

MgBr₂·OEt₂ mediated protection of alcohols with hexamethyldisilazane: An efficient catalytic route for the preparation of silyl ethers under solvent-free conditions

Mohammad M. Mojtahedi*, Hassan Abbasi, M. Saeed Abaee

Chemistry and Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran, Iran

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Abstract

Various types of alcohols and phenols were rapidly protected by hexamethyldisilazane in good to excellent yields at room temperature in the presence of catalytic amount of magnesium bromide ethyl etherate under solvent-free conditions. Good to excellent chemoselectivity was demonstrated for competitive protection of primary hydroxyls in the presence of secondary and tertiary alcohols. Highly selective protection of phenols in the presence of aromatic amines was also demonstrated successfully.

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Keywords: Silyl ethers; HMDS; Magnesium bromide ethyl etherate; Solvent-free; Catalytic reaction

1. Introduction

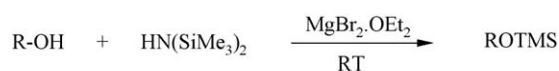
Protected hydroxyl functionalities are very important for their organic [1] and analytical chemistry [2] applications. Many multi-step syntheses and chemical transformations require at least one step of alcohol group protection [3]. One of the most popular strategies for this purpose is to convert alcohols into their corresponding silyl ethers [4]. Treatment of alcohols by silyl chlorides and silyl triflates in the presence of a base has been a very common tool for the preparation of silyl ethers [5]. However, some of the reported procedures suffer from drawbacks such as limited reactivity and cumbersome removal of by-produced amine salts from the reaction mixture.

1,1,1,3,3,3-Hexamethyldisilazane (HMDS) is a cheap and commercially available reagent frequently used for trimethylsilylation of hydroxyl groups, giving ammonia as the only by-product [6]. Handling of this reagent does not require special precautions and the work up of the reaction mixture is easy and rapid. However, the poor silylation power is a main limitation for application of HMDS [7]. This limitation dictates the use of harsher reaction conditions and longer times. Several

catalytic systems have been developed to ease HMDS silylation processes by using trimethylchlorosilane [8], liquid amine [9], microwave irradiation [10], montmorillonite K-10 [11], kaoline [12], Al₂O₃/KF [13], zirconium based catalysts [14], H₃PW₁₂O₄₀ [15], triflates of metal ions [16], LiClO₄ [17], copper complexes [18], phosphomolybdic acid [19], and very recently CuSO₄ in acetonitrile [20]. Although these methods improve reaction conditions and shorten the reaction time, in many cases still drastic conditions are necessary for completion of the process, tedious work is required, or very expensive reagents are used.

Use of magnesium bromide ethyl etherate (MgBr₂·OEt₂) as an efficient Lewis acid catalyst for various synthetic transformations is well established [21] due to ready availability and ease of preparation [22]. The oxophilic and coordinating nature of MgBr₂·OEt₂ has been demonstrated by its use as a bidentate chelating Lewis acid in a variety of chelation-controlled transformations such as cycloadditions [23], asymmetric aldol and anti-aldol reactions [24], *N*-acylation of amides [25], deprotection of ethers [26], ring opening of epoxides [27], diastereoselective addition of nucleophiles [28], rearrangement processes [29], radical reactions [30], hydrogen transfers [31], diastereoselective cyanohydrin formations [32], acylation of alcohols [33], stereoselective reductions [34], anomerization reactions [35], and most recently Cannizzaro reactions [36]. In continu-

* Corresponding author. Tel.: +98 21 88036145; fax: +98 21 88037185.
E-mail address: mojtahedi@ccerci.ac.ir (M.M. Mojtahedi).



R = aryl, primary, secondary, and tertiary alkyls

Scheme 1.

ation of our experiences on the use of such reaction conditions [23a,36] and our previous studies on alcohols protection techniques [10,37], we established a mild and efficient procedure for the synthesis of the title compounds in the presence of catalytic quantities of $\text{MgBr}_2 \cdot \text{OEt}_2$ at room temperature under solvent-free conditions (Scheme 1).

2. Experimental

2.1. General remarks

Reactions were monitored by GC and TLC. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer and absorptions were reported as wave numbers (cm^{-1}). ^1H NMR spectra were obtained on a Bruker AC 80 MHz instrument as CDCl_3 solutions and the chemical shifts are expressed as δ units with Me_4Si as the internal standard. GC experiments were carried out using a Fisons 8000 apparatus. All chemicals and reagents were purchased from commercial sources.

