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Alum: An Efficient Catalyst for Trimethylsilylation of Alcohols and Phenols with Hexamethyldisilazane

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A highly convenient method for the trimethylsilylation of alcohols and phenols *via* treatment by hexamethyldisilazane in the presence of alum as a catalyst has been developed. A wide variety of hydroxyl groups were selectively protected in CH_3CN under mild conditions.

**Key Words: Alcohol, Phenol, Trimethylsilyl ether, Alum, Catalysis.**

INTRODUCTION

Protection of hydroxyl functional group is an important process in multi-step synthesis[1]. One of the popular methods for this purpose is to transfer hydroxyl group into their corresponding silylether[2]. Generally, the formation of silylether was carried out by the treatment of alcohols with silylchlorides or silyltriflayes under the influence of basic condition[3-7]. However, these methods frequently suffered from drawbacks such as lack of reactivity and the difficulty in removal of ammonium salts. Hexamethyldisilazane (HMDS) is a cheap and commercially available compound that can be used for the preparation of trimethylsilylethers from hydroxyl compound. O-Silylation of alcohol using hexamethyldisilazane is an attractive alternative, since the only by-product of the reaction is ammonia. Even though the handling of this reagent is easy, its main drawback is its poor silylating power, which needs forceful condition and long reaction time[8]. A variety of catalysts have been reported for the activation of hexamethyldisilazane in the literature, $Sn(IV)(TPP)(BF_4)_2$[9], SiO_2-$ZnCl_2$[10], $La(NO_3)_3$[11], $TiCl_2(OTf)$-SiO_2[12], $Fe(ClO_4)_3$[13], 1,3-dichloro-5,5-dimethyl-hydantoin[14], $Bi(OTf)_3$[15], $TiCl_3(OTf)$[16], nafion SAC-13[17], $NaHSO_4$-SiO_2[18], NBS[19], Al_2O_3-$HClO_4$[20], silica-$FeCl_3$[21], $Al(H_2PO_4)_3$[22], $ZrO(OTf)_2$[23], ZnO[24], $Fe(HSO_4)_3$[25], silica sulfuric acid[26], ferric chloride[27], [bmim][BF_4][28], montmorillonite K-10[29] are important systems. Although these procedures provide improvement, many of these catalysts or activators require long reaction time and drastic reaction condition.

Recently, alum $(KAl(SO_4)_2 \cdot 12H_2O)$, which is relatively nontoxic and inexpensive catalyst, has emerged as an efficient alternative catalyst for a variety of prominent organic reactions

such as Biginelli[30], Pechmann reaction[31] and also used for the synthesis of 1,8-dioxo-octahydroxanthenes[32], isoquinolonic acids[33], trisubstituted imidazoles[34], 1'*H*-spiro[isoindoline-1,2'-quinazoline]-3,4'(3'*H*)-diones[35], 1,3,4-oxadiazoles[36] and 1,5-benzodiazepines[37].

In this paper, we wish to report a rapid and highly efficient method for trimethylsilylation of alcohols and phenols with hexamethyldisilazane (HMDH) catalyzed by alum at room temperature (**Scheme-I**).
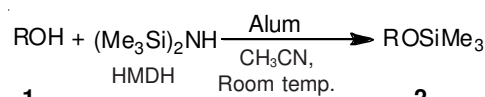
Scheme-I

EXPERIMENTAL

NMR spectra were determined on Bruker AV-400 spectrometer at room temperature using TMS as internal standard, coupling constants (*J*) were measured in Hz; elemental analysis were performed by a Vario-III elemental analyzer; melting points were determined on a XT-4 binocular microscope and were uncorrected; commercially available reagents were used throughout without further purification unless otherwise stated.

General procedure for the preparation of 2: To a mixture of hexamethyldisilazane (1 mmol) and alum (0.05 mmol) in CH_3CN (1 mL) an alcohol or phenol (1 mmol) was added and the mixture was stirred at room temperature for the specified time (Table-3). Then reaction was quenched with water (5 mL) and organic phase dried over Na_2SO_4 (3 g) after 5 min. Evaporation of the solvent under reduce pressure gave almost pure

product. The desired pure products were characterized by comparison of their NMR data with those of known compounds. The spectral data of some new trimethylsilylethers are given below:

(1-(3-Bromophenyl)ethoxy)trimethylsilane: (2i): ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.40-7.31 (m, 4H), 4.82 (q, J = 8.4, 1H), 1.49 (d, J = 4.4, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.3, 135.1, 130.2, 127.4, 125.8, 124.2, 68.9, 26.9, 0.08; anal. calcd. (%) for C$_{11}$H$_{17}$BrSi: C 48.35, H 6.27; found (%): C 48.28, H 6.35.

