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Synthesis of ^{18}F -Difluoromethylarenes from Aryl (Pseudo) Halides

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Abstract

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We report a general method for syntheses of [^{18}F]CHF₂-arenes from [^{18}F]fluoride for radiopharmaceutical discovery. The method is practical, operationally simple, tolerates a wide scope of functional groups, enables labeling of a variety of arenes and heteroarenes with radiochemical yields (RCYs, not decay corrected) from 10% to 60%. The ^{18}F -fluorination precursors are readily prepared from aryl chlorides, bromides, iodides and triflates, respectively. Seven ^{18}F -difluoromethylarene drug analogs and radiopharmaceuticals including claritin, fluoxetine (prozac), and [^{18}F]DAA1106 were synthesized to show the potential of the method for applications in PET radiopharmaceutical design.

Keywords

^{18}F -difluoromethylarene; aryl (pseudo) halides; fluorine-18; positron emission tomography; radiopharmaceuticals

Fluorine-18 (^{18}F) is the most commonly used radionuclide for molecular imaging by positron emission tomography (PET).¹ Over the past five years, several modern fluorination reactions have been developed with ^{18}F , many of which are achieved with high specific activity (SA) [^{18}F]fluoride.² Development of modern ^{18}F -multi-fluoromethylation reactions, for example to incorporate ^{18}F into trifluoromethyl groups, are now also addressed, due to the prospects of having more labeled chemotypes available for imaging.³ A challenge in the preparation of ^{18}F -labeled compounds that contain more than one fluorine atom, especially when located on the same carbon atom, is the probability of isotope exchange that can substantially lower the specific activity. Here we describe a general method for difluoromethyl [^{18}F]CHF₂-arenes from [^{18}F]fluoride. The method is practical and general over a wide variety of arenes and heteroarenes. On a fundamental level, the crucial but unusual C-F bond formation occurs by nucleophilic substitution on a fully substituted carbon.

The most extensive work to date on multi-fluorinated ^{18}F -labeled molecules has been directed at the synthesis of ^{18}F -trifluoromethyl groups.³ Gouverneur and co-workers have established a practical method based on [^{18}F]CuCF₃ species, with large substrate scope.^{3f} A year later, three other groups independently reported different methods to prepare [^{18}F]CuCF₃, which was also explored for [^{18}F]trifluoromethylation of aryl boronic acids.^{3g-3i} Groves and co-workers have reported a direct C-H to C- ^{18}F transformation based on Mn-salen-catalyzed benzylic fluorination with [^{18}F]fluoride,^{2j} which was also extended to ^{18}F -trifluoromethylarenes.^{3j} [^{18}F]CHF₂ arenes such as [^{18}F]4-(difluoromethyl)-1,1'-biphenyl, can be synthesized through decarboxylative ^{18}F -fluorination with [^{18}F]Selectfluor generated from [^{18}F]F₂ or Ag^I-mediated halogen-exchange with [^{18}F]fluoride ion.^{3e,k} Gouverneur's group improved the substrate scope of Ag^I-mediated halogen-exchange; but the CHFCl-arene starting materials still require several synthetic steps for preparation.^{3m} To date, no method has been reported for the ^{18}F -labeling of difluoromethylarenes with high specific activity. Here, we describe progress toward the goal of high-specific-activity difluoromethylation in a practical and general reaction.

To overcome the challenge of C-F bond formation to achieve ^{18}F -difluoromethylation from [^{18}F]fluoride, we have designed an ^{18}F -difluoromethylation reaction that features a benzoyl

auxiliary, which controls the chemoselectivity of C–H functionalization; [^{18}F]fluoride introduction is observed only at the desired benzylic position. The auxiliary can be installed from aryl (pseudo) halides, and quickly cleaved in situ after radiofluorination to generate ^{18}F -difluoromethylarenes (Scheme 1).

The labeling procedure entails (1) C–H bromination to α -Br- α -F-acetophenone; (2) *in situ* halogen-exchange with [^{18}F]fluoride; and (3) benzophenone cleavage.⁴ Treatment of aryl acetophenones **2** with *N*-bromophthalimide and [^{18}F]fluoride in the presence of tetraethylammonium bicarbonate (TEAB) in chlorobenzene and acetonitrile at 100 °C,⁵ followed by addition of an aqueous KOH solution after 5 min, gave [^{18}F]CHF₂-arenes **3** (Table 1). The procedure was successfully applied to the ^{18}F -difluoromethylation of a wide range of substrates, including both electron-deficient and electron-rich aromatics. The radiochemical yields (RCYs, non-decay corrected; relative to starting [^{18}F]fluoride) range from 10% to 60%.⁶ Halide, alcohol, ether, aldehyde, ketone, ester, amide, carbamate, cyanide, nitrate, cyclopropane and alkyne functional groups are tolerated. The method is also compatible with heterocycles (e.g. **3m–p**). Moisture is tolerated; water-saturated chlorobenzene gave the same radiochemical yield within error ([^{18}F]**3m**, 47% vs. 49% RCY). For aniline derivative **2g**, no expected product was generated under the standard condition: We surmised that the basic nitrogen was oxidized by *N*-bromophthalimide instead of basic nitrogen was oxidized by *N*-bromophthalimide instead of the α -C–H bond of acetophenone. Given that bromo-arylammonium can be reduced to aniline, after ^{18}F -labeling of **2g**, addition of sodium thiosulfate to the reaction mixture afforded [^{18}F]CHF₂-aniline ([^{18}F]**3g**) in 16% RCY.

