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Efficient Method for the *t*-Butyldimethylsilylation of Alcohols with *N,O*-Bis(*t*-butyldimethylsilyl)acetamide

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Abstract: The efficient *t*-butyldimethylsilylation of alcohols—including tertiary and sterically hindered secondary alcohols—can be achieved using *N,O*-bis(*t*-butyldimethylsilyl)acetamide (BTBSA) in the presence of catalytic amounts (0.01-0.05 equiv) of tetrabutylammonium fluoride (TBAF) and other fluoride ion sources. The judicious choice of solvent and amount of catalyst permits the selective silylation of primary alcohols.

Recently we reported a new procedure for the trimethylsilylation of alcohols using *N,O*-bis(trimethylsilyl)acetamide (BSA) and 1,3-bis(trimethylsilyl)urea (BSU) in the presence of catalytic tetrabutylammonium fluoride (TBAF).[1,2] We have now extended our studies to the preparation of *t*-butyldimethylsilyl (TBS) ethers using this silyl transfer methodology. Many of the methods commonly employed for the introduction of the TBS group[3] often suffer from a lack of reactivity and/or selectivity. Here we describe the efficient *t*-butyldimethylsilylation of alcohols—including tertiary and sterically hindered secondary alcohols—as well as the chemoselective silylation of primary alcohols with *N,O*-bis(*t*-butyldimethylsilyl)acetamide (BTBSA, **1**) in the presence of catalytic TBAF and other fluoride ion sources.

Treatment of alcohols with BTBSA[4] and a catalytic amount of TBAF (0.02-0.05 equiv) in an aprotic solvent afforded the corresponding silyl ethers in good to excellent yield (Table 1). The silylation reactions, which produced neutral, water-soluble or volatile by-products, were essentially complete in a few minutes at room temperature in the case of primary and secondary alcohols.

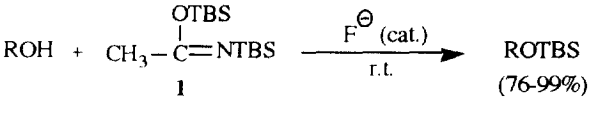


Table 1. Preparation of *t*-Butyldimethylsilyl Ethers with BTBSA/cat. TBAF

Starting Material	BTBSA (equiv)	TBAF (equiv)	Solvent	Time (h)	Isolated Yield, %[a]
Benzyl alcohol	0.6	0.02	THF	0.5	96
Glycerol	1.8	0.03	NMP	0.75	99[b]
1-Phenyl-1,2-ethanediol	1.2	0.03	NMP	0.5	95[c]
2-Methyl-1-phenyl-1-propanol (**2**)	0.6	0.03	NMP	0.5	95
2-Phenyl-2-propanol (**3**)	1.2	0.05	NMP	16	97
2-Methyl-1-phenyl-2-propanol	1.2	0.05	NMP	16	76

[a]All reactions were carried out at r.t. at a concentration of 0.5*M*. Following aqueous work-up, products were purified by flash or radial chromatography and characterized by ^{1}H- and ^{13}C-NMR. [b]Yield of 1,2,3-tris(*t*-butyldimethylsilyloxy)propane. [c]Yield of 1,2-bis(*t*-butyldimethylsilyloxy)-1-phenylethane.

The silylation of alcohols with the BTBSA/cat. TBAF system is more solvent dependent than the analogous trimethylsilylation reaction (Figure 1).[5] Greater amounts of TBAF were required in CH_2Cl_2 and THF than in *N*-methylpyrrolidinone (NMP) to achieve the same degree of benzyl alcohol silylation. Little or no silyl ether formation was observed in the absence of fluoride ion.The hindered phenylpropanol derivatives **2** and **3** were the most sensitive to solvent polarity but nonetheless were converted into the corresponding TBS ethers in quantitative yield in NMP. (In comparison, yields of the TBS ethers of **2** and **3** using the classical method—TBS-Cl/imidazole/DMF[6]—were 40 and 6%, respectively, and 90% in the tertiary case with TBS triflate/2,6-lutidine.[7]) The silyl ethers of benzyl alcohol and **2** could be obtained in excellent yield with 0.6 molar equivalents of BTBSA indicating that both TBS groups of the reagent are utilized in the reaction. For cumyl alcohol (**3**), however, silylation was always incomplete unless a full equivalent of BTBSA was employed.

