Tris(dimethylamino)sulfonium Difluorotrimethylsilicate, a Mild Reagent for the Removal of Silicon Protecting Groups

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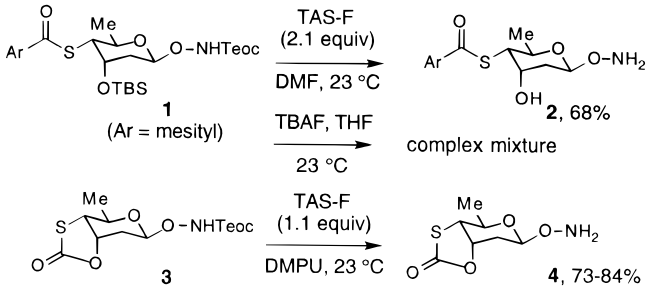
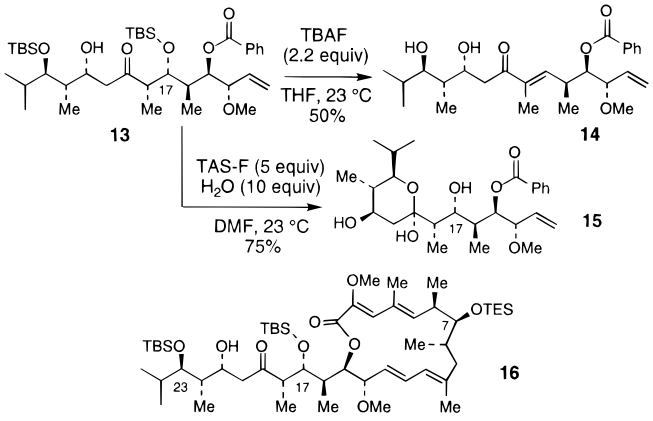
Numerous methods have been developed for the introduction and selective removal of silicon-containing protecting groups, which are used extensively in organic synthesis.[2−4] Nevertheless, there remains a great need for the development of ever milder and more selective methods for silyl group deprotection for use with base- and/or acid-sensitive substrates. Herein, we report the use of TAS-F [tris(dimethylamino)sulfonium difluorotrimethylsilicate, $(Me_2N)_3S^+ F_2SiMe_3^-$][5,6] for the deprotection of a range of silyl ethers and 2-(trimethylsilyl)ethyl carbamates and esters. Particularly striking are the TAS-F-mediated deprotections of the base-sensitive substrates **1**, **3**, **5**, **11**, and **13**, which could not be deprotected cleanly or efficiently by using tetra-*n*-butylammonium fluoride (TBAF).



As part of our studies on the synthesis of the calicheamicin A−B−E trisaccharide,[7,8] we needed to deprotect the 2-(trimethylsilyl)ethyl carbamate (Teoc-NHR)[9] unit of glycoside **1**. However, attempts to remove the Teoc and *tert*-butyldimethylsilyl (TBS) groups from **1** by using TBAF gave a complex mixture of products, presumably due to acyl transfer and/or hydrolysis of the thioester. A search of the literature prompted us to consider TAS-F as a fluoride source for the removal of these protecting groups. TAS-F has been used to generate "naked" enolates from silyl enol ethers[5] and, to a lesser extent, for the cleavage of Si−C bonds (e.g., generation of cyclopentadienyl anions)[10] and the removal of silyl protecting groups from phenols.[11] Several examples of TAS-F-mediated deprotection of silyl ethers have also been reported recently.[12,13] Accordingly, addition of TAS-F to **1** in DMF provided glycoside **2** in 68% yield. Equally impressive was the deprotection of the Teoc unit of **3**, which provided **4** in 84% yield. The thiocarbonate unit of this compound is highly base sensitive and was readily cleaved during attempted deprotection of **3** with TBAF.

In studies directed toward the synthesis of damavaricin D, culminating in the total synthesis of 24,27-dimethyl dihydrodamavaricin D,[14,15] we needed to deprotect the Teoc group and the 2-(trimethylsilyl)ethyl ester[16] of **5**. Unfortunately, treatment of **5** with TBAF in DMF produced **6** in 65−80% yield as well as 10−15% of enoate **7** arising from elimination of the C(11) acetate. Similar results were obtained when this reaction was performed in the presence of 4 Å molecular sieves or with CH_3CN or THF as solvent. However, treatment of **5** with 4 equiv of TAS-F in DMF afforded amino acid **6** exclusively in 95% yield (crude). This protocol proved crucial to the success of our damavaricin D total synthesis, which proceeded by way of the bis-MOM-protected dihydroquinone **8**. In this case, deprotection of **8** with TAS-F provided crude seco acid **9**, which was used directly in the subsequent macrolactamization reaction (76% yield of macrocycle).[17] In related work, we have demonstrated that it was possible to deprotect the 2-(trimethylsilyl)ethyl ester of intermediate **11** in the presence of a primary *tert*-butyldiphenylsilyl (TBDPS) ether by treatment of **11** with 2.1 equiv of TAS-F in DMF (93% yield of **12**) (Scheme 1).

