SHORT PAPER

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Phosphomolybdic acid, an efficient catalyst for the trimethylsilylation of alcohols†

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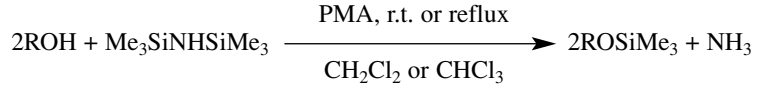
An easy method for the preparation of trimethylsilyl ethers of alcohols with 1,1,1,3,3,3-hexamethyl- disilazane (HMDS) catalysed by phosphomolybdic acid (PMA) under mild conditions has been carried out in excellent yields.

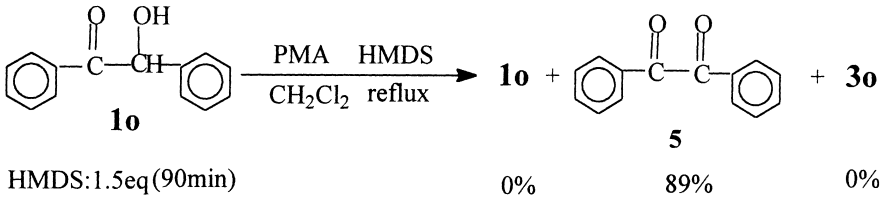
Keywords: phosphomolybdic acid, protection, trimethylsilyl ethers, heteropoly acid

The protection of hydroxyl groups by the formation of silyl ethers has been extensively used in organic synthesis.[1] Silyl ethers are easy to form, resistant to oxidation, have good heat stability, low viscosity and easy of recovery to their parent compounds.[2] Silylation has also become an important part of gas–liquid partition and thin-layer chromatographic (TLC) analyses due to its general effect of reducing intermolecular hydrogen bonding and thus increasing volatility and solubility.[3]

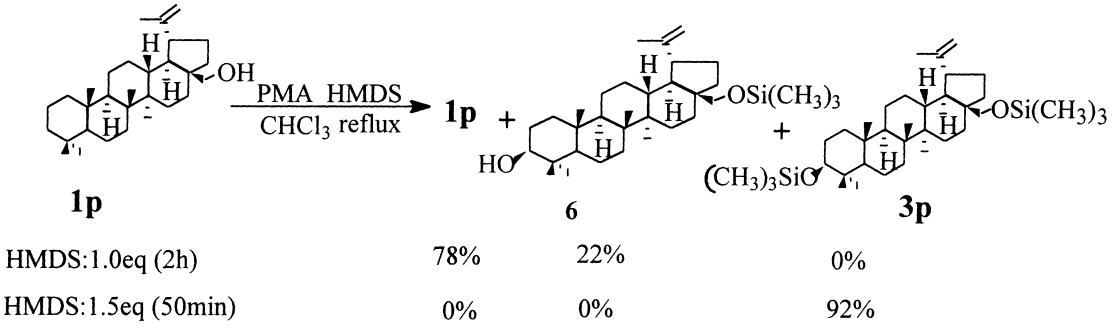
HMDS has been found to be a convenient reagent for converting alcohols to their trimethlsilyl derivates.[2,4–6] HMDS is a cheap and commercially available reagent, giving ammonia as the only byproduct and the products are separated from excess of HMDS by a simple distillation.[7] Its handling does not need special precaution and the reaction work-up is not time consuming. The main drawback of this reagent is its poor silyating power, which needs forceful conditions in many instances and reactions.[5] The activity of HMDS has been increased drastically by using some catalysts. Chlorotrimethlsilane,[2] sulfuric acid,[1] zinc chloride,[8] X–NH–Y(where at least one of X or Y is an electron-withdrawing group)[5] and montmorillonite K-10[3,9,10] as catalysts are employed for the preparation of trimethylsilyl ethers. These catalysts have their advantages, but they also have some disadvantages. For example, the use of conventional strong acid as catalyst associates with the formation of a large amount of byproduct such as HCl-amine salt, entails problems



Scheme 1



Scheme 2



Scheme 3

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

of corrosivity, tedious work-up, pollution and non-recoverable of catalyst, as well some catalysts needing long reaction times. Consequently, there is a genuine need for efficient and heterogeneous catalytic methods for this reaction using inexpensive, non-pollution and easily handled catalysts.

