Mild and Highly Efficient Method for the Silylation of Alcohols Using Hexamethyldisilazane Catalyzed by Iodine under Nearly Neutral Reaction Conditions

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Received May 21, 2000

The role of silyl groups has already been recognized, of late, as an important part of organic chemistry from both analytical and synthetic point of view, especially as protecting group in many syntheses of reasonable complexity.[1] Generally, the formation of silyl ethers 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 suffered from drawbacks such as lack of reactivity or the difficulty in removal of amine salts derived from the reaction of by-produced acid 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 special precautions. However, the low silylating power of HMDS is a main drawback for its application, which needs forceful conditions and long reaction times in many instances. A variety of catalysts such as $(CH_3)_3SiCl$,[5] sulfonic acids,[6] $ZnCl_2$,[7] nitrogen ligand complexes of metalchlorides,[8] zirconium sulfophenyl phosphonate,[9] K-10 montmorilonite,[10] and especial types of catalysts, having the general formula X^1-NH-X^2 in which at least one of the groups X^1, X^2 is electron-withdrawing such as ester or amide groups, has also been reported for the silylation of a wide range of functional groups using HMDS.[11] Although these procedures provide an improvement, in most cases reaction with hindered alcohols do not take place,[5] or required forceful conditions and prolonged reaction time.[12] In our development of new methods for functional group transformation, we are especially interested in exploring the potential use of various types of neutral or nearly neutral catalyst.[13] In continuation of these studies, herein, we wish to describe a new protocol for the mild and rapid trimethylsilylation of a wide variety of alcohols using HMDS and a catalytic amount of iodine (Scheme 1).

Compounds that were trimethylsilylated in this way are primary, allylic, benzylic, hindered and unhindered secondary, tertiary, and acid-sensitive tertiary alcohols (Tables 1 and 2). Generally, in the cases of primary and secondary alcohols the reactions were completed within less than 3 min in CH_2Cl_2 at room temperature accompanied by a fast evolution of NH_3 gas from the reaction mixture (Table 1, entries 1−12). However, in a separate experiment, we observed that HMDS alone (as solvent) is not suitable for the silylation of benzhydrol and tertiary alcohols such as adamantanol, and no reaction occurred even under reflux conditions (Table 1, entry 13; Table 2, entry 1). On the other hand, the representative results of the silylation of these substrates under iodine catalyzed conditions clearly indicate the remarkable catalytic activity of iodine for such a transformation (Table 1, entry 14; Table 2, entry 2). Recently, we have shown that $ZnCl_2$ in refluxing acetonitrile and nitrogen ligand complexes of metal chlorides are highly efficient catalyst for chemoselective silylation of various types of alcohols.[7,8] However, we found that these catalysts were not suitable for silylation of acid-sensitive alcohols such as diarylalkyl carbinols, and produce the corresponding alkenes as sole products.[14] This observation encouraged us to investigate the ability of the protocol for the efficient conversion of highly crowded tertiary alcohols to their corresponding trimethylsilyl ethers.

Inspection of the data in Table 2 clearly shows that different types of highly hindered tertiary alcohols were successfully converted to the corresponding silyl ethers in almost quantitative yields at room temperature (Table 2). Due to the nearly neutral nature of the reaction medium, no elimination by- products were observed at all. To the best of our knowledge this method describes the first example of highly efficient trimethylsilylation of highly acid-sensitive and hindered diarylalkyl carbinols using HMDS (Table 2, entries 4 and 5).

The mechanism for these transformations is unclear. One idea may be that I_2 produces trace amounts of HI or TMSI, which might be the actual catalyst for the silylation reaction. However, a brief survey of the literature shows that silylation reaction with HMDS in the presence

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(12) Reference 11, Table 1, entry 10.

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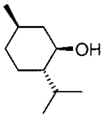
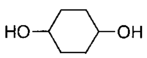
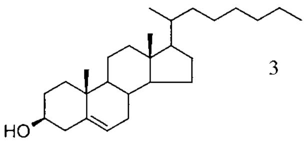
10.1021/jo005519s CCC: $19.00

Scheme 1

$$\text{R-OH} \xrightarrow[\text{CH}_2\text{Cl}_2,\ \text{rt}]{\text{HMDS (0.8 equiv.), I}_2\text{ (0.01 equiv.)}} \text{R-OSiMe}_3$$