The last step of our bafilomycin A_1 synthesis,[18] involving the removal of two TBS ethers and a TES ether from **16**, was modeled by the conversion of **13** to **15**. Previous work in our laboratory had established that hemiketal units of related intermediates are unstable under mildly acidic conditions, especially when C(17)-OH is protected.[19] Attempts to deprotect **13** by using HF−pyridine gave no reaction (24 h), whereas treatment of **13** with TBAF resulted in elimination of the C(17)-OTBS group and provided enone **14** as the major product. This elimination was also observed when **13** was treated with TAS-F in DMF (anhydrous). However, treatment of ketone **13** with 5 equiv of TAS-F and 10 equiv of water in DMF generated the sensitive hemiketal **15** in 75% yield.



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(2) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991.
(3) Kocienski, P. *Protecting Groups*; Georg Thiem Verlag: Stuggart, 1994.
(4) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.
(5) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223.
(6) Middleton, W. J. In *Organic Syntheses*; Freeman, J. P., Ed.; Wiley: New York, 1990; Vol. VII, p 528.
(7) Roush, W. R.; Follows, B. C. *Tetrahedron Lett.* **1994**, *35*, 4935.
(8) Follows, B. C. Ph.D. Thesis, Indiana University, 1997.
(9) Carpino, L. A.; Tsao, J.-H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358.
(10) Wessel, J.; Behrens, U.; Lork, E.; Mews, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 443.
(11) Siamoto, H.; Kusano, Y.; Hiyama, T. *Tetrahedron Lett.* **1986**, *27*, 1607.

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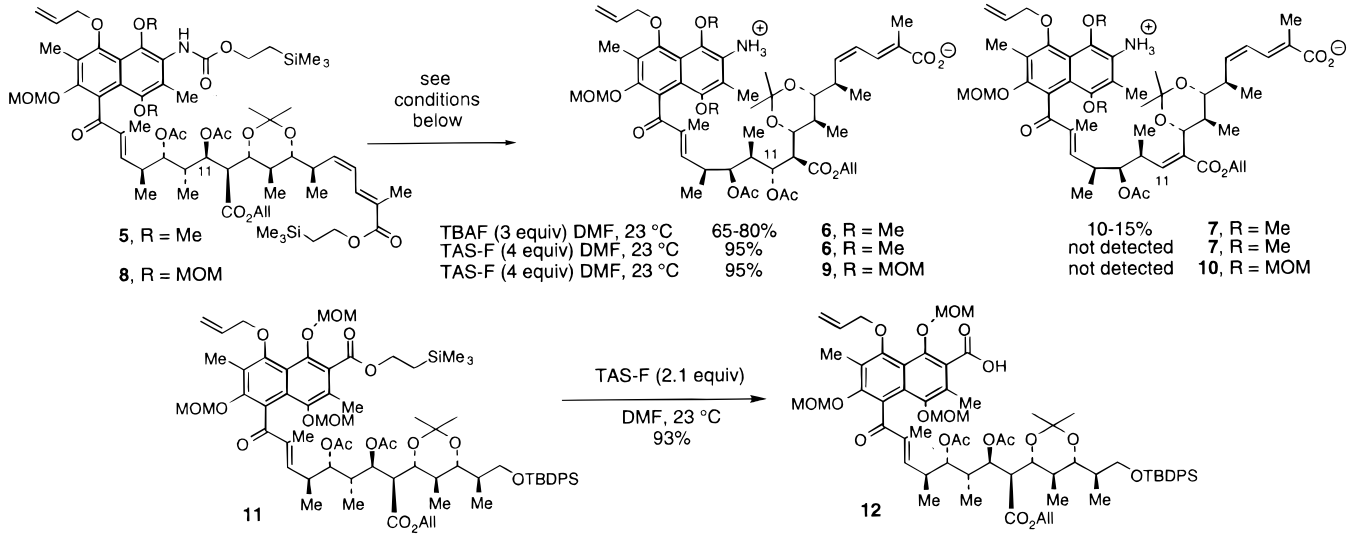
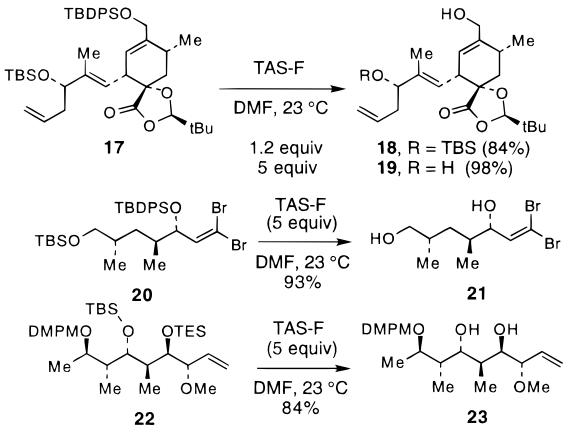
Scheme 1