In recent years, PMA, a kind of heteropoly acid (HPA) has been found to be useful catalyst in a variety of organic reactions.[11,12] HPA is superior to common inorganic acids. It has many advantages, since it has high reactivity, and is non-toxic, inodorous, non-corrosive, non-pollution, non-volatile and has excellent stability.[13–15] Furthermore, HPA can be used not only as acid catalyst, but also as an oxidative and bifuntional catalyst.[14] It has been reported that HPA has good catalytic activity for the etherisation.[16] The reactions catalysed by PMA are usually carried out under mild conditions with high yields and the work-up of the reactions is very simple, usually only removal of the catalyst by filtration and evaporation of the solvent are involved. Herein we report the protection of hydroxy group by formation of trimethylsilyl ethers under catalysis of PMA.

In the presence of PMA, treatment of a variety of alcohols (**1**) with HMDS in dichloromethane or chloroform (except for those in absence of solvent) at mild temperature gave the corresponding trimethylsilyl ethers (**3**) in good to excellent yields. The results are shown in Table 1. The present procedure for preparation of trimethylsilyl ethers is quite general as a wide range of hydroxy containing compounds such as primary alcohols (**1a, 1b, 1f**, **1g, 1h, 1i, 1j, 1m** and **1n**), secondary alcohols (**1c**, **1e**, **1p** and **1q**) were protected in excellent yields.

If the substance is easily oxidised, the corresponding product (**3**) could not be obtained due to oxidation by PMA. For example, Benzoin (**1o**) reacting with HMDS in presence of PMA did not give its trimethlsilyl ether, but gave the product of oxidation, that is benzil (m.p. 95°C, yellow crystal from alcohol). So PMA could not be the catalyst for the silylation reaction of Benzoin (Scheme 2).

Treatment of Betulin (**1p**) with HMDS gave different amounts of mono- and di-silylated products by using different equivalents of HMDS. For example, it only offorded 28-trimethysiloxy-3β-hydroxylup-20(29)-ene (**6**) by employing 1 equivalent of HMDS (Scheme 3). Tertiary alcohols showed the lowest activity, though they were silylated with HMDS in presece of PMA at higher temperature and longer reaction time, only a low yields (**3**) were obtained. For example, triphenylmethanol (**1l**) required a longer reaction time (6h), higher temperature (reflux) and gave product (**3l**) in a lower yield (68%). Therefore, primary alcohols could be protected more easily than secondary alcohols and secondary alcohols could be protected more easily than tertiary alcohols.

In a word, we have developed preparative procedures for trimethylsilyl ethers with the advantages of operational simplicity, high yields, short reaction times and a recyclable and environment-friendly catalyst.

Experimental

*General procedure for the preparation of trimethylsilyl ethers (**3**):* A mixture of alcohol (3mmol) and HMDS (4.5mmol) in dry dichloromethane or chloroform (5ml) (except for those in absence of solvent) was stirred in the presence of PMA (100mg) at room or refluxing temperature for the length of time as indication in Table 1. The reaction was monitored by TLC. After completion of the reaction, mixture was filtered and the catalyst was washed with dichloromethane or chloroform (2×5 ml). Removal of the solvent under reduced pressure furnished the essentially pure product (**3**). Further purification was achieved by distillation or column chromatograph on silica gel with light petroleum (b.p. 60–90°C) as eluent wherever necessary. Products were characterised by their melting points, spectral characteristics (IR and ^{1}H NMR) and comparison with authentic samples. IR spectra were recorded on a Bio-Rad FTS-40 spectrometer (KBr). ^{1}H NMR spectra were determined in D-chloroform solution on a FT-NMR Bruker 300 (300MHz), and reported in δ ppm using tetramethylsilane as the standard.

