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$Fe(HSO_4)_3$ Promoted Trimethylsilylation of Alcohols and Phenols in Solution and Under Solvent-Free Conditions

Farhad Shirini[1,*], **Mohammad A. Zolfigol**[2], and **Abdol-Reza Abri**[1]

[1] Department of Chemistry, College of Science, Guilan University, Rasht, I.R. Iran
[2] College of Chemistry, Bu-Ali Sina University, Hamadan, I.R. Iran

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Summary. Alcohols and phenols are efficiently converted to their corresponding trimethylsilyl ethers with hexamethyldisilazane (*HMDS*) in the presence of $Fe(HSO_4)_3$ in solution and under solvent-free conditions.

Keywords. Alcohols; $Fe(HSO_4)_3$; Phenols; Trimethylsilylation; Solvent-free conditions.

Introduction

Trimethylsilylation is largely used to protect alcohols and phenols especially in the chemistry of steroids, sugars, and natural product synthesis, and a number of procedures are available for this purpose [1–6]. The use of some silylating agents is limited by their unavailability, toxicity, or the laborious processes of purifying the products. Hexamethyldisilazane (*HMDS*) [7, 8], a cheap and commercially available reagent, is one of the most widely used reagents for silylation of hydroxyl groups. Its handling does not require special precautions, and the work-up is not time-consuming, because the by-product of the reaction is ammonia, which is simple to remove from the reaction medium. However, the low silylating power of *HMDS* is the main drawback to its application. Therefore, a variety of reagents have been reported to improve the silylating power of *HMDS*, as *e.g.*, zirconium sulfophenyl phosphonate [9], sulfonic acids [10], nitrogen ligand complexes of metal chlorides [11], K-10 montmorillonite [12], chlorotrimethylsilane [13], $LiClO_4$ [14], *N,N′,N″,N‴*-tetramethyltetra-2,3-pyridinoporphyrazinato copper(II) [15], and $ZrCl_4$ [16]. Although these procedures provide an improvement, in most cases long reaction times, drastic reaction conditions, or tedious work-up is needed. In addition, some of the reagents are expensive and toxic or have to be prepared in a time-consuming procedure.

Results and Discussion

In our development of new methods for functional group transformation, we are interested in the protection of hydroxyl groups as trimethylsilyl ethers. Along these lines, we have introduced silica chloride [17] and $Al(HSO_4)_3$ [18] as new reagents for the promotion of silylation of hydroxyl groups with *HMDS*. Even though the activity of *HMDS* has been increased drastically in the presence of these reagents, this method suffers from limitations. In the presence of silica chloride, the reaction can not be performed under solvent-free conditions [19] and the protection of phenols needs longer reaction times [17]. On the other hand, *HMDS* is not able to protect phenols in the presence of $Al(HSO_4)_3$ [20].

In view of this, we decided to overcome these limitations by conducting the silylation reactions in the presence of $Fe(HSO_4)_3$ [21]. Herein, we report that $Fe(HSO_4)_3$ efficiently catalyzes the silylation of

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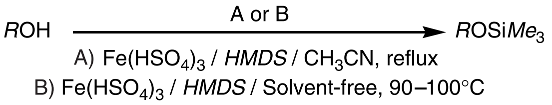
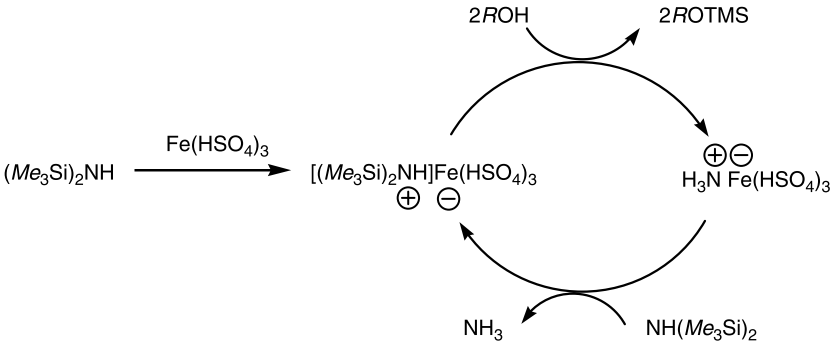
* Corresponding author. E-mail: shirini@guilan.ac.ir or fshirini@yahoo.com



Scheme 1

alcohols and phenols in solution and under solvent-free conditions (Table 1, Scheme 1).

Trimethylsilylation of different types of alcohols (including benzylic and primary, secondary, and ter-



Scheme 2

Table 1. Trimethylsilylation of alcohols and phenols in solution and under solvent-free conditions[a,b]