The utility of TAS-F for the selective deprotection of silyl ethers was explored using **17**, **20**, and **22** as substrates. Treatment of **17** with 1.2 equiv of TAS-F selectively removed the primary TBDPS, leaving the secondary TBS ether intact (84% yield of **18**). This constitutes, to our knowledge, the mildest set of conditions yet reported for the selective deprotection of primary TBDPS ethers.[2−4] Both the TBS and TBDPS ethers were removed when **17** was treated with 5 equiv of TAS-F (98% yield of **19**). It was not possible to accomplish selective deprotections of either **20** (competition between primary TBS and secondary TBDPS ethers) or **22** (competition between secondary TES and TBS ethers) by using 1.2 equiv of TAS-F. However, complete desilylation of **20** (93%) and **22** (84%) was easily accomplished by using excess TAS-F.



The examples reported herein demonstrate that TAS-F is a mild and highly effective reagent for the deprotection of silyl ethers, 2-(trimethylsilyl)ethyl esters, and 2-(trimethylsilyl)ethyl carbamates and that selective deprotections may be achieved with this reagent. Hypervalent silicon reagents have been used previously as sources of highly nucleophilic fluoride ion for substitution reactions ($Bu_4N^+Ph_3SiF_2^-$)[20,21] and as reagents for deprotection of silyl ethers (H_2SiF_6),[22,23] but to the best of our knowledge TAS-F has not been employed as an alternative to TBAF for the deprotection of base- or acid-sensitive compounds. Most of the side reactions encountered in the attempted TBAF deprotections of **1**, **3**, **5**, and **13** may be attributed to tetrabutylammonium hydroxide present in TBAF, which is highly hygroscopic and notoriously difficult to dry.[24−26] By contrast, TAS-F is commercially available as an anhydrous solid (and also can be prepared by an *Organic Syntheses* procedure),[6] and our experience suggests that even the hydrated reagent does not promote undesired base-catalyzed reactions observed with TBAF as the fluoride source (see deprotection of **13**). Hypervalent fluoride complexes of tin[27] and phosphorus[28] have also been used as nucleophilic fluoride sources and are also potentially applicable to the removal of silicon protecting groups.

We anticipate that TAS-F will find numerous applications in organic synthesis as a alternative to TBAF, especially for the deprotection of base- and/or acid sensitive substrates.

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Supporting Information Available: Representative experimental procedures and characterization data (13 pages).

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(12) Barrett, A. G. M.; Peña, M.; Willardsen, J. A. *J. Org. Chem.* **1996**, *61*, 1082.
(13) Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6627.
(14) Roush, W. R.; Coffey, D. S.; Madar, D. J.; Palkowitz, A. D. *J. Brazil Chem. Soc.* **1996**, *7*, 327. This paper is the text of a lecture presented at the VIIth Brazilian Meeting on Organic Synthesis, Sept 1996.
(15) Coffey, D. S. Ph.D. Thesis, Indiana University, 1997.
(16) Sieber, P. *Helv. Chim. Acta* **1977**, *60*, 2711.
(17) Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331.
(18) Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. Manuscript in preparation.
(19) Bannister, T. D. Ph.D. Thesis, Indiana University, 1991.
(20) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166.
(21) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901.
(22) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492.
(23) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1993**, *58*, 5130.
(24) Cox, D. P.; Terpinski, J.; Lawrynowicz, W. *J. Org. Chem.* **1984**, *49*, 3216.
(25) Clark, J. H. *Chem. Rev.* **1980**, *80*, 429.
(26) Sharma, R. K.; Fry, J. L. *J. Org. Chem.* **1983**, *48*, 2112.
(27) Gingras, M. *Tetrahedron Lett.* **1991**, *32*, 7381.
(28) Bensoam, J.; Leroy, J.; Mathey, F.; Wakselman, C. *Tetrahedron Lett.* **1979**, *4*, 353.