS PENTOXIDE SUPPORTED ON SILICA GEL

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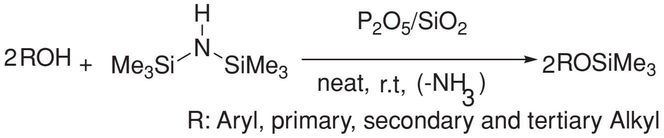
GRAPHICAL ABSTRACT



Abstract *An eco-friendly and mild protocol for trimethylsilyl protection of alcohols over phosphorus pentoxide supported on silica gel using hexamethyldisilazane has been described. Solvent-free and ambient reaction conditions, easy workup, short reaction times, excellent yields, and reusability of the catalyst are the noticeable features of this methodology.*

Keywords Alcohols; hexamethyldisilazane; P_2O_5/SiO_2; trimethylsilylation

INTRODUCTION

Trimethylsilyl protection of alcohols has been recognized as an important part of organic, inorganic, and analytical chemistry.[1] This synthetic methodology was used especially as a protecting group approach in many multistep syntheses with reasonable complexity for masking hydroxyl functional groups.[2] This transformation enhances solubility in nonpolar solvents, has low viscosity, increases thermal stability, and is resistant to oxidation; in addition, trimethylsilylation of hydroxyl compounds is used extensively to increase the volatility of the compounds for gas chromatography and mass spectrometry.[3]

The preparation of silyl ethers can be carried out by treatment of alcohols with silyl chlorides in the presence of a stoichiometric amount of an organic base[4] or silyl triflates with $R_3Si–H$ activated by dirhodium (II) perfluorooctanoate.[5] However, these methods suffer from drawbacks such as lack of reactivity or the difficulty in removal of amine salts.[4,5] 1,1,1,3,3,3-Hexamethyldisilazane (HMDS), an inexpensive and readily available compound, has been used for the preparation of trimethylsilyl ethers from hydroxyl compounds.[6] The only by-product of this reaction is NH_3 gas, which is a notable advantage of

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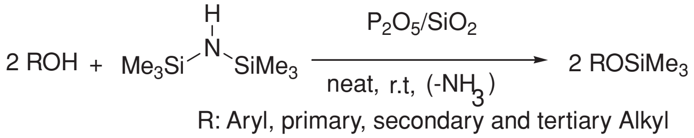
the method.[6] Even though the handling of this reagent is easy, the low silylation power of HMDS is the main drawback to its application[7]; therefore, there are a variety of catalysts to activate this reagent, such as Envirocat EPZGO,[8] tungstophosphoric acid,[9] K-10 montmorillonite,[10] cupric sulfate pentahydrate,[11] lithium perchlorate supported on silica gel,[12] sulfonic acid–functionalized silica,[13] magnesium triflate,[14] alumina-supported heteropolyoxometalates,[15] iron (III) trifluoroacetate,[16] silica-supported perchloric acid,[17] superparamagnetic iron oxide,[18] barbutric acid,[19] and $TiCl_2(OTf)$-SiO_2.[20] Recently, an uncatalyzed method for the silylation of alcohols and phenols with HMDS in CH_3NO_2 was reported.[21] Even though these catalytic systems enhance the ability of HMDS for the silylation, some of the catalysts require a long reaction time, a high temperature, and an excess amount of reagent. The lack of a facile and general synthetic methodology under essentially mild reaction conditions has prompted us to develop an efficient, convenient, and practical procedure for the silylation of alcohols under solvent-free conditions 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 phosphorus pentoxide supported on silica gel (P_2O_5/SiO_2) as a catalyst at room temperature under solvent-free conditions (Scheme 1).



Scheme 1

Phosphorus pentoxide-methanesulfonic acid was used for the first time as a convenient alternative to polyphosphoric acid by Eaton et al.[22] to escape the difficulties encountered with polyphosphoric acid (PPA). Then, P_2O_5 supported on SiO_2 as an inexpensive, heterogeneous, stable, free-flowing, white powder was prepared.[23a] This compound is safe, easy to handle, environmentally benign, and presents fewer disposal problems.[23] To the best of our knowledge there has been no report available on trimethylsilyl protections of alcohols over P_2O_5/SiO_2 as a catalyst in the literature.

RESULTS AND DISCUSSION

To optimize the amount of the catalyst in the mentioned reaction, we carried out a model study of benzyl alcohols with HMDS in the presence of different amounts of P_2O_5/SiO_2 (7% w/w)[24] as a catalyst under solvent-free conditions at room temperature (Table 1). It was found that 0.06 g of the catalyst showed a maximum yield (95%) in minimum a reaction time (3 min). Further increasing the catalyst amount (0.08, 0.1 g) decreased the yield of the product in 2 min.