Entry	Substrate	Silylation in CH_3CN		Solvent-free silylation	
		Time/h	Yield/%[c]	Time/h	Yield/%[c]
1	Benzyl alcohol	1.7	70	0.21	90
2	2-Bromobenzyl alcohol	2	60	0.17	90
3	2-Chlorobenzyl alcohol	1.9	60	0.2	95
4	4-Chlorobenzyl alcohol	2	55	0.18	90
5	2-Nitrobenzyl alcohol	0.5	85	0.25	95
6	3-Nitrobenzyl alcohol	0.5	87	0.25	90
7	4-Nitrobenzyl alcohol	0.4	85	0.28	90
8	2-Methylbenzyl alcohol	2.2	60	0.25	80
9	4-*tert*-Butylbenzyl alcohol	2.7	50	0.23	90
10	4-Benzyloxybenzyl alcohol	1.7	60	0.25	85
11	3,4-Methylenedioxybenzyl alcohol[d]	0.3	85	0.22	90
12	1-Phenylethanol	1.3	72	0.4	80
13	Benzhydrol[d]	0.83	75	0.7	85
14	3-Phenyl-1-propanol	2.3	70	0.15	95
15	2-Phenyl-1-propanol	2.1	60	0.18	85
16	1-Phenyl-2-propanol	2.2	60	0.3	80
17	Cyclohexanol	0.7	75	0.32	80
18	(−)-Menthol[d]	1.2	70	0.7	88
19	2-Adamantanol[d]	2.2	80	0.72	90
20	Cholesterol[d]	0.5	80	0.33	85
21	1-Adamantanol[d]	2.5	70	0.5	82
22	Cinnamyl alcohol	0.5	–[e]	0.3	–[e]
23	Phenol	0.7	90	0.17	95
24	2-Chlorophenol	0.25	90	0.12	93
25	2,4-Dichlorophenol	0.73	85	0.25	95
26	4-Fluorophenol	1	60	0.42	95
27	Hydroquinone[f]	0.5	80	0.2	95
28	Resorcinol[f]	2.7	60	0.7	90

[a] Products were identified spectroscopically and also by the conversion of the products to their corresponding starting materials; [b] Under solvent-free conditions: trimethylsilylation of alcohols and phenols was performed at 90 and 100°C; [c] Isolated yields; [d] The reaction was performed using 1.5 mmol of *HMDS*; [e] Mixture of products; [f] Yields are related to the products with two protected hydroxyl groups

tiary aliphatic ones) and phenols was investigated in the absence of solvent by *HMDS* in the presence of $Fe(HSO_4)_3$ (Table 1). In a simple procedure, a mixture of reactants was stirred in an oil bath (90–100°C) for the appropriate time (Table 1). Both types of the above-mentioned compounds reacted efficiently and the corresponding silyl ethers were isolated in good to high yields. No oxidation product was observed during the course of the reaction. However, this method is not useful for the silylation of allylic alcohols (Table 1, entry 22).

In order to compare the obtained results with those obtained in solution, we studied the silylation in refluxing acetonitrile. As shown in the Table 1, there are appreciable differences between the results obtained in solution and those under solvent-free conditions. In conclusion, by omitting the solvent in addition to ease of the work-up procedure, the reaction time was reduced and the need for solvent is avoided.

Although the actual role of $Fe(HSO_4)_3$ is not clear, on the basis of the previously reported mechanism for the silylation of alcohols with *HMDS* in the presence of $Al(HSO_4)_3$ [18] the mechanism that is shown in Scheme 2 is selected as the most probable one.

To illustrate the efficiency of the proposed method, Table 2 compares some of our results with some of those reported for relevant reagents in the literature [14, 17, 18], which demonstrates its significant superiority.

In conclusion, the present method demonstrates that trimethylsilylation of alcohols and phenols with *HMDS* is effectively promoted in the presence of $Fe(HSO_4)_3$. The relatively short reaction times, good to high yields of the products, the simple and clean work-up, and the mild reaction conditions make this method a useful addition to the present methodologies for the silylation of alcohols and phenols.

Table 2. Comparison of some of the results obtained by silylation of alcohols and phenols with *HMDS* in the presence of $Fe(HSO_4)_3$ (1) with some of those reported by $LiClO_4$ (2) [14], silica chloride (3) [17], and $Al(HSO_4)_3$ (4) [18]

Entry	Substrate	Time/h/Yield/%			
		(1)	(2)	(3)	(4)
1	4-Chlorobenzyl alcohol	11/90	1.8/67	30/92	40/92
2	(−)-Menthol	40/88	3/76	–	60/95
3	Phenol	10/95	–	60/80	–
4	2-Naphthol	6/92	1.6/75	375/60	–

Experimental

Chemicals were purchased from Fluka, Merck, and Aldrich Chemical Companies. All of the trimethylsilyl ethers are known compounds and were characterized on the basis of their spectroscopic data (IR and NMR), and by comparison with those reported in literature [14, 16, 22–25], and also by regeneration of the corresponding alcohols. All yields refer to the isolated products. The purity determination of the substrate and reaction monitoring was executed by TLC on silica-gel polygram SILG/UV 254 plates.

General Procedure for Silylation of Alcohols and Phenols in CH_3CN

To a mixture of 1 mmol substrate and 0.087 g $Fe(HSO_4)_3$ (0.25 mmol) in 4 cm^3 CH_3CN, 0.161 g *HMDS* (1 mmol) was added dropwise within 5 min with stirring under reflux condition. After completion of the reaction (TLC or GC), 10 cm^3 water were added and the organic layer was separated, dried ($MgSO_4$), and filtered. Evaporation of the solvent gave almost pure product(s). Further purification proceeded by bulb-to-bulb distillation under reduced pressure or recrystallization to afford the pure silyl ether.

General Procedure for Silylation of Alcohols and Phenols under Solvent-Free Conditions

A mixture of 1 mmol substrate, 0.087 g $Fe(HSO_4)_3$ (0.25 mmol) and 0.161 g *HMDS* (1 mmol) was shaken in an oil bath (90–100°C) for the specified time (Table 1). The progress of the reaction was monitored by TLC. 10 cm^3 water were added and the mixture was extracted with $3 \times 10\,cm^3$ diethyl ether. The organic layer was separated and dried ($MgSO_4$). Evaporation of the solvent gave almost pure product(s). Further purification proceeded by bulb-to-bulb distillation under reduced pressure or recrystallization to afford pure silyl ether.

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