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Published on Web 11/23/2006

A New Class of S_N2 Reactions Catalyzed by Protic Solvents: Facile Fluorination for Isotopic Labeling of Diagnostic Molecules

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Abstract: Aprotic solvents are usually preferred for the S_N2 reactions, because nucleophilicity and hence S_N2 reactivity are severely retarded by the influence of the partial positive charge of protic solvents. In this work, we introduce a remarkable effect of using tertiary alcohols as a reaction medium for nucleophilic fluorination with alkali metal fluorides. In this novel synthetic method, the nonpolar *protic tert*-alcohol enhances the nucleophilicity of the fluoride ion dramatically in the absence of any kind of catalyst, greatly increasing the rate of the nucleophilic fluorination and reducing formation of byproducts (such as alkenes, alcohols, or ethers) compared with conventional methods using dipolar aprotic solvents. The great efficacy of this method is a particular advantage in labeling radiopharmaceuticals with [^{18}F]fluorine ($t_{1/2}$ = 110 min) for positron emission tomographic (PET) imaging, and it is illustrated by the synthesis of four [^{18}F]fluoride-radiolabeled molecular imaging probes—[^{18}F]FDG, [^{18}F]FLT, [^{18}F]FP-CIT, and [^{18}F]FMISO—in high yield and purity and in shorter times compared to conventional syntheses.

Introduction

Noninvasive imaging of molecular and biological processes in living subjects with positron emission tomography (PET) provides exciting opportunities to monitor metabolism and detect diseases in humans and in small-animal models.[1] Measuring these processes with PET requires the preparation of specific molecular imaging probes labeled with positron-emitting radioisotopes. In this regard, fluorine is particularly useful: (a) Because fluorine can replace hydrogen with minimal steric interference, labeling pharmaceuticals with [^{18}F]fluorine often enables the fluorine-substituted analogue to be used to trace biochemical processes while maintaining favorable interaction with the target; (b) fluorine is also often used as a substituent in pharmaceuticals because it can increase the activity, potency, and stability of biologically active compounds;[2] (c) finally, because of its relatively long half-life of 110 min, [^{18}F]labeled radiopharmaceuticals can be produced regionally and shipped for imaging studies to nearby hospitals and laboratories that are not equipped with particle accelerators for radionuclide production.

The typical method for introducing fluorine at a specific aliphatic molecular site is the nucleophilic displacement of the corresponding sulfonate or halide by fluoride ion.[3] Although alkali metal fluorides have traditionally been used for this purpose, fluorination with these reagents is known to proceed only under vigorous conditions due to their limited solubility in organic solvents and low nucleophilicity. As an alternative, a "*naked*" fluoride ion, which is not solvated tightly by bulky cations or solvent molecules, is usually used to improve these reactions,[4] and over the past several decades, numerous kinds of phase-transfer type protocols, such as crown ether and quaternary ammonium fluoride derivatives, have been developed to enhance the nucleophilicity and solubility of fluoride ions in organic media and to accelerate this substitution reaction.[5] Although the naked fluoride ion generated from phase transfer

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(1) (a) Phelps, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 9226−9233. (b) Marx, V. *Chem. Eng. News* **2005**, *83*, 25.
(2) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1320−1367. (b) Filler, R. In *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Ed.; Studies in Organic Chemistry 48; Elservier; New York, 1993; pp 1−23.
(3) For reviews on nucleophilic fluorination, see: (a) Gerstenberger, M. R. C.; Haas, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 647−667. (b) Mascaretti, O. A. *Aldrichim. Acta* **1993**, *26*, 47−58.
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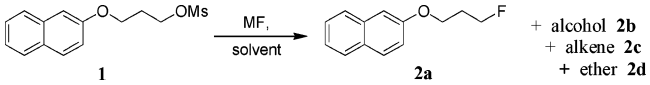
10.1021/ja0646895 CCC: $33.50

Table 1. Fluorinations of Mesylate **1** with Metal Fluoride under Various Reaction Conditions[a]



