Efficient O-Trimethylsilylation of Alcohols and Phenols with Trimethylsilyl Azide Catalyzed by Tetrabutylammonium Bromide under Neat Conditions

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A very efficient procedure for the trimethylsilylation of a wide variety of alcohols, including primary, allylic, benzylic, secondary, hindered secondary, tertiary, and phenols is reported. The reactions were carried out under neat conditions with trimethylsilyl azide (TMSN$_3$) and, when necessary, in the presence of a catalytic amount (20 mol %) of tetrabutylammonium bromide (TBABr) at 30 or 70 °C. Under catalytic conditions, the yields of the corresponding trimethylsilyl ethers were greater than 91%. This procedure also allows the selective protection of primary and secondary alcohols in the presence of tertiary ones.

Introduction

As a consequence of serious pollution problems, the adoption of "cleaner production" methods is an urgent priority. Four main approaches have recently been developed to synthesize compounds in an environmentally friendly manner: (i) use water or supercritical fluids instead of organic solvent, (ii) use no solvent at all, (iii) use catalytic amounts of metal instead of stoichiometric amounts, and (iv) use biosynthetic processes.[1]

For several years, we have been investigating organic processes in an exclusively aqueous medium,[2] and recently we discovered that even Lewis acids, such as AlCl$_3$, recommended for use under anhydrous conditions, are excellent catalysts in aqueous medium.[3] Here, we report an efficient protocol to silylate primary, secondary, and tertiary alcohols and phenols under neat conditions.

The use of a silyl ether function as a protecting group of the hydroxy functionality is well documented in organic synthesis.[4] Among the most efficient reagents to introduce the trimethylsilyl group we can recall: trimethylsilyl chloride in the presence of a base,[5] Li$_2$S,[6] or Mg,[7] ketene methyltrialkylsilyl acetals,[8] allyl silanes,[9] ethyl

trimethylsilyl acetate,[10] N,N-bis(trimethylsilylurea),[11] and methyl 3-(trimethylsilyloxy)crotonate.[12] Hexamethyldisilazane has been used in the presence of a variety of catalysts (Me$_3$SiCl,[13] sulfonic acids,[14] ZnCl$_2$,[15] nitrogen ligand complexes of metal chlorides,[16] zirconium sulfophenyl phosphonate,[17] K-10 montmorillonite,[18] R$_1$R$_2$NH compounds in which R$_1$ and R$_2$ are ester or amide groups,[19] I$_2$[20]). N-Trimethylsilyl-2-oxazolidinone[21] and N,O-bis(trimethylsilyl)acetamide[22] were used in the presence of Me$_3$SiCl and tetrabutylammonium fluoride, respectively.

With some exceptions,[5a,7,20,22] these reagents are not able to silylate, or only partly silylate, secondary hindered

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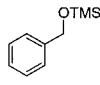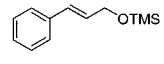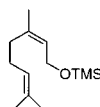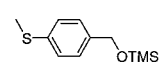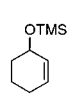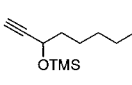
and tertiary alcohols. Moreover, protection under neat conditions is rarely used.[21]

Results and Discussion

Trimethylsilyl azide, a commercially available reagent, is widely used in the azidolysis of epoxides,[23] but there is only one report[24] of its use for the trimethylsilylation of alcohols and phenol. This reaction was performed in organic solvent (THF, CH_2Cl_2, M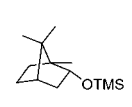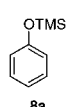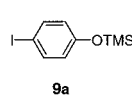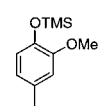eCN), and good results were only obtained for primary and secondary unhindered alcohols.[24] The silylation of tertiary or hindered alcohols does not occur. We hypothesized that this is due to the fact that the silicon atom in $TMSN_3$ has a low electrophilic character and that coordination with a halogen ion should make the silicon atom more electrophilic,[25] favoring the nucleophilic attack of a hydroxy group. The goal was attained by using a catalytic amount of TBABr, which allows a highly efficient trimethylsilylation of tertiary alcohols and phenols by $TMSN_3$ to be achieved under neat conditions.

