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Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

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To cite this Article Akhlaghinia, Batool(2007) 'A New and Efficient Method for the Protection of Alcohols and Phenols by Using Hexamethyldisilazane in the Presence of Anhydrous Ferric Chloride under Mild Reaction Conditions', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 182: 3, 687 — 694

To link to this Article: DOI: 10.1080/10426500601047487

URL: <http://dx.doi.org/10.1080/10426500601047487>

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A New and Efficient Method for the Protection of Alcohols and Phenols by Using Hexamethyldisilazane in the Presence of Anhydrous Ferric Chloride under Mild Reaction Conditions

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Damghan, Iran

Alcohols and phenols are protected with hexamethyldisilazane in the presence of anhydrous ferric chloride in good to excellent yields in acetonitrile. This method is highly selective for the conversion of primary alcohols in the presence of secondary and tertiary alcohols and also for conversion phenols.

Keywords Alcohol; ferric chloride; hexamethyldisilazane HMDS; phenol; trimethylsilylether

INTRODUCTION

The importance of hydroxyl-group functionality in organic chemistry is reflected by the continuous appearance in the literature of methods for developing complex structures based on the chemical interconversion of this functional group. A limiting factor in some cases is the presence of more than one oxygen function of comparable reactivity in the molecule to be transformed. This difficulty is circumvented by the use of protective groups, which is a practice that in theory allows free manipulation of the desired functionality. However, it is only in a few cases that this practice reaches an acceptable practical level, mostly due to the difficulties involved in the selectivity of protecting and of regenerating specific hydroxyl groups. The role of silyl groups has already been recognized as an important part of organic chemistry from both analytical and synthetic points of view, especially as a protecting group in many syntheses of reasonable complexity.¹ Generally the formation of

Received July 29, 2005; accepted August 21, 2006.

The authors gratefully acknowledge the partial support of this study by the Damghan University Research Council.

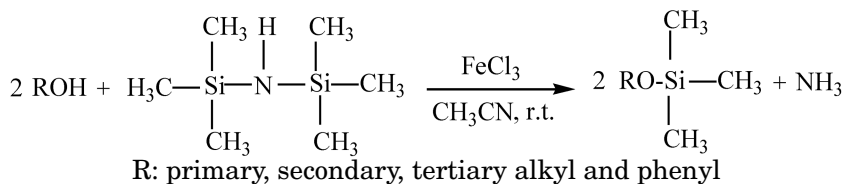
Address correspondence to Batool Akhlaghinia, Department of Chemistry, Damghan University of Basic Sciences, Damghan, Iran. E-mail: b.akhlaghinia@dubs.ac.ir

silyl ethers is carried out by treatment of alcohols with silyl chlorides or silyl triflates in the presence of a base,² Li_2S ,³ and sometimes a nonionic super base catalyst.⁴ However, some of these methods frequently suffer from drawbacks, such as a lack of reactivity or difficulty in the removal of amine salts derived from the reaction of byproduced acids and co-bases during the silylation reaction. 1,1,1,3,3,3-Hexamethyldisilazane (HMDS) is a stable, commercially available, and cheap reagent for trimethylsilylation of hydrogen-labile substrates,^{1a} giving ammonia as the only byproduct. On the other hand, silylation using this silazan-type reagent is nearly neutral and does not need precautions. However, the low silylating power of HMDS is the main drawback for its application, which needs forceful conditions and long reaction times in many cases. A variety of catalysts, such as $(\text{CH}_3)_3\text{SiCl}$,⁵ sulfonic acids⁶ ZnCl_2 ,⁷ complexes of metal chlorides with nitrogen ligands,⁸ zirconium sulfophenyl phosphonate,⁹ K-10 montmorillonite,¹⁰ and a special type of catalyst having the general formula $\text{X}^1\text{-NH-X}^2$ in which at least one of the groups X^1 , X^2 , is electron-withdrawing, such as an ester or amide group, has also been reported for the silylation of a wide range of functional groups using HMDS.¹¹