((4-Chlorocyclohexa-2,4-dienyl)(4-chlorophenyl)-methoxy)trimethylsilane (2j): ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.60-7.53 (m, 4H), 7.28-7.20 (m, 4H), 5.89 (s, 1H), 0.28 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.8, 158.2, 141.2, 140.2, 116.3, 115.0, 76.2, 0.10; Anal. calcd. (%) for C$_{16}$H$_{18}$OCl$_2$Si: C 59.07, H 5.58; found (%): C 59.01, H 5.63.

(4-(4-Methoxyphenyl)butoxy)trimethylsilane (2o): ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.10 (d, J = 8.4, 2H), 6.82 (d, J = 8.4, 2H), 3.72 (s, 3H), 3.70-3.67 (m, 2H), 2.58-2.54 (m, 2H), 1.65-1.60 (m, 2H), 1.65-1.60 (m, 2H), 1.47-1.40 (m, 2H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.2, 132.1, 130.4, 114.2, 65.2, 55.9, 36.8, 33.1, 26.9, 0.12; Anal. calcd. (%) for C$_{14}$H$_{24}$O$_2$Si: C 66.61, H 9.58; found (%): C 66.72, H 9.48.

RESULTS AND DISCUSSION

First, we tried to convert benzyl alcohol (1 mmol) to its corresponding benzylsilylether with alum (0.05 mmol) and hexamethyldisilazane (1 mmol) in the presence of various solvents (Table-1). The results in Table-1 show that amongst these solvents, acetonitrile was the solvent of choice in terms of time and product yield.

TABLE-1
SOLVENT OPTIMIZATION FOR THE SYNTHESIS OF OPTIMIZATION FOR THE SYNTHESIS OF BENZYLTRIMETHYLSILYL ETHER*

Entry	Solvent	Time (min)	Yield (%)**
1	THF	40	89
2	CH$_2$Cl$_2$	25	90
3	EtOAc	30	86
4	n-Hexane	45	73
5	CHCl$_3$	30	85
6	CH$_3$CN	25	97

*Reaction conditions: benzyl alcohol (1 mmol); HMDS (1 mmol); Alum (0.05 mmol); Room temperature **Isolated yield.

To determine the appropriate concentration of the catalyst alum, we investigated the model reaction at different concentrations of catalyst like 1, 2, 3, 4, 5, 6, 7 and 8 mol %. The product formed in 65, 72, 82, 90, 97, 96, 97 and 96 % yield, respectively. This indicates that 5 mol % of alum is sufficient for the best result (Table-2, Entry 6).

Using these optimized reaction conditions, a series of alcohols has been subsequently experimented. As shown in Table-3, benzylic alcohols, cyclic alcohols and aliphatic alcohols were silylated with hexamethyldisilazane at room temperature within 35 min in excellent yields after the addition of the catalyst alum. It is interesting to check whether the same catalyst could be employed for trimethysilylation of phenolic compounds. Under the same conditions as above, most of the

TABLE-2
AMOUNT OF CATALYST OPTIMIZATION FOR THE SYNTHESIS OF BENZYL TRIMETHYLSILYL ETHER*

Entry	Alum (mol %)	Time (h)	Yield (%)**
1	0	60	0
2	1	45	65
3	2	30	72
4	3	30	82
5	4	25	90
6	5	25	97
7	6	25	96
8	7	20	97
9	8	20	96

*Reaction conditions: benzyl alcohol (1 mmol); HMDS (1 mmol); Room temperature **Isolated yield.

