Utilization of Tetrabutylammonium (Triphenylsilyl)difluorosilicate as a Fluoride Source for Nucleophilic Fluorination

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Over the past several decades, a growing number of fluorinated drugs have found use in medical applications including cardiovascular, central nervous system, anticancer, antibacterial, and antiviral therapies.[1] Medicinal chemists frequently use fluorine to modify the properties of a potential drug. While replacement of a hydrogen with fluorine does not alter the steric size of a molecule, it provides for increased lipophilicity, hydrogen bonding, and polar interactions.[1] In some instances, replacement of hydrogen by fluorine blocks an unwanted biochemical reaction. The ability to incorporate fluorine into organic molecules is becoming increasingly important as the number of biologically active fluorinated compounds continues to grow.

The most common method of introducing fluorine at a specific molecular site is by nucleophilic displacement.[2] Alkali metal fluorides have traditionally been used for this purpose; however, these reagents require vigorous reaction conditions and long reaction times due to their limited solubility in organic solvents.[3] More recently, metal fluorides have been largely supplanted by tetraalkylammonium fluorides, with tetrabutylammonium fluoride (TBAF) being the most popular reagent. These salts are advantageous in that they are soluble in polar organic solvents and their reactions are fast at room temperature or below.[3] Unfortunately, they have their own problems associated with them. Although the nucleophilicity of tetraalkylammonium fluorides is greatly increased relative to that of metal fluorides, these reagents are also very basic, promoting elimination of the substrate leaving group in addition to displacement.[3] Another problem is that these salts are available only as hydrates or solutions containing water, and it is virtually impossible to dehydrate them entirely.[3] Water in the presence of fluoride generates hydroxide, which may act as a nucleophile, forming hydroxy products as well as the desired fluoro products.[3]

In a recent article, we discussed the benefits of using fluorosilicic acid (H_2SiF_6) as a reagent for the deprotection of silyl ethers.[4] Having found that fluorosilicate complexes such as H_2SiF_6 were useful reagents, we chose to extend the investigation to search for tetrabutylammonium fluorosilicates that could serve as hypervalent silicon alternatives to current fluoride sources in S_N2 reactions. Ideally, a fluoride source should be soluble in organic solvents, anhydrous, and nonhygroscopic, and solutions of the reagent should be close to pH neutral. We have found that tetrabutylammonium (triphenylsilyl)difluorosilicate (TBAT) meets these requirements. TBAT is an anhydrous, white, crystalline solid with a melting point of 150−151 °C. This salt is not hygroscopic and is soluble in most organic solvents. Compared to TBAF, TBAT is less nucleophilic, but it is also less basic. Additionally, TBAT avoids the problems caused by the presence of water. As our results indicate (*vide infra*), TBAT is a promising new fluoride source for nucleophilic displacement reactions.

The synthesis of TBAT is straightforward and is analogous to the traditional methods for the synthesis of fluorosilicates.[5,6] Although other tetraalkylammonium organofluorosilicates have been known for some decades, their synthetic uses as fluoride sources have not been explored.

$$\underset{\mathbf{1}}{Ph_3SiOH} \xrightarrow[MeOH,\ 99\%]{\text{aqueous HF}} \underset{\mathbf{2}}{Ph_3SiF} \xrightarrow[CH_2Cl_2,\ 95\%]{\text{TBAF/THF}} \underset{\mathbf{3}\ (TBAT)}{Bu_4N^+\ Ph_3SiF_2^-}$$

Table 1 summarizes the TBAT fluorination reaction results. For comparison, results reported in the literature using other fluorination reagents have been included. With primary alkyl halides, TBAT provides the fluoride in excellent yield and with minimal contamination from the alkene and/or alcohol byproducts. Entries 1−4 show that alkyl bromides give better results than chlorides or iodides. A comparison of entries 1 and 3 demonstrates the superiority of TBAT to TBAF for this substrate. The fact that TBAF gave almost as much octanol as octyl fluoride is indicative of the problems that the presence of water in solutions of TBAF can cause. Entries 5 and 6 demonstrate that sulfonates are the leaving group of choice for both TBAT and TBAF reactions. The situation is different for displacements at secondary centers in that the halides are poor substrates (entries 7−14). Halides predominantly undergo elimination with any of the displacement protocols (entries 7 and 8). Again, sulfonates provide better results than either the