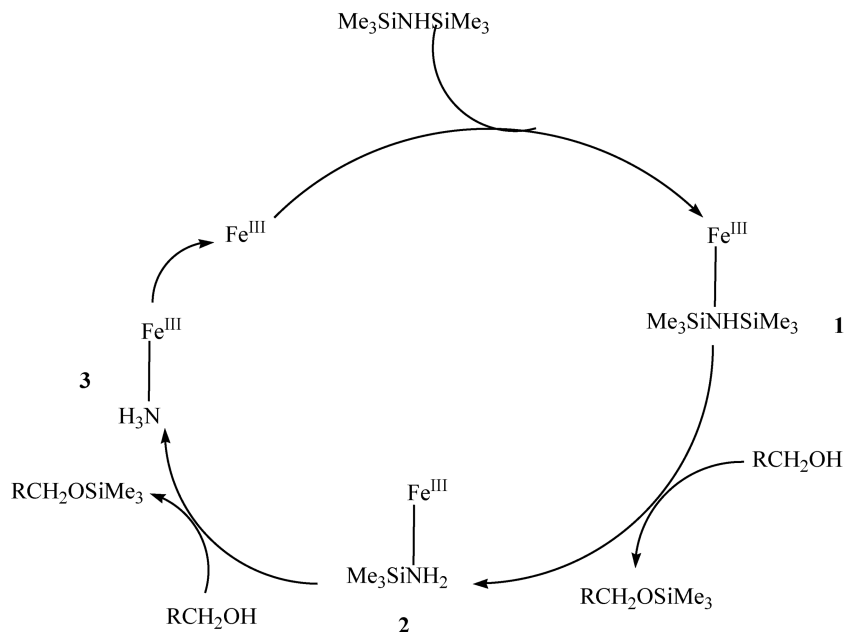
As part of our ongoing research to develop new synthetic methodologies involving various new reagents,¹² we perceived that anhydrous ferric chloride, which is readily available, might be a useful catalyst for trimethylsilylation because of its mild Lewis acidity. In this article we report that anhydrous ferric chloride can be used as an efficient catalyst for the trimethylsilylation of alcohols and phenols.

RESULTS AND DISCUSSION

In the present study the trimethylsilylation of alcohols and phenols in the presence of a catalytic amount of FeCl_3 was investigated. The protection of benzyl alcohol under the catalytic effect of FeCl_3 was studied. Benzyl trimethylsilylether was produced immediately in a quantitative yield. We applied these reaction conditions for the protection of structurally different alcohols and phenols (Scheme 1).



SCHEME 1

**SCHEME 2**

In order to optimize reaction conditions, we first examined the effect of different molar ratios of the alcohol/HMDS/catalyst. The best results were obtained using the ratio 1:0.7:0.07. Trimethylsilyl ethers were produced in quantitative yields (Table I).

Compounds that were trimethylsilylated in this way are primary, secondary, and tertiary alcohols and phenols. Generally, the reactions were completed at r.t. and were accompanied by the evolution of NH_3 gas from the reaction mixture.

The mechanism of these transformations is unclear. One hypothesis may be that FeCl_3 acts as a Lewis acid, which may polarize the Si-N bond in HMDS to produce the effective silylating agent **1** (Scheme 2). A rapid reaction of **1** with alcohol yields **2** with a concomitant release of the corresponding silyl ether. The reaction of **2** with a second molecule of alcohol produces the corresponding silyl ether and the $\text{Fe}(\text{III})$ ammine complex **3**. The cleavage of **3** leads to the fast evolution of NH_3 and release of the catalyst, which re-enters the catalytic cycle (Scheme 2).

This method was found to be highly selective. In a binary mixture of benzyl alcohol and 3-phenyl-1-propanol, benzylic alcohol was completely converted to the corresponding silyl ether, while only a 5% conversion was observed for the propanol derivative (Table II). Excellent

TABLE I Trimethylsilylation of Alcohols and Phenols Catalyzed by FeCl₃ in Dry Acetonitrile

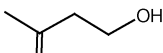
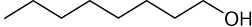

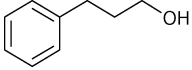
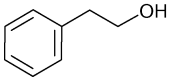
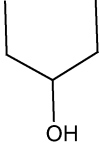

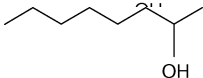
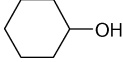
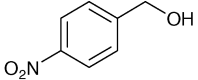
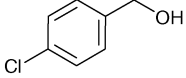
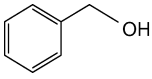
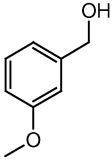
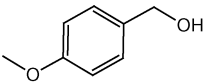
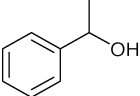
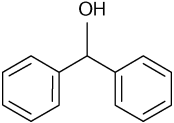

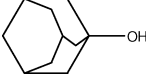
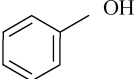
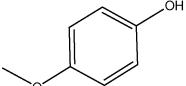
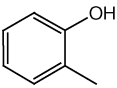
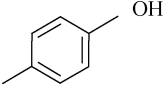
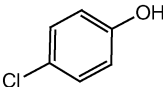
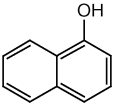
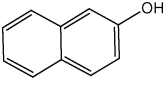
ROH	Reaction time	Conversion (%) ^a	Isolated yield (%)
	Immediately	100	92
	2.5 h ²	100	90
	Immediately	100	93
	10 min	100	96
	Immediately	100	98
	5 h	100	97
	3 h	100	96
	3 h	100	98
	3.5 h	100	97
	20 min	100	91
	10 min	100	92
	Immediately	100	98
	Immediately	100	95

TABLE I Trimethylsilylation of Alcohols and Phenols Catalyzed by FeCl₃ in Dry Acetonitrile (*Continued*)

ROH	Reaction time	Conversion (%) ^a	Isolated yield (%)
	Immediately	100	95
	Immediately	100	99
	Immediately	100	90
	46 h	100	94
	32 h	80	60
	10 min	100	95
	30 min	100	97
	70 min	100	90
	25 min	100	94
	2 h	100	95
	75 min	90	85
	1.5 h	65	58

^aYields were determined by GC using an internal standard.

