

Silylation of Alcohols and Phenols Using HMDS Catalyzed by SiO₂-Cl in Solution and Solvent-Free Conditions

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Abstract

Trimethylsilylation of a variety of alcohols and phenols, in the presence of silica chloride, using hexamethyldisilazane (HMDS) in solution and under solvent-free conditions is reported. Trimethylsilyl ethers were formed in excellent yields both for aliphatic alcohols and phenols without having an electron-withdrawing group. In addition, SiO₂-Cl can be recovered and reused after drying.

Keywords: Silylation; Hexamethyldisilazane; Alcohols; Phenols; Silica chloride; Solvent-free conditions

Introduction

Trimethylsilyl ether formation is not only a fundamental process in the synthesis of functional organosilicon compounds but also an important technique for protection of reactive hydroxyl groups during multistep synthesis of natural products. Due to the enhanced stability under a variety of conditions, solubility in non-polar solvents, thermal stability and the ease of removal which is simply accomplished by acid or base induced hydrolysis giving only uncreative siloxane as byproduct [1,2]. It is also used extensively for the derivation of hydroxyl group to increase their volatility for gas chromatography and mass spectrometry.

Several reagents have been used for this conversion, including the trimethylsilylhalides in the presence of stoichiometric amount of a tertiary amine, trimethylsilyl triflate, allylsilanes in the presence of a catalytic amount of *p*-toluenesulfonic acid [4,5], iodine [6], trifluoromethanesulfonic acid [7], and Sc(OTf)₃ [8].

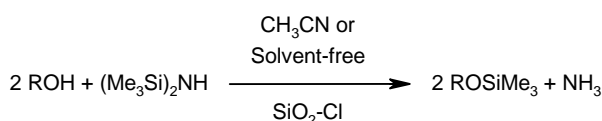
One of the most common silylating reagents used for the trimethylsilylation of hydroxyl groups is hexamethyldisilazane (HMDS), which is a stable, commercially available, cheap reagent, and is nearly neutral, so its handling does not need special precautions. The low silylating power of HMDS is the only disadvantage for this agent. Therefore, there are a variety of catalysts for activating of this reagent [9-17]. Some of these reagents are moisture sensitive or expensive. In addition, in most of these cases a long reaction time or tedious work-up is needed.

Silica chloride has been reported to be an efficient reagent for the selective thioacetalization of carbonyl compounds, transformation of sulfoxides to thioethers, dehydration of tertiary benzylic alcohols, deprotection of thioacetals, and ring expansion of cyclic thioacetals [18-23]. Recently, silica chloride/HMDS was used as a catalyst for the silylation of alcohols and phenols [24]. In that report, the silylation reactions were carried out in refluxing methylene chloride with 70-95% yields for alcohols and 50-80% yields for phenols and naphthols.

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Results and Discussion

In continuation of our exploration of the potential catalyst for efficient, convenient, and nearly neutral conditions to protect hydroxyl groups [25,26], we also found that silica chloride is a suitable catalyst for silylation of alcohols and phenols with HMDS. But by using CH_3CN as solvent or under solvent free conditions, both alcohols and phenols are silylated in excellent yields (Scheme 1, Table 1). Silylation reaction in the other polar solvent and in the presence of silica chloride gave low yields of products.



R= alkyl or aryl

Scheme 1

The silylated products were formed in almost quantitative yields for alcohols and in high yields for phenols in short reaction time. The work-up procedure under solvent free conditions is very simple. By adding CH_2Cl_2 to the reaction mixture, $\text{SiO}_2\text{-Cl}$ can be easily recovered by filtration and the crude product is obtained by removing the solvent under reduced pressure.