$TMSN_3$ (1.5 mol/equiv) at 30 °C converts under neat conditions primary alcohols into the corresponding trimethylsilyl ethers in 30 min (Table 1, entries 1, 3, 5, and 7); when the reaction was carried out in the presence of TBABr (0.1 mol/equiv), the silylation occurs quantitatively in a few seconds (Table 1, entries 2, 4, 6, and 8). Secondary alcohols give OTMS products in a few hours when only $TMSN_3$ is used (Table 1, entries 9, 11, and 14); by adding 0.1 or 0.2 mol/equiv of TBABr to the reaction mixture, the time was reduced to 0.5–10 min (Table 1, entries 10, 13, and 16). The reactivity of phenols to $TMSN_3$ is very low (Table 1, entries 18, 21, and 24); by using 20 mol % of TBABr, the reaction was greatly accelerated (Table 1, entries 19, 22, and 25). An extraordinary catalytic effect of TBABr was found in the silylation of tertiary alcohols. No silylation reaction of 2-methyl-1-phenyl-2-propanol (**11**) was observed after 4 h at 70 °C in the absence of the ammonium salt even with 4 mol/equiv of $TMSN_3$ (Table 2, entry 1). In the presence of 0.1 mol/equiv of catalyst, the reaction at 70 °C was complete in 2 h (Table 2, entry 2) and with 2.5 mol/equiv of $TMSN_3$ and 0.2 mol/equiv of TBABr, the reaction occurred quantitatively in only 30 min (Table 2, entry 5). This protocol was extended to other tertiary alcohols, and the results are illustrated in Table 3. In all cases, the trimethylsilyl ether derivatives were isolated in high yields (92–99%), and the reactions were completed in a relatively short time (0.5–7 h). The methyl *trans*-2-azido-1-hydroxycyclohexane carboxylate (**16**) was an unusually difficult substrate to silylate. Under standard conditions, only 73% of the corresponding silyl ether was obtained after 17 h (Table 3, entry 12). To increase the conversion, the reaction was carried out with 4 mol/equiv of $TMSN_3$, and in this way, a 93% yield of **16a** after 6 h was reached (Table 3, entry 13). In contrast, 1-adamantanol (**12**) was silylated very easily and only 1.5 mol/equiv of $TMSN_3$ were needed to protect it completely after only 12 min (Table 3, entry 4). The data in Table 3 clearly show that the presence of TBABr is fundamental for the effectiveness of the reaction;

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Table 1. O-Trimethylsilylation of Primary and Secondary Alcohols and Phenols with 1.5 Mol/Equiv of $TMSN_3$ at 30 °C

| Entry	Alcohol	TBABr (mol/eq)	Time (min.)	Silyl ether	Yield[a] (%)
1	**1**	-	30	**1a**	99
2		0.1	0.2		
3	**2**	-	30	**2a**	98
4		0.1	0.2		
5	**3**	-	30	**3a**	99
6		0.1	0.2		
7	**4**	-	30	**4a**	98
8		0.1	0.2		
9	**5**	-	60	**5a**	98
10		0.1	0.5		
11		-	600	**6a**	99
12	**6**	-	10		8
13		0.2	10		98
14		-	780	**7a**	95
15	**7**	-	10		2
16		0.2	10		96
17		-	1440	**8a**	98
18	**8**	-	150		59
19		0.2	150		99
20		-	1440	**9a**	94
21	**9**	-	120		55
22		0.2	120		96
23		-	1440	**10a**	92
24	**10**	-	240		51
25		0.2	240		98

[a] Yield of isolated product.

without the catalyst, only traces of protected alcohols were observed. The use of $TMSN_3$ is also important because, by using trimethylsilyl chloride as trimethylsilylating agent, a large percentage of the corresponding elimination products was detected.

We also explored the ability of $TMSN_3$ to discriminate between different kinds of hydroxy groups (primary, secondary, tertiary, benzylic, and phenolic) present in the

Table 2. O-Trimethylsilylation of 2-Methyl-1-phenyl-2-propanol 11 with TMSN$_3$–TBABr at 70 °C
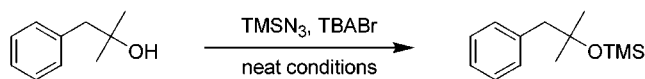
entry	TMSN$_3$ mol/equiv	TBABr mol/equiv	time (h)	conversion[a] (%)
1	4.0		4.0	2
2	4.0	0.1	2.0	97
3	1.2	0.2	2.0	90
4	2.0	0.2	2.0	96
5	2.5	0.2	0.5	>99

[a] Conversion based on GC analysis.

Table 3. TBABr-Catalyzed O-Trimethylsilylation of Tertiary Alcohols at 70 °C

Entry	Alcohol	TMSN$_3$ mol/eq	TBABr mol/eq	Time (h)	Silyl ether	Yield[a] (%)
1	11	2.5	-	0.5	11a	-
2		2.5	0.2	0.5		98
3	12	1.5	-	0.2	12	-
4		1.5	0.2	0.2		96
5	13	2.5	-	3.0	13a	2
6		2.5	0.2	3.0		99
7	14	2.5	-	2.0	14a	4
8		2.5	0.2	2.0		98
9	15	2.5	-	7.0	15a	-
10		2.5	0.2	7.0		92
11		4.0	-	6		1
12	16	2.5	0.2	17	16a	73
13		4.0	0.2	6		93

[a] Yield of isolated product.

same compound. The results obtained are reported in Table 4. In the presence of secondary benzylic and phenolic hydroxy groups, the reaction is completely unselective and only produces the bis-silylated product **17a** (Table 4, entry 1). In the reaction of the phenyl ethanediol **18**, the process results in a 81/19 mixture of compound **18a** with only the primary silylated hydroxy group and the completely silylated compound **18b** (Table 4, entry 2). An analogous result was obtained in the case of 1,2-octanediol **19** (Table 4, entry 3). Trimethysilylation

