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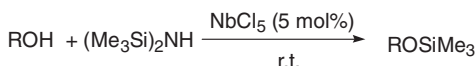
RAPID AND EFFICIENT TRIMETHYLSILYL PROTECTION OF HYDROXYL GROUPS CATALYZED BY NIOBIUM(V) CHLORIDE

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GRAPHICAL ABSTRACT



Abstract An efficient and convenient procedure for the trimethylsilylation of a wide variety of alcohols, including primary, benzylic, secondary, and phenols with hexamethyldisilazane, has been developed. The reactions were carried out at room temperature in the presence of a catalytic amount of niobium(V) chloride and afforded the corresponding trimethylsilyl ethers in high to excellent yields in short time.

Keywords Hexamethyldisilazane; hydroxyl groups; niobium pentachloride; phenols; trimethylsilylation

INTRODUCTION

Protection of hydroxyl groups plays an essential role in multistep organic synthesis, and a large number of reagents and methods have been developed. Among the protecting groups for protection of alcohols, silyl ethers have been introduced as suitable protection groups for this purpose due to their easy of formation and cleavage, and their reasonable stability to the nonacidic media conditions. Trimethylsilylation is one of the most often used silylating methods. Some silylating agents such as trimethylsilyl chloride, ketene methyl-trialkylsilyl acetals, allyl silanes, ethyl trimethylsilyl acetate, *N,N*-bis(trimethylsilylurea), methyl 3-(trimethylsilyloxy)crotonate, and trimethylsilyl azide have been reported for trimethylsilyl (TMS) protection of hydroxyl groups.¹ The use of some silylating agents

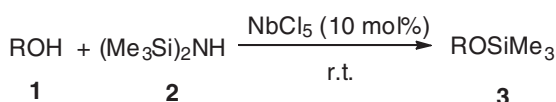
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is limited by their unavailability, toxicity, or the laborious processes of purifying the products. Hexamethyldisilazane (HMDS) is a commercially available and cheap reagent, giving ammonia as the only byproduct, and the products are separated from excess of HMDS by a simple distillation. However, the low silylating power of HMDS is the main drawback to its application. Therefore, a variety of reagents have been reported to improve its silylating power.^{2–26} Although these procedures worked nicely in many cases, sometimes, however, some of these procedures are associated with one or more shortcomings such as long reaction time, low yield, the lack of generality, requirement of excess of reagents, the use of expensive or less easily available catalysts, and vigorous reaction conditions.

In recent years, niobium(V) chloride has been considered as an efficient Lewis acid catalyst for a variety of organic transformations.^{27,28} For example, it has been used to catalyze regioselective dealkylation of alkyl aryl ethers,²⁹ and in the selective acetylation of amines and thiols,³⁰ the cyanosilylation of aldehydes,³¹ chemoselective synthesis of 1,1-diacetates,³² and one-pot Mannich-type reaction,³³ as well as deprotection of methoxy methyl ether.³⁴ It also serves as the catalyst for opening of epoxide rings,³⁵ the synthesis of 1,5-benzodiazepine derivatives,³⁶ bis(indol)alkanes,³⁷ trisubstituted alkenes,³⁸ and pyrano[3,2-*c*]quinolines.³⁹ As part of our continuing interest in the development of new synthetic methodologies,^{40–44} we report in this article an efficient and convenient procedure for the trimethylsilylation of alcohols and phenols with HMDS in the presence of a catalytic amount of NbCl₅ at room temperature (Scheme 1).



Scheme 1 Trimethylsilylation of alcohols and phenols catalyzed by NbCl₅.

RESULTS AND DISCUSSION

In an optimized procedure, the reaction of 9-fluorenylmethanol with hexamethyldisilazane was carried out by varying the catalyst loading in CH₂Cl₂ at room temperature. It was found that when increasing the amount of NbCl₅ from 1 to 5, 10, and 15 mol%, the yields increased from 50 to 70, 95, and 96, respectively. Use of 10 mol% of NbCl₅ is sufficient to catalyze the required transformation within a span of 5 min. Any excess of NbCl₅ beyond this loading did not show any further in conversion and yield. Use of less than the required catalyst loading resulted in low yields. Only trace product was detected under similar condition in the absence of catalyst at long reaction time (1 h).