3f: n^{25} 1.4208; IR (KBr): υ_{max} 2960, 2860, 1458, 1380, 1252, 1102, 874, 842, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$): σ_H 3.56 (2H, t, *J*=6.2 Hz, OCH_2), 1.27 (16H, brs, $8 \times CH_2$), 0.88 (3H, t, *J*=6.4 Hz, CH_3), 0.10 (9H, s, $SiMe_3$)

3p: m.p. 127–129°C (colourless platelets from cyclohexane); IR (KBr): υ_{max} 3065, 2960, 2880, 1638, 1456,1376,1258, 1088, 886, 842, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$): σ_H 4.67 (1H, brs, 29-H), 4.58 (1H, brs, 29-H′), 3.67 (1H, d, *J*=9.8 Hz, 28-H), 3.22 (1H, d, *J*=9.8 Hz, 28–H′), 3.15 (1H, m, 3-H), 2.05-1.02 (complex, CH_2, CH), 1.68 (3H, s, 30-Me), 1.02, 0.97, 0.87, 0.83, 0.73 (15H, all s, $5 \times$ Me), 0.10 (18H, s, $2 \times SiMe_3$)

3q: m.p. 128–129°C (colourless needles from cyclohexane); IR (KBr): υ_{max} 2958, 2875, 1462, 1378, 1256, 1098, 902, 842, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$): σ_H 5.32 (1H, d, *J*=4.4 Hz, 6-H), 3.49 (1H, m, 3α-H), 1.16 (3H, s, 19-Me), 0.97 (3H, d, *J*=6.2 Hz, 21-Me), 0.88 (6H, d, J=6.6 Hz, 26, 27-Me), 0.69 (3H, s, 18-Me), 0.12 (9H, s, $SiMe_3$).

3r: m.p. 88–90°C (colourless platelets from cyclohexane); IR (KBr): υ_{max} 2960, 1460, 1378, 1252, 1098, 900, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$): σ_H 5.32 (1H, d, *J*=4.2 Hz, 6-H), 3.48 (1H, m, 3α-H), 1.06 (3H, s, 19-Me), 0.68 (3H, s, 18-Me), 0.11 (9H, s, $SiMe_3$).

28-trimethysiloxy-3β-hydroxylup-20(29)-ene (**6**): m.p. 121–122°C (colourless platelets from cyclo-hexane); IR (KBr): υ_{max} 3358, 3075, 2958, 1640, 1456, 1372, 1252, 1096, 1040, 882, 840, 740 cm^{-1} ; ^{1}H

Table 1 Silylation of alcohols by using HMDS in presence of PMA

Entry	Alcohols	Solvent	Reaction condition	Reaction time min/(h)	Yields/%[a]
1	*n*-Butyl alcohol (**1a**)	None	r. t.	5	96
2	*iso*-Butyl alcohol (**1b**)	None	r. t.	10	95
3	*sec*-Butyl alcohol (**1c**)	None	r. t.	(1)	90
4	*tert*-Butyl alcohol (**1d**)	None	Reflux	(3)	80
5	Cyclohexanol (**1e**)	None	r. t.	14	91
6	*n*-Decanol (**1f**)	None	r. t.	13	95
7	*n*-Octyl alcohol (**1g**)	None	r. t.	11	94
8	2-Ethyl hexanol (**1h**)	None	r. t.	10	95
9	Octadecyl alcohol (**1i**)	$CHCl_3$	r. t.	15	92
10	Benzyl alcohol (**1j**)	None	r. t.	5	94
11	Benzhydrol (**1k**)	CH_2Cl_2	r. t.	15	88
12	Triphenylmethanol (**1l**)	CH_2Cl_2	Reflux	(6)	68
13	Phenoxy ethyl alcohol (**1m**)	None	r. t.	40	95
14	2-Phenylethanol (**1n**)	CH_2Cl_2	r. t.	30	92
15	Benzoin (**1o**)	CH_2Cl_2	Reflux	90	89[b]
16	Betulin (**1p**)	$CHCl_3$	Reflux	50	92[c]
17	Cholesterol (**1q**)	CH_2Cl_2	Reflux	20	93
18	β-Sitosterol (**1r**)	CH_2Cl_2	r. t.	50	84

[a]Yields refers to isolated products.
[b]Yield refers to the oxidative product of benzoin.
[c]Yield refers to disilylated product.

NMR ($CDCl_3$): σ_H 4.67 (1H, brs, 29-H), 4.58 (1H, brs, 29-H′), 3.67 (1H, d, *J*=9.7 Hz, 28-H), 3.23 (1H, d, *J*=9.7 Hz, 28-H'), 3.17 (1H, m, 3-H), 2.05–1.04 (complex, CH_2, CH), 1.69 (3H, s, 30-H), 1.04 (3H, s, Me), 0.98 (3H, s, 2 × Me), 0.84 (3H, s, Me), 0.76 (3H, s, Me), 0.11 (9H, s, $SiMe_3$)

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