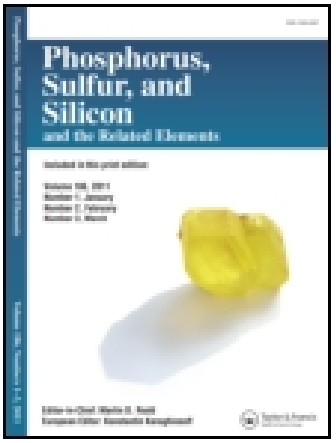

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Melamine-Trisulfonic-Acid-Catalyzed Trimethylsilylation of Alcohols and Phenols

Liqiang Wu [a] , Pengli Sun [a] & Fulin Yan [a]
[a] School of Pharmacy , Xinxiang Medical University , Xinxiang, Henan, China
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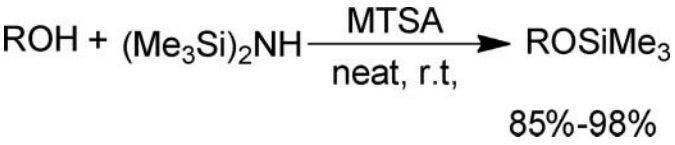
MELAMINE-TRISULFONIC-ACID-CATALYZED TRIMETHYLSILYLATION OF ALCOHOLS AND PHENOLS

Liqiang Wu, Pengli Sun, and Fulin Yan
School of Pharmacy, Xinxiang Medical University, Xinxiang, Henan, China

GRAPHICAL ABSTRACT



Abstract *A highly convenient method for the trimethylsilylation of alcohols and phenols via treatment by hexamethyldisilazane in the presence of melamine trisulfonic acid as a catalyst has been developed. A wide variety of hydroxyl groups were selectively protected under solvent-free conditions.*

Keywords trimethylsilylation; hexamethyldisilazane; melamine trisulfonic acid; solvent-free

INTRODUCTION

The protection of hydroxyl groups by the formation of silyl ethers has been extensively used in organic synthesis.[1] Among many reagents which have been used for the protection, hexamethyldisilazane (HMDS), a cheap, stable, and commercially available reagent, is selected as one of the best candidates for this purpose. Its handling does not require special precautions and the workup is not facile because the by-product of the reaction is ammonia, which is simple to remove from the reaction medium.[2] However, the low silylating power of HMDS is the main drawback to its application. Therefore, there are a variety of catalysts for the activation of this reagent, such as $Sn^{IV}(TPP)(BF_4)_2$,[3] SiO_2–$ZnCl_2$,[4] $La(NO_3)_3$,[5] $TiCl_2(OTf)$–SiO_2,[6] $Fe(ClO_4)_3$,[7] 1,3-dichloro-5,5-dimethylhydantoin,[8] $ZrCl_4$,[9] trichloroisocyanuric acid,[10] $LaCl_3$,[11] $NaHSO_4$–SiO_2,[12] NBS,[13] $H_3PW_{12}O_{40}$,[14] alumina-supported heteropolyoxometalates,[15] $InBr_3$,[16] $CuSO_4$,17 ZnO,[18] $Fe(HSO_4)_3$,[19] $HClO_4$–SiO_2,[20] ferric chloride,[21] I_2,[22] and tribromomelamine.[23] However, many of these methodologies are associated with one or more disadvantages such as (i) harsh reaction conditions, e.g., treatment with air sensitive agents such as trichloroisocyanuric acid at CH_2Cl_2 for 4 h,[10] heating at 85 °C in PhMe catalyzed by alumina-supported heteropolyoxometalates,[15] heating in

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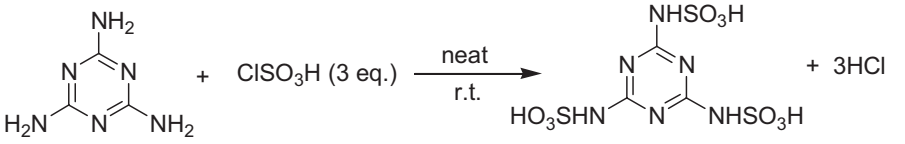
Address correspondence to Liqiang Wu, School of Pharmacy, Xinxiang Medical University, Xinxiang, Henan 453003, China. E-mail: wliq1974@sohu.com