Table 1. Silylation of Alcohols Using HMDS in the Presence of Iodine

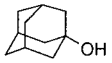
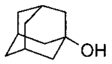
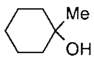
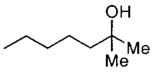
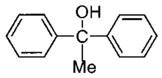
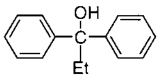
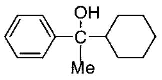
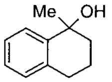
Entry	ROH	time (min)	yield[a,b] (%)
1	$PhCH_2OH$	2	98
2	$4\text{-}(CH_3)C_6H_4CH_2OH$	2	96
3	$2,6\text{-}(Cl)_2C_6H_3CH_2OH$	3	98
4	4-(*i*-Pr)$C_6H_4CH_2OH$	2	98
5	$PhCH{=}CHCH_2OH$	2	99
6	n-octylOH	3	92
7	$PhCH_2CH_2CH_2OH$	3	98
8	$PhCH(OH)CH_3$	3	96
9	$PhCH(OH)CH_2CH_3$	3	95
10		4	99
11		4	97[c]
12		3	97
13	PhCH(OH)Ph	3h	NR
14	PhCH(OH)Ph	4	96

[a] Isolated yield. [b] All products gave satisfactory FT-IR and NMR spectra spectra. [c] 1.6 equiv of HMDS was used, and yields refer to the corresponding disilyl compound.

of protic and Lewis acid catalysts are much slower than those observed in the presented protocol. Therefore, it seems that I_2 represents an extraordinary effect over that expected from simple in situ generation of HI or TMSI in the reaction medium. Another plausible idea is that I_2 polarizes the Si–N bond in HMDS to produce reactive silylating agent **1** (Scheme 2). A rapid reaction with alcohol then ensues, leading to the iodoammonium silylating species **2** and concomitant release of the corresponding silyl ether then results in the formation of the unstable ammonia–iodine complex **3**. Irreversible cleavage of **3**, leading to the fast evolution of NH_3 and release of I_2, which re-enters to the catalytic cycle (Scheme 2). Nevertheless, at this time there is no experimental evidence for this feature of I_2, and the actual role of this reagent should be further studied in detail.

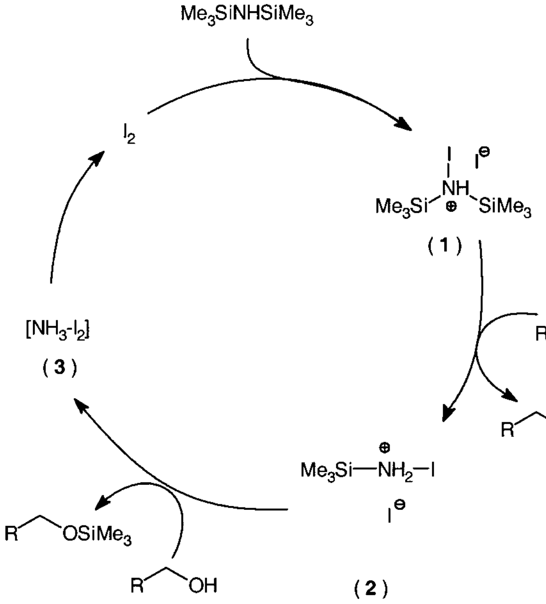
In summary, we have demonstrated that iodine is a new, efficient and practically neutral catalyst for trimethylsilylation of a variety of alcohols using HMDS. Work on catalytic effect of iodine on the reaction of other types of silazanes with alcohols is currently ongoing in our laboratory.

Table 2. Silylation of Highly Hinderd Tertiary Alcohols Using HMDS in the Presence of Iodine

entry	ROH[a]	Time (min)	Yield[b,c] (%)
1		5h	NR
2		6	99
3		4	99
4		5	94
5		30	98
6		45	99
7		20	93
8		18	96

[a] The starting alcohols were either obtained commercially or prepared according to the known Grignard procedures. Isolated yield without any distillation. [b] All products gave satisfactory FT-IR spectra.

Scheme 2



Experimental Section

General Procedure for Silylation of Alcohols Using HMDS Catalyzed with I_2 (Large Scale). To a stirred solution of alcohol (10 mmol) and I_2 (0.1 mmol) in CH_2Cl_2 (40 mL) was added HMDS (8 mmol in 10 mL CH_2Cl_2) dropwise within 5 min. After completion of the reaction (TLC or GC), finely powdered $Na_2S_2O_3$ (≈3 g, portion wise) was added, the mixture was stirred for additional 30 min, and the resulting mixture was filtered through a short pad of silica gel. The filter cake was washed twice with CH_2Cl_2 (35−40 mL). Evaporation of the solvent under reduced pressure gave almost pure product(s) (Tables 1 and 2). Further purification was proceeded by vacuum distillation or recrystallization to afford pure silyl ethers.

Acknowledgment. The authors acknowledge the Institute for Advanced Studies in Basic Sciences (IASBS) Research Council for support of this work.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

JO005519S