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Mild, Effective and Selective Method for the Silylation of Alcohols Using Silazanes Promoted by Catalytic Tetrabutylammonium Fluoride

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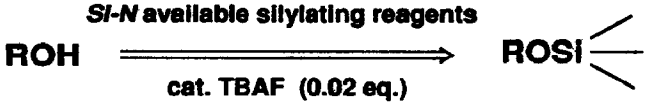
Abstract: The presence of catalytic amounts (~0.02 equiv.) of tetrabutylammonium fluoride (TBAF) significantly promoted the silylation of alcohols using a variety of available silazanes under mild conditions with high chemoselectivity, wherein the choice of silazanes allowed an alternative method for the powerful silylation of various kinds of alcohols or the highly regioselective silylation of primary alcohols.

Silylations of hydroxyl groups, especially trimethylsilylation (TMS) and *t*-butyldimethylsilylation (TBDMS), are presently well established not only as the most popular and reliable protective methods in organic syntheses[1] but also in the diverse field of silicon(e) chemistry.[2] In view of the expanding and elaborate syntheses of complex polyhydroxy compounds, mild and selective silylations and desilylations of alcohols are becoming more and more important. Many of these methods, therefore, have been already exploited. The most commonly used silyl chlorides or silyl triflates/base combination frequently lacks in reactivity and/or chemoselectivity, and requires delicate conditions to scavenge these by-produced acids.

On the other hand, silylation using silazane-type reagents is mild (nearly neutral), the use of co-bases to capture the acid is not needed, and operationally more convenient due to the ease of their preparation and handling. Accordingly, several silazanes are commonly used and commercially available for this purpose. But, the reactivity of these silazane-reagents is often low or unsatisfactory.

Meanwhile, tetrabutylammonium fluoride (TBAF) is now put to general use in the desilylation of silyl ethers. We now wish to described here that catalytic amounts (0.02 equiv.) of TBAF significantly promoted the silylation of alcohols using a variety of available silazane-reagents under mild conditions, i.e., cat. TBAF plays a role as a smooth silyl transfer catalyst from nitrogen to the hydroxyl group.[3]