When we used 2 mmol of primary, secondary alcohols, or phenols, 0.05 g of silica chloride was sufficient for the completion of the reaction. But in the case of tertiary alcohols 0.1 g of silica chloride is needed for 2 mmol of tertiary alcohol. With this method, primary, allylic, benzylic, hindered primary alcohols, secondary, tertiary, acid sensitive alcohols, and phenols were readily transferred into their corresponding trimethylsilyl ethers. The results are summarized in Table 1. In the case of 1,1-diphenyl ethanol, we also found 45% of the dehydration by-product [20].

This method is highly selective for silylation of primary and secondary alcohols in the presence of a tertiary alcohol. But, it is not selective for primary and secondary alcohols in the presence of phenols (Scheme 2).

Reusability of silica chloride was investigated for the silylation reaction of benzhydrol and 2,5-dimethylphenol with HMDS. We found out that after four times of silylation in the presence of silica chloride in acetonitrile, the reactivity of catalyst does not change and we have seen the same yield with the same reaction time.

Silylation reaction does not take place with

hydroxyquinolines and nitrophenols as it is shown in Table 1 (entry 28-31) [22,23], maybe due to electron-withdrawing property of the aromatic ring. In the case of 4-aminophenol, we only observed O-silylation, Table 1, entry 27.

In summary, we have modified the reported procedure for the application of $\text{SiO}_2\text{-Cl}$ as a new, efficient and practically neutral catalyst for trimethylsilylation of a variety of alcohols and phenols using HMDS under solution and solvent free conditions with high yields and easy work-up procedure. In addition, $\text{SiO}_2\text{-Cl}$ can be recovered and reused after drying.

Experimental

The General Procedure for the Preparation of Trimethylsilyl Ethers

To a mixture of HMDS (0.7 mmol) and silica chloride (0.05 g for primary, secondary alcohols and phenols and 0.1 g for tertiary alcohols) was added the alcohol (1 mmol), and the mixture was stirred at room temperature for specified time (Table 1). After completion of the reaction, CH_2Cl_2 was added and silica chloride removed by filtration. The solvent and the excess HMDS were removed by rotary evaporation, and almost pure trimethylsilyl ether was isolated. Further purification was carried out by short-column chromatography on silica gel (ethyl acetate/petroleum ether) if needed. The procedure in solution was the same as above, but it was carried out in acetonitrile (1 mL) as solvent. All compounds were characterized on the basis of spectroscopic data (IR, NMR, MS) and by comparison with those reported in the literature.

Selected spectroscopic data: 2-Methoxy naphthalene (Table 1, entry 26), Solid, mp, 69-72 °C (lit., mp 70-73 °C); ^1H NMR (500 MHz, CDCl_3), δ , 3.98 (s, 3H), 7.30-7.32 (m, 1H), 7.39-7.41 (m, 1H), 7.53-7.56 (m, 1H), 7.64-7.67 (m, 1H), 7.90-7.98 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3), δ , 55.7 (CH₃), 106.4 (CH), 119.4 (CH), 124.1 (CH), 126.9 (CH), 127.8 (CH), 128.4 (CH), 129.6 (C), 130.1 (CH), 135.3 (C), 158.3 (C). IR (KBr), ν , 3059.5, 3030.7, 3000.0, 2953.2, 1600.3, 1498.6, 1247.6, 1040.4, 784.6, 690.1 cm^{-1} .

Acknowledgments

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Table 1. Silylation of alcohols and phenols with HMDS in presence of SiO₂-Cl

