PROTECTION OF HYDROXY GROUPS AS TRIMETHYLSILYL ETHERS USING 1,1,1,3,3,3-HEXAMETHYLDISILAZANE (HMDS) CATALYZED BY POLY(4-VINYLPYRIDINIUM TRIBROMIDE)

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A very efficient procedure for the protection of alcohols and phenols is presented. The mixture of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and catalytic amounts of poly(4-vinylpyridinium tribromide) was found to be effective for the trimethylsilylation of alcohols and phenols. Protection reaction is very simple and performs heterogeneously in acetonitrile at room temperature under mild conditions.

Keywords: Poly(4-vinylpyridinium tribromide); Alcohols; Phenols; Protection; Trimethylsilylation; Hexamethyldisilazane (HMDS); Protecting groups; Silylation.

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked. Many protective groups have been, and are being, developed for this purpose. A protective group must fulfill a number of requirements. It must react selectively in good yield to give a protected substrate that is stable to the projected reactions. The protective group must be selectively removed in good yield by readily available, preferably nontoxic reagents that do not attack the regenerated functional group[1]. Silyl ethers are the most popular protecting groups of alcohols and phenols in synthetic organic chemistry and a various types of silyl ethers have been reported[2–5]. Also trimethylsilylation is widely used to protect alcoholic and phenolic compounds[6–10]. Even though various approaches have been emerged in the recent years for the silylation of hydroxy group[11–16], these methods suffer from some disadvantages like low selectivity, long reaction times, low yields of products, toxicity, delicate purification step, lack of reactivity or

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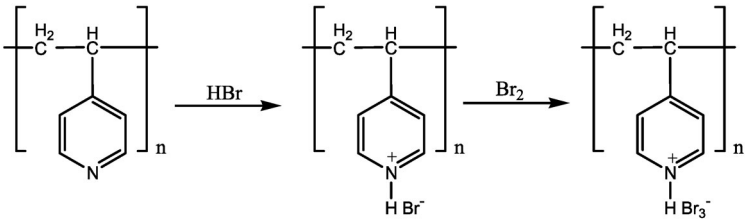
the difficulty in removal of by-products. 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) as a cheap, stable and commercially available reagent is one of the most widely used silylating agent for silylation of alcohols and phenols. Its handling does not require special precautions and the workup is not time-consuming, because the by-product of the reaction is ammonia, which is simple to remove from the reaction media. However, the low silylating power of HMDS is the main drawback to its application. Therefore, an appropriate catalyst should be used for activation of this reagent.

RESULTS AND DISCUSSION

Our recent studies are focused on application of new reagents or catalysts in the organic functional group transformations[17–21]. In continuation of this investigation we decided to explore a metal free catalyst for the trimethylsilylation of alcohols and phenols by 1,1,1,3,3,3-hexamethyldisilazane (HMDS). In this light we prepared poly(4-vinylpyridinium tribromide) from poly(4-vinylpyridine) as is outlined in Scheme 1.



SCHEME 1

To check the solvent effect on the outcome of the trimethylsilylation reaction and to find appropriate solvent, different solvents were applied for the trimethylsilylation of 2,4-dichlorobenzyl alcohol, as a typical example, by hexamethyldisilazane and poly(4-vinylpyridinium tribromide) as catalyst. The summarized results in Table I shown that acetonitrile is the most effective solvent, so it was employed in all reactions.

With optimal conditions in hand, we report here chemoselective trimethylsilylation of different types of hydroxy groups including primary, secondary, hindered secondary, and tertiary alcohols and a variety of phenols using 1,1,1,3,3,3-hexamethyldisilazane (**1**) in the presence of a catalytic amount of poly(4-vinylpyridinium tribromide) (**2**) in acetonitrile at room temperature (Scheme 2 and Table II).