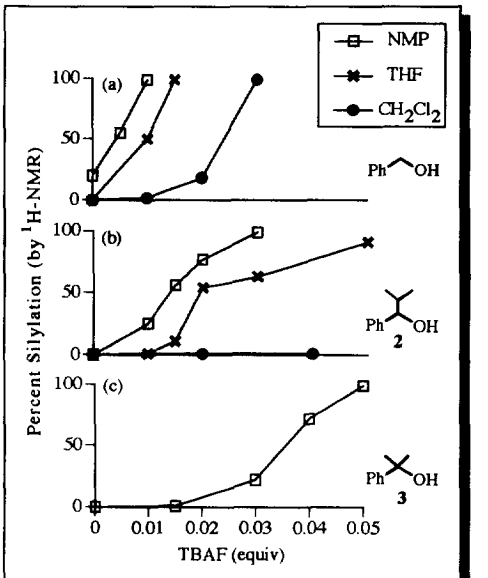
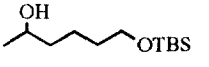
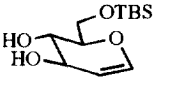
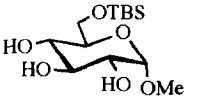
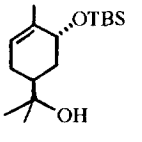


Fig. 1. Effect of TBAF on Percent Silylation: (a), (b) 45 min, 0.6 equiv BTBSA, (c) 16 h, 1.2 equiv BTBSA.

The judicious choice of solvent and amount of TBAF catalyst readily permitted the selective silylation of primary hydroxyl groups in the presence of secondary ones (Table 2).[8] As anticipated, we found even greater preference in the formation of secondary TBS ethers over tertiary ones using this protocol. One limitation of the method, however—and attributable to the migratory propensity of the TBS group in the presence of basic fluoride ion[9]—appears to be the selective silylation of 1,2-diols: 1-phenyl-1,2-ethanediol gives a 2:1:1 mixture of primary and secondary mono- and disilyl ethers, respectively, with BTBSA/cat. TBAF in CH_2Cl_2.

Table 2. Selective *t*-Butyldimethylsilylations with BTBSA/cat. TBAF

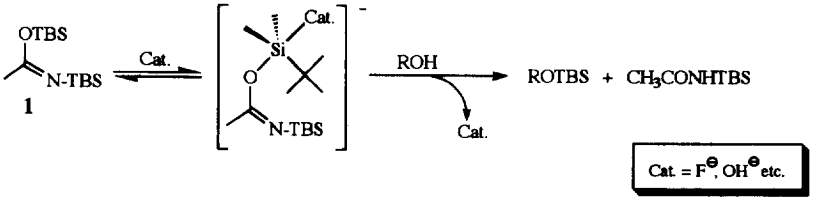
Starting Material	Reaction Conditions[a]	Product	Isolated Yield, %[b]
1,5-Hexanediol	TBAF 0.03 eq CH_2Cl_2 24 h		96
D-Glucal	TBAF 0.015 eq THF 24 h		89
Methyl α-D-glucopyranoside	TBAF 0.01 eq NMP 24 h		95
(±)-*trans*-Sobrerol	TBAF 0.03 eq NMP 12 h		97

[a]All reactions were carried out at r.t. using 0.6 equivalents of BTBSA. [b]All products gave satisfactory ^{1}H- and ^{13}C-NMR spectra.

Prolonged reaction times (16 h) led to a significant amount of desilylation of the TBS ether of benzyl alcohol with catalytic TBAF in THF or NMP (but not CH_2Cl_2) which was proportional to the amount of catalyst used (5 and 25% deprotection using 0.01 and 0.02 equiv TBAF, respectively). Silyl ether cleavage is due presumably to the presence of water (~5%)—and thus nucleophilic hydroxide—in commercial TBAF solutions.[10] In order to evaluate the effect of contaminating water (3-4 mol/mol TBAF) on the reaction and speculate on the mechanism of this fluoride-promoted silylation we examined other fluoride ion sources as well as organic soluble hydroxide equivalents in the reaction.

Both "anhydrous" TBAF[11] and tetrabutylammonium difluorotriphenylstannate[12] (TBAS) were more potent sources of nucleophilic fluoride than TBAF with respect to the minimum amount of catalyst needed for quantitative *t*-butyldimethylsilylation of benzyl alcohol in CH_2Cl_2 or THF. However, whereas TBAS (0.01-0.03 equiv) produced no detectable silyl ether cleavage after 16 hours, "anhydrous" TBAF was a more potent base (25% deprotection with 0.01 equiv) than TBAF in this respect. TBAS was the most effective catalyst of the three at promoting the *t*-butyldimethylsilylation of **2** in THF (>99% yield by ^{1}H-NMR with 0.04 equiv TBAS; cf. Fig. 1b), but the least effective at silylating tertiary alcohols and for silylations carried out in dipolar aprotic solvents in general.