1 **2a**

entry	solvent	MF	temp (°C)	time (h)	yield of product[b] (%) 1	2a	2b	2c	2d
1	*t*-BuOH	CsF	80	6	trace	92	-	-	7
2	*n*-BuOH	CsF	80	6	4[c]	64	-	-	30
3	CH_3CN	CsF	80	6	91	7[c]	-	trace	-
4	DMF	CsF	80	6	33	48	8[c]	9[c]	-
5	1,4-dioxane	CsF	80	6	94	-	-	-	-
6	benzene	CsF	80	6	97	-	-	-	-
7	*tert*-amyl alcohol	CsF	80	6	-	93	-		5(5[c])
8	*tert*-amyl alcohol	CsF	90	2.5	-	94	-	-	4(5[c])
9	*t*-BuOH	CsBr	80	6	94	4[d]	-	-	trace
10	CH_3CN	CsBr	80	6	68	32[d]	-		-
11	*tert*-amyl alcohol	RbF	90	24	13	76	-		9
12	*tert*-amyl alcohol	KF	90	24	90	trace	-		7[c]

[a] All reactions were carried out on a 1.0 mmol reaction scale of mesylate **1** using 3 mmol of metal fluoride in 4.0 mL of solvent. [b] Isolated yield. [c] Yield determined by NMR. [d] Yield of 2-(3-bromopropoxy)naphthalene.

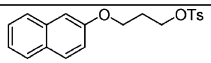
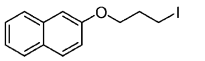
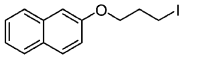
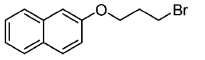
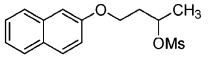
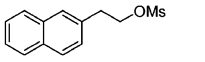
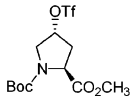
methods (e.g., tetrabutylammonium fluoride, TBAF, or KF-kryptfix complex) is a good nucleophile, its synthetic utility can be limited by its strong basicity.[6] When alkali metal salts are used, it is also well-known that polar aprotic solvents, such as acetonitrile and dimethylformamide (DMF), are much better than protic solvents for nucleophilic displacement; in polar aprotic solvents, the nucleophilicity of the anions is enhanced by selective solvation of the cation, whereas, in protic solvents, anion nucleophilicity is reduced by interaction with the partial positive charge of protic solvents.[7] Recently, it was found that nucleophilic fluorination with a metal fluoride may be catalyzed by a fluorinase enzyme. In this enzymatic reaction, hydrogen bonding among the enzyme, fluoride, and substrate plays a crucial role in synthesis of C−F bonds.[8]

In this report, we introduce the phenomenal efficiency of using tertiary alcohols as a reaction media for the nucleophilic fluorination with alkali metal fluoride. In this method, the nonpolar, protic *tert*-alcohol media—in the absence of any kind of catalyst—actually enhances the nucleophilicity of the alkali metal fluoride dramatically, increasing the rate of nucleophilic fluorination compared with conventional methods and reducing formation of typical byproducts (e.g., alkenes, alcohols, or ethers).[3,6,9]

Results and Discussion

Table 1 presents the results of the fluorination of a model compound, 2-(3-methanesulfonyloxypropoxy)naphthalene (**1**), with various alkali metal fluorides under various reaction conditions. The fluorination of mesylate **1** with 3 equiv of CsF under typical reaction conditions produced the 2-(3-fluoropropoxy)naphthalene product (**2a**) in low to very low yields, with alcohol **2b** and alkene **2c** being formed as byproducts; this was the case not only in polar aprotic solvents such as CH_3CN and DMF (7 and 48%, respectively, entries 3 and 4) but also in nonpolar aprotic solvent such as 1,4-dioxane and benzene (zero yield, entries 5 and 6). The same reaction in *t*-BuOH, however, proceeded almost to completion within 6 h, providing the fluoroalkane **2a** in very high yield (92%, entry 1), together with only small amounts of the ether byproduct **2d** (7%). It is of note that under these conditions, the reaction mixture forms a solid at 30 min. A denser solid formed in the reaction of entry 1, Table 2 compared to the reaction of entry 8, Table 1.

