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High Efficiency Synthesis of F-18 Fluoromethyl Ethers: An Attractive Alternative for C-11 Methyl Groups in Positron Emission Tomography Radiopharmaceuticals

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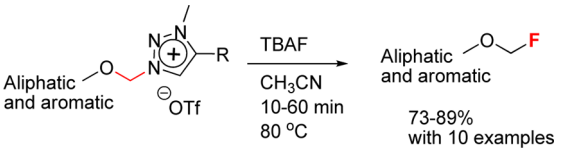
ABSTRACT



A rapid and efficient method for the synthesis of *O*-fluoromethyl aliphatic and aromatic ethers is presented. This method is so mild that it can be used for the preparation of positron emission tomography (PET) radiopharmaceuticals bearing *O*-[^{18}F]fluoromethyl groups.

The carbon-11 radionuclide, widely used in positron-emission tomography (PET), is generally produced locally by cyclotron bombardment, according to the $^{14}N(p,\alpha)^{11}C$ nuclear reaction.[1] The primary radiochemical products, [^{11}C]CO_2 or [^{11}C]CH_4, are then transformed into other precursors ([^{11}C]CO, [^{11}C]CH_3OH, [^{11}C]CH_3I, [^{11}C]CH_3OTf, [^{11}C]HCN, etc.) that are used for radiolabeling more complex PET radiopharmaceuticals, with heteroatom methylations (CH_3–X; X = O, N, S) with CH_3I or CH_3OTf being most commonly used for this purpose. These C-11 labeled radiopharmaceuticals are good for research; their commercialization, however, is very challenging because the short half-life of C-11 ($t_{1/2}$ = 20 min) makes mass production and FDA-mandated cGMP qualification analysis very impractical. Thus, many researchers have sought F-18 labeled alternatives for the RX-$^{11}CH_3$ group, namely, RX-$CH_2{}^{18}F$, RX-$CH_2CH_2{}^{18}F$, and RX-$CH_2CH_2CH_2{}^{18}F$ groups, which, because of the longer half-life of F-18 ($t_{1/2}$ = 110 min), enable regional production and distribution.[2−5] In the case of fluoroalkoxy groups (X = O), Tsukada et al. showed a nice

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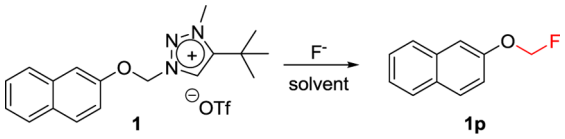
comparison of the D- and L-isomers of *O*-^{18}F-fluoromethyl, *O*-^{18}F-fluoroethyl, and *O*-^{18}F-fluoropropyl tyrosine as tumor imaging agents in mice.[3d] In this comparison, D-isomers were more metabolically stable in vivo than L-isomers, but the stabilities of different chain lengths, from fluoromethyl to fluoropropyl, were similar. It is notable, however, that due to synthetic difficulties, there are very few reports of the synthesis of RX-$CH_2{}^{18}F$ systems; typical radiochemical yields are less than 5%, which is insufficient for commercial production.[6] For $RNHCH_2CH_2{}^{18}F$ and $RNHCH_2CH_2CH_2{}^{18}F$ syntheses, mass production was still difficult until our development of tertiary alcohol labeling conditions.[7] Fluoroalkyl groups have also been added to aryl or alkenyl units,[8] and a study of the in vivo stability of fluoromethyl, fluoroethyl, and fluoropropyl arenes showed the fluoromethyl to be only somewhat more unstable than the others.[8c] There are, of course, many RX-$^{11}CH_3$ compounds that behave well as PET radiopharmaceuticals,[9] but if one replaces the ^{11}C-methyl group with a fluoroethyl or fluoropropyl group, the analog becomes not only larger but also more lipophilic by the addition of a $CH_2{}^{18}F$ or $CH_2CH_2{}^{18}F$ unit onto the methyl group. Given the small size of a fluorine atom, replacement of a ^{11}C-methyl group with a $^{18}FCH_2$ group is a more isostructural change.

During a study of alcohol protecting groups, we examined a triazolium methyl group (compound **1**) as a replacement for a benzyl group, and we found that this group functioned as a very good nucleofuge for displacement by the fluoride ion. Herein, we describe a convenient method for the fluoromethylation of alcohols that can be used for the synthesis of *O*-[^{18}F]fluoromethylated PET radiopharmaceuticals.