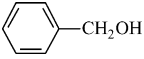
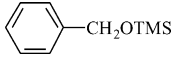
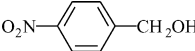
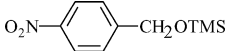
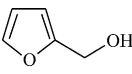
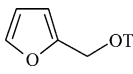
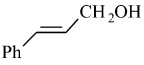
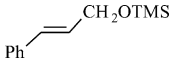
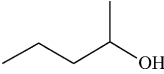
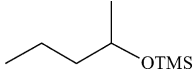
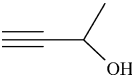
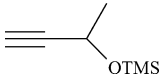

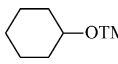
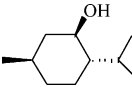
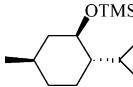
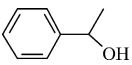
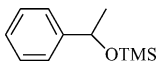
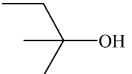
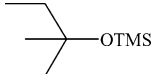

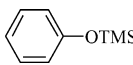
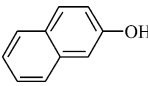
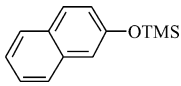
2.2. General procedure for the preparation of trimethylsilylethers

To a mixture of alcohol (5.0 mmol) and HMDS (3.0 mmol) was added $\text{MgBr}_2 \cdot \text{OEt}_2$ (0.25 mmol) and the mixture was stirred at ambient temperature for an appropriate length of time as appear in Table 1. The reaction mixture was extracted twice by 10 ml portions of diethyl ether after TLC and GC monitoring showed completion of the reaction. The combined ethereal phases were washed by water and dried over anhydrous Na_2SO_4 . The product was obtained after evaporation of the volatile portion and was purified with column chromatography over silica gel or by bulb to bulb distillation, if necessary.

3. Results and discussion

Initially, hydroxyl protection of primary alcohols with HMDS was examined in the presence of various amounts of $\text{MgBr}_2 \cdot \text{OEt}_2$ and the process was found to be catalytic (Table 1). Treatment of *n*-hexanol with HMDS in the presence of 5 mol% $\text{MgBr}_2 \cdot \text{OEt}_2$ at room temperature afforded 91% of the corresponding TMS derivative of the alcohol in 10 min (entry 1). The product was easily separable by diethyl ether from the reaction medium. Other primary aliphatic and benzylic alcohols were also protected in the same manner in short reaction times yielding more than 90% of the desired TMS ethers (entries 2–6). The methodology proved to be efficient in conversion of secondary alcohols into their respective TMS ethers as well. Reactions of 2-

Table 1
 $\text{MgBr}_2 \cdot \text{OEt}_2$ catalyzed silylation of alcohols using HMDS

Entry	Substrate	Product	Time (min)	Yield (%) ^a
1	$\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{OH}$	$\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{OTMS}$	10	91
2	$\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{OH}$	$\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{OTMS}$	10	96
3			5	98
4			8	92
5			6	89
6			10	94
7			10	90
8			15	85
9			10	92
10			15	86
11			5	97
12			20	92
13			20	92
14			40	94

^a Isolated yields.

pentanol (entry 7), butyn-2-ol (entry 8), cyclohexanol derivatives (entries 9 and 10), and 1-phenylethanol (entry 11) resulted in rapid formation of the products under the same conditions. Further generality of this procedure was demonstrated by high yield protection of tertiary alcohols (entry 12) and phenols (entries 13 and 14).

Due to the importance of the selectivity in synthetic organic chemistry, competitive reactions were designed to evaluate the chemoselectivity of the protocol. The results summarized in Table 2 clearly indicate that phenols are easily protected in the presence of aromatic amines with very high chemoselectivity (entries 1 and 2). This is also the case when primary alcohols are subjected to react with HMDS in the presence of tertiary hydroxyl groups (entries 3 and 4). Under similar conditions, primary alcohols can still be protected preferentially in competition with secondary alcohols (entries 5 and 6) while mixture of secondary and tertiary alcohols exhibits slight preference for formation of secondary TMS ethers (entry 7).

Table 2
Competitive TMS protection of alcohols in the presence of HMDS and MgBr₂·OEt₂

Entry	Product 1	Product 2	1:2
1			>100:1
2			>100:1
3			>100:1
4			>100:1
5			4.7:1
6			3.3:1
7			1.3:1

4. Conclusion

The present protocol involves mild reaction conditions at ambient temperature with high yields of isolated products in short reaction times. The silyl ether products are easily separable from the reaction mixtures by simple extraction with diethyl ether. Use of catalytic amounts of MgBr₂·OEt₂ as the only additive for transformation of alcohols to silyl ethers in a solvent-free environment and excellent to good chemoselectivity for the protection of primary alcohols are other advantages of the procedure.

Acknowledgment

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