



Rapid and highly efficient trimethylsilylation of alcohols and phenols with hexamethyldisilazane (HMDS) catalyzed by reusable zirconyl triflate, [ZrO(OTf)₂]

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ABSTRACT

In this paper, rapid and efficient trimethylsilylation of alcohols and phenols with hexamethyldisilazane in the presence of catalytic amounts of ZrO(OTf)₂ is reported. Primary, secondary and tertiary alcohols as well as phenols were efficiently converted to their corresponding TMS ethers in short reaction times at room temperature. It is noteworthy that this method can be used for chemoselective silylation of primary alcohols in the presence of secondary and tertiary alcohols and phenols.

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1. Introduction

Conversion of hydroxy functional groups to silyl ether groups is a frequently used protection method both in synthesis of fine chemicals and natural products [1,2]. Commonly, silyl ethers are prepared by treatment of hydroxyl compounds with silyl chlorides or silyl triflates in the presence of bases such as imidazole [3], 4-(*N,N*-dimethylamino)pyridine [4], *N,N*-diisopropylethylamine [5] and Li₂S [6]. However, some of these silylation methods suffer from disadvantages such as the lack of reactivity or the difficulty in removal of amine salts derived from the reaction of by-product acids and co-bases during the silylation reaction. An alternative method for the preparation of silyl ethers from hydroxyl compounds is to use 1,1,1,3,3,3-hexamethyldisilazane (HMDS) as silylating agent, because it is a stable, commercially available, cheap reagent and gives ammonia as the only by-product. On the other hand, silylation with HMDS is nearly neutral and does not need special precautions. However, the main drawback of HMDS is its poor silylating power which needs forceful conditions and long reaction times in many cases [7]. Therefore, a variety of

catalysts have been developed for activation of this reagent, such as (CH₃)₃SiCl [8], sulfonic acids [9], ZnCl₂ [10], K-10 montmorillonite [11], LiClO₄ [12], H₃PW₁₂O₄₀ [13], iodine [14], InBr₃ [15], nitrogen-ligand complexes of metal chlorides [16], zirconium sulfophenyl phosphonate [17], CuSO₄ · 5H₂O [18], sulfonic acid-functionalized nanoporous silica [19], MgBr₂ · OEt₂ [20], LaCl₃ [21] and poly(*N*-bromobenzene-1,3-disulfonamide) and *N,N,N',N'*-tetrabromobenzene-1,3-disulfonamide [22]. Although these procedures provide an improvement, but many of these catalysts or activators need long reaction times, drastic reaction conditions or tedious workups, moisture sensitive or expensive. Hence, introduction of new procedures to circumvent these problems is still in demand.

In this paper, we report a rapid and efficient method for trimethylsilylation of alcohols and phenols with hexamethyldisilazane catalyzed by ZrO(OTf)₂ at room temperature.

2. Experimental

Chemicals were purchased from Fluka and Merck chemical companies. ¹H NMR spectra were recorded in CDCl₃ solvent on a Bruker AM 80 MHz or a Bruker AC 500 MHz spectrometer using TMS as an internal standard. Infrared spectra were run on a Philips PU9716 or Shimadzu IR-435 spectrophotometer. All analyses were performed on a Shimadzu GC-16A instrument with a flame

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ionization detector using silicon DC-200 or Carbowax 20M columns and *n*-decane was used as internal standard.

2.1. Preparation of the catalyst

To a solution of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ (0.646 g, 0.2 mmol) in deionized water (25 mL), AgCF_3SO_3 (1.03 g, 0.4 mmol) was added. The solu-

Table 1

Silylation of 4-chlorobenzyl alcohol with HMDS and in the presence of zirconium salts at room temperature^a

Entry	Yield (%) ^b			Time (min)
	ZrCl ₄	ZrOCl ₂	ZrO(OTf) ₂	
1	5	10	100	1
2	13	15		2
3	22	27		3
4	46	39		4

^a Reaction conditions: 4-chlorobenzyl alcohol (1 mmol), HMDS (2 mmol), catalyst (1 mol%), CH_3CN (1 ml).

^b GC yield.

tion was stirred for 10 min. The AgCl precipitate was filtered through a 0.45 μm filter. The $\text{ZrO}(\text{OTf})_2$ crystals were obtained by evaporation of solvent. The catalyst was characterized by FT-IR and elemental analysis techniques. The FT-IR spectrum of this catalyst shows bands at 640 (C–S), 1024 (Zr=O), 1168 and 1248 (S–O) cm^{-1} .