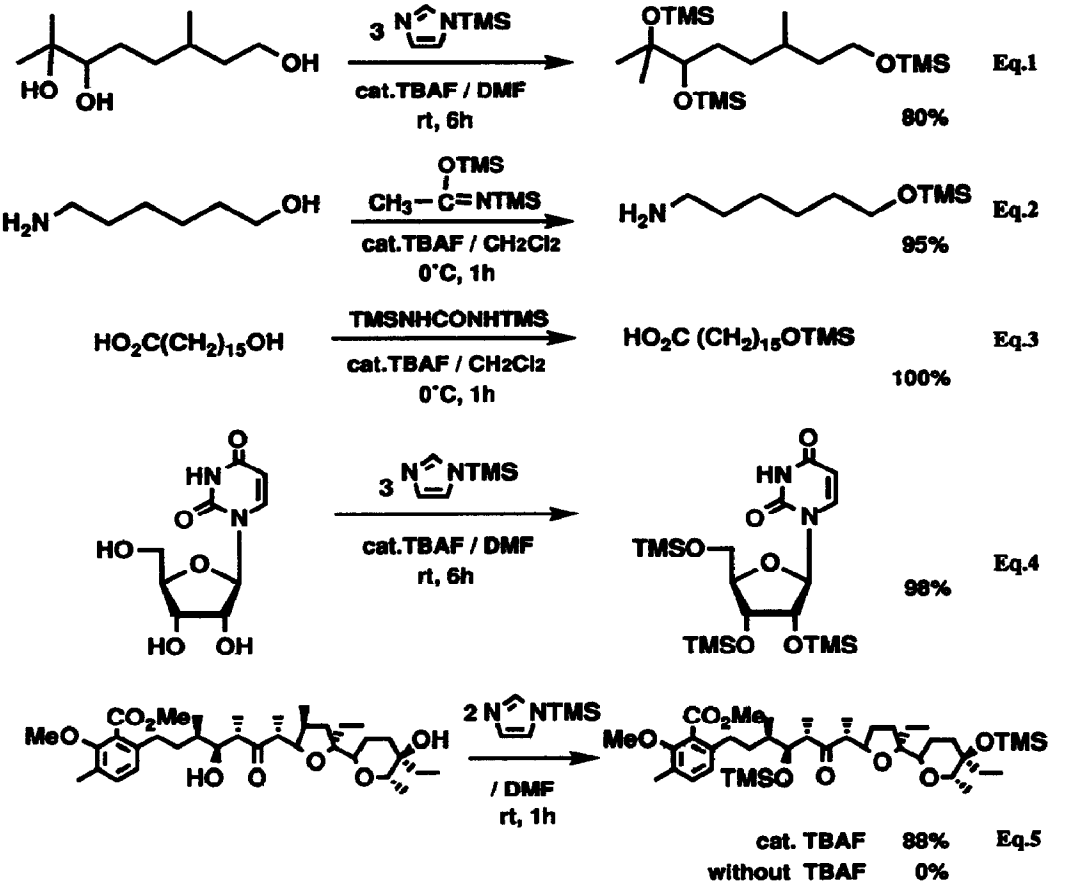


First, several commercially available silazanes/cat. TBAF systems were examined, and these representative results indicate the remarkable effects of catalytic TBAF as shown in Table 1. Equations 1~5 attest that the present silylation is applicable for a wide range of alcohols. The manipulation is quite simple and exemplified by the following typical procedure: To a *N,N*-dimethylformamide (DMF) solution (2 ml) of 3-methyl-1-phenyl-3-pentanol (178 mg, 1.00 mmol) and *N*-(TMS) imidazole (280 mg, 2.00 mmol) was added a TBAF (1M THF solution, 20 μ l, 0.02 mmol) at 0 °C. After 10 min, water was added and the usual work up followed by SiO_2-column chro-matographic purification (hexane) gave 3-methyl-3-trimethylsiloxy-1-phenylpentane (230 mg) in 92% yield.

Table 1. Silyations of Alcohols Using Available Silazanes / cat. TBAF (0.02 equiv.) Systems

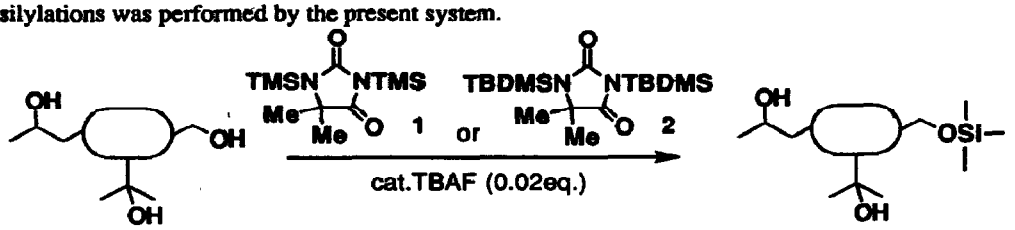
Entry	Alcohol[a)]	Silazane	Equiv.	Solvent	Temp/°C	Time (min)	Yield/% [b)]
1	A	$(TMS)_2NH$	5.0	DMF	40	180	100 (<5%)[c)]
2	B	*N,O*-bis(TMS) acetamide	1.0	THF	0	15	100 (80)
3	B	*N*-(TMS) acetamide	1.5	DMF	0	60	100 (trace)
4	B	*N*-(TMS) imidazole	2.0	DMF	20	30	100 (trace)
5	B	*N*-(TMS) imidazole	2.0	DMF	0	60	100 (trace)
6	B	*N,N*-bis(TMS) urea	1.0	DMF	0	20	100 (trace)
7	A	*N*-(TBDMS) imidazole	2.0	DMF	20-30	30	99 (20)

a) A: 1-octanol; B: 3-methyl-1-phenyl-3-pentanol (a tertiary alcohol). b) Determined by GLC analysses (widebore column DB-1701; 15 m x 0.545 mm). c) Parentheses mean the yields *without* the TBAF catalyst.