TABLE II The Selective Reaction of Different Binary Mixtures with HMDS/FeCl₃

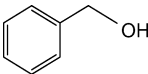
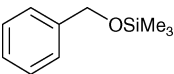
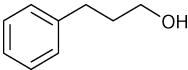
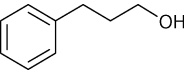
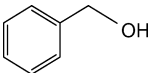
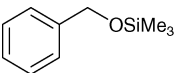
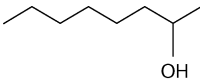
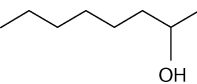
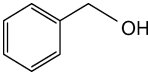
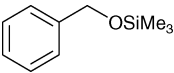
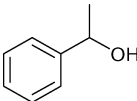
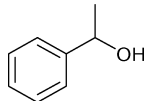
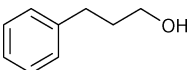
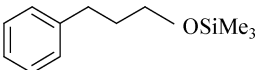
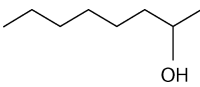
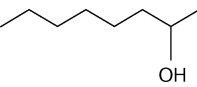
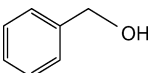
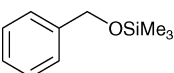
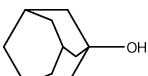
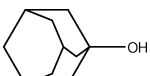
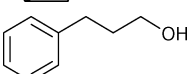
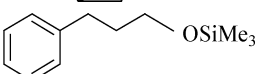
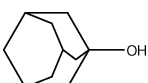
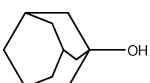
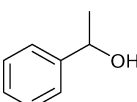
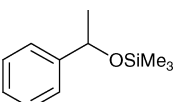
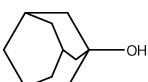
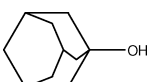
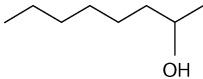
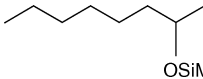
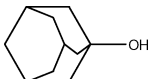
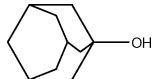
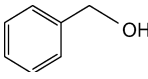
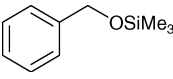
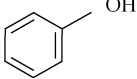
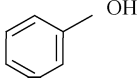
Binary mixture	Products	Reaction time	Yield (%) ^a
		Immediately	100
			95
		Immediately	100
			100
		Immediately	100
			96
		4.5 h	100
			100
		Immediately	100
			100
		Immediately	100
			95
		Immediately	100
			97

TABLE II The Selective Reaction of Different Binary Mixtures with HMDS/ FeCl_3

Binary mixture	Products	Reaction time	Yield (%) ^a
		6.5 h	100
			97
		Immediately	100
			97

^aYields were determined by an GC using internal standard.

selectivity was also observed for the conversion of primary alcohols in the presence of a secondary alcohol as well as of secondary alcohols in the presence of tertiary ones (Table II). Selectivity was observed in the conversion of benzyl alcohol in the presence of phenol (Table II).

In conclusion, the methodology described in this article shows that FeCl_3 is an effective catalyst for the trimethylsilylation of alcohols and phenols. Advantages of our protocol are simplicity, short reaction times, mild reaction conditions, as well as good yields. We expect this method to be a useful addition to modern synthetic methodologies.

EXPERIMENTAL

Chemicals were obtained from Merck (Darmstadt, Germany) or Fluka (Buchs, Switzerland). FTIR spectra were recorded on a Perkin Elmer (Norwalk, Connecticut, USA) RXI spectrometer. NMR spectra were recorded on a Bruker Avance DPX 250 MHz instrument. Products were purified by column chromatography, and purity determination of the products was accomplished by GLC on a Shimadzu model GC 10-A instrument using *n*-octane as an internal standard or by TLC on a silica-gel polygram on SIL G/UV 254 plates.

Typical Procedure for the Protection of Benzyl Alcohol

To a mixture of benzyl alcohol (0.108 g, 1 mmol) and HMDS (0.112 g, 0.7 mmol) in dry CH_3CN (3–5 mL), FeCl_3 (0.011 g, 0.07 mmol) was added, and the reaction mixture was stirred at room temperature. GC

analysis showed that the reaction was completed immediately. The reaction mixture was filtered. Column chromatography of the filtrate on silica gel using *n*-hexane as an eluent gave benzyl trimethylsilylether in a 98% yield.

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