Table 2. Fluorinations of Various Alkyl Halides and Mesylates Using CsF in *tert*-Amyl Alcohol[a]

entry	Compound	temp (°C)	reaction time (h)	yield[b] (%)	comment
1		90	2	93	trace SM
2		90	24	73	18% alkene, trace SM
3		reflux	12	72	22% alkene
4		reflux	18	88	6% alkene[c]
5		90	3.5	81	12% alkenes
6		90	2.5	92	trace alkene
7		25	1.5	69	15% alkenes

[a] Unless otherwise noted, all reactions were carried out under the same conditions as those for entry 8 in Table 1, and an ether compound was detected in the all reactions in 4−5% yield, except entry 7. [b] Isolated yield. [c] Yield determined by NMR.

Comparison of Table 1 entries 3 and 10 shows that CsBr is much more reactive for nucleophilic displacement than CsF in a polar aprotic solvent such as CH_3CN, presumably due to weaker ionic bonding in CsBr compared to CsF, as well as to the greater nucleophilicity of the bromide ion compared to the fluoride ion. By contrast, the nucleophilic bromination reaction using CsBr proceeded remarkably slowly in *t*-BuOH, converting only 4% of mesylate **1** to the corresponding bromide (2-(3-bromopropoxy)naphthalene) in 6 h at 80 °C (entry 9). These results should be compared with the fluorination reactions with CsF in *tert*-butyl or *tert*-amyl alcohols, which were complete within 6 h and produced the fluoroalkane **2a** in very high yield (92−94%, entries 1 and 7). The other alkali metal fluorides, RbF and KF, exhibit lower reactivity for fluorination in *tert*-alcohol media, with either 76% and trace yields being obtained, respectively (entries 11 and 12, respectively), after extended reaction times (24 h). *tert*-Amyl alcohol, which has a large steric hindrance as well as a high boiling point, was found to be the best solvent among alcohols examined for this reaction; the

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product fluoroalkane was produced in 94% yield (entry 8) with a reaction time of only 2.5 h.[10] The importance of alcohol steric hindrance is evident from comparisons of reactions run with CsF in the *tert*-alcohols (entries 1, 7, and 8) compared to *n*-butanol (entry 2).

Table 2 illustrates further characteristics of this fluorination reaction with various primary and secondary halide or sulfonate precursors using 3 equiv of CsF in *tert*-amyl alcohol (entries 1−5). In all cases, the corresponding fluorine-substituted compounds are produced in comparable or greater yields than previously reported by other methods. The fluorination of haloethyl or alkanesulfonyloxyethyl aromatic compounds using *"naked"* fluoride, which is a strong base as well as a strong nucleophile, is known to be difficult because of the competing elimination to give the vinylarene by product. The merit of this method is evident in the fluorination of 2-(2-mesyloxyethyl)-naphthalene to 2-(2-fluoroethyl)naphthalene, which proceeds almost to completion, producing the corresponding fluoroalkane in 92% yield with only trace quantities of alkene byproduct (Table 2, entry 6).

The fluorination reaction of mesylates or tosylates has been reported to be less than twice as fast as that of iodides. Comparison of entries 1 and 2, however, shows that the fluorination rate of a tosylate is approximately 12 times faster than that of the corresponding iodide. This result suggests that the reaction rate is determined not only by the nature of the leaving group but also by other types of interactions, such as those between the solvent (*tert*-alcohol) and the leaving group. For example, H-bonding between the alcohol solvent and the oxygen atoms in the alkanesulfonate leaving group may enhance its nucleofugic (leaving group) character. Remarkably, using this fluorination procedure, we were able to prepare a fluoroproline derivative in good yield after only 1.5 h at room temperature from the corresponding triflate precursor (Table 2, entry 7). It is notable that a triflate has six sites for H-bonding with the solvent alcohol (three oxygens and three fluorines). By contrast, fluorination of reactants with halide groups in the *tert*-amyl alcohol media required long reaction times as well as vigorous conditions, although the reactions did eventually produce the fluorine-substituted product in high yields, as shown in entries 3 and 4 (72 and 88%, respectively).