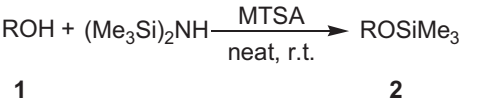
CH_3CN in the presence of 25 mol% $Fe(HSO_4)_3$ at reflux for 1.7 h;[19] (ii) prolonged reaction time;[10,14,16] (iii) requirement for hazardous and carcinogenic organic solvents such as CH_3CN,[3,9,12,17,19,20,21,23] CH_2Cl_2,[7,8,10,11,16,22] PhMe;[15] (iv) use of toxic, costly, or air sensitive catalysts.[3,8,10,13,18,23] Thus, the development of environmentally benign, high-yielding, and clean approaches for the silylation of hydroxyl groups in demand.

Recently, melamine trisulfonic acid (MTSA) has emerged as a promising solid acid catalyst for acid-catalyzed reactions, such as acetylation of alcohols, phenols, and amines;[24] oxathioacetalyzation of aldehydes;[25] and methoxymethylation of alcohols.[26] This catalyst is safe, easy to handle, environmentally benign, and presents fewer disposal problems. MTSA as a solid acid catalyst was prepared from the reaction of melamine with neat chlorosulfonic acid at room temperature (see Scheme 1).



Scheme 1

In this article, we wish to report a rapid and highly efficient method for trimethylsilylation of alcohols and phenols with HMDS catalyzed by MTSA at room temperature (Scheme 2).



Scheme 2

RESULTS AND DISCUSSION

Initially, we screened different solvents for the trimethylsilylation of benzyl alcohol with HMDS in the presence of a catalytic amount of MTSA. As can be seen from Table 1,

Table 1 Solvent optimization for the synthesis of benzyl trimethylsilyl ether[a]

Entry	Solvent	Yield (%)[b]
1	$CHCl_3$	83
2	CH_2Cl_2	90
3	EtOAc	82
4	*n*-Hexane	74
5	THF	90
6	CH_3CN	92
7	Solvent-free	95

[a]Reaction conditions: benzyl alcohol (1 mmol); HMDS (1 mmol); MTSA (0.05 mmol) r.t.; 15 min.
[b]Isolated yield.

Table 2 The amount of catalyst optimization for the synthesis of benzyl trimethylsilyl ether[a]

Entry	MTSA (mol%)	Time (min)[b]	Yield (%)[b]
1	0	60	0
2	1	25	71
3	2	20	83
4	3	15	96
5	4	15	96
6	5	15	95
7	6	15	95

[a]Reaction conditions: benzyl alcohol (1 mmol); HMDS (1 mmol); r.t.
[b]Based on 3 runs.

benzyl alcohol was silylated in the solvent-free conditions faster than the other solvents. Thus, solvent-free conditions were used throughout the work due to its high reaction rate and easy workup procedures.

To optimize the catalyst loading, 0, 1, 2, 3, 4, and 5 mol% of MTSA was tested, respectively. The results are summarized in Table 2. A 3 mol% loading of MTSA was sufficient to push the reaction forward and 2 mol% of MTSA was not enough. Higher amounts of MTSA did not lead to significant change in the reaction yields.

Table 3 Trimethylsilylation of alcohols and phenols catalyzed by MTSA[a]

Entry	Substrate	Time (min)	Products	Yield (%)[b]	Ref.
1	Benzyl alcohol	15	**2a**	96 (90, 87, 88, 85, 82, 80)[c]	23
2	4-Chlorobenzyl alcohol	10	**2b**	97	23
3	3-Nitrobenzyl alcohol	15	**2c**	90	27
4	4-Nitrobenzyl alcohol	10	**2d**	94	23
5	4-Methylbenzyl alcohol	15	**2e**	89	28
6	4-Methoxylbenzyl alcohol	15	**2f**	91	27
7	2,4-Dichlorobenzyl alcohol	20	**2g**	93	23
8	3,4-Methylenedioxybenzyl alcohol	25	**2h**	88	29
9	1-(3-Bromophenyl)ethanol	20	**2i**	91	The work
10	(4-Chlorocyclohexa-2,4-dienyl) (4-chlorophenyl)methanol	15	**2j**	90	The work
11	Cyclohexanol	20	**2k**	93	23
12	Menthol	30	**2l**	86	23
13	Cholesterol	30	**2m**	85	23
14	2-Adamantanol	25	**2n**	88	23
15	(4-(4-methoxyphenyl)butoxy) trimethylsilane	20	**2o**	86	The work
16	Lauryl alcohol	20	**2p**	89	28
17	2,2-Dimethylpropan-1-ol	15	**2q**	87	28
18	Pentan-1-ol	10	**2r**	94	23
19	Phenol	10	**2s**	98	23
20	4-Chlorophenol	10	**2t**	98	29
21	4-Nitrophenol	10	**2u**	95	29
22	4-Methylphenol	15	**2v**	92	20
23	4-Methoxylphenol	15	**2w**	90	23

