Novel and Efficient Method for the Silylation of Hydroxyl Groups with Hexamethyldisilazane (HMDS) under Solvent-Free and Neutral Conditions

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Summary: Various alcohols and phenols were silylated to trimethylsilyl ethers with hexamethyldisilazane in the presence of solid lithium perchlorate under very mild, neutral, and solvent-free conditions in good to excellent yields.

Perhaps one the most important uses of trimethylsilyl groups in organic synthesis is for the protection of hydroxyl groups of alcohols, phenols, and carboxylic acids. Several chemical conversions and multiple-sequence syntheses often require protection of hydroxyl groups. The trimethylsilyl group is one of the most popular and widely used groups for protecting the hydroxyl function and often is used in analytical chemistry to prepare silyl ethers as volatile derivatives of alcohols and phenols.[1]

Several methods have been reported for this conversion, including the reaction of an alcohol with trimethylsilyl halides in the presence of a stoichiometric amount of a tertiary amine,[2] with trimethylsilyl triflate, which is more reactive than the chloride,[3] with allylsilanes in the presence of a catalytic amount of *p*-toluenesulfonic acid,[3] with iodine,[4] with trifluoromethanesulfonic acid,[5] and with $Sc(OTf)_3$.[6]

Hexamethyldisilazane (HMDS) is frequently used for the trimethylsilylation of hydroxyl groups. HMDS is an inexpensive and commercially available reagent. Its handling does not require special precautions, and the workup is not time-consuming, because the byproduct of the reaction is ammonia, which is simple to remove from the reaction medium. The low silylation power of HMDS is the main drawback to its application; therefore, there are a variety of catalysts for activating of this reagent, such as I_2,[7] $(CH_3)_3SiCl$,[8] and K-10 montmorillionite.[9,10] However, in most of these cases a long reaction time, drastic reaction conditions, or tedious workup is needed. In addition, many of these reagents are moisture sensitive or expensive. The lack of a facile and general synthetic methodology for the silylation of hydroxyl groups (alcohols, phenols), under essentially neutral conditions, prompted us to develop an efficient, convenient, and practical procedure for the protection of hydroxyl groups under solvent-free conditions.

In continuation of our interest in the application of solid $LiClO_4$ in organic synthesis,[11] we report here the use of readily available HMDS for silylation of hydroxyl groups in the presence of solid $LiClO_4$ under environmentally benign and natural conditions. We examined the potential of HMDS for silylation of alcohols in the presence of solid $LiClO_4$ without using a solvent. Upon addition of HMDS to an alcohol in the presence of solid $LiClO_4$, the silylated product was formed in high yield and in a short time. The workup procedure is very simple. By addition of petroleum ether or CH_2Cl_2 to the reaction mixture, $LiClO_4$ is recovered easily by filtration and the crude product can be obtained by distilling the solvent.

To find out the best reaction conditions for the protection of alcohol in the presence of solid $LiClO_4$, benzyl alcohol and HMDS were used with different amounts of solid $LiClO_4$ (Scheme 1).

Scheme 1

$$\underset{1.0\ \text{mol}}{2PhCH_2OH} + \underset{0.7\ \text{mol}}{(Me_3Si)_2NH} \xrightarrow[0.5\ \text{mol, room temp}]{LiClO_4\ (\text{solid})} 2PhCH_2OSiMe_3 + NH_3$$

In the case of simple alcohols 20 mol % of solid $LiClO_4$ was sufficient for the completion of the reaction. However, the optimal molar ratio of ROH, HMDS, and $LiClO_4$ is 1:0.7:0.5. With the mixture of HMDS and $LiClO_4$, primary, allylic, benzylic, and hindered primary alcohols, unhindered secondary, tertiary, and acid-sensitive alcohols, and phenols were readily transformed into their corresponding trimethylsilyl ethers in high yield. The results are summarized in Table 1.

To show the accelerating effect of solid $LiClO_4$, the reactions of HMDS and various alcohols were examined in the absence of lithium perchlorate as catalyst. However, these reactions remained incomplete and low

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Table 1. Silylation of Alcohols and Phenols with HMDS in the Presence of Solid $LiClO_4$ and under Solvent-Free Conditions

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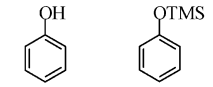
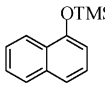
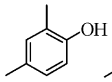
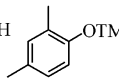
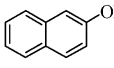
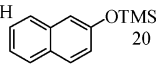
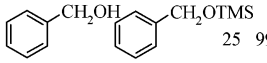
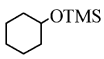
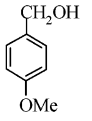
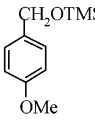
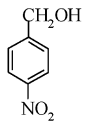
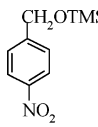
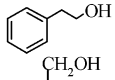
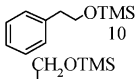
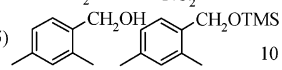
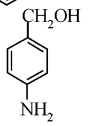
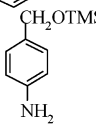
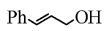
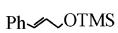
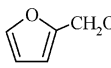
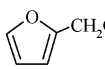
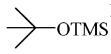
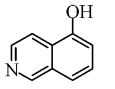
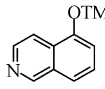
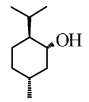
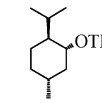
		20	96(64)			20	80(68)
		20	90(70)			20	84(65)
						80	99(70)
		25	99(67)			10	95(60)
		10	97(63)			10	95(54)
		10	98(65)			10	98(62)
		10	98(60)			25	99(50)
		30	90(40)			20	96(60)
		10	99(45)			25	98(40)
		20	82(60)			50	99(55)

[a] Conversion yields. [b] Yields for the silylation reaction in the absence of $LiClO_4$ are shown in prentheses.

yields of products were obtained (Table 1). Further investigations to broaden the scope and synthetic applications of solid $LiClO_4$ under solvent-free conditions are under way in our laboratory.

In conclusion, solid $LiClO_4$ is found to be an efficient catalyst for the silylation of various hydroxyl groups with HMDS under very mild, neutral, and solvent-free conditions. The present procedure provides a novel, efficient, and general methodology for the preparation of trimethylsilyl ethers in high yield with an easy workup procedure. In addition, $LiClO_4$ can be quantitatively recovered and reused after activation.

Experimental Section

General Procedure for the Preparation of Trimethylsilyl Ethers. To a mixture of HMDS (7 mmol) and $LiClO_4$ (5.0 mmol) was added the alcohol (10 mmol), and the mixture was stirred at room temperature under an argon atmosphere for the specified time (Table 1). After completion of the reaction, CH_2Cl_2 or petroleum ether was added and $LiClO_4$ was removed by filtration. The solvent and 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).

Caution! Although we did not have any accidents while using or drying $LiClO_4$, it is advisable to work in a fume hood using a suitable lab shield.

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