Elemental analysis data: Calcd. C, 5.92; S, 15.82; Zr, 22.51. Found: C, 5.45; S, 15.44; Zr, 22.35%.

2.2. General procedure for the silylation reaction

To a mixture of alcohol or phenol (1 mmol) and HMDS (2 mmol) in CH_3CN (1 ml) was added $\text{ZrO}(\text{OTf})_2$ (0.5 ml%). The mixture was stirred at room temperature for a specified time (Table 2). The progress of the reaction was monitored by GC. After completion of the reaction, the solvent was evaporated, Et_2O (15 ml) was added and then the catalyst was filtered. The filtrates were washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude product, which was confirmed by ^1H NMR and IR spectral data.

Table 2

Trimethylsilylation of alcohols and phenols with HMDS catalyzed by $\text{ZrO}(\text{OTf})_2$ at room temperature^a

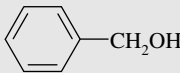
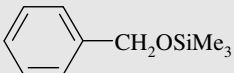
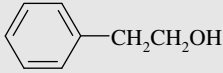
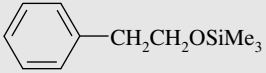
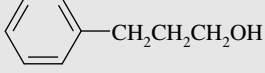
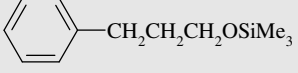
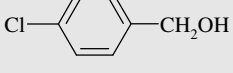
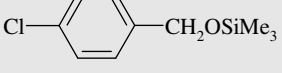
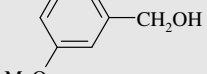
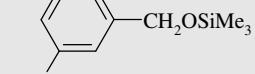
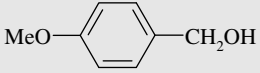
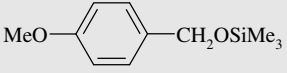
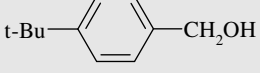
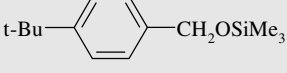
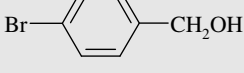
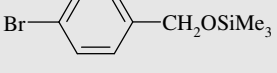
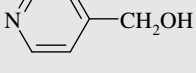
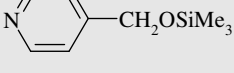
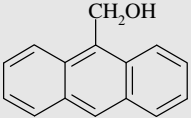
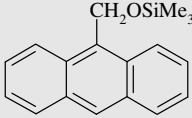
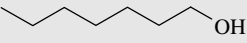
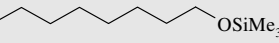
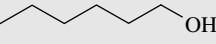
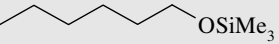
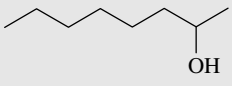
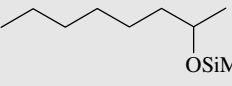
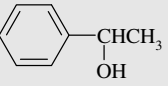
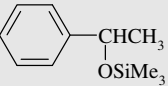
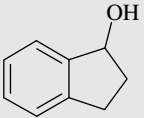
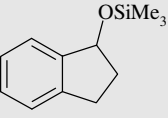
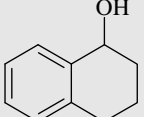
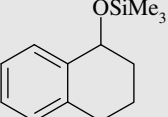
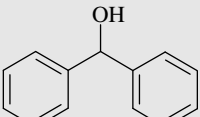
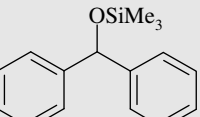
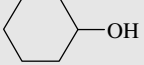
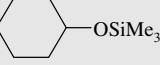
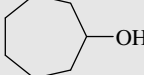
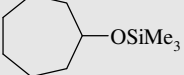
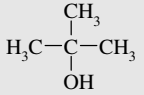
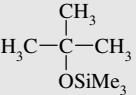
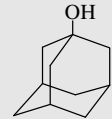
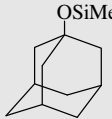
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3			1	100
4			1	100 (95)
5			1	100
6			1	100
7			1	100
8			1	100 (95)
9			1	100

Table 2 (continued)