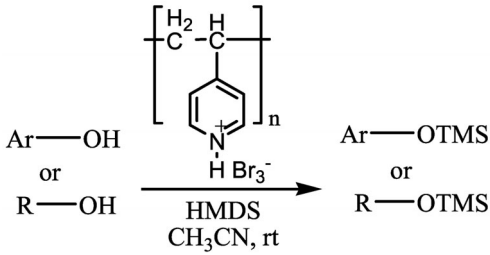
The result of this investigation was excellent. Trimethylsilylated products were prepared easily by mixing of an alcohol or phenol, hexamethyl-

TABLE I
Trimethylsilylation of 2,4-dichlorobenzyl alcohol using HMDS and a catalytic amount of poly(4-vinylpyridinium tribromide) in different solvents[a]

Entry	Solvent	Time, min	GC yield, %
1	acetonitrile	10	100
2	acetone	180	79
3	chloroform	180	83
4	dichloromethane	180	70
5	ethyl acetate	180	48
6	diethyl ether	180	43

[a] Substrate/HMDS/Catalyst 1:0.8:0.02 (mmol).

disilazane and 2 mole % of poly(4-vinylpyridinium tribromide) in acetonitrile followed by stirring of this mixture at room temperature for appropriate time (see Table II). After reaction completion, the reaction quenched with water and dichloromethane was added to the mixture. Pure product can be easily isolated from the reaction media by drying organic phase over Na_2SO_4, simple filtration and evaporation of the solvent.



SCHEME 2

As it is evident from Table II, the good range of turn over number (TON) of catalyst is observed. To investigate the role of poly(4-vinylpyridinium tribromide) as a catalyst, 2,4-dichlorobenzyl alcohol was trimethylsilylated by HMDS in the absence of catalyst. However, trimethyl(2,4-chlorophenoxy)silane was obtained in 57% yield after 3 h (Table II, entry 11). Interestingly, when the same reaction was performed in the presence of 2 mole % poly(4-vinylpyridinium tribromide), the silylated product was obtained in 90% yield after 10 min (Table II, entry 10).

TABLE II

Trimethylsilylation of alcohols and phenols to the corresponding trimethylsilyl alcohols and phenols using HMDS in the presence of a catalytic amount of poly(4-vinylpyridinium tribromide) in acetonitrile at room temperature

Entry	Substrate	Product	Substrate/HMDS/Cat. (mmol)		Time min	Yield %[a]	TON
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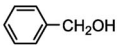
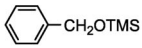
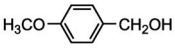
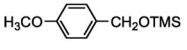
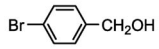
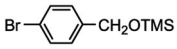
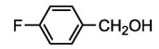
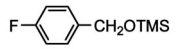
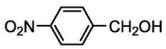
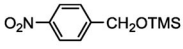
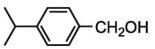
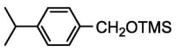
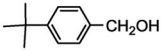
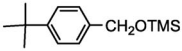
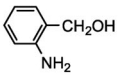
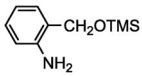
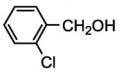
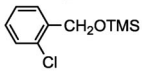
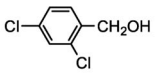
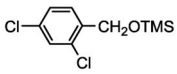
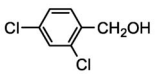
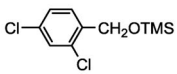
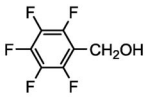
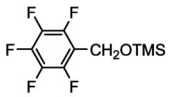
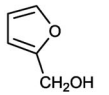
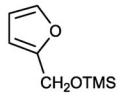
1			0.8	0.02	7	96	48
2			0.8	0.02	2	95	47.5
3			0.8	0.02	12	82	41
4			0.8	0.02	5	99	49.5
5			1	0.02	50	86	43
6			0.8	0.02	10	98	49
7			0.8	0.02	3	86	43
8			1	0.02	2	98	49
9			1	0.02	5	87	43.5
10			0.8	0.02	10	90	45
11			0.8	–	180	57[a,b]	–
12			1	0.02	3	98	49
13			0.8	0.02	2	92	46