Using these optimized reaction conditions, 60 mg of P_2O_5/SiO_2 (7% w/w), the scope and efficiency of the reaction were explored for the synthesis of a wide range of structurally diverse and functionalized alcohols, phenols, and naphthols at room temperature (Table 2). Generally, in all cases of benzylic alcohols, primary, secondary, and tertiary alcohols and phenols and naphthols were converted to corresponding trimethylsilyl ethers within less

Table 1 Optimization amount of the P_2O_5/SiO_2 as a catalyst in the synthesis of benzyl trimethylsilyl ether under solvent-free and mild conditions

Entry	Amount P_2O_5/SiO_2 (Catalyst) (g)	Time (min)	Yield (%)
1	0.04	8	80
2	0.06	3	95
3	0.08	2	90
4	0.1	2	88

[a] A molar ratio of benzyl alcohol/HMDS was chosen (1:0.75), and yields refer to isolated pure products.

than 30 min by evolution of NH_3 gas from the reaction mixture. There was not much difference in reactivity with the variation of aliphatic and aromatic compounds containing hydroxyl functional groups. Only tertiary alcohols (Table 2, entries 16, 17) took a longer time to complete the reaction, which is due to steric hindrance. Phenols containing an amino functional group were regioselectively O-silylated (Table 2, entry 19), whereas the amino group was intact.

To show the merit of the present work in comparison with reported results in the literature, we compared results of P_2O_5/SiO_2 with $Cu(OTf)_2$,[25] $Mg(OTf)_2$,[14] cupric sulfate pentahydrate,[11] alumina-supported heteropolyoxometalates,[15] and $LiClO_4$[26] in the synthesis of trimethyl(phenoxy)silane. As shown in Table 3, P_2O_5/SiO_2 can act as an effective catalyst with respect to reaction times, amount of the catalyst, and yields of the obtained products. Thus, the present protocol with P_2O_5/SiO_2 catalyst is convincingly superior to some reported catalytic methods.

From the context of a green approach, the reusability study of the catalyst was performed with the *O*-silyl protection of benzyl alcohol (Table 2, entry 1). After completion of the reaction (checked by thin-layer chromatography [TLC]), the reaction mixture was solved using ethylacetate and filtered to separate the catalyst. It was washed well with ethyl acetate (2 × 5 mL) and then dried at 100 °C for 2 h before being further used. It was observed that on five successive runs with P_2O_5/SiO_2 as the catalyst, the reactivity in all runs remained almost unchanged (Figure 1).

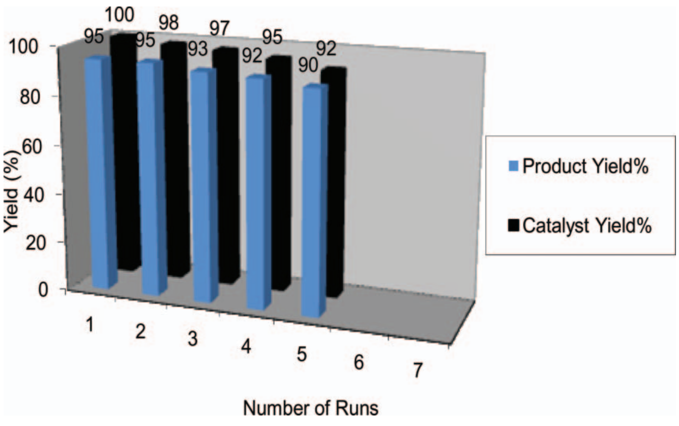
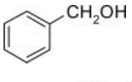
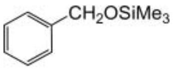
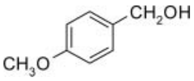
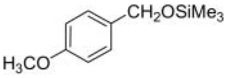
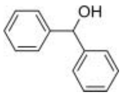
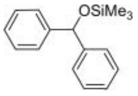
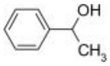
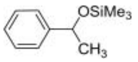
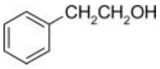
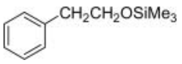


Figure 1 The reusability study of the P_2O_5/SiO_2 as the catalyst in *O*-silyl protection of benzyl alcohol.

