An efficient method for the silylation of hydroxyl groups with hexamethyldisilazane (HMDS) catalyzed by aluminum tris(dihydrogen phosphate) under solvent-free and ambient conditions

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Abstract: A highly efficient and mild procedure for the trimethylsilylation of a wide variety of alcohols, including primary, benzylic, secondary, hindered secondary, tertiary, phenols, and oximes with hexamethyldisilazane (HMDS), using $Al(H_2PO_4)_3$ as a recyclable heterogeneous catalyst at room temperature in a few minutes with excellent yields under solvent-free conditions is described.

Key words: trimethylsilylation, hexamethyldisilazane, aluminum tris(dihydrogen phosphate) [$Al(H_2PO_4)_3$], solvent-free, hydroxyl groups.

Résumé : On a mis au point une méthode douce et très efficace de triméthylsilylation d'une grande variété d'alcools, y compris les alcools primaires, benzyliques, secondaires, secondaires empêchés et tertiaires, ainsi que des phénols et des oximes, qui implique l'utilization de l'hexaméthyldisilazane (HMDS) en présence de $Al(H_2PO_4)_3$ comme catalyseur hétérogène réutilizable et qui s'effectue en quelques minutes à la température ambiante, avec d'excellents rendements et des conditions sans solvant.

Mots-clés : triméthylsilylation, hexaméthyldisilazane, tris(phosphate diacide) d'aluminium [$Al(H_2PO_4)_3$], sans solvant, groupements hydroxyles.

[Traduit par la Rédaction]

Introduction

Trimethylsilylation of organic compounds having labile hydrogen atoms is an important organic transformation. It is a frequently used protection method in multi-step sequence synthesis of natural products due to the enhanced stability under a variety of conditions, solubility in nonpolar solvents, thermal stability, and the ease of removal, which is simply accomplished by acid- or base-induced hydrolysis giving only unreactive siloxane as the by-product (1). It is also used extensively for the hydroxyl compounds to increase their volatility for gas chromatography and mass spectrometry (1, 2). Several methods have been reported for this conversion, including the reaction of an alcohol with trimethylsilylhalides in the presence of a stoichiometric amount of a tertiary amine (3), with trimethylsilyl triflate and trimethylsilylmethallylsulfinates, which are more reactive than the chloride (4), allylsilanes in the presence of a catalytic amount of *p*-toluenesulfonic acid (4) iodine (5), trifluoromethanesulfonic acid (6), and $Sc(OTf)_3$ (7). 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 by-product 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 a variety of catalysts for activating this reagent, such as $(CH_3)_3SiCl$ (8), K-10 montmorillionite (9), sulfonic acids (10), zirconium sulfophenyl phosphonate (11), $ZnCl_2$ (12), Envirocat EPZGO (13), tungstophosphoric acid (14), iodine (15), lithium perchlorate (16), cupric sulfate pentahydrate (17), H–β Zeolite (18), $MgBr_2$ (19), lithium perchlorate supported on silica gel (20), $Al(HSO_4)_3$ (21), $Al(OTF)_3$ (22), magnesium triflate (23), copper triflate (24), $ZrCl_4$ (25), silica-$HClO_4$ (26), lanthanum trichloride (27), trichloroisocyanuric acid (28), and sulfonic acid-functionalized ordered nanoporous silica (29). However, in most cases a long reaction time, drastic reaction conditions, or tedious workup is needed. In addition, trimethylsilyl azide is expensive and toxic. We now show that O-trimethylsilylated compounds can be produced using $Al(H_2PO_4)_3$ (30) as an efficient, recyclable heterogeneous catalyst at room temperature under solvent-free conditions (Scheme 1).

This catalyst is safe, easy to handle, environmentally benign, presents fewer disposal problems, and is stable in reaction media.