TABLE II
(*Continued*)

Entry	Substrate	Product	Substrate/HMDS/Cat (mmol)		Time min	Yield %[a]	TON
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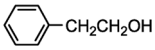
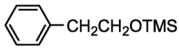
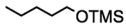
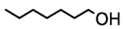
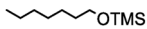
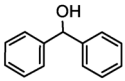
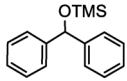
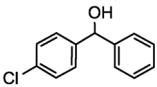
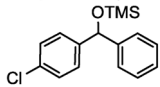
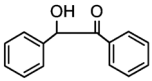
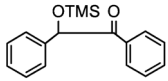
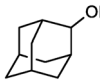
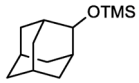
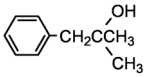
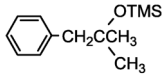
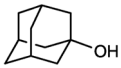
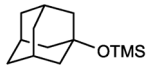
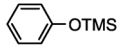
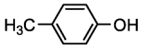
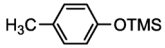
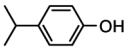
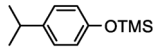
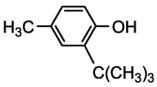
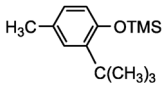
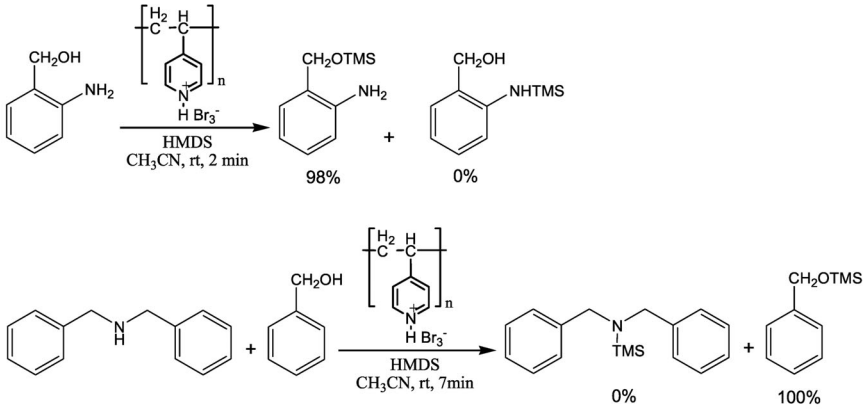
14			0.8	0.02	2	98	49
15			0.8	0.02	2	96	48
16			0.8	0.02	15	95	47.5
17			1.5	0.02	10	96	48
18			1.5	0.02	8	91	45.5
19			1.2	0.02	6	92	46
20			1.2	0.02	2	95	47.5
21			1.8	0.02	180	86	43
22			1.5	0.02	32	95	47.5
23			1.0	0.02	40	85	42.5
24			1.2	0.02	11	95	47.5
25			0.8	0.02	6	92	46
26			0.8	0.02	4	99	49.5

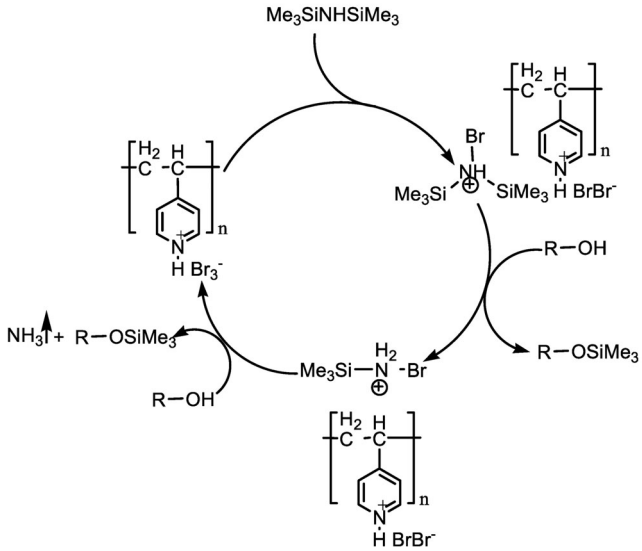
[a] GC yield. [b] In the absence of catalyst.