Table 2 Trimethylsilylation of benzylic alcohols; primary, secondary, and tertiary alcohols; and phenols and naphthols with HMDS in the presence of solid heterogeneous P_2O_5/SiO_2 as a catalyst (0.06 g) under ambient conditions

Entry	Substrate	Product	Time (min)	Yield (%)[a]	Literature References for Known Product[b]
1			3	95	16, 17, 27
2			4	95	16, 17
3			7	89	16, 17, 27
4			8	91	16, 17, 27
5			4	97	16, 17, 27
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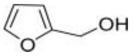
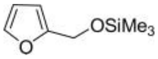
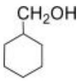
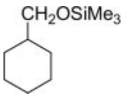
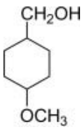
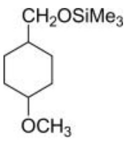
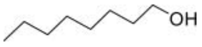
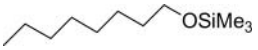
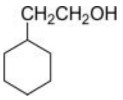
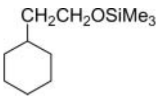
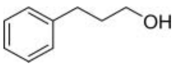
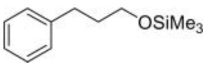
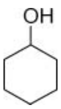
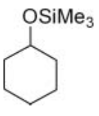
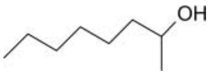
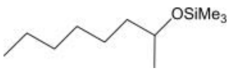
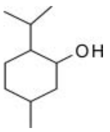
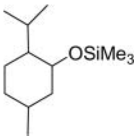
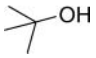
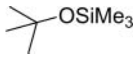
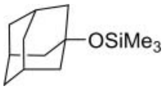
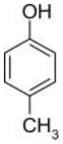
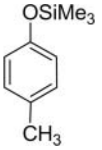
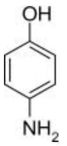
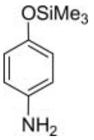
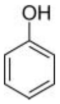
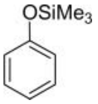
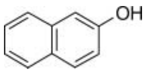
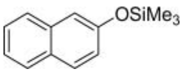
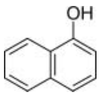
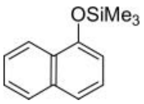
7			18	95	27
8			3	92	17
9			2	94	17
10			4	95	17
11			4	88	17
12			10	90	17, 27
13			15	91	17, 27
14			8	93	16, 17, 27
15			15	95	17

Table 2 Trimethylsilylation of benzylic alcohols; primary, secondary, and tertiary alcohols; and phenols and naphthols with HMDS in the presence of solid heterogeneous P_2O_5/SiO_2 as catalyst (0.06 g) under ambient conditions *(Continued)*

Entry	Substrate	Product	Time (min)	Yield (%)[a]	Literature References for Known Product[b]
16			35	89	17
17			30	95	16, 17, 27
18			3	97	17
19			5	91	17
20			3	97	16, 17, 27
21			5	91	17
22			6	91	16, 17, 27

[a] A molar ratio of substrate/HMDS was chosen (1:0.75). Yields refer to the pure isolated products.

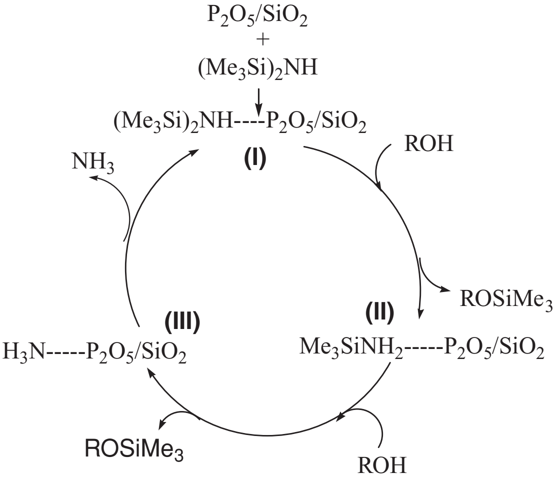
[b] The structure of all known products was confirmed by comparison of their spectral data (FTIR and ^1H and ^{13}C-NMR) with those of known samples in the literature.[16,17,27]

According to our chemical reaction observation and literature survey[16–18,21,27] for the investigated process, the following mechanism can be proposed for this transformation. According to the evolution of NH_3 in the reaction conditions, the interaction between the acidic nature of P_2O_5/SiO_2 and Lewis base nature of nitrogen (nonbonding electrons) of HMDS polarizes the N–Si bond to produce the reactive silylating agent (**I**). A rapid reaction with alcohol then ensues, leading to the ammonium-silylating species (**II**) with concomitant release of the corresponding silyl ether. Irreversible cleavage of (**II**) with alcohol leads to $ROSiMe_3$ and formation of (**III**). The mechanism clearly shows one mole of HMDS molecule reacting with two moles of alcohols. The P_2O_5/SiO_2-NH_3 complex ends up with the evolution of gaseous ammonia and the recycling of P_2O_5/SiO_2. The evolution of ammonia was confirmed by its strong, pungent odor and the use of red litmus