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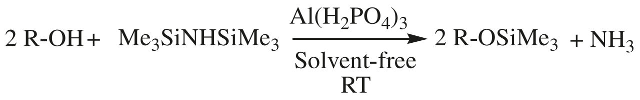
Scheme 1. Preparation of trimethylsilyl ethers.



$$2\ \text{R-OH} + \text{Me}_3\text{SiNHSiMe}_3 \xrightarrow[\text{Solvent-free, RT}]{\text{Al(H}_2\text{PO}_4)_3} 2\ \text{R-OSiMe}_3 + \text{NH}_3$$

R= aryl, primary, secondary, tertiary and benzylic alcohol, oxime

Results and discussion

First, silylation of benzyl alcohols with HMDS in the presence of solid aluminum tris(dihydrogen phosphate) as catalyst in various solvents and also under solvent-free conditions at room temperature was investigated. The results were summarized in Table 1. As shown in Table 1, the solvent-free condition is obviously the best choice for these reactions. Solvent-free reactions promise to be an essential facet of ‘Green Chemistry’. This type of organic reaction possesses some advantages over traditional reactions in organic solvents. Solvent-free reactions make it possible to reduce the consumption of environmentally unfriendly solvents and lead to new environmentally benign procedures to save resources and energy.

To determine the optimum quantity of $Al(H_2PO_4)_3$, the reaction of benzyl alcohol (1 equiv.) and HMDS (0.8 equiv.) was carried out under the solvent-free conditions using different quantities of catalyst at room temperature. The use of 50 mg of catalyst resulted in the highest yield in 5 min (Table 2).

Thus, we prepared a range of O-trimethylsilylated compounds under the optimized reaction conditions (Table 3).

A wide range of structurally diverse and functionalized phenols, alcohols, and oximes underwent silylation by this procedure to provide the corresponding TMS ethers (trimethysilyl ethers) in good to excellent isolated yields as shown in Table 3 (entries 1–24, 26, 28). Primary alcohols mostly reacted faster than secondary and tertiary alcohols. Generally, in all cases of benzyl, primary, secondary, and tertiary alcohols the reactions were completed within less than 65 min in solvent-free conditions accompanied by evolution of NH_3 gas from the reaction mixture. Inspection of the data in Table 3 clearly shows that different types of hindered secondary and tertiary alcohols were successfully converted to the corresponding silyl ethers at ambient conditions (Table 3). Amines (Table 3, entries 26, 27) and thiols (Table 3, entry 25) remained unaffected under the reaction conditions. To examine the functional group compatibility, we tested some more alcohols having other functional groups such as carbonyl group, amino group, alkene, and ethers. Alcohols were successfully converted to the corresponding silyl ethers, whereas, other functional groups were intact (Table 3, entries 2, 16, 26, 28).

The suggested mechanism of the $Al(H_2PO_4)_3$ catalyzed silylation of hydroxyl groups is shown in Scheme 2. $Al(H_2PO_4)_3$ can act as Brønsted acid and also Lewis acid owing to the empty aluminum *p*-orbital. Thus, in this mechanism, the operation process chart (OPC) of the catalyst in this works is unknown but according to observations such as the evolution of NH_3 in the reaction conditions, we have suggested that an acid–base interaction in $Al(H_2PO_4)_3$ as catalyst and nitrogen in HMDS polarizes the N–Si bond of HMDS to produce a 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 leading to the fast evolution of ROTMS (trimethysilyl ethers) and also formation of the unstable complexes of $Al(H_2PO_4)_3$ with ammonia (III). Cleavage of this complex with HMDS leads to the fast evolution of NH_3. Release of $Al(H_2PO_4)_3$ as catalyst from the intermediate (III) re-enters the catalytic cycle (Scheme 2).

Table 1. Preparation of benzyl trimethylsilyl ether using aluminum tris(dihydrogen phosphate) (0.05 g) as the catalyst under solvent and solvent-free conditions at room temperature.

Entry	Solvent	Time (min)	GC yield (%)	Yield (%)^a
1	Dichloromethane	27	100	89
2	Chloroform	20	100	93
3	Ethyl acetate	35	100	91
4	*n*-Hexane	35	100	92
5	Acetonitrile	15	100	89
6	Solvent-free	5	100	98

[a] Isolated yield and the product gave satisfactory IR and NMR spectra.

Table 2. Optimization of the catalyst in the synthesis of benzyl trimethylsilyl ether.

Entry	Catalyst (g)	Time (min)	Isolated yield (%)
1	0.1	3	94
2	0.05	5	98
3	0.025	50	90
4	0.01	75	86

$Al(H_2PO_4)_3$ is an inexpensive and nonhazardous solid acid catalyst, which can be handled easily and removed from the reaction mixtures by simple filtration. The recovered catalyst was reused five times without any loss of activity (Table 4).

