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Note

Simple procedure for the preparation of trimethylsilyl ethers of carbohydrates and alcohols

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The trimethylsilyl group has been used extensively for the protection of alcohols in organic synthesis. As a result, several methods and reagents have been developed for the preparation of trimethylsilyl ethers[1]. Chlorotrimethylsilane or a mixture of chlorotrimethylsilane and hexamethyldisilazane in pyridine generally is employed for the per-*O*-silylation of simple carbohydrate derivatives[2]. For the silylation of less reactive compounds, however, rigorous conditions[3] or expensive reagents[1,4] are often required, thus rendering many methods unsuitable for sensitive compounds and large scale reactions. We report herein a new procedure for the facile silylation of carbohydrates and sterically hindered alcohols under very mild conditions.

Treatment of alcohols and carbohydrate derivatives with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) * and a catalytic amount of tetrabutylammonium fluoride (TBAF) in an aprotic solvent afforded the corresponding silyl ethers in very good yield (Table I). The silylation reactions, which were essentially complete in a few minutes at room temperature, produced neutral, water-soluble or volatile byproducts, thereby simplifying isolation of the silylated products. Although less polar solvents could be employed successfully in the reaction, pyridine and dipolar aprotic solvents such as *N*-methylpyrrolidinone (NMP) and *N*,*N*-dimethylformamide (DMF) facilitated the reaction and permitted dissolution of the polyhydroxy compounds. Owing to its volatility, pyridine is a useful silylation solvent for analytical procedures[12].

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* For large scale reactions, 1,3-bis(trimethylsilyl)urea, which forms urea as a byproduct, can be substituted for BSA.

TABLE I

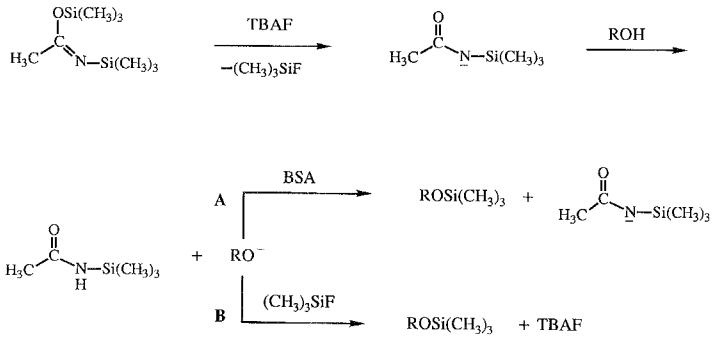
Preparation of trimethylsilyl ethers

Entry	Starting material	Product	Yield [a] (%)	Bp (°C/mmHg) or mp (°C)	$[\alpha]_D^{22}$ (c) in $CHCl_3$
1	α-D-Glucose	1,2,3,4,6-Pentakis-*O*-(trimethylsilyl)-α-D-glucopyranose	93	b 107–110/0.1 [b]	+65.4° (3.3)[b]
2	1,6-Anhydro-β-D-glucose	1,6-Anhydro-2,3,4-tris-*O*-(trimethylsilyl)-β-D-glucopyranose	75 [c]	b 87–88/0.1 [d]	−39.4° (3.2) [d]
3	Methyl α-D-glucopyranoside	Methyl 2,3,4,6-tetrakis-*O*-(trimethylsilyl)-α-D-glucopyranoside	95	b 101/0.15 [e]	+85.7° (1.6) [e]
4	Trehalose dihydrate	2,3,4,6,2′,3′,4′,6′-Octakis-*O*-(trimethylsilyl)-α,α-trehalose	98 [f]	m 79–81 [f]	+100° (1.0) [f]
5	1,2-*O*-Isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-glucofuranose [g]	1,2-*O*-Isopropylidene-6-*O*-*p*-tolylsulfonyl-3,5-bis-*O*-(trimethylsilyl)-α-D-glucofuranose	83 [h]	m 110–111.5	−16.6° (1.0)
6	2-Phenyl-2-propanol	2-Phenyl-2-(trimethylsiloxy)-propane	87	b 74–75.5/4.4 [i]	
7	2-Methyl-1-phenyl-1-propanol	2-Methyl-1-phenyl-1-(trimethylsiloxy)propane	94	b 73–74/2.6 [j]	