The general applicability of this method was further evaluated for structurally diverse alcohols and phenols under optimized reaction conditions, and the results are depicted in Table 1. The results clearly show that primary, benzylic, and secondary alcohols as well as phenols are all good substrates in this reaction, and the corresponding trimethylsilyl ethers are formed in good to excellent yields. Moreover, when the alcoholic and phenolic hydroxyl groups are present in the same substrate (Table 1, entry 21), they are transformed to the corresponding disilylated product. This method was also found to be efficient for the trimethylsilylation of allylic alcohol (Table 1, entry 15). However, tertiary alcohol such as triphenylmethanol (Table 1, entry 25) was not silylated during the course of the reaction. It is noteworthy that the substituents on the phenol moiety play a significant

Table 1 Protection of alcohols or phenols by formation of trimethylsilyl ethers catalyzed by NbCl₅

Entry	Alcohols or phenols	Product	Solvent	Time (min)	Yield (%) ^a	Ref.
1	<i>n</i> -Dodecanol	3a	CH ₂ Cl ₂	30	87	2
2	9-Fluorenylmethanol	3b	CH ₂ Cl ₂	5	95	3
3	2-Phenylethyl alcohol	3c	None	4	95	4
4	1-Adamantanemethanol	3d	CH ₂ Cl ₂	30	90	45
5	2-Phenylethanol	3e	None	4	94	5
6	Benzyl alcohol	3f	None	5	93	4
7	<i>p</i> -Tolylmethanol	3g	None	4	90	8
8	4-Nitrophenylmethanol	3h	CH ₂ Cl ₂	30	93	8
9	Cyclohexanol	3i	None	30	95	8
10	Diphenylmethanol	3j	CH ₂ Cl ₂	30	90	4
11	2-Thiophenemethanol	3k	None	30	91	13
12	1-Phenylethanol	3l	None	10	95	4
13	(4-Methoxyphenyl)methanol	3m	None	8	93	8
14	1- <i>o</i> -Tolyloxy-propane-1,3-diol	3n	CH ₂ Cl ₂	20	90 ^b	
15	Cinnamyl alcohol	3o	None	20	91	8
16	Phenol	3p	None	20	92	4
17	4-Aminophenol	3q	CH ₂ Cl ₂	15	94	4
18	4-Methylphenol	3r	CH ₂ Cl ₂	15	95	9
19	4-Bromophenol	3s	CH ₂ Cl ₂	30	70	46
20	Salicylaldehyde	3t	CH ₂ Cl ₂	30	51	10
21	4-Hydroxymethylphenol	3u	CH ₂ Cl ₂	15	93 ^b	11
22	α -Naphthol	3v	CH ₂ Cl ₂	5	95	9
23	β -Naphthol	3w	CH ₂ Cl ₂	30	90	8
24	4-Nitrophenol	3x	CH ₂ Cl ₂	60	0	12
25	Triphenylmethanol	3y	CH ₂ Cl ₂	60	0	12

^aIsolated yield.^bYields refer to disilylated products.

role in this process. The presence of an electron-releasing group, such as methyl and amino, enhanced the product formation as indicated by short reaction times. Phenol with an electron-withdrawing group, such as a bromo and aldehyde group (Table 1, entries 19 and 20), required relatively longer reaction times to render lower yield. Nitrophenol (Table 1, entry 24) failed to convert into the corresponding trimethylsilyl ether when the mixture was stirred for 1 h in the presence of NbCl₅.

Finally, in order to show the efficacy of NbCl₅ with respect to the reported catalysts, we compared the reaction time and yield for trimethylsilylation of α -naphthol. As demonstrated in Table 2, the yield/time ratios of the present method are better or comparable with the reported methods.

In conclusion, we have demonstrated that NbCl₅ is a highly efficient catalyst for the trimethylsilylation of a wide range of structurally varied alcohols and phenols. The advantages, such as mild reaction conditions, short reaction times, and high yields, make our method a valuable contribution to the existing processes in the field of protection of hydroxyl groups.

EXPERIMENTAL

IR spectra were obtained using a Bruker Tensor 27 spectrometer instrument. NMR spectra were taken on a Bruker DRX-500 spectrometer. Elemental analyses were carried out on a Vario EL III CHNOS elemental analyzer.

Table 2 Comparison of the activity of some catalyst in the trimethylsilylation of α -naphthol

Entry	Catalyst	Conditions	Time	Yield (%)	Ref.
1	Silica-FeCl ₃	Solvent-free/rt	6 min	93	5
2	Al(H ₂ PO ₄) ₃	Solvent-free/rt	7 min	94	7
3	1,3-Dibromo-5,5-dimethylhydantoin	Solvent-free/rt	20 min	95	9
4	FeCl ₃	CH ₃ CN/rt	75 min	85	14
5	InBr ₃	CH ₂ Cl ₂ /rt	4 h	94	15
6	Fe(CF ₃ CO ₂) ₃	Solvent-free/rt	20 min	92	16
7	ZnO	Solvent-free/rt	5 min	90	17
8	Fe(NO ₃) ₃ ·9H ₂ O/NaI	CH ₂ Cl ₂ /rt	8 min	95	20
9	<i>N</i> -Bromosuccinimide	CH ₂ Cl ₂ /rt	3 h	93	23
10	CuSO ₄ ·5H ₂ O	CH ₃ CN/rt	38 h	50	24
11	Silica chloride	CH ₂ Cl ₂ /rflux	4 h	65	25
12	LiClO ₄	Solvent-free/rt	20 min	68	26
13	NbCl ₅	CH ₂ Cl ₂ /rt	5 min	95	This work