[a]Reaction conditions: alcohol or phenol (1 mmol); HMDS (1 mmol); MTSA (0.03 mmol); neat; r.t.
[b]Isolated yield.
[c]Yields after three times of catalyst recovery.

Table 4 MTSA-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%); refiux	CH_3CN	100	70	[19]
2	$TiCl_2(OTf)$–SiO_2 (1 mol%)	Neat	10	87	[6]
3	$Sn^{IV}(TPP)(BF_4)_2$ (1 mol%)	CH_3CN	1	100	[3]
4	$ZrCl_4$ (2 mol%)	CH_3CN	1	95	[9]
5	Trichloroisocyanuric acid (6 mol%)	CH_2Cl_2	240	90	[10]
6	Trichloromelamine (3 mol%)	CH_2Cl_2/CH_3CN	30	92	[8]
7	$HClO_4$–SiO_2 (2.5 mol%)	CH_3CN	10	93	[20]
8	Tribromomelamine (3 mol%)	CH_2Cl_2/CH_3CN	10	98	[23]
9	MTSA (3 mol%)	Neat	15	96	This work

On the basis of 3 runs, the reaction conditions were optimized. As shown in Table 3, benzylic alcohols, cyclic alcohols, and aliphatic alcohols were silylated with HMDS at room temperature within 30 min in excellent yields after the addition of the acid catalyst MTSA. We were then interested in whether the same catalyst could be employed for trimethysilylation of phenolic compounds. Under the same conditions as above, all of the tested phenols were smoothly converted into the corresponding silyl ethers in good yields. No elimination and rearrangement by-products were observed at all.

The reusability of the catalyst was tested in the synthesis of benzyl trimethylsilyl ether. The catalyst was recovered after each run, washed with CH_2Cl_2, dried in an oven at 100 °C for 30 min prior to use, and tested for its activity in the subsequent run and fresh catalyst was not added. The catalyst was tested for 6 runs. It was seen that the catalyst displayed very good reusability (Table 3, entry 1).

To illustrate the efficiency of the proposed method, Table 4 compares some of our results with some of those reported for relevant reagents in the literature, which demonstrates its significant superiority. Compared with some of the reported methods in Table 4, the present method has a short reaction time, good yield, and solvent-free conditions. In addition, MTSA is a stable, cost effective, recyclable, and noncorrosive catalyst with high efficiency.

CONCLUSION

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

EXPERIMENTAL

NMR spectra were determined on Bruker AV-400 spectrometer at room temperature using tetramethylsilane (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; and MTSA was prepared according to reference [24]; Commercially available reagents were used throughout without further purification unless otherwise stated.

General Procedure for Trimethylsilylation of Alcohols and Phenols

A mixture of alcohol or phenol (1 mmol), MTSA (0.03 mmol), and HMDS (1 mmol) was prepared and stirred at room temperature for appropriate time (Table 3). After completion of the reaction (TLC), 10-mL water was added and the mixture was extracted with diethyl ether (3 × 10 mL). The organic layer was separated, dried ($MgSO_4$), and filtered. Evaporation of the solvent under reduced pressure gave the highly pure product without further purification. 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 $C_{16}H_{18}Cl_2OSi$: 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), 1.47–1.40 (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 $C_{14}H_{24}O_2Si$: C 66.61, H 9.58; found: C 66.72, H 9.48.

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