Table 4. Selective O-Trimethylsilylation of Diols 17–22 with 1.5 Mol/Equiv of TMSN$_3$

Entry	Alcohol	Temp. (°C)	Time (min)	Silyl ether[a]
1	17	50[b]	120[b]	**17a** 100%
2	18	30[b]	10	**18a** 81% **18b** 19%
3	19	0	0.5	**19a** 87% **19b** 13%
4	20	30	10	**20a** 98% **20b** 2%
5	21	30	30	**21a** 100%
6	22	30	600	**22a** 100%

[a] Silyl ether ratios were determined by GC analysis. [b] Different reaction conditions (amount of TMSN$_3$, time, and temperature) were used but better selectivity was not observed.

of compound **20** furnished the phenol **20a** with high selectivity (Table 4, entry 4). Primary and secondary hydroxy groups react faster than the tertiary ones, and the monosilylated alcohol was isolated in almost quantitative yield (Table 4, entries 5 and 6).

Mechanistically, we suggest that the silicon atom of TMSN$_3$ gives a pentacoordinated species, by coordinating with the bromide ion of TBABr and then undergoes nucleophilic attack by the OH group forming the OTMS functionality and regenerating the TBABr.

In summary, TMSN$_3$ is not only an effective silylating agent for primary and secondary unhindered alcohols but also for secondary hindered, and tertiary ones and phenols if the silicon atom is activated to nucleophilic attack. TBABr is an excellent catalyst that allows the reaction to be performed in neat conditions with excellent yield. The degree of selectivity of primary over secondary, tertiary and phenolic hydroxy groups and secondary ones is from good to excellent.

Experimental Section

General Procedures. All chemicals were purchased and used without further purification. GC analyses were performed

with an SPB-5 fused silica capillary column (30 m, 0.25 mm diameter), an "on column" injector system, an FID detector, and hydrogen as the carrier gas. GC−MS analyses were carried out with 70 eV electron energy. ^{1}H and ^{13}C NMR spectra were recorded at 400, 200, 100.6, and 50.3 MHz, respectively, in CDCl$_3$ and CD$_3$COCD$_3$. IR spectra were recorded with a FT-IR instrument, using CCl$_4$ as solvent. The alcohols and phenols **1−3** and **5−14** are commercially available. Alcohol **4** was obtained by reducing the corresponding aldehyde in water with NaBH$_4$. Alcohol **15** was synthesized from the corresponding alkene through epoxidation (MCPA/water), hydrolysis (H$_2$SO$_4$/water), and selective acetylation of the secondary hydroxy group (Ac$_2$O/pyridine). Compound **16** was synthesized starting from 1-cyclohexene-1-carboxylic acid by means of epoxidation (Oxone,water/acetone), azidolysis (NaN$_3$/AlCl$_3$, water), and the final COOH protection was carried out with an ether solution of diazomethane. The diols **18**, **19,** and **21** were synthesized through epoxidation (MCPA/water) and subsequent hydrolysis (H$_2$SO$_4$/water), from the corresponding alkenes. Compounds **17** and **20** were obtained through the reduction of the corresponding carbonyl compounds (NaBH$_4$/water). Diol **22** was synthesized through syn dihydroxylation of the corresponding alkene (OsO$_4$/CH$_2$Cl$_2$). Silyl ethers **1a**,[6] **2a**,[6] **5a**[6] and **3a**,[26] **6a**,[15] **7a**,[27] **8a**,[6] **9a**,[28] **10a**,[29] **12a**,[7] **13a**,[12] **14a**,[30] **15a**,[31] **18a**, **18b**,[16] **20a**, and **20b**[18] are known compounds. Silyl ethers **4a**, **11a**, **16a**, **17a**, **19a**,**b**, **21a**, and

22a are new compounds and are described in the Supporting Information.

General Procedure for O-Trimethylsilylation of Alcohols and Phenols Using TMSN$_3$ Catalyzed by TBABr. TBABr was added to a stirred solution of alcohol (1 mmol) and TMSN$_3$ at 30 or 70 °C (see Tables 1−3). When the reaction was complete (TLC or GC analysis), 2 mL of water was added and the mixture was extracted with Et$_2$O; to eliminate TBABr, the resulting ether solution was filtered through a thin pad of silica gel and then silica gel was washed twice with Et$_2$O. The combined organic layers were dried over Na$_2$SO$_4$ and evaporated under reduced pressure to give the pure O-trimethylsilylated alcohol as indicated in Tables 1−3.

Supporting Information Available: Properties, identification data (^{1}H and ^{13}C NMR, IR, mass spectral data), and elemental analysis of newly synthesized silyl ethers **4a**, **11a**, **16a**, **17a**, **19a**,**b**, **21a**, and **22a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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