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11			1	100
12			1	100
13			1	100
14			4	100
15			4	100
16			3	100
17			4	100 (96)
18			1	100
19			1	100
20			1	100
21			4	100

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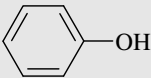
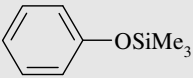
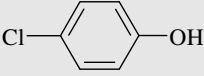
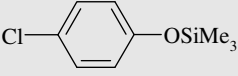
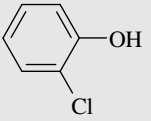
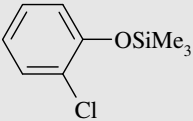
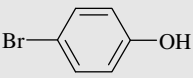
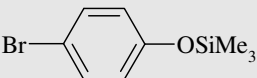
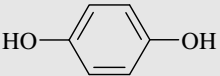
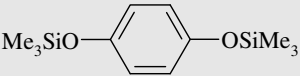
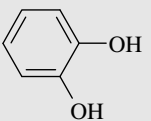
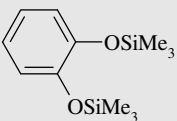
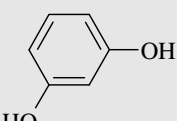
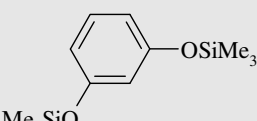
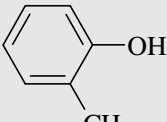
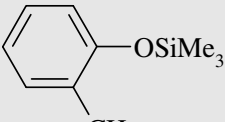
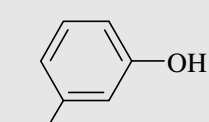
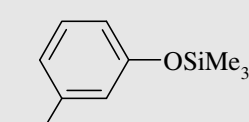
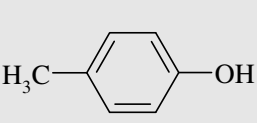
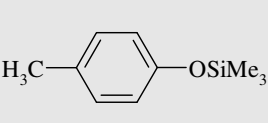
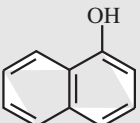
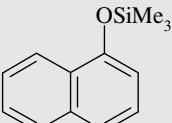
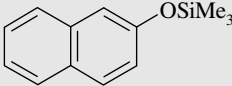
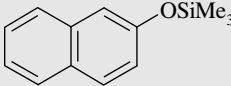
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25			4	100 (94)
26 ^d			4	100
27 ^d			4	100
28 ^d			4	100
29			1	100
30			1	100
31			1	100
32			2	100

Table 2 (continued)

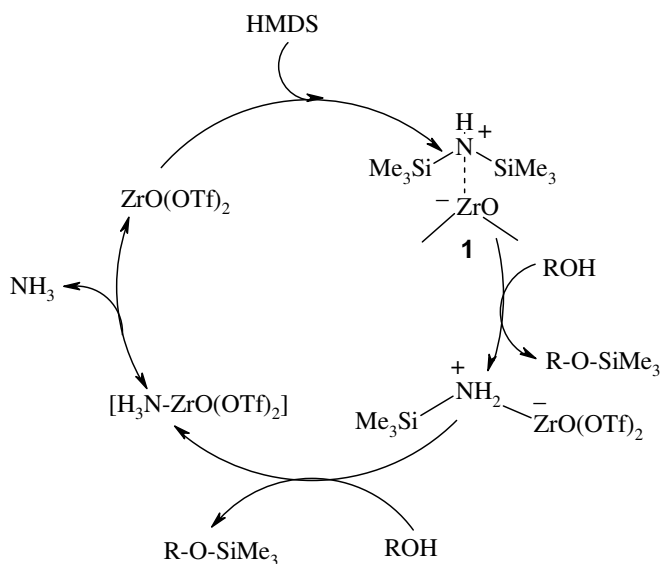
Entry	Hydroxy compound	TMS ether	Time (min)	Yield (%) ^{b,c}
33			4	100 (95)

^a Reaction conditions: ROH (1 mmol), HMDS (2 mmol), catalyst (0.5 mol%), CH₃CN (1 ml).

^b GC yield.

^c Yields in the parentheses are isolated yields.

^d Reaction was performed with 3 mmole of HMDS.



Scheme 1.

