Fluoride Sources

DOI: 10.1002/anie.200803150

Tetrabutylammonium Tetra(*tert*-Butyl Alcohol)-Coordinated Fluoride as a Facile Fluoride Source**

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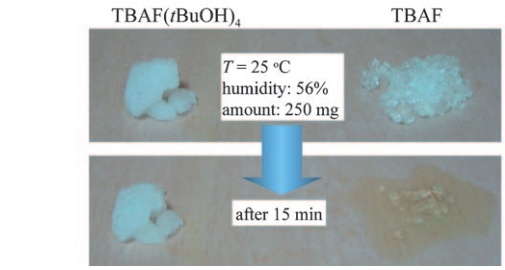
The generally favorable pharmaceutical properties of many low fluorinated compounds and ^{18}F-labeled radiopharmaceuticals for positron emission tomography (PET) molecular imaging studies have made the incorporation of fluorine atoms into organic molecules increasingly important.[1] Nucleophilic substitution is the method typically used to introduce a fluorine atom at a specific molecular site,[2] and numerous phase-transfer-type protocols and reagents for this reaction have been developed over the past several decades.[2–4] Among the various reagents used, tetraalkylammonium fluorides, which are represented by tetrabutylammonium fluoride (TBAF), are used most widely for nucleophilic fluorination on account of their good solubility and nucleophilicity in organic solvents.[2] However, their hygroscopic character makes them available only in the form of a hydrate. Hydroxide typically competes with fluoride, leading to hydroxylations to form alcohols as a side reaction.[5] To solve this problem, some protocols of "anhydrous" TBAF ($TBAF_{anh}$), generated by heating under a dynamic vacuum[6] or prepared directly through the S_NAr reaction of hexafluorobenzene using tetrabutylammonium cyanide (TBACN) in polar aprotic solvent,[7] have been reported. However, although reactions using "naked" fluoride from $TBAF_{anh}$ as a good nucleophile are very fast at room temperature or below, these reaction systems are generally strongly basic. This restricts their synthetic utility because of the possibility of side reactions, such as elimination of alkyl halide or sulfonates to form alkenes. In addition, these materials are difficult to handle and maintain their dehydrated state owing to their very high hygroscopicity.[2,5] Tetrabutylammonium triphenyldifluorosilicate (TBAT), which was developed by DeShong and co-workers, allows anhydrous and less basic conditions than with TBAF. However, the fluorination reaction using TBAT requires vigorous reaction conditions and an excess of TBAT for the reaction to proceed on account of its low reactivity.[5] Therefore, an ideal fluoride source should have 1) good nucleophilicity with low basicity to reduce the number of side reactions; 2) good solubility in organic solvents; 3) a dehydrated state for anhydrous reaction conditions; and 4) low hygroscopicity for easy handling. Herein, we introduce tetrabutylammonium tetra(*tert*-butyl alcohol) coordinated fluoride, $TBAF(t\text{BuOH})_4$ (**1**), as a promising new fluoride source that meets the above requirements for nucleophilic fluorinations.

$TBAF(t\text{BuOH})_4$ was prepared simply by using the procedure shown in Scheme 1. Commercially available TBAF hydrate was heated in *t*BuOH/hexane to 90 °C for 30 min, and recrystallized at room temperature to afford $TBAF(t\text{BuOH})_4$ as an anhydrous, white, crystalline solid in 92% yield. The structure of $TBAF(t\text{BuOH})_4$ was characterized by X-ray crystallography (Figure 1). Its X-ray crystal structure shows



Scheme 1. Preparation of tetrabutylammonium tetra(*tert*-butyl alcohol) coordinated fluoride.

Figure 1. Top: X-ray crystal structure of $TBAF(t\text{BuOH})_4$ (**1**). Bottom: Demonstration of the hygroscopicity of $TBAF(t\text{BuOH})_4$ and commercially available TBAF.