TABLE-3
TRIMETHYLSILYLATION OF ALCOHOLS AND PHENOLS CATALYZED BY ALUM*

Entry	Substrate	Time (min)	Products	Yield (%)**
1	Benzyl alcohol	25	**2a**	97
2	4-Chlorobenzyl alcohol	20	**2b**	100
3	3-Nitrobenzyl alcohol	25	**2c**	92
4	4-Nitrobenzyl alcohol	20	**2d**	95
5	4-Methylbenzyl alcohol	25	**2e**	88
6	4-Methoxylbenzyl alcohol	25	**2f**	92
7	2,4-Dichlorobenzyl alcohol	30	**2g**	92
8	3,4-Methylenedioxybenzyl alcohol	35	**2h**	89
9	1-(3-Bromophenyl)ethanol	30	**2i**	94
10	(4-Chlorocyclohexa-2,4-dienyl)(4-chlorophenyl) methanol	20	**2j**	92
11	Cyclohexanol	25	**2k**	90
12	Menthol	35	**2l**	85
13	Cholesterol	35	**2m**	82
14	2-Adamantanol	30	**2n**	87
15	4-(4-Methoxyphenyl)butan-1-ol	30	**2o**	92
16	Lauryl alcohol	30	**2p**	85
17	2,2-Dimethylpropan-1-ol	20	**2q**	88
18	Pentan-1-ol	20	**2r**	95
19	Phenol	20	**2s**	99
20	4-Chlorophenol	20	**2t**	100
21	3-Nitrophenol	25	**2u**	92
22	4-Nitrophenol	20	**2v**	96
23	4-Methylphenol	30	**2w**	98
24	4-Methoxylphenol	25	**2x**	92
25	2,4-Dichlorophenol	30	**2y**	94

*Reaction conditions: alcohol or phenol (1 mmol); HMDS (1 mmol); alum (0.05 mmol); neat; Room temperature **Isolated yield.

tested phenols were smoothly converted into the corresponding silyl ethers in good yields. No elimination and rearrangement by-products were observed at all.

A plausible mechanism has been shown in **Scheme-II**. Lewis acid-base interaction between the alum and nitrogen of hexamethyldisilazane polarizes the N-Si bond to produce the reactive silylating agent (I), which rapidly reacts with alcohol to give the corresponding silyl compounds and complex (II). This complex (II) reacts with another molecule of alcohol to produce the corresponding silyl derivative. Finally the complex (III) collapses to the formation of ammonia and liberation of the catalyst. The evolution of ammonia was confirmed by its strong, pungent odor and using the red litmus paper which turns to blue.
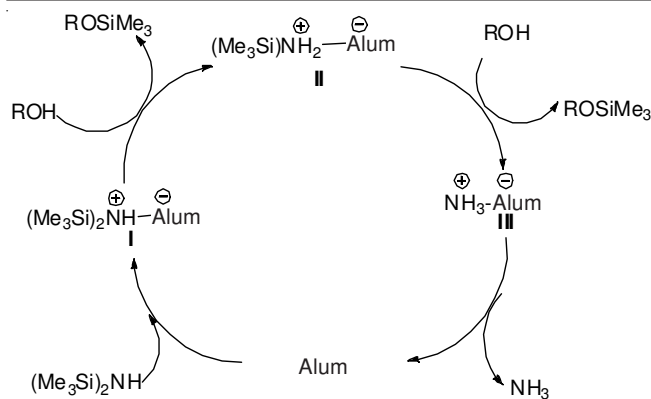
Scheme-II

In order to show the merit of alum in comparison with other catalysts used for the similar reaction, we have tabulated some of the results in Table-4. As it is evidence from the results, alum found to be effective catalyst for trimethylsilylation of alcohols and phenols with hexamethyldisilazane.

TABLE-4
ALUM CATALYZED TRIMETHYLSILYLATION OF BENZYL ALCOHOL IN COMPARISON WITH OTHER LITERATURES

Entry	Catalyst and conditions	Solvent	Time (min)	Yield (%)	Ref.
1	$Fe(HSO_4)_3$ (25 mol %); reflux	CH_3CN	100	70	[25]
2	$TiCl_2(OTf)$-SiO_2 (1 mol %)	Neat	10	87	[12]
3	Trichloromelamine (3 mol %)	CH_2Cl_2/ CH_3CN	30	92	[14]
4	Silica sulfuric acid (83 mg/mmol)	Neat	10	93	[26]
5	Alum (5 mol %)	CH_3CN	25	98	The study

Conclusion

We have developed a simple, mild and environmentally benign method for trimethylsilylation of alcohols and phenols with hexamethyldisilazane catalyzed by alum at room temperature. This method offers the advantage of shorter reaction times, high chemoselectivity and easy workup. It is believed that this methodology could be an important addition to the existing methodologies.

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