To demonstrate the potential utility of the ^{18}F -labeling procedure, we examined a variety of well-known biologically active molecule analogues, including fenofibrate (cholesterol scavenger), fluoxetine (selective serotonin reuptake inhibitor), DAA-1106 (translocator protein 18 kDa radiotracer), SC-58125 (COX₂ inhibitor) and analepticon (respiratory stimulant). The labeling method was selective on a claritin derivative, which possesses five benzylic C–H bonds and four allylic C–H bonds. To achieve ^{18}F -labeling of tertiary amines, a stepwise method was developed, with bromination carried out separately, prior to fluorination (Scheme 2). Specifically, the enolate of precursor **2**, generated by deprotonation with LiHMDS at low temperature, was trapped by NBS. Without separation, the crude brominated precursor was subjected to radiofluorination, which afforded the corresponding ^{18}F -labeled amines, including [^{18}F]CHF₂-hydroquinidine ester in 26% RCY.

Obtaining high specific activity (SA) is an ongoing challenge for ^{18}F -labeling of multi-fluoromethyl-compounds due to undesired isotope exchange reactions,^{3e–3l} with recent progress reported for ^{18}F -trifluoromethylation.^{3g} The reactions conditions provided in Table 1 are useful to readily access ^{18}F -labeled difluoromethyl arenes, but only with low specific activity (e.g. 0.49 mCi/ μmol for [^{18}F]**3m**). To achieve high specific activity, we attempted to identify the undesired pathway that led to the formation of non-radioactive compounds **3**. Control experiments showed that $^{19}\text{F}/^{18}\text{F}$ isotope exchange did not occur for **2r**, **2r'**, and **3r** in the presence of [^{18}F]fluoride/TEAB at 100 °C (Scheme 3a). In the absence of additional fluoride, treatment of α -phenyl- α -Br- α -F-acetophenone (**2r'**), with TEAB gave **2r''** in 9% yield, determined by NMR spectroscopy. The results demonstrated that decomposition of

2r' by TEAB released ^{19}F -fluoride ion, which fluorinated **2r'** to form the non-radioactive byproduct **2r''**. However, use of a weaker base, tetrabutylammonium methanesulfonate (TBAOMs), did not decompose α -Br- α -F-acetophenone **2m'**, but ^{18}F -fluorination was not observed when TEAB was replaced by TBAOMs. To increase the nucleophilicity of ^{18}F , organic bases such as *N,N*-diisopropylethylamine (DIPEA) were explored to promote ^{18}F -fluorination.⁷ With 0.5 μmol of precursor **2m'** and a reaction temperature of 80 $^{\circ}\text{C}$, we determined a specific activity for [^{18}F]**3m** at 81 mCi/ μmol (3.0 GBq/ μmol), with only 39 mCi of starting [^{18}F]fluoride after bombardment (Scheme 3b) for a reaction yielding over 3 mCi of product, which could be sufficient for preclinical PET imaging studies. Given the anticipated increase of specific activity with larger amounts of activity in the mCi range (Scheme 3b), we propose that, with appropriate automation, specific activity higher than 81 mCi/ μmol (3.0 GBq/ μmol) will be achievable.

Starting material preparation from aryl halides and pseudo halides is robust and practical: Prior to our work, palladium-catalyzed cross-coupling of aryl halide with α -fluoroacetophenone was not a general reaction, and yields were generally low (e.g. 17%).⁸ We extended the transformation to be general, from aryl chlorides, bromides, iodides and triflates, including sterically hindered arenes (full table of Pd-catalyzed fluoroacetophenonation of arenes is shown in the supporting information). To highlight the convenience of precursor preparation, we show six examples in Table 2.