The mechanism of this silylation is not clear. Kuwajima[13] employed a mixture of ethyl trimethylsilylacetate and TBAF to silylate alcohols and ketones and speculated that the *in situ* generated fluorotrimethylsilane was the active silylating agent in the reaction. However, we found that the silylation of benzyl alcohol with BTBSA in NMP proceeds in quantitative yield with tetrabutylammonium hydroxide (0.02 equiv) and nearly as well (~95%) when potassium *t*-butoxide or potassium trimethylsilanolate are substituted for TBAF.[14] In contrast, amine bases are ineffective catalysts in the reaction.[15] These results are consistent with a mechanism in which fluoride ion and other nucleophiles (*e.g.*, hydroxide) having a high affinity towards silicon generate a reactive pentavalent silicate[16,17] which is susceptible to nucleophilic displacement (Scheme 1). Evidence for the formation of *N*-(*t*-butyldimethylsilyl)acetamide (TBSA) was obtained from ^{1}H-NMR studies of the reaction of benzyl alcohol and **3** with BTBSA/cat. TBAF in CD_2Cl_2 and DMF-d_7, respectively.[18]



Scheme 1

We also examined commercially available 4-(*t*-butyldimethylsilyloxy)-3-penten-2-one and *N*-(*t*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide as silyl transfer reagents in the reaction; these reagents have been used for the silylation of alcohols in the presence of acidic catalysts.[4,19] While both of these monoTBS reagents led to the efficient silylation of benzyl alcohol in THF in the presence of TBAF (0.02 equiv), neither gave rise to any silyl ether formation in the case of **2** or **3** (0.03-0.05 equiv TBAF, NMP).[20]

In summary, the versatility and efficiency of the BTBSA/cat. TBAF system make it an attractive method for the preparation of TBS ethers under very mild conditions.[21] Preliminary results using BTBSA with other catalysts indicate that the anhydrous fluoride source TBAS exhibits a better reactivity profile than TBAF for the synthesis of base-sensitive and/or moderately hindered TBS ethers.

REFERENCES AND NOTES

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7. Corey, E.J.; Cho, H.; Rücker, C.; Hua, D.H. *Tetrahedron Lett.* **1981**, *22*, 3455-3458.
8. Treatment of an equimolar mixture of benzyl alcohol and **2** in THF with BTBSA (0.6 equiv)/TBAF (0.015 equiv) at r.t. for 45 min led to selective primary silylation (>99:1 by ^{1}H-NMR) in 95% isolated yield.
9. Wuts, P.G.M.; Bigelow, S.S. *J. Org. Chem.* **1988**, *53*, 5023-5034 and references cited therein.
10. The use of excess BTBSA (0.9 equiv) circumvented silyl deprotection and led to an increase in the formation of the 1,3-di-*t*-butyl-1,1,3,3-tetramethyldisiloxane. Minimal deprotection (≤2%) was observed for the TBS ether of **2** with BTBSA (0.6 equiv)/TBAF (0.03 equiv) in NMP after 16 hours.
11. "Anhydrous" TBAF contains 0.1-0.3 molar equivalents of water and ~10% tetrabutylammonium bifluoride: Cox, D.P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216-3219.
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14. When the reaction is carried out in THF, however, the TBS ether of benzyl alcohol is formed in low to moderate yield in the presence of hydroxide synthons (0.02 equiv, cf. Fig. 1a). The order of oxide potency (n-Bu_4NOH >> KOTMS > KO*t*-Bu) may reflect the degree of steric crowding in a pentacoordinated silicon intermediate.[16]
15. Treatment of benzyl alcohol in NMP and other solvents with BTBSA and stoichiometric quantities of triethylamine or 4-dimethylaminopyridine failed to improve the yield of the silyl ether *vis-à-vis* BTBSA alone. This result argues against a mechanism involving heterolytic cleavage of the Si-O bond and subsequent alcohol deprotonation by an amidate intermediate.[1]
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18. TBSA (bp 70-73°C/2.3 mm), prepared from acetamide and TBS-C1 (1.1 equiv) according to Mawhinney's general method[4], was ineffective at silylating **3** (but not primary and secondary alcohols), thus explaining the observed stoichiometry in the reaction of tertiary alcohols with BTBSA. ^{1}H-NMR data (300 MHz, $CDCl_3$) for TBSA: δ 4.83 (br s, 1H), 2.01 (s, 3H), 0.90 (s, 9H), 0.20 (s, 6H).
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20. Reference 2 gives two examples of the selective silylation of a primary alcohol with 1.2 equivalents of 5,5-dimethyl-1,3-bis(TBS)hydantoin.
21. Satisfactory elemental analyses were obtained for all new compounds.

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