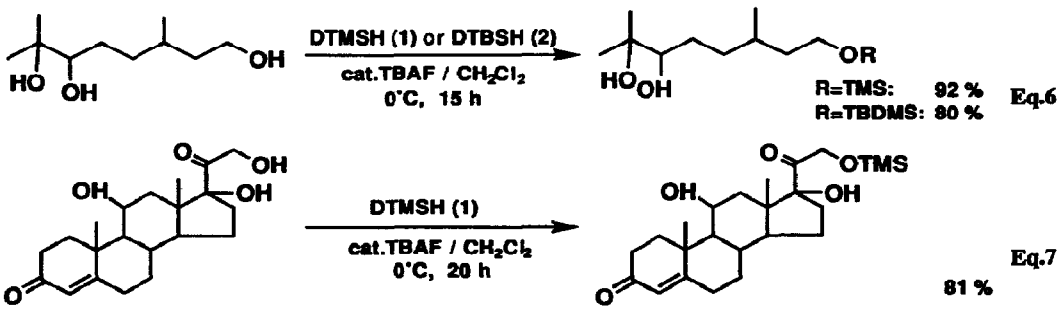


Based on the aforementioned results, the novel and highly regio- and chemoselective silazane agents, 5,5-dimethyl-1,3-bis(TMS)hydantoin (DTMSH, 1[4]) or 5,5-dimethyl-1,3-bis(TBDMS)hydantoin (DTBSH, 2[5a])/ cat. TBAF system for primary alcohols were next introduced. These reagents were designed by placing more a transferable silyl group in the hindered site (*N*-1) to suppress access of secondary or tertiary alcohols.

The structural assumption was actually supported by the X-ray crystallography of 2[5b]. It is worth noting that strict kinetic selection of primary alcohols *vs.* secondary and tertiary ones, especially in the difficult case of trimethylsilylations was performed by the present system.



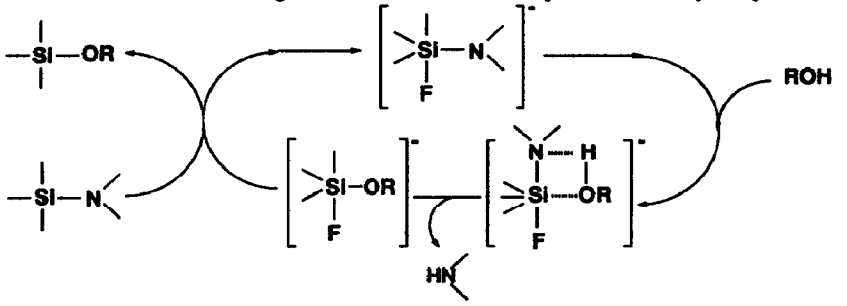
Very high regioselectivity is demonstrated by the competing reaction of an equimolar mixture of hard-to-distinguish 1-octanol and 2-octanol with DTMSH (**1**, 1.0 equiv.)/cat. TBAF at -20°C for 5h in CH_2Cl_2 where the ratio of the primary silylation to the secondary one was efficiently 98.0 : 2.0 (checked by GLC; widebore column DB-1701; 15 m x 0.545 mm) in 99% isolated yield. A similar experiment employing 1-octanol and 3-octanol had a 99.5 : 0.5 selection in 98% isolated yield. Employing DTBSH (**2**, 1.2 equiv.) against an equimolar mixture of 1-octanol and 2-octanol at rt for 15h resulted in the sole formation of the TBDMS ether of 1-octanol in 98% isolated yield. Applications to other functionalized substrates such as a triol and hydrocortizone were depicted in Eqs **6** and **7**, wherein only the primary hydroxy groups were silylated.



Notable features of the new method are demonstrated as follows: (1) The TBAF catalyst[6] generally promoted the silylation using several types of commercially available silazane reagents[7]; $(TMS)_2NH$, *N,O*-bis(TMS) acetamide, *N*-(TMS) acetamide, *N*-(TMS) imidazole, and *N,N*-bis(TMS) urea which increase in that order. (2) The introduction of the TBDMS group was also accelerated using commercially available *N*-(TBDMS) imidazole[7] and DTBSH (**2**). (3) High chemoselectivities toward ketone, enone, epoxy, amino, and carboxy groups were generally observed. A complex lasalocid derivative bearing several labile functional groups could be silylated wherein the silylation virtually did not proceed without TBAF (Eq. 5). (4) A solvent effect[3b] was observed: polar solvents such as DMF were superior when compared with THF and CH_2Cl_2, especially when sterically crowded alcohols were employed. (5) DTMSH (**1**) and DTBSH (**2**) are both crystals that are conveniently handled and easily prepared.[4,5] (6) Reagents **1** and **2** were found to release the silyl groups on the crowded *N*(1) positions to primary alcohols, which is proved by fact that reagent **2** was converted into 5,5-dimethyl-3-(TBDMS)hydantoin after the reaction. (7) The 5,5-dimethyl substituent adjacent to the reactive *N*-1 silyl group in DTMSH (**1**) is indispensable for the high regioselectivity. Actually, the control