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[**] This study was supported by grant from the Atomic Energy Technology and Development Program of KOSEF (M20704000037-08M0400-03711 and M20702000003-08N0200-00310 to D.W.K). We also thank Prof. John A. Katzenellenbogen for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803150.

four *t*BuOH molecules coordinated around a single fluoride ion through hydrogen bonds each 1.83 Å long. This result provides further evidence that a "flexible" fluoride source is generated in the fluorination system using an alkali metal fluoride catalyzed by a nonpolar protic alcohol.[8] Figure 1 shows that TBAF(*t*BuOH)$_4$ is significantly less hygroscopic than TBAF, which is expected to provide easy handling and anhydrous conditions maintained during the reaction process. The stability of the tetra(*tert*-butyl alcohol) coordinated fluoride structure in solution was shown indirectly by carrying out a desilylation reaction using TBAF(*t*BuOH)$_4$ or TBAF in THF (Figure 2A). The reaction using TBAF(*t*BuOH)$_4$ proceeded much more slowly than with TBAF, which means that the tetra(*t*BuOH) coordinated fluoride structure can be maintained in an organic solution at room temperature to some extent. Figure 2B shows that TBAF(*t*BuOH)$_4$ could produce a similar reaction rate in the nucleophilic fluorination reaction at 60 °C in CH_3CN to that using TBAF, which means that TBAF(*t*BuOH)$_4$ can be a good alternative reagent for nucleophilic fluorination.

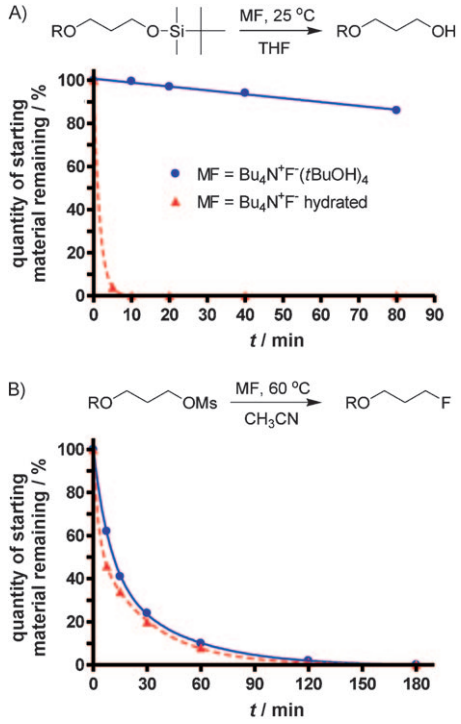
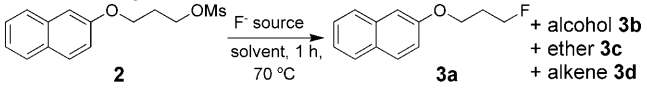


Figure 2. A) Desilylation using TBAF(*t*BuOH)$_4$ or TBAF. B) Reactivity of TBAF(*t*BuOH)$_4$ and TBAF in a nucleophilic fluorination reaction. The quantity of starting material remaining was determined by ^{1}H NMR spectroscopy. R = naphthyl, Ms = methanesulfonyl.

Table 1 shows the results of the fluorination of mesylate **2** as a model compound using TBAF(*t*BuOH)$_4$ or other reagents in various solvents. The fluorination using TBAF(*t*BuOH)$_4$ in various organic solvents proceeded almost quantitatively at 70 °C in 1 h without forming any alcohol by-product **3b** owing to its anhydrous character (Table 1, entries 1–3), whereas 3–5% alcohol by-product **3b** was formed in the same fluorination using TBAF in various organic solvents, including *t*BuOH (Table 1, entries 4–6). Moreover, TBAF(*t*BuOH)$_4$ was proven to be significantly reactive compared with alkali metal fluoride catalyzed by *tert*-butyl alcohol or crown ether. In particular, the fluorination using CsF in *tert*-butyl alcohol has the drawback that alkoxylation by the alcohol solvent itself is a another side reaction, affording 7% of the ether by-product **3c**. Therefore, it is favorable to use TBAF(*t*BuOH)$_4$ in a polar aprotic solvent, which forms very little ether by-product in the fluorination reaction.