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(6) TBAT is synthesized as follows. (i) Synthesis of triphenylsilyl fluoride (**2**): triphenylsilanol (100.0 g, 361.8 mmol) was dissolved in 350 mL of MeOH in a 1-L polyethylene bottle. After the solution was chilled to 5 °C in an ice bath (some precipitation), aqueous HF (52 mL of a 48% solution, 1.447 mol) was added, causing further precipitation. The reaction mixture was allowed to warm to ambient temperature, and after 30 min, distilled water (200 mL) was added to induce further precipitation of the product. The slurry was then vacuum filtered and rinsed with 4 × 150 mL of H_2O. After suction drying for 2 h, triphenylsilyl fluoride (105.3 g, quantitative) was obtained as damp (calculated 4% water) white crystals, which were used without further purification. A sample was dried under vacuum for analysis: mp 62−63 °C; IR (CCl_4) 3074 (m), 3055 (m), 3005 (m), 1959 (w), 1889 (w), 1823 (w), 1593 (m), 1430 (s), 1124 (s), 1111 (m), and 850 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.67−7.61 (m, 6H), 7.52−7.36 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 135.0, 132.5 (d, J_{C-F} = 17 Hz), 130.8, 128.1; ^{19}F NMR ($CDCl_3$) δ (F_3COOH = 0.0 ppm) −147.0 (Si−F satellites, J_{Si-F} = 141 Hz). The spectral data were identical to those previously reported.[1-3] (ii) Synthesis of tetrabutylammonium triphenyldifluorosilicate (TBAT) (**3**): triphenylsilyl fluoride (25.85 g wet, 89.1 mmol) was dissolved in CH_2Cl_2 (100 mL) in a 500-mL flask, and $MgSO_4$ (4 g) was added to dry the solution. Tetrabutylammonium fluoride (89 mL of a 1.0 M solution in THF) was added in one portion (mild exotherm). The slurry was vacuum filtered into a 1-L flask, and the filtrate was concentrated at reduced pressure. Ethyl acetate (750 mL) was added to the pasty concentrate. Approximately 250 mL of the EtOAc was distilled off under N_2 to azeotropically remove water. Another 250 mL of EtOAc was then added and distilled off, leaving a clear, colorless solution of the salt in 500 mL of EtOAc. The solution was allowed to cool to 25 °C and then stored at −20 °C for 8 h. After filtration, 45.70 g (95%) of the TBAT salt was obtained as large white spears: mp 150−151 °C; IR (CCl_4) 3066 (m), 3046 (m), 2961 (vs), 2876 (m), 1487 (m), 1475 (m), 1460 (m), 1429 (m), 1123 (s), 1100 (m), 887 (m), 841 (m), and 705 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (bs, 3H), 7.68 (m, 3H), 7.32 (m, 6H), 7.16 (bs, 3H), 2.67 (t, 8H, 8), 1.21 (m, 16H), 0.92 (t, 12H, 6); ^{13}C NMR ($CDCl_3$) δ 137.1, 135.2, 128.2 (d, J_{C-F} = 163 Hz), 126.5, 57.5, 23.5, 19.4, 13.6; ^{19}F NMR ($CDCl_3$) δ (F_3COOH = 0.0 ppm) −19.6 (J_{Si-F} = 250 Hz); ^{29}Si NMR ($CDCl_3$) δ −106.3 (t, J_{Si-F} = 252 Hz); LRMS (70 ev) *m/z* (relative intensity) 386 (8), 278 (33), 259 (75), 201 (94), 186 (50), 185 (50), 184 (58), 154 (49), 142 (100). Anal. Calcd for $C_{34}H_{51}NSiF_2$: C, 75.64; H, 9.52. Found: C, 76.11; H 9.61. X-ray crystal data are included in the supplementary material.