The starting 1,2,3-triazolium triflates were prepared from the corresponding chloromethyl ethers (see procedure in Supporting Information (SI)): Upon treatment with sodium azide, *O*-chloromethyl ethers were converted to *O*-azidomethyl ethers; the triazole was formed by a Click reaction with an alkyne in EtOAc, and treatment with methyl triflate in CH_3CN gave the 1,2,3-triazolium triflates. Most of the starting 1,2,3-triazolium triflates and imidazolium triflate are stable after freezer storage for two months at −15 °C (see details in SI). As shown in Table 1, triazolium salt **1**, prepared as a model substrate, was subjected to nucleophilic fluorination under various reaction conditions. When **1** was treated with 3 equiv of KF at 80 °C for 24 h in CH_3CN, starting material (**1**) was recovered quantitatively (entry 1). However, treatment with CsF under the same conditions gave the desired *O*-fluoromethylated product **1p** in 38% yield, with 57% recovered starting material **1** (entry 2). When TBAF was used, the reaction was complete within 1 h in good yield (64% at 15 min, entry 4; 89% at 1 h, entry 5). The reaction proceeded slowly at rt (entry 3), but curiously, starting material **1** could not be recovered. Careful NMR analysis showed that under these conditions the triflate anion of **1** was immediately replaced by the fluoride ion; this anion exchange did not occur under the conditions of entries 1 and 2, presumably because the fluoride ion has a very tight ionic interaction with potassium or cesium (see NMR in SI). In searching for the optimal reaction solvent, we explored fluorination with TBAF at 80 °C in other solvents (*t*-BuOH, acetone, THF, and DMF)

Table 1. Optimization of Fluorination of 1,2,3-Triazolium Triflate **1**[a]



					yield[b] (%)	
entry	MF	solvent	temp (°C)	time (h)	**1**	**1p**
1[c]	KF	CH_3CN	80	24	100	0
2[c]	CsF	CH_3CN	80	24	57	38
3	TBAF	CH_3CN	rt	24	–[d]	19
4	TBAF	CH_3CN	80	15 min	–[d]	64
5	TBAF	CH_3CN	80	1	–[d]	89
6	TBAF	*t*-BuOH	80	1	–[d]	81
7	TBAF	acetone	80	1	–[d]	45
8	TBAF	THF	80	40 min	–[d]	85
9	TBAF	DMF	80	20 min	–[d]	79
10	KF/K_{222}	CH_3CN	rt	24	–[d]	37
11	KF/K_{222}	CH_3CN	40	1	–[d]	19
12	KF/K_{222}	CH_3CN	60	1	–[d]	62
13	KF/K_{222}	CH_3CN	80	15 min	–[d]	84

[a] All reactions were carried out on a 1.0 mmol reaction scale of triazolium salt **1** using 1.5 mmol of fluoride in 4.0 mL of organic solvent in a sealed reaction vial. [b] Isolated yield. [c] 3 mmol of fluoride were used. [d] The triflate anion of starting material was immediately changed to fluoride.

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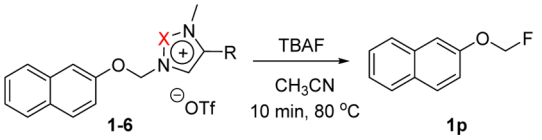
(entries 6–10). All solvents gave comparable yields, except acetone (entry 7). Because a short reaction period is essential for F-18 labeling, the more rapid reaction in DMF, which was complete in 20 min, would be advantageous (entry 9). Another powerful fluorination reagent KF/K_{222} was also tested in CH_3CN and proved to be superior to the others (entries 10–13), giving some product even at rt (entry 10) and complete reaction within 15 min at 80 °C (entry 13). As the reaction even proceeds at 60 °C (entry 12), this fluoromethylation protocol appears promising for labeling thermally sensitive materials, such as amino acids, oligopeptides, and potentially even proteins, without causing epimerization.

Table 2. Optimization of Substituents in Fluorination of 1,2,3-Triazolium Triflates **1**–**5** and Imidazolium Triflate **6**[a]