The characteristics of the nucleophilic substitution reaction with fluoride in *tert*-alcohol, described above, are striking. First, hindered protic solvents (*tert*-butanol and *tert*-amyl alcohol in the present work) are much better than aprotic solvents, indicating a catalytic activity of the protic solvent. This finding is striking, because in S_N2 reactions polar, aprotic solvents are known to be much more efficient. Second, product yield is highly dependent on the cation (Cs^+ is much better than K^+), which provides experimental evidence for an important influence of Coulombic interactions by the cation on the reaction. Third, the relative reactivity of the halide ion nucleophile appears to be reversed (F^- much more reactive than Br^-) from that typical for halide ions in protic solvents ($F^- < Cl^- < Br^-$, etc), the latter sequence being that predicted by simply considering the differential solvation of the nucleophile. Fourth, the effect of the leaving group seems to be much larger than that for the conventional S_N2 reactions, suggesting that some sort of interaction between the leaving group and the other constituents of the reaction (the nucleophile, cation, or the solvent molecule) is affecting the reaction rate.

To test the practical utility of this new fluorination method in an important application where speed and efficiency are critical, namely, F-18 radiolabeling of important PET radiopharmaceuticals, we selected as targets the widely used and commercially available agent 2-[^{18}F]fluoro-2-deoxyglucose ([^{18}F]FDG) as well as three other promising candidate radiopharmaceuticals that are challenging to label. The results are given in Table 3, and overall, we obtained high radiochemical yields under favorable reaction conditions.

3′-Deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT) is under clinical trial (phase III) in Korea (July 2004 by Asan Medical Center) and the United States (December 2004 by NCI and GE) for PET imaging of tumor cell proliferation. Previously, [^{18}F]FLT was prepared from the [^{18}F]fluoride ion in a radiochemical yield of 50 ± 5.2%, under conventional conditions using a large amount of precursor (40 mg) and reaction at 150 °C; a 15 ± 5.4% yield was obtained at 110 °C with 20 mg of precursor.[11] As automated synthesis modules that typically use plastic valves and tubes do not tolerate temperatures of 150 °C, these systems cannot be utilized for routine synthesis. During the optimization of [^{18}F]FLT using an automatic module, we have found that the tetrabutylammonium cation is generally better than the cesium cation in a *tert*-alcohol system. In this study, we obtained higher radiochemical yields (65.5 ± 5.4%) of [^{18}F]FLT with a small amount of precursor at 120 °C (Table 3, entry 2) using $TBAHCO_3$. This condition enabled us to use an automated synthesis system.

N-[^{18}F]Fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{18}F]FP-CIT) is a well-known radiopharmaceutical for PET imaging of dopamine transporters. It has not been used routinely, however, because of difficulties in its preparation (only 1% yields have been obtained).[12] In Europe, the radioiodine-labeled analogue of CIT, namely [^{123}I]FP-CIT, has been used in place of [^{18}F]FP-CIT for single photon emission imaging. Using our new [^{18}F]fluorination method, we prepared [^{18}F]FP-CIT in 35.8 ± 5.2% yield at 100 °C for 20 min in one step (Table 3, entry 3). Thus mass production of [^{18}F]FP-CIT can enable us to begin clinical trials (phase III) in Korea (June 2006 by Asan Medical Center). [^{18}F]FDG is the only commercially available radiopharmaceutical and by far the most widely used one. The new fluorination method could facilitate its commercial production (Table 3, entry 1) and advance the availability of this important fluorinated radiopharmaceutical, as well as that of other ones to be developed in the future, for routine clinical use.