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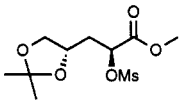
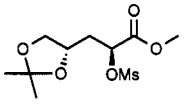
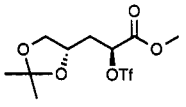
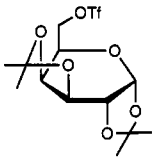
Table 1. Fluorination Using TBAT: Comparison with Results Reported Using Other Methods

entry	substrate (RX)	reagent	solvent	temp	time (h)	yield[a] (RF) (%)	comments
1[b]	$CH_3(CH_2)_7Br$ (**4**)	2 equiv of TBAF, "anhydrous"	none	25 °C	1	48[b]	12% alkene,[b] 40% octanol
2	$CH_3(CH_2)_7Cl$ (**5**)	6 equiv of TBAT	CH_3CN	reflux	24	70	30% alkene
3	$CH_3(CH_2)_7Br$ (**4**)	6 equiv of TBAT	CH_3CN	reflux	24	85	15% alkene
4	$CH_3(CH_2)_7I$ (**6**)	4 equiv of TBAT	CH_3CN	reflux	24	74	26% alkene
5[b]	$CH_3(CH_2)_7OTs$ (**7**)	2 equiv of TBAF, "anhydrous"	none	25 °C	1	98[b]	2% alkene[b]
6	$CH_3(CH_2)_7OTs$ (**7**)	4 equiv of TBAT	CH_3CN	reflux	24	99	trace alkene
7	$CH_3(CH_2)_5CHBrCH_3$ (**8**)	4 equiv of TBAT	CH_3CN	reflux	24	34	66% alkenes
8	$CH_3(CH_2)_5CHICH_3$ (**9**)	6 equiv of TBAT	CH_3CN	reflux	2	19	4% s.m. 77% alkenes
9[b]	$CH_3(CH_2)_5CH(OTs)CH_3$ (**10**)	2 equiv of TBAF, "anhydrous"	none	25 °C	1	58[b]	32% alkenes,[b] 7% octanol
10	$CH_3(CH_2)_5CH(OTs)CH_3$ (**10**)	6 equiv of TBAT	CH_3CN	reflux	24	98	2% alkenes
11[c]	$CH_3(CH_2)_9CH(OMs)CH_3$ (**11**)	2 equiv of TBABF	50% THF, 50% HMPT	95 °C	20	51[c]	14% alkenes[c]
12	$CH_3(CH_2)_9CH(OMs)CH_3$ (**11**)	6 equiv of TBAT	CH_3CN	reflux	32	85	15% alkenes
13[d]	 **12**	saturated KF	acetamide	reflux	2.5	55[d]	syn:anti[d] 90:10
14	 **12**	6 equiv of TBAT	CH_3CN	reflux	48	73	syn:anti 68:32
15	 **13**	6 equiv of TBAT	CH_3CN	reflux	48	76	syn only
16	 **14**	6 equiv of TBAT	CH_3CN	reflux	48	92	

[a] Yields were determined by GC except for entries 13−15, which represent isolated yields. [b] Reference 3. [c] Reference 7. [d] Reference 8.

bromide or the iodide substrates. TBAT displacement of a secondary tosylate (entry 10) proceeds smoothly with nearly total conversion to the fluoroalkane, while TBAF gives only mediocre yields of the fluoro derivative. Entries 11 and 12 show that while TBAT is preferred to tetrabutylammonium bifluoride (TBABF) for the fluorination of secondary alkyl mesylates, a greater amount of alkene is formed than with tosylates. In entries 13 and 14, TBAT provides a higher yield for the fluorination of an α-mesylate ester than KF; however, the diastereomeric excess is reduced due to epimerization under the reaction conditions. This problem is eliminated by mating TBAT with the optimal sulfonate leaving group for this substrate (entry 15). Changing the mesylate to a triflate prevents epimerization and proves that the displacement proceeded with inversion of stereochemistry. In the final example (entry 16), a fluoro sugar is produced in good yield by displacement of the triflate.

These results indicate that TBAT is significantly more effective than traditional methods for nucleophilic fluorination of primary and secondary substrates. The sole limitation of this protocol is that 4−6 equiv of TBAT are required for reasonable reaction rates; however, this drawback is ameliorated since excess TBAT can be recovered easily and recycled.

Reaction optimization studies with TBAT are underway in an attempt to define a protocol that requires a stoichiometric quantity of TBAT to be employed while maintaining the high yields of product. We are also studying other organofluorosilicate complexes to determine the most efficacious ligand combination. Indeed, preliminary screens have identified organofluorosilicates with a better reactivity profile than TBAT.

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Supplementary Material Available: Experimental details including X-ray crystal data for TBAT, representative fluorination procedures using TBAT, and characterization of the compounds synthesized (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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