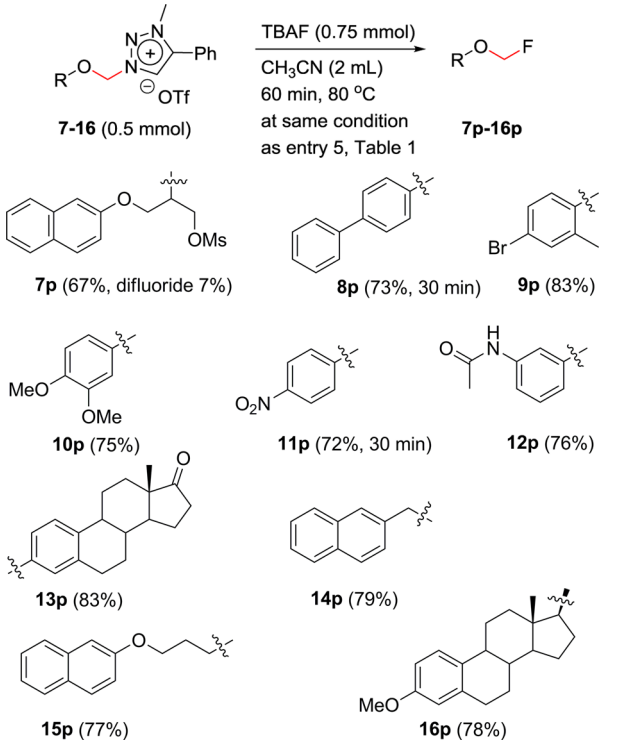
entry	X	R, compound	yield[b]
1	N	-*t*-Bu, **1**	66
2	N	-$COOCH_3$, **2**	42
3	N	-Ph, **3**	87
4	N	-4-CH_3O-Ph, **4**	72
5	N	-3,5-$(CF_3)_2$-Ph, **5**	89
6	CH	-Ph, **6**	57

[a] All reactions were carried out on a 1.0 mmol reaction scale of triazolium salt using 1.5 mmol of fluoride in 4.0 mL of CH_3CN. [b] Isolated yield.

To find the optimal heterocyclic leaving group for this fluorination reaction, four triazolium salts and an imidazolium salt were prepared and examined under the same fluorination conditions (1.5 equiv of TBAF, 80 °C, 10 min, CH_3CN, Table 2). We expected that electron-withdrawing groups (EWGs) on the triazolium salt might accelerate the reaction rate by labilizing the methylene–nitrogen bond of the precursor and electron-donating groups (EDG) would decrease the rate by stabilizing this bond. Although measuring yields at 10 min does not provide accurate reaction kinetics, the triazolium salt with an EWG, (3,5-ditrifluoromethyl)phenyl, gave the best yield (89%, entry 5). The triazolium salt with a methyl ester (EWG), however, gave a lower yield (42%, entry 2), presumably because of poor precursor stability. Other triazolium salt precursors afforded comparable yields (entries 1, 3, 4), implying that the reaction proceeded rapidly regardless of the electronic nature of the salt. Comparison of phenyl-substituted triazolium and imidazolium salts (entries 3, 6) showed that the triazolium salt (87%) was superior to the imidazolium salt (57%).

After establishing the optimal reaction conditions and best salt form, the reaction (1.5 equiv of TBAF, 80 °C, CH_3CN) was applied to more complicated triazolium salts (Scheme 1), and in all cases the desired products were obtained in comparable yields. The precursor **7**, having both a primary mesylate and a triazolium salt, gave principally the desired fluoromethyl compound **7p** in 67% yield, along with some difluorinated product (7%). Even though a mesylate is a better leaving group than a triazolium salt, these oxymethylene triazolium salts have very high reactivity toward fluoride ion substitution because the ether oxygen labilizes the C–N bond and would also stabilize any incipient carbocation character in the transition state. Thus, fluoride attack on the methylene group is doubly activated, by oxygen as well as by the triazolium group.

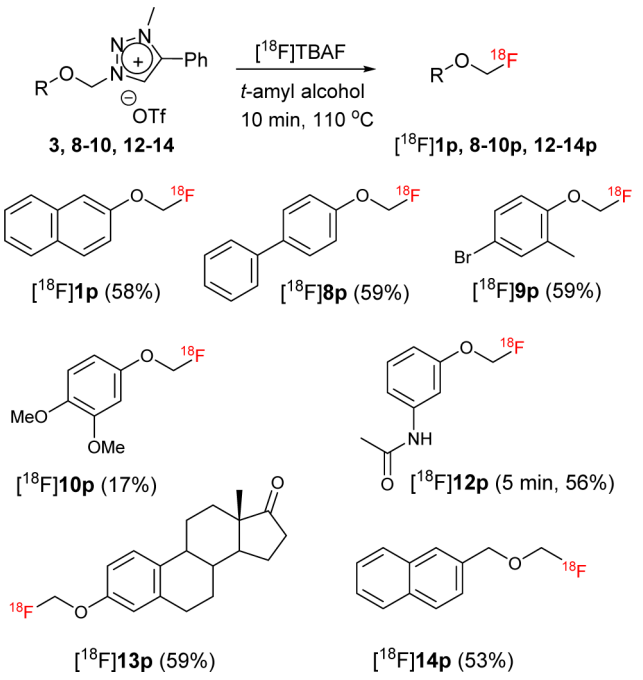
Scheme 1. Fluorinations of Various Compounds (Isolated Yield)