In conclusion, we have reported a general method for ^{18}F -labeling of difluoromethylarenes via aryl (pseudo) halides with broad functional group compatibility. The strategy outlined herein will augment the pool of radiochemical methodologies and enable ^{18}F -labeled difluoromethylarenes to be considered in PET radiotracer design.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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5. For optimization of labeling conditions, see supporting information Table S2..
6. RCY (SPE): reaction mixture was purified by solid-phase extraction (SPE) to separate ^{18}F -labeled product from polar by-products and unreacted ^{18}F fluoride. The radiochemical yield was measured based on the filtrate, and is reported relative to starting ^{18}F fluoride activity. The filtrate was also analyzed by radio-HPLC in conjunction with radio-TLC to determine radiochemical purity. RCY (HPLC): reaction mixture was purified by semi-preparative HPLC to separate ^{18}F -labeled product. The radiochemical yield was measured based on the fraction corresponding to radiolabeled product, and is reported relative to starting ^{18}F fluoride activity. The filtrate was also analyzed by radio-HPLC. RCY (SPE) and RCY (HPLC) for ^{18}F difluoromethyl-SC-58125, ^{18}F 6-difluoromethylquinoline, and ^{18}F difluoromethyl-fenofibrate were consistent (see supporting information Table S3).
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Scheme 1. Auxiliary Facilitated [^{18}F]Difluoromethylarene Formation

Scheme 2.

Step-wise ¹⁸F-Difluoromethylarene Formation of Tertiary Amines. Reaction conditions:

Arene **2** (10 μmol), LiHMDS (1.0 M in THF, 1.3 equiv), THF (0.25 mL), -78 °C, 45 min.

then NBS (1.0 equiv), THF (0.1 mL), -78 °C, 45 min. (b) TEAB (3.5 mg), chlorobenzene

(0.2 mL), MeCN (20 μL), 100 °C, 5 min, then KOH aqueous solution (45 w%, 40 μL),

100 °C, 15 min.

Scheme 3.

a. Control Experiments. b. Improvement of Specific Activity.

Table 1

 ^{18}F -Difluoromethylarene Formation of Aryl-acetophenones.^[a]

[^{18}F]3a 29% $\pm$ 2% ($n = 3$)	[^{18}F]3b 29% $\pm$ 1% ($n = 3$)
[^{18}F]3c 54% $\pm$ 3% ($n = 3$)	[^{18}F]3d 36% $\pm$ 3% ($n = 3$)
[^{18}F]3e 61% $\pm$ 2% ($n = 3$)	[^{18}F]3f 50% $\pm$ 1% ($n = 3$)
[^{18}F]3g^b 16% $\pm$ 2% ($n = 3$)	<div> [^{18}F]CHF₂-DAA1106 36% $\pm$ 5% ($n = 3$) </div> <div> [^{18}F]CHF₂-Fenofibrate 47% $\pm$ 3% ($n = 3$) 39% RCY (HPLC) </div>
[^{18}F]3h 47% $\pm$ 3% ($n = 3$)
[^{18}F]3i 41% $\pm$ 1% ($n = 3$)
[^{18}F]3j^c 26% $\pm$ 2% ($n = 3$)
[^{18}F]3k 13% $\pm$ 2% ($n = 3$)
[^{18}F]3l 46% $\pm$ 2% ($n = 3$)	<div> [^{18}F]CHF₂-Claritin^c 21% $\pm$ 2% ($n = 3$) </div> <div> [^{18}F]CHF₂-SC-58125 47% $\pm$ 2% ($n = 3$) 37% RCY (HPLC) </div>
[^{18}F]3m 49% $\pm$ 3% ($n = 3$) 47% $\pm$ 2% ($n = 3$) ^d 43% RCY (HPLC) SA = 0.49 mCi/ μ mol
[^{18}F]3n 37% $\pm$ 1% ($n = 3$)
[^{18}F]3o 40% $\pm$ 3% ($n = 3$)
[^{18}F]3p 47% $\pm$ 3% ($n = 3$)
[^{18}F]CHF₂-Boc-Fluoxetine^{c,e} 17% $\pm$ 2% ($n = 3$)	[^{18}F]CHF₂-Estrone^{c,e} 11% $\pm$ 1% ($n = 3$)

General conditions: [a] Arene **2** (10 μ mol), *N*-bromophthalimide (2.0 mg), TEAB (3.5 mg), chlorobenzene (0.2 mL), MeCN (20 μ L), 100 $^{\circ}\text{C}$, 5 min, then KOH aqueous solution (45 w%, 40 μ L), 100 $^{\circ}\text{C}$, 15 min. [b] *N*-bromophthalimide (4.2 mg), then $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ (5.0 mg) was added in the second step. [c] KOH aqueous solution (45 w%, 60 μ L). [d] Chlorobenzene was replaced by water saturated chlorobenzene (0.2 mL). [e] Chlorobenzene was replaced by benzene (0.2 mL). Yield ranges are provided; n = number of independent reactions; RCY (SPE): reaction mixture was purified by solid-phase extraction (SPE); RCY (HPLC): reaction mixture was purified by semi-preparative HPLC.⁶

Table 2Selected Examples of Pd-Catalyzed Fluoro-acetophenonation of Arenes.^[a]