Table 1: Fluorination of mesylate **2** with TBAF(*t*BuOH)$_4$ or the stated alternative reagent.[a]



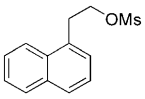
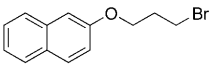
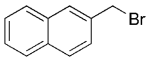
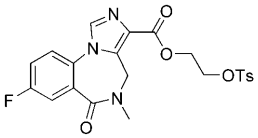
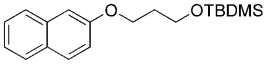
2 **3a**

Entry	F⁻ source (2 equiv)	Solvent	Yield [%][b]				
			2	**3a**	**3b**	**3c**	**3d**
1	TBAF(*t*BuOH)$_4$	CH_3CN	–	99 (98)[c]	–	<0.5	–
2	TBAF(*t*BuOH)$_4$	DMF	–	99 (97)[c]	–	<0.5	–
3	TBAF(*t*BuOH)$_4$	*t*BuOH	–	98	–	2	–
4	TBAF	CH_3CN	–	93 (92)[c]	5	–	2
5	TBAF	DMF	–	94 (92)[c]	3	–	2
6	TBAF	*t*BuOH	–	94	3	2	–
7	CsF	*t*BuOH	68	30		2	
8[d]	CsF (3 equiv)	*t*BuOH	trace	92	–	7	–
9	KF/[18]crown-6	DMF	95	4	1	–	–

[a] Unless otherwise noted, all reactions were carried out on a 1.0 mmol scale of mesylate **2** with 2 mmol of fluoride source in 4.0 mL of solvent for 1 h at 70 °C. [b] Yield determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product in parentheses. [d] Reference [8a]; this reaction was performed at 80 °C for 6 h.

Table 2 summarizes the results of fluorination reactions using TBAF(*t*BuOH)$_4$. To investigate its influence on the reactions, the fluorination was carried out on two model compounds that have some potential for elimination as a side reaction when using TBAF(*t*BuOH)$_4$ in CH_3CN. The level of fluorination was compared with the same reactions using an anhydrous "naked" fluoride source, such as TBAF$_{anh}$, generated in situ, and commercially available TBAF (Table 2, entries 1–6). The fluorination of 1-(2-mesylethyl)naphthalene using TBAF(*t*BuOH)$_4$ proceeded efficiently and provided the corresponding fluoride in 71% yield and the styrene by-product in 28% yield (Table 2, entry 1). In contrast, the same reaction using TBAF$_{anh}$ and TBAF afforded the styrene in 91% and 61% yield, respectively, and the desired fluoro product in only 9% and 33% yield, respectively. (Table 2, entries 2 and 3; 5% alcohol was also formed in entry 3). The use of *t*BuOH as a solvent to study the *tert*-butyl alcohol solvent effect[8] also allowed the fluorination with TBAF(*t*BuOH)$_4$ to proceed much more selectively compared with the use of a polar aprotic solvent such as CH_3CN (Table 2, entry 4).[9] The second example (Table 2, entries 5–7) with a bromide substrate showed a similar trend. TBAF(*t*BuOH)$_4$, which is an anhydrous fluoride source shielded by *t*BuOH molecules (mildly basic "flexible" fluoride), allowed the fluorination to proceed much more selectively, by reducing the elimination reaction significantly, than with TBAF$_{anh}$ or

Table 2: Nucleophilic fluorinations of the various substrates.

Entry	Substrate	Method[a]	Yield [%][b] product[c]	alkene	alcohol
1		A	71	29	–
2		B	9	91	–
3		C	33	61	5
4		D	88	10	–
5		A	80	19	–
6		B	22	78	–
7		C	63	30	6
8		A	98[d]	–	–
9		A	93[d]	–	–
10		A	–	–	100

[a] Method A: reactions were carried out on a 1.0 mmol scale of substrate with 2.0 equiv of TBAF(*t*BuOH)$_4$ at 70 °C for 1 h in 4.0 mL of CH_3CN; B: from the protocol of reference [7a]; the reaction was carried out using 0.2 mmol scale of the substrate with 2.0 equiv of $TBAF_{anh}$ generated in situ in CD_3CN at 25 °C; C: TBAF was used; D: TBAF(*t*BuOH)$_4$ in *t*BuOH. [b] Yield determined by ^{1}H NMR spectroscopy. [c] Desired fluoro product. [d] Yield of isolated product. [e] TBDMS = *tert*-butyldimethylsilyl, Ts = 4-toluenesulfonyl.