A variety of structurally diverse phenol derivatives **8**–**13** were smoothly converted to the corresponding fluoromethylated phenyl products **8p**–**13p** in moderate to excellent yield. Electronic environment variations on the aromatic substituent had little influence on the reaction although EWGs seemed to increase the reaction rate. The precursor bearing a 3-acetamidophenol derivative **12** also gave a good yield of **12p** (76%), indicating tolerance of the amide functionality. Similarly, the steroid having a ketone also gave a good yield (**13p**), implying similar tolerance of carbonyl groups. Fluorination on the benzylic (**14**), primary alkyl (**15**), or secondary alkyl (**16**) positions also proceeded smoothly to afford the fluoromethoxy products in very good yields (77–79%).

With completion of the F-19 fluorination study with a variety of precursors, this protocol was extended to F-18

Scheme 2. Fluorinations of Various Compounds with [^{18}F]Fluoride (Nondecay Corrected Isolated Radiochemical Yield)



radiolabeling. Several selected precursors were subjected to a [^{18}F]fluorination condition ([^{18}F]TBAF, 110 °C, *tert*-amyl alcohol) to check the utility of this method in F-18 labeling. The results are given in Scheme 2, and overall, reasonable yields were obtained under favorable reaction conditions. [^{18}F]Fluorination of **1** afforded [^{18}F]fluoromethoxy naphthalene ([^{18}F]**1p**) in 58% isolated, nondecay corrected radiochemical yield after 10 min. The overall preparing time including HPLC was 45 min with 230 GBq/μmol specific activity. In other cases, the corresponding [^{18}F]fluorine-substituted compounds were produced in great yields, except for precursor **10** including EDGs such as dimethoxy groups. A noteworthy advantage of using this triazolium salt as a labeling precursor is that it is so simple to separate the small amount of labeled product from excess starting material by simple chromatographic retention of the precursor salt and elution of the neutral product.

To find the effect of the triazolium ring in a fluorination reaction, we performed the fluorination reaction in an NMR tube. All protons' peaks of starting compound **1** changed their chemical shifts when tetrabutylammonium fluoride (TBAF) was added (see SI, Figure S5). NMR spectra were taken before adding TBAF, 10 min later at 0 °C after adding TBAF, at 60 min later at rt after removal of the ice bath, and 10 min later at 80 °C. The C5 proton peak shown at 8.60 ppm completely disappeared at 10 min later at 0 °C after adding TBAF, due to the acidity of that proton.[10] At 60 min later at rt, the tiny peak at 9.63 ppm which is presumably the C5 proton peak of triazolium fluoride was shown. At 10 min later at 80 °C, the tiny peak at 9.63 ppm disappeared with completion of fluorination. Based on this experiment, the proposed mechanism of intramolecular fluorination for the synthesis of fluoromethyl ether was shown in Figure 1. *N*-Heterocyclic zwitter ionic carbene is a favored form in equilibrium at rt. The displacement of fluoride proceeds slowly at 80 °C from triazolium fluoride.

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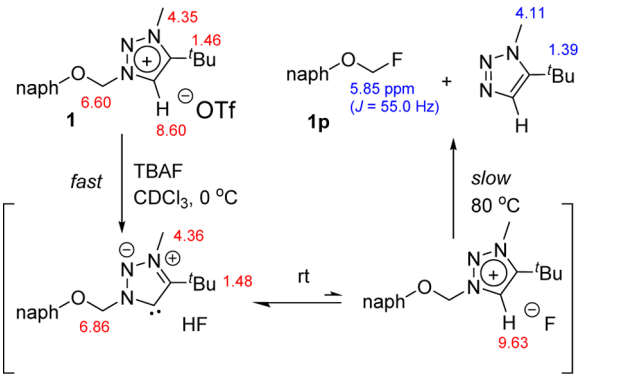

Figure 1. Proposed mechanism of intramolecular fluorination for the synthesis of fluoromethyl ether (numbers are chemical shifts of protons).

In conclusion, the method we have described for the preparation of *O*-fluoromethylated aliphatic and aromatic ethers should enable the facile preparation of a number of compounds bearing *O*-fluoromethyl groups of varying structure. In addition, because this method is efficient and rapid, it will be of use for the preparation of *O*-fluoromethylated compounds labeled with the PET radionuclide fluorine-18 ($t_{1/2}$ = 110 min) and could expand the availability of commercially viable F-18 labeled radiopharmaceuticals considerably. We are currently expanding this chemistry to *S*- and *N*-fluoromethylation.

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Supporting Information Available. Typical procedure for the preparation of starting triazolium salts and fluorination, F-18 fluorination, NMR experiment for finding mechanism of fluorination, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.