Procedure for Trimethylsilylation of Alcohols or Phenols

A mixture of alcohol or phenol (5 mmol), HMDS (5 mmol), and NbCl₅ (0.50 mmol, 10 mol%) in CH₂Cl₂ (5 mL) or in the absence of solvent was stirred at room temperature. After completion of the reaction (monitored by TLC or GC), the mixture was diluted with CH₂Cl₂ and washed with water. The organic layer was dried over anhydrous MgSO₄ and evaporated under reduced pressure. Then the crude product was subjected to column chromatography over silica gel using hexane as eluent to afford the pure trimethylsilyl ether.

All of the products were liquids. Compounds **3** except for **3n** are known compounds and their structures were identified by comparison of their physical and spectroscopic data with those previously reported. The new product **3n** was characterized on the basis of its elemental analysis and IR, ¹H NMR, and ¹³C NMR spectra.

(9*H*-Fluoren-9-ylmethoxy)trimethylsilane (**3b**)

IR (neat): 2956, 1616, 1577, 1477, 1466, 1450, 1379, 1321, 1251, 1109, 999, 896, 839, 738 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ _H 0.13 (s, 9H), 3.81 (d, *J* = 8.0 Hz, 2H), 4.08 (t, *J* = 8.0 Hz, 1H), 7.28 (td, *J* = 7.5, 1.0 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.62 (dd, *J* = 7.5, 1.0 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 2H) ppm; Anal. Calcd for C₁₇H₂₀OSi: C, 76.07; H, 7.51. Found: C, 75.82; H, 7.76.

Trimethylphenethyloxysilane (**3e**)

IR (neat): 2954, 1604, 1496, 1454, 1382, 1250, 1094, 927, 881, 842, 748, 698 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ _H 0.15 (s, 9H), 2.97 (t, *J* = 7.5 Hz, 2H), 3.84 (t, *J* = 7.5 Hz, 2H), 7.27–7.36 (m, 5H) ppm; Anal. Calcd for C₁₁H₁₈OSi: C, 67.98; H, 9.34. Found: C, 68.18; H, 9.20.

Trimethyl-(4-nitrobenzyloxy)silane (3h)

IR (neat): 2956, 1608, 1520, 1456, 1348, 1251, 1203, 1097, 1014, 842, 748, 688 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ_{H} 0.19 (s, 9H), 4.79 (s, 2H), 4.78 (d, $J = 8.5$ Hz, 2H), 6.19 (d, $J = 8.5$ Hz, 2H) ppm; Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_3\text{Si}$, C, 53.31; H, 6.71; N, 6.22. Found: C, 53.50; H, 6.56, N, 6.05.

1-(1,3-Bis(trimethylsilyloxy)propoxy)-2-methylbenzene (3n)

IR (neat): 2956, 2873, 1635, 1604, 1593, 1497, 1437, 1250, 1122, 1053, 989, 842, 748 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ_{H} 0.13 (s, 9H), 0.16 (s, 9H), 2.23 (s, 3H), 3.61–3.72 (m, 2H), 3.89–4.02 (m, 2H), 4.06–4.10 (m, 1H), 6.81 (d, $J = 8.0$, 1H), 6.85 (d, $J = 8.0$, 1H), 7.12–7.15 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} –0.48, 0.30, 16.51, 64.55, 69.63, 72.05, 110.95, 120.36, 126.70, 126.78, 130.67, 157.04 ppm; Calcd for $\text{C}_{16}\text{H}_{30}\text{O}_3\text{Si}_2$, C, 58.84; H, 9.26. Found: C, 59.02; H, 9.05.

Trimethyl-(3-phenylallyloxy)silane (3o)

IR (neat): 2956, 1628, 1419, 1122, 1068, 1001, 936, 852, 617 ppm; ^1H NMR (500 MHz, CDCl_3) δ_{H} 0.13 (s, 9H), 4.31 (dd, $J = 5.5$, 1.5 Hz, 2H), 6.29 (dt, $J = 15.5$, 5.5 Hz, 1H), 6.58 (dt, $J = 15.5$, 1.5 Hz, 1H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.29 (t, $J = 7.5$ Hz, 2H), 7.37 (d, $J = 7.5$ Hz, 2H) ppm; Calcd for $\text{C}_{12}\text{H}_{18}\text{OSi}$, C, 69.84; H, 8.79. Found: C, 70.01; H, 8.52.

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