In order to consider chemoselectivity of the described system, some competitive reactions were designed as outlined in Scheme 3. As it is shown in Table II (entry 8) and Scheme 3, the hydroxy group was silylated selectively in the presence of an amino group.



SCHEME 3

A plausible mechanism for the silylation reaction is outlined in Scheme 4.



SCHEME 4

To show the efficiency of the described system in comparison with procedures previously reported in the literature, we compared our results of trimethylsilylation of 2-adamantanol (as a typical example) with the best results from the literature as shown in Table III.

TABLE III
Comparison of the different methods used for the trimethylsilylation of 2-adamantanol

Entry	Catalyst	HMDS/Catalyst mmol	Time min	Yield %[a]	Ref.
1	poly(4-vinylpyridinium tribromide)	1.2:0.02	2	95	this work
2	tribromomelamine	0.9:0.04	90	99	6
3	1,3-dichloro-5,5-dimethylhydantoin	0.8:0.05	120	89	7
4	trichloromelamine	1.3:0.09	30	93	7
5	$Fe(HSO_4)_3$	1.5:0.25	140	80	14
6	KBr	1.4:0.15	30	90	22
7	$Al(HSO_4)_3$	0.75:0.06	240	50	23
8	silica sulfonic acid	0.6:0.03	80	99	24

CONCLUSION

In summary, herein we report a new catalytic method for efficient trimethylsilylation of compounds containing hydroxy groups under metal-free, mild and heterogeneous conditions. This method offers the advantage of shorter reaction times, high selectivity, non-toxic conditions and easy workup.

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies. The silylated products were characterized by comparison of their spectral (IR, ν in cm^{-1}; ^1H NMR, δ in ppm) and physical data with authentic samples. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL FX 90 Q, tetramethylsilane (TMS) was used as an internal standard. Infrared spectra were recorded on a Perkin–Elmer GX FT IR spectrometer. Thin-layer chromatography (TLC) was used for checking of reaction progress.

Preparation of Poly(4-vinylpyridinium tribromide)

In a 50-ml round-bottomed flask, HBr (1 ml, 47%) and poly(4-vinylpyridine) (1.85 g) were stirred for 1 h, then kept at 50 °C for 24 h to obtain dry poly(4-vinylpyridinium bromide).

In the next step, Br_2 (1.2 ml) was added to the resulting powder, this mixture was stirred for 2 h and an orange crystalline solid of **2** was obtained quantitatively.

Trimethylsilylation of 2-Adamantanol with HMDS
Catalyzed by Poly(4-vinylpyridinium tribromide). General Procedure

To a mixture of 2-adamantanol (0.152 g, 1 mmol) and HMDS (0.194 g, 1.2 mmol) in CH_3CN (10 ml), poly(4-vinylpyridinium tribromide) (**2**; 7 mg, 0.02 mmol) was added and the mixture was stirred at room temperature for 2 min (reaction progress was monitored by TLC). Then the reaction was quenched with water (10 ml) and CH_2Cl_2 (20 ml) was added. The organic phase was dried over Na_2SO_4 (3 g) and evaporation of the solvent gave pure trimethyl-(2-adamantanoxy)silane (0.213 g, 95%). ^{1}H NMR (90 MHz, $CDCl_3$): 3.78 m, 1 H; 1.35–2.25 m, 14 H; 0.08 s, 9 H (CH_3). IR (Nujol): 2853, 1450, 1354, 1249, 1133, 1093, 880, 839, 752.

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