Table 3 Comparison result of P_2O_5/SiO_2 with $Cu(OTf)_2$,[26] $Mg(OTf)_2$,[14] cupric sulfate pentahydrate,[11] alumina-supported heteropolyoxometalates,[15] and $LiClO_4$[27] in the silylation of phenol with HMDS

Entry	Catalyst	Conditions	Amount of Catalyst (g)	Time (min)	Yield (%)[a]
1	$Cu(OTf)_2$	Solvent (CH_3CN), RT	0.03	120	70
2	$Mg(OTf)_2$	Solvent free, RT	0.03	60	70
3	Cupric sulfate pentahydrate	Solvent (CH_3CN), RT	0.02	90	95
4	Alumina-supported heteropolyoxometalates	Solvent (Toluene), 85 °C	0.1	90	100
5	$LiClO_4$	Solvent free, RT	0.5	20	96
6	P_2O_5/SiO_2	Solvent free, RT	0.06 (7% w/w)	3	97 (Present work)

[a]Yields refer to isolated products.



Scheme 2

paper. Released P_2O_5/SiO_2 as catalyst from intermediate (**III**) reenters catalytic cycle (Scheme 2).

P_2O_5/SiO_2 has improved storage stability in moisture in comparison to P_2O_5, which is very sensitive to moisture and showed much more reactivity than unsupported P_2O_5.[23] P_2O_5/SiO_2 can react with ammonia in an acid–base interaction, but gaseous ammonia is an excellent driving force for easy cleavage of P_2O_5/SiO_2-NH_3 and recycling the catalyst for continuation catalytic cycle in the mechanism. Finally, P_2O_5/SiO_2, a heterogeneous catalyst, was removed from the organic product by simple filtration.

CONCLUSION

In summary, we have demonstrated that P_2O_5/SiO_2 is a new, efficient, and heterogeneous catalyst for trimethylsilylation of a variety of hydroxyl groups using HMDS under solvent-free, mild, and ambient conditions. The reactions were carried out at room temperature with a short reaction time and produce the corresponding trimethylsilyl ethers in good to excellent yields. The catalyst can be recovered from reaction mixtures by a simple filtration procedure and reused.

EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. P_2O_5/SiO_2 was prepared according to the reported procedure.[24] All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (Fourier transform infrared [FTIR] and ^{1}H-NMR and ^{13}C-NMR spectra). The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance DPX 500 MHz instrument. The spectra were measured in $CDCl_3$ relative to tetramethylsilane (TMS; 0.00 ppm). FTIR spectra were recorded on a Jasco FTIR 460 plus spectrophotometer. TLC was performed on silica-gel polygram SIL G/UV 254 plates.

General Procedure for Trimethylsilylation of Alcohols Using HMDS Catalyzed with P_2O_5/SiO_2

To a stirred solution of alcohols (10 mmol) and HMDS (7.5 mmol) was added P_2O_5/SiO_2 (0.6 g) and the mixture was stirred at room temperature for the time specified in Table 2. The reaction was followed by TLC (*n*-hexane-EtOAc, 9:1). After completion of the reaction (checked by TLC), the reaction mixture was solved using ethyl acetate and filtered to separate the catalyst. It was washed well with ethyl acetate (2 × 5 mL) and then dried at 100 °C for 2 h before being further used. Then, the filtered solution was evaporated and purified by passing through a short pad column of silica gel using *n*-hexane as eluent (2 × 20 mL). Evaporation of the solvent under reduced pressure gave pure product(s) (Table 2). The desired pure product(s) were characterized by comparison of their physical data with those of known compounds.[16,17,27]

Selected Spectral Data

Trimethyl(benzyloxy) silane (Table 2, entry 1): colorless liquid, ^{1}H-NMR ($CDCl_3$, 500 MHz): $\delta = 7.36–7.35$ (5H, m), 4.72 (2H, s), 0.18 (9H, s) ppm; ^{13}C-NMR ($CDCl_3$, 125 MHz): $\delta = 138.32$, 128.36, 127.45, 127.35, 67.85, 0.29; IR (CCl_4): 2957, 1496, 1454, 1377, 1250, 1207, 1096, 1027, 842, 727, 695 cm^{-1}.

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