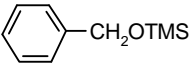
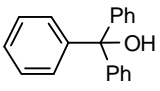
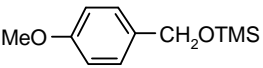
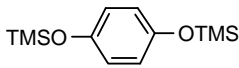
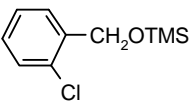
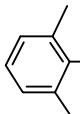
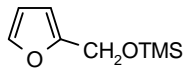
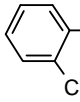
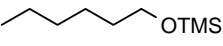
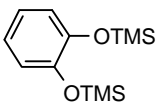
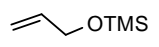
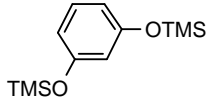
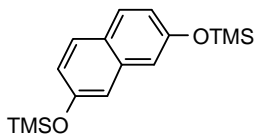
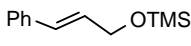
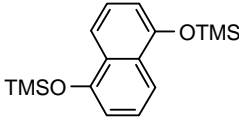
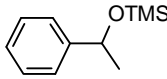
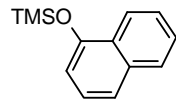
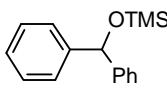
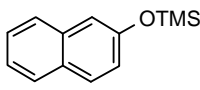
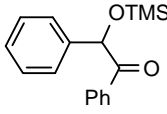
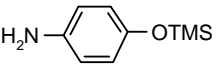
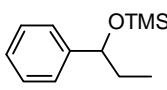
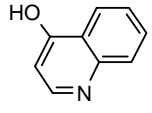
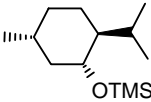
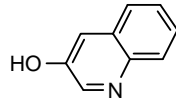
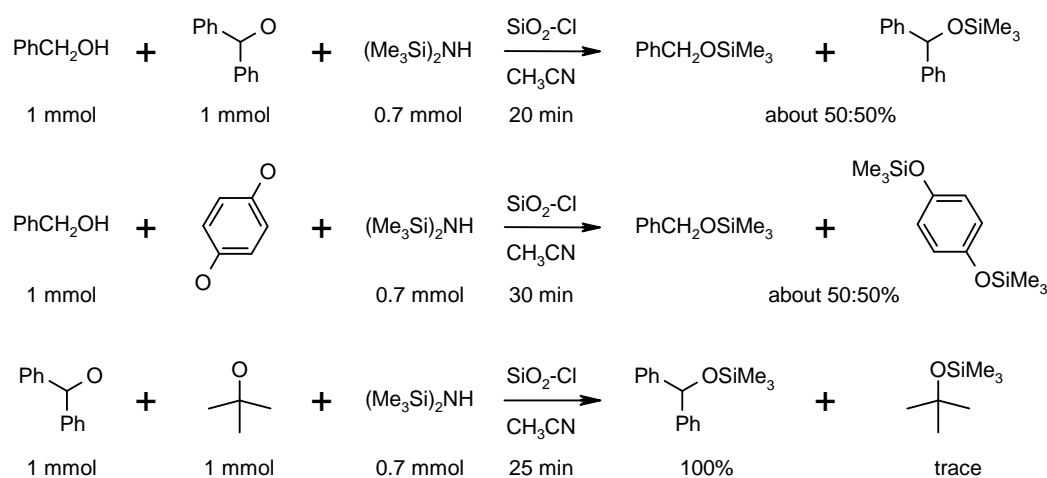
Entry	Product	Time (min)	Yield ^a (%)		Entry	Product	Time (min)	Yield ^a (%)	
			Solvent-free	CH ₃ -CN				Solvent-free	CH ₃ -CN
1		20	98	100	17		24 h	NR	NR
2		15	100	100	18		10	95	98
3		10	90	95	19		20	96	93
4		20	100	100	20		10	90	95
5		20	100	100	21		10	94	98 (95 ^b)
6		15	–	95	22		10	100 (92 ^b)	98
7	$C_{15}H_{31}CH_2OTMS$	20	100	85	23		40	95	97
8		20	100	100	24		50	96	93
9		30	100	100	25		70	98	97
10		50	100	100	26		45	100	95
11		60	100	–	27		20	100	100
12		25	100	100	28		120	trace	–
13		60	84	–	29		120	–	trace

Table 1. Continued

14		120	-	100	30		24 h	100	NR
15		120	-	95	31		72 h	NR	NR
16		5 h	NR	50					

^a Conversion yield; ^b Isolated yield; NR: No Reaction



Scheme 2

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