[a] Isolated yield of pure distilled or recrystallized product, unless otherwise indicated. See Experimental for general procedure. [b] Contained ~5% of the β anomer (axial anomeric proton) from ^1H NMR data ($CDCl_3$, 270 MHz) for H-1: α anomer, δ 5.01 (d, *J* 3.0 Hz); β anomer, δ 4.47 (d, *J* 7.1 Hz); *cf.* ref. 5. Lit. physical constants: bp 104–106°C/0.001 mm; $[\alpha]_D^{20}$ +76.7° (*c* 0.4, $CHCl_3$)[6], bp 115°C/0.08 mm; $[\alpha]_D^{20}$ +34.1° (*c* 3.17, cyclohexane)[7]. The anomeric ratio was not reported in refs. 6 or 7. [c] Reaction carried out at room temperature for 16 h. [d] Lit. bp 93°C/0.04 mm; $[\alpha]_D^{20}$ −34.3° (*c* 2.9, $CHCl_3$)[7]. [e] Lit. bp 109–110°C/0.1 mm; $[\alpha]_D^{20}$ +91.3° (*c* 1.5, $CHCl_3$)[7]. [f] Yield of crude crystalline product, very pure by TLC and NMR analysis; Lit. mp 80–82°C; $[\alpha]_D^{25}$ +95° (*c* 1, $CHCl_3$)[8]. [g] See ref. 9. [h] Recrystallized from petroleum ether. Lit.: mp and $[\alpha]_D$ not reported[10]. However, a sample prepared according to ref. 10 exhibited mp 106–109°C, $[\alpha]_D^{20}$ −15.9° (*c* 1.0, $CHCl_3$). [i] Lit. bp 73°C/4.5 mm[11]. [j] Lit. bp 74–77°C/3.5 mm[11].

This new procedure compares very favorably with existing methods for the silylation of sterically hindered alcohols. For example, treatment of 2-phenyl-2-propanol in NMP with BSA (1 mol equiv) and TBAF (0.005 mol equiv) provided the corresponding silyl ether in 87% yield (Entry 6, Table I). In comparison, silylation of this tertiary alcohol according to Olah's procedure[11] with a mixture of chlorotrimethylsilane and lithium sulfide leads to the recovery of a considerable amount of starting material.

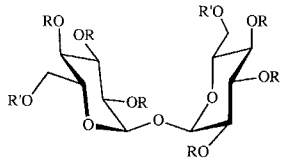
Although BSA is an inexpensive and popular silylating agent[13], elevated temperatures and large excesses of this reagent are often required for less reactive alcohols[14]. In fact, no silyl ether formation was observed when 2-phenyl-2-propanol was treated with a large excess (10 mol equiv) of BSA in NMP in the absence of fluoride ion. Similarly, treatment of trehalose in NMP or pyridine with BSA alone led to very little silylation even at elevated temperatures (< 10% complete after 2



Scheme 1.

h at 80°C in NMP), whereas per-*O*-silylation occurs facilely at room temperature in the presence of 0.05 mol equiv of TBAF (Entry 4, Table I).

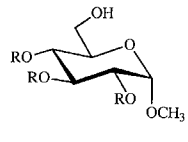
The mechanism for this fluoride-induced silylation is not clear. Nakamura et al.[15] employed a mixture of ethyl trimethylsilylacetate and TBAF to silylate alcohols and ketones, and speculated that in situ generated fluorotrimethylsilane was the active silylating agent in the reaction. However, we found that the per-*O*-silylation of trehalose dihydrate with BSA (7–8 mol equiv) proceeds nearly as well when potassium *tert*-butoxide (0.05 equiv) is substituted for TBAF. This result suggests that the silylation reaction is explicable in terms of alcohol deprotonation by an in situ generated quaternary ammonium amidate followed by silylation with BSA (path A, Scheme 1). Thus, it appears that TBAF is acting as an initiator, and not a catalyst, in this case. Nevertheless, a reaction pathway involving silylation of the deprotonated alcohol by fluorotrimethylsilane and regeneration of the TBAF catalyst cannot be unequivocally ruled out (path B, Scheme 1). Since the silyl ethers can be obtained in good yield with as little as 0.6 mol equiv of BSA (1.2 mol of trimethylsilyl groups per mol of hydroxyl groups), both trimethylsilyl groups of the reagent can be utilized in the reaction.



1a R=R'=H

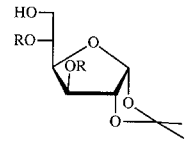
1b R=R'=$Si(CH_3)_3$

1c R=$Si(CH_3)_3$, R'=H



2a R=H

2b R=$Si(CH_3)_3$



3a R=H

3b R=$Si(CH_3)_3$

This silylating method is also amenable to the one-pot, two-step synthesis of 2,3,4,2′,3′,4′-hexakis-*O*-(trimethylsilyl)-α,α-trehalose (**1c**) directly from trehalose dihydrate (**1a**) via selective methanolysis[8,16] of the trimethylsilyl groups on the primary (6,6′) positions. Diol **1c** is a useful intermediate in the synthesis of biologically-important trehalose diesters[8,17]. Accordingly, without workup of the silylation reaction mixture, the octakis derivative **1b** was converted to diol **1c** in 83% overall yield by the action of potassium carbonate in methanol at 0°C. Methyl 2,3,4-tris-*O*-(trimethylsilyl)-α-D-glucopyranoside (**2b**) was prepared in 76% yield from methyl α-D-glucopyranoside (**2a**) via an analogous procedure. Application of this persilylation–desilylation protocol to the preparation of furanose derivatives such as **3b** from 1,2-*O*-isopropylidene-D-glucofuranose (**3a**) resulted in the nonselective cleavage of trimethylsilyl groups on the per-*O*-silylated intermediate to give a mixture of products.