(10) *Typical Procedure in Table 1*: CsF (290 mg, 3.0 mmol) was added to the mixture of 2-(3-methanesulfonyloxypropoxy)naphthalene (**1**, 280 mg, 1.0 mmol) in *tert*-amyl alcohol (3.0 mL). The mixture was stirred over 2.5 h at 90 °C. After evaporation of solvent, the reaction mixture was extracted with ethyl ether (7 mL × 3). The organic layer was dried over anhydrous sodium sulfate and evaporated under a reduced pressure. The residue was purified by flash column chromatography (20% CH_2Cl_2/hexanes) to obtain 192 mg (94%) of 2-(3-fluoropropoxy)naphthalene (**2a**).

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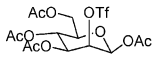
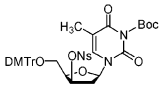
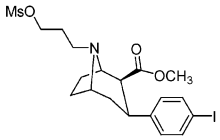
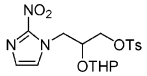
Table 3. Automatic Preparations of the Key Fluorine-18 Labeled PET Radiopharmaceuticals Using Alcohol Solvent System

entry	compound	[^{18}F]fluorination temp. (°C)	time (min)	precursor (mg)	radiochemical yield (%)	product
1		100	10	20	85.4±7.8[a] (n = 10)	[^{18}F]FDG
2		120	10	20	65.5±5.4[b] (n = 10)	[^{18}F]FLT
	Method in literature[11]	110	7.5	20	15.0±5.4 (n = 3)	[^{18}F]FLT
3		100	20	4	35.8±5.2[c] (n = 14)	[^{18}F]FP-CIT
	Method in literature[12]	90	10	10	Only 1%	[^{18}F]FP-CIT
4		120	15	10	69.6±1.8[d] (n = 10)	[^{18}F]FMISO
	Method in literature[13]	105	6	10	15.0±5.4 (n = 3)	[^{18}F]FMISO

[a] Radiochemical yield after [^{18}F]fluorination in the manual synthesis (n = 10). The product was 2-[^{18}F]fluoro-2-deoxyglucose. [b] 3′-Deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT), radiochemical yield after HPLC purification in the automatic synthesis with GE TracerLab FX module (n = 10). [c] *N*-2-[^{18}F]Fluoropropyl-2β-carbomethoxypropyl-3β-(4-iodophenyl)nortropane ([^{18}F]FP-CIT), radiochemical yield after HPLC purification in the automatic synthesis with GE TracerLab FX module (n = 14). [d] 1-[^{18}F]Fluoro-3-(2-nitroimidazol-1-yl)propan-2-ol ([^{18}F]FMISO), radiochemical yield after HPLC purification in the automatic synthesis with GE TracerLab MX module (n = 1).

Conclusions

In summary, we have described a novel method for the nucleophilic fluorination of some halo- and alkanesulfonyloxy alkane systems to the corresponding fluoroalkanes using alkali metal fluorides in *tert*-alcohol media. The nonpolar protic solvent enhances the reactivity of alkali metal fluorides tremendously, which facilitates the synthesis of organofluorine compounds by enabling efficient, high yielding S_N2 substitution that is rapid and proceeds under relatively mild conditions. These characteristics are especially important in the labeling of PET radiopharmaceuticals with [^{18}F]fluoride, where the short half-life of the radionuclide ($t_{1/2}$ = 110 min) and its availability at high specific activity only at the tracer level place a premium on reaction speed and efficiency. Since our findings are in marked contrast with the predictions made from the conventional mechanism, elucidating the mechanism of the presented reactions in *tert*-alcohol would be of keen interest.

Acknowledgment. We gratefully acknowledge the National Research and Development Program of MOST, Korea (2005-03184, D.Y.C.), Real-time Molecular Imaging Program (S.J.O.), and the KOSEF for financial support (R01-2005-000-10117-0, S.Y.L.). We also thank Professors John A. Katzenellenbogen and Peter Beak for helpful discussions.

Supporting Information Available: Experimental procedures of labeling for [^{18}F]FDG, [^{18}F]FLT, [^{18}F]FP-CIT, [^{18}F]FMISO, and a picture of solid formations. This material is available free of charge via a Internet at http://pubs.acs.org.

JA0646895