To show the merit of the present work in comparison with reported results in the literature, we compared reactions of $Al(H_2PO_4)_3$ with iodine (15), lithium perchlorate (16), cupric sulfate pentahydrate (17), magnesium triflate (23), and copper triflate (24) in the synthesis of trimethylsilyl ethers. As shown in Table 5, $Al(H_2PO_4)_3$ is a better catalyst with respect to reaction times and yields of the obtained products. Thus, the present protocol with $Al(H_2PO_4)_3$ as catalyst is convincingly superior to the reported catalytic methods.

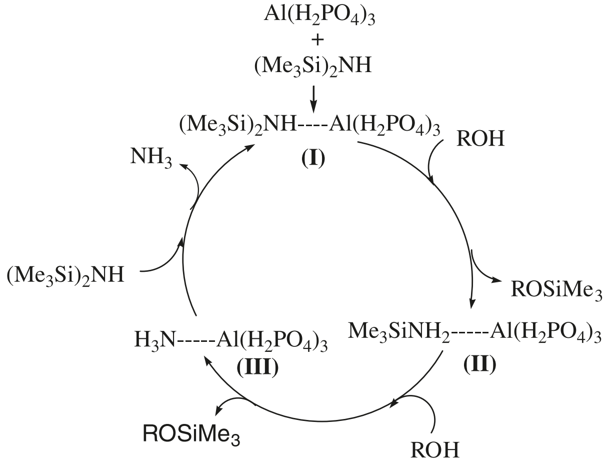
The catalyst stability was assessed to evaluate if the catalyst could be disturbed by solvent or not. In a controlled experiment, preparation of 2-naphthyl trimethylsilyl ether in CH_2Cl_2 as solvent was examined (Table 3, entry 20), after 7 min, the catalyst was removed by simple filtration. The reaction was continued further and it was observed that the reaction stopped (GC monitoring) in absence of solid catalyst particles (Fig. 1). This suggests to us that the catalyst is heterogeneous and stable in reaction medium. When the separated catalyst was transferred to this media, the reaction was progressed and completed. To reconfirm that there were no active catalyst species in solution or to show that the process

Table 3. Silylation of alcohols, phenols, naphthols, and oximes with HMDS in the presence of solid aluminum tris(dihydrogen phosphate) as the catalyst (0.05 g) under solvent-free conditions at room temperature.

Entry	Substrate	Time (min)	Yield (%)[a]
1	Benzyl alcohol	5	98
2	4-Methoxybenzyl alcohol	4	96
3	2-Phenyl ethanol	7	98
4	Diphenyl methanol	9	93
5	1-Phenyl ethanol	8	92
6	1-Butanol	6	83
7	3-Methyl-1-butanol	8	87
8	Cyclohexanol	19	94
9	*tert*-Butanol	65	89
10	Tetrahydro-2-furylmethanol	12	96
11	5-Methyl-2-(1-ethylmethyl) cyclohexanol	9	96
12	1,4-Butandiol	7	91
13	Tricyclo[3,3,1,$1^{3,7}$] doc-1-ol	56	97
14	1-Octanol	9	94
15	2-Octanol	11	95
16	(3β)-Choest-4-en-3-ol	10	98
17	Phenol	6	97
18	4-Methylphenol	6	96
19	1-Naphthol	7	94
20	2-Naphthol	6	95
21	4,4′-Biphenol	6	96
22	Acetophenone oxime	6	95
23	Benzaldehyde oxime	5	93
24	4-Methyl acetophenone oxime	6	90
25	1,3-Propanditiol	7	—
26	4-Aminophenol	7	92
27	Aniline	7	—
28	Benzoin	21	80

[a] The pure isolated products were characterized by comparison of their physical data with those of known compounds (8–30).

Scheme 2. The suggested mechanism of the $Al(H_2PO_4)_3$ catalyzed silylation of hydroxyl groups.



is truly heterogeneous, the catalyst was subjected to vigorous stripping in CH_2Cl_2 for 30 min. The catalyst was filtered and the filtrate was used as reaction medium. No noticeable transformation of 2-naphthyl trimethylsilyl ether confirmed heterogeneity of the catalyst in the reaction conditions. This evidence showed that the process is heterogeneous and no leaching occurs.

Table 4. Reusability of the catalyst based on the preparation of benzyl trimethylsilyl ether.