This fluoride-promoted silylation procedure should find useful application to carbohydrate derivatives and unreactive alcohols in general. It also provides an efficient one-pot, two-step synthesis of pyranoside derivatives such as **1c** and **2b** in which only the secondary hydroxyls are protected as trimethylsilyl ethers.

EXPERIMENTAL

General methods.—Melting points were determined with a Mel-Temp capillary melting-point apparatus and are uncorrected. TLC was performed on Silica Gel 60 F_{254} (Merck) with detection by dipping in phosphomolybdic acid (5% in 95% EtOH) or anisaldehyde (2.5% in 75:3:1 EtOH–concd H_2SO_4–acetic acid) followed by heating. Flash chromatography was performed on Silica Gel 60 (Merck, 230–400 mesh). Optical rotations were determined with a Jasco DIP-140 digital polarimeter. ^{1}H NMR spectra were obtained on a Varian EM 360-A spectrometer (60 MHz) or a Bruker HX-270 multinuclear Fourier transform spectrometer (270 MHz). Infrared spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrophotometer.

All starting materials and reagents were commercially available and used without purification unless otherwise indicated. Solvents were dried according to standard methods.

General procedure for the trimethylsilylation of alcohols.—To a vigorously stirred solution of the alcohol (1 mmol) in dry *N*-methylpyrrolidinone (NMP, 2–4 mL) at 15°C under N_2 was added *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 0.6–1.0 mol per mol of hydroxyl groups). The resulting colorless solution was then treated dropwise over 5 min with tetrabutylammonium fluoride (TBAF, 1.0 M in THF, 0.005 mol per mol of hydroxyl), during which time the solution generally turned pink or purple and became turbid. The color change was accompanied by a slight evolution of heat. After stirring 15–30 min at room temperature, the excess BSA was quenched with MeOH (0.5 mL) and the reaction mixture was diluted with hexanes (25 mL), washed with water (15 mL), and dried ($MgSO_4$). Removal of volatiles in

vacuo afforded the almost pure silyl ethers, which could be purified further by distillation or recrystallization. IR and ^{1}H NMR spectra of the products were in agreement with the assigned structures and their reported spectral data.

2,3,4,2',3',4'-Hexakis-O-(trimethylsilyl)-α,α-trehalose (**1c**).—To a solution of trehalose dihydrate (**1a**, 0.25 g, 0.66 mmol) in dry DMF (1 mL) at 15°C under N_2 was added BSA (1.4 mL, 5.7 mmol) followed by TBAF (1.0 M in THF, 0.04 mL, 0.04 mmol) dropwise over 5 min. The reaction mixture was vigorously stirred at room temperature for 30 min and then quenched with 2-propanol (0.25 mL). The resulting mixture was diluted with dry MeOH (15 mL), cooled to 0°C, and treated dropwise over 20 min with a solution of K_2CO_3 (0.091 g, 0.66 mmol) in dry MeOH (20 mL). After stirring for 2 h at 0°C, the solution was neutralized with acetic acid (0.1 mL) and the MeOH was removed in vacuo at 35°C. The resulting residue was partitioned between ether (25 mL) and brine (25 mL) and the layers separated. The ethereal layer was dried ($MgSO_4$) and concentrated in vacuo to afford 0.49 g (96%) of the crude diol which crystallized on standing (mp 97–105°C). Flash chromatography over silica gel with 1:4 (v/v) EtOAc–hexanes furnished 0.42 g (83%) of pure diol **1c** as a colorless solid; mp 115–117°C, $[\alpha]_D^{25}$ + 103° (*c* 1, $CHCl_3$); Lit.[8] mp 115–118°C; $[\alpha]_D^{20}$ + 100° ($CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.91 (d, 2 H, *J* 3.0 Hz, H-1,1'), 3.95–3.58 (m, 8 H), 3.48 (t, 2H, *J* ~ 9 Hz), 3.42 (dd, 2 H, *J* ~ 3, 9 Hz), 1.74 (br s, 2 H, 2 O*H*), 0.16, 0.15, and 0.12 (3 s, 18,18, and 18 H, 6 $OSiMe_3$).

Methyl 2,3,4-tris-O-(trimethylsilyl)-α-D-glucopyranoside (**2b**).—Methyl α-D-glucopyranoside (**2a**, 0.20 g, 1.0 mmol) was per-*O*-silylated (3 mmol BSA) and selectively deprotected (0.5 mmol K_2CO_3) as in the preparation of **1c** to give 0.31 g (76%) of compound **2b** after flash chromatography with 3:17 (v/v) EtOAc–hexanes; mp 97–98°C; $[\alpha]_D^{25}$ + 93° (*c* 5.0, $CHCl_3$); lit.[16] mp 98.5–99.5°C; $[\alpha]_D^{25}$ + 91.48° ($CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.61 (d, 1 H, *J* 3.5 Hz, H-1), 3.83–3.43 (m, 6 H), 3.75 (s, 3 H, OMe), 1.82 (br s, 1 H, O*H*), 0.18, 0.16, and 0.15 (3 s, 9,9, and 9 H, 3 $OSiMe_3$).

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