TBAF. The displacement of a benzylic bromide using TBAF-(*t*BuOH)$_4$ proceeds smoothly with nearly complete conversion to the fluoride (Table 2, entry 8). A fluoro-flumazenile, which can be a molecular probe for PET,[10] was produced in 93% yield by reaction with the corresponding tosylate precursor (Table 2, entry 9). In the final example, the desilylation reaction at 70 °C using TBAF(*t*BuOH)$_4$ proceeded quantitatively within 30 min (Table 2, entry 10).

In summary, we report tetrabutylammonium tetra(*tert*-butyl alcohol) coordinated fluoride, TBAF(*t*BuOH)$_4$, as a highly effective nucleophilic fluorination reagent along with its characteristics. TBAF(*t*BuOH)$_4$ has various favorable properties, such as a unique and stable structure surrounded by four bulky nonpolar protic *tert*-butyl alcohol molecules (a "flexible" fluoride form), a dehydrated state for anhydrous reaction conditions, low hygroscopicity, and good nucleophilicity with low basicity. These favorable properties not only suppress the side reactions (hydroxylation, alkoxylation, and elimination) in the fluorination reaction but also allow easy handling. Further studies on the development of a more efficient protocol with an alcohol coordinated fluoride species and the application of ^{18}F labeling for radiopharmaceuticals for PET are currently underway.

Experimental Section

Preparation of TBAF(*t*BuOH)$_4$: Commercially available TBAF hydrate (1.0 g, 3.17 mmol) was added to *t*BuOH (88 mL) and *n*-hexane (22 mL). The mixture was stirred for 30 min at 90 °C. During this time TBAF dissolved completely. The solution was cooled to room temperature, and a white crystalline solid precipitated. The crystalline solid was filtered and washed rapidly with 40 mL of 70% *t*BuOH/hexane. The filtrate was kept in vacuum for 15–20 min to remove residual solvent, and TBAF(*t*BuOH)$_4$ (**1**, 1.63 g, 2.92 mmol) was obtained as white crystalline solid in 92% yield. ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.01$ (t, $J = 9.0$ Hz, 12H), 1.27 (s, 36H), 1.42–1.48 (m, 8H), 1.66–1.71 (m, 8H), 3.44 ppm (t, $J = 9.0$ Hz, 8H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 13.6$, 19.6, 24.0, 31.1, 58.5, 68.2 ppm.

Typical procedure for fluorination (Table 1, entry 1, or Method A in Table 2): **1** (1.1 g, 2 mmol) was added to a solution of mesylate **2** (280 mg, 1.0 mmol) in CH_3CN (4.0 mL). The mixture was stirred for 1.0 h at 70 °C. The residue was dissolved in water (6.0 mL) and extracted from the aqueous phase with diethyl ether (6.0 mL × 3). The organic layer was dried (sodium sulfate) and evaporated under reduced pressure. The residue was purified by short flash column chromatography (5% EtOAC/hexane) to give 2-(3-fluoropropoxy)-naphthalene (**3a**, 200 mg, 98%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.14$–2.39 (m, 2H), 4.24 (t, $J = 6.2$ Hz, 2H), 4.72 (dt, $J = 46.8$, 5.8 Hz, 2H), 7.16–7.22 (m, 2H), 7.34–7.53 (m, 2H), 7.76–7.83 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 30.4$ (d, $J = 20.1$ Hz), 63.6 (d, $J = 5.3$ Hz), 80.8 (d, $J = 163.9$ Hz), 106.8, 118.8, 123.6, 126.4, 126.7, 127.6, 129.1, 129.4, 134.6, 156.7 ppm; MS (EI) *m*/*z* 204 [M^+]; HRMS (EI) *m*/*z* calcd for $C_{13}H_{13}FO$ [M^+] 204.0950, found 204.0932.

Received: July 1, 2008
Published online: September 29, 2008

Keywords: alcohols · fluorination · fluorine · nucleophilic substitution · tetrabutylammonium fluoride

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