Entry	Run no.	Yield (%)
1	Cycle 1	97
2	Cycle 2	96
3	Cycle 3	96
4	Cycle 4	95
5	Cycle 5	94

Conclusion

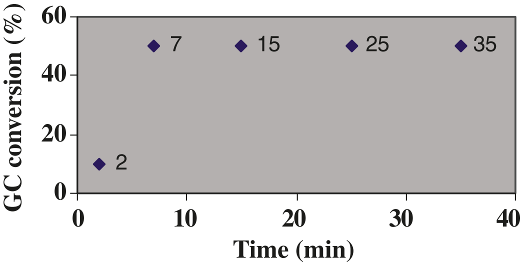
In conclusion, a reliable, rapid, and environmentally benign method for the preparation of trimethylsilyl ethers in a high to excellent yield under solvent-free and ambient conditions has been developed, which involves the use of recyclable $Al(H_2PO_4)_3$. In addition to the purity of the products, the short reaction times and ease of work-up make the method

Table 5. Comparison of our results with results obtained by some metal salts.

Entry	Catalyst	Conditions [molar ratio of catalyst]	Time, yield (%)
1	Iodine	CH_2Cl_2, RT [0.01]	—
2	$LiClO_4$	Solvent-free, RT [0.5]	20 min, 96
3	Cupric sulfate pentahydrate	CH_3CN, RT [0.01]	1.5 h, 95
4	$Cu(OTf)_2$	CH_3CN, RT [0.01]	120 min, 70
5	$Mg(OTf)_2$	Solvent-free, RT [0.01]	60 min, 70
10	$Al(H_2PO_4)_3$	Solvent-free, RT [0.16]	6 min, 97

Note: Based on phenol/HMDS (1:0.8 equiv.).

Fig. 1. Evaluation of the catalyst stability in the preparation of 2-naphthyl trimethylsilyl ether.



advantageous. We are currently exploring further applications of $Al(H_2PO_4)_3$ for other types of functional group transformations in our laboratories.

Experimental

General

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. $Al(H_2PO_4)_3$ was prepared according to the reported procedure (30). All yields refer to isolated products after purification. Products were characterized by comparison with authentic samples and by spectroscopy data (IR, ^{1}H NMR spectra). The NMR spectra were recorded on a Bruker Avance DPX 300 and 500 MHz instrument. The spectra were measured in $CDCl_3$ relative to TMS (0.00 ppm). GC analysis was run with Shimadzu GC-14A. IR spectra were recorded on a JASCO FT-IR 460plus spectrophotometer. TLC was performed on Silica-gel polygram SIL G/UV 254 plates.

Preparation of $Al(H_2PO_4)_3$ (30)

The catalyst was prepared by taking a mixture of alumina (neutral) and concentrated phosphoric acid (88%) in a silica boat maintaining the molar ratio of alumina–H_3PO_4 as 1:3 and heating at 200–220 °C on a hot sand bath. The mixture was stirred at the stipulated temperature until the swampy mass solidified and then the temperature was reduced to around 100 °C. The whole was then placed in a vacuum desiccator and cooled to ambient temperature. The catalyst thus prepared was finally transferred and stored in an air tight sample vial. The catalyst has been reported previously in the literature and was characterized by comparison of IR spectroscopy and the powder XRD with known samples (30). IR spectrum and powder XRD pattern matched well with the literature ($Al(H_2PO_4)_3$: 317.84 g mol^{-1}).

$$Al_2O_3 + H_3PO_4 \xrightarrow{\text{Heat}} Al(H_2PO_4)_3 + H_2O \uparrow$$

General procedure for silylation of alcohols using HMDS catalyzed with $Al(H_2PO_4)_3$

$Al(H_2PO_4)_3$ (0.05 g) was added to a stirred solution of alcohol (1 mmol) and HMDS (0.7 mmol) and the mixture was stirred at room temperature for the time specified in Table 3. The reaction was followed by GC and TLC (*n*-hexane–EtOAc, 9:1). After completion of the reaction, *n*-hexane was added and the heterogeneous catalyst was filtered and the resulting mixture was passed through a short pad of silica gel. Then, the pad column was washed with *n*-hexane (2 × 10 mL). Evaporation of the solvent under reduced pressure gave pure product(s) (Table 3). The separated catalyst was washed by ethyl acetate and dried in oven at 100 °C for 3 h. The desired pure product(s) was characterized by comparison of their physical data with those of known compounds (8–30).

Acknowledgements

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