reaction of 1,3-bis(TMS) hydantoin lacking a 5,5-dimethyl group showed poor regioselectivity in the preceding experiment of 1-octanol and 2-octanol (6% of TMS ether of 2-octanol was obtained even with 63% total conversion). (8) The reaction was relatively unaffected by the presence of contaminating water in the range of 0~500 ppm. in the solvent used.

A tentative mechanism is proposed as follows. The TBAF catalyst first attacks the silazane reagent to form the reactive pentavalent silicate[8], which in turn condenses with an alcohol to eliminate the amines. The fluoride anion is transferred from the alkoxy(fluoro)silicate to the remaining silazane to release the silyl ether and to reform the aminofluorosilicate. A slight excess of silazane completes the catalytic cycle.



The silylation system would be expected to be applicable to practical or industrial uses by choosing the appropriate silazane. Further, the TBAF catalyzed silyl-transfer reactions using other silicon compounds are now under investigation.

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References and Notes

1. Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; 2nd. ed.; John Wiley: New York, **1991**; pp 68-87.
2. (a) *Comprehensive Organometallic Chemistry;* Sir Wilkinson, G. TRS Ed., Pergamon: Oxford, **1982**; Vol 2, pp 1-397. (b) *The Chemistry of Organic Silicon Compounds* Patai, S.; Rappoport, Z. Ed., Wiley: Chichester, **1989**; part 1 and 2.
3. It was reported that (a) ethyl (TMS)acetate conducts trimethylsilylation of alcohols by the action of cat. TBAF wherein a nucleophilic carbanion is generated: Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346, and that (b) some heteroatom-silicon bonds are activated by fluoride anion, however, no example of trimethylsilylation or *t*-butyldimethylsilylation is shown: Corriu, R. J. P.; Perz, R.; Reye, C. *Tetrahedron* **1983**, *39*, 999; Corriu, R. J. P. *Pure Appl. Chem.* **1988**, *60*, 99; Borar-Law, R. P.; Davis, A. P.; Dorgan, B. J. *Tetrahedron Lett.* **1990**, *31*, 6721.
4. A mixture of 5,5-dimethylhydantoin (2.56 g, 0.02 mol) and hexamethyldisilazane (16.1 g, 0.10 mmol) in 1,2-dichloroethane (20 ml) was refluxed for 15h. The mixture was dried under reduced pressure to give BTMSH (1, 5.26 g, 96%) which can be used without any further purification. Colorless crystals; mp 52-55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.36 (9H, s), 0.42 (9H, s), 1.35 (6H, s).
5. (a) To a stirred solution of 5,5-dimethylhydantoin (3.84 g, 0.03 mol), cat. *N,N*-dimethylaminopyridine (183 mg) and triethylamine (6.58 g, 0.065 mol) in DMF (30 ml) was added *t*-butyldimethylchlorosilane (11.31 g, 0.075 mol) portion by portion at rt and stirred for 10 h. After the usual work up and purification with column chromatography (hexane/ethyl acetate=10:1) gave DTBSH (2, 8.68 g, 81%). Colorless crystals; mp 62-67 °C; (b) The X-ray data of 2 is the supplementary material available.
6. 1M THF solution of TBAF (commercial grade) was used without any drying or purification.
7. All of the reagents are commercially available in large amounts and are inexpensive except TBDMS imidazole which can be easily prepared from imidazole and TBDMSCl.
8. (a) Corriu, R. J. P.; Young, J. C. In *The Chemistry of Organic Silicon Compounds*; Patai, S. Rappoport, Z. Ed.; John Wiley: New York, **1989**; pp 1241-1288. (b) Tamao, K. *J. Synth. Org. Chem., Jpn.* **1990**, *48*, 457. (c) Hatanaka, Y.; Hiyama, T. *ibid*. **1990**, *48*, 834.

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