3. Results and discussion

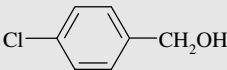
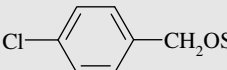
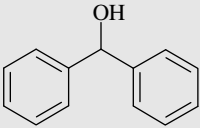
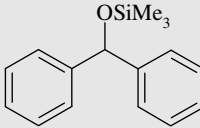
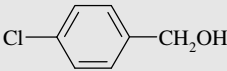
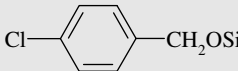
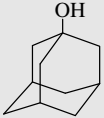
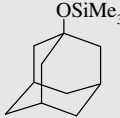
3.1. Silylation of alcohols and phenols with HMDS catalyzed by ZrO(OTf)₂

First, we investigated the ability of different zirconium salts for the silylation of 4-chlorobenzylalcohol with HMDS in CH₃CN as solvent at room temperature. As shown in Table 1, ZrO(OTf)₂ is superior in terms of reaction time and product yield. Under the same reaction conditions, a wide variety of alcohols were converted completely to their corresponding silyl ether with 2 mmol of HMDS in the presence of 0.5 mol% of ZrO(OTf)₂ at room temperature. When the reaction of 4-chlorobenzyl alcohol was carried out with 1.4, 1.6 and 1.8 mmol of HMDS, the yields were 75–90%. While with 2 mmol of HMDS the reaction was completed. The obtained results for silylation of different primary, secondary (including aliphatic and aromatic alcohols) and tertiary alcohols showed that the reaction was immediately completed for all alcohols at room temperature and no alcohol was detected by TLC or GC (Table 2). In the absence of catalyst, the reaction was much less efficient for the conversion of alcohols to silyl ethers. In the case of benzylic alcohols, the nature of substituents had no significant effect on the yields of silyl ethers.

The ability of this catalyst in the silylation of phenols with HMDS was also investigated. The reaction of phenols with HMDS

Table 3

Selective silylation of alcohols and phenols catalyzed by ZrO(OTf)₂ in CH₃CN

Row	ROH	Silyl ether	Time (min)	Yield (%)
1			1	100
			1	1
2			1	100
			1	0

(continued on next page)

Table 3 (continued)

Row	ROH	Silyl ether	Time (min)	Yield (%)
3			1	100
			1	12
4			1	100
			1	0

in the presence of 0.005 molar equivalent of $ZrO(OTf)_2$ in CH_3CN , as solvent, was carried out and the desired silyl ethers were obtained in excellent yields at room temperature (Table 2, entries 22–35). The silylation of dihydroxybenzenes such as hydroquinone, pyrocatechol and resorcinol, was also achieved. The results showed that all hydroxyl groups were silylated and the desired bis(trimethylsilyl ether) were obtained in excellent yields (Table 2, entries 26–28).

A probable mechanism has been shown in Scheme 1. In this mechanism, it is suggested that the Lewis acid–base interaction between metal triflate and nitrogen in HMDS polarizes N–Si bond of HMDS to produce a reactive silylating agent (**1**), which effectively silylates the hydroxyl compounds. The fast evolution of ammonia gas is a good indication for the proposed mechanism.

The selectivity of this method was also investigated. As shown in Table 3, primary alcohols were completely converted to the corresponding silyl ether in the presence of a secondary or tertiary alcohols or phenols (Table 3, entries 1, 2 and 4). Also, in a binary mixture of 4-chlorobenzyl alcohol and 1-hexanol, the benzylic alcohol was completely converted to the corresponding silyl ether, while only a 12% conversion was observed for the aliphatic alcohol (Table 3, entry 3).

3.2. Catalyst reuse and recovery

The recovery and reusability of the catalyst was investigated in the silylation of 4-chlorobenzyl alcohol (10 mmol) with HMDS (20 mmol). After completion of the reaction, the solvent was evaporated and Et_2O (40 ml) was added and then the catalyst was filtered. The recovered catalyst was used in the next run. The results showed that the catalyst can be reused several times (four consecutive runs were checked) without significant loss of its activity.

4. Conclusion

In this paper, a rapid, efficient and chemoselective method for the silylation of alcohols and phenols catalyzed by zirconyl triflate, $ZrO(OTf)_2$, is reported. In addition, short reaction times, excellent

yields, easy work-up, stability, reusability and relatively non-toxicity of the catalyst are noteworthy advantages of this method which make this procedure as a useful addition to the existing methodologies for the protection reactions.

Other applications of this catalyst in organic transformations are under investigation.

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