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Synthesis and Reactivity of ^{18}F-Labeled α,α-Difluoro-α-(aryloxy)acetic Acids

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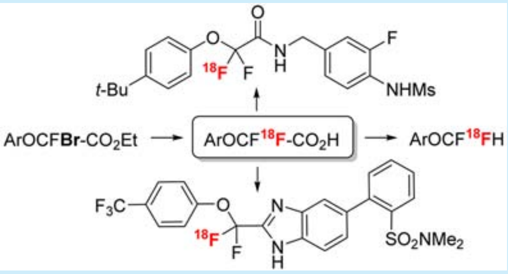
S *Supporting Information*

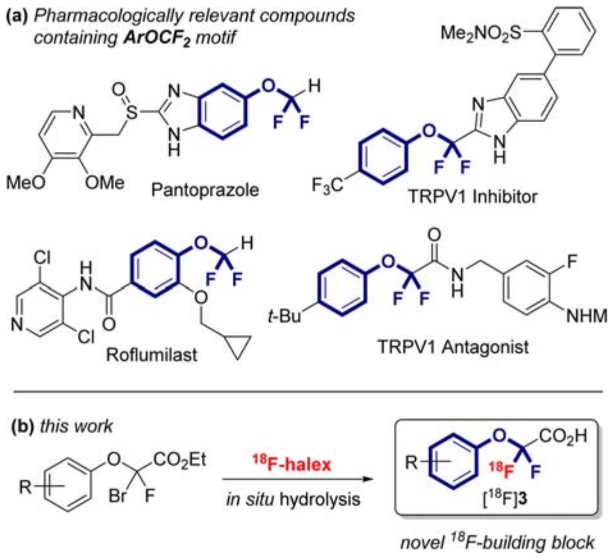
ABSTRACT: In this work, we describe the ^{18}F-labeling of α,α-difluoro-α-(aryloxy)acetic acid derivatives and demonstrate that these building blocks are amenable to post-^{18}F-fluorination functionalization. Protodecarboxylation offers a new entry to ^{18}F-difluoromethoxyarene, and the value of this approach is further demonstrated with coupling processes leading to representative ^{18}F-labeled TRPV1 inhibitors and TRPV1 antagonists.



Fluorine-18 (^{18}F) is one of the most commonly used radionuclides for the production of positron emission tomography (PET) radiotracers; PET is a noninvasive molecular imaging modality that allows quantitative in vivo observation of biochemical and physiological processes.[1] This technique is utilized as a tool for clinical diagnosis[2] and to facilitate drug development.[3] To date, access to radiotracers has relied mostly on radiosynthetic methodologies leading to [^{18}F]alkyl−F or [^{18}F]aryl−F bond formation.[4] With the aim of expanding the chemical space available for radioligand discovery, recent efforts have focused on the development of innovative protocols for the ^{18}F-labeling of perfluoroalkyl substituents. In this context, molecules featuring the α,α-difluorinated aryl ether motif ($ArOCF_2$) are of interest because of their increasing importance in medicinal chemistry (Scheme 1a).[5] Difluoromethyl aryl ethers are prominent motifs in drug development because the polarized C−H bond can act as a hydrogen bond donor, a property that could enhance potency without affecting microsomal stability.[6,7] Moreover, the replacement of OCH_3 with $OCHF_2$ does not increase P-gp efflux liability, an advantage when designing neuro-PET radioligands. As a result, methodologies for accessing ^{18}F-labeled $ArOCF_2H$ have recently appeared.[8] Compounds featuring a $ArOCF_2$−C bond are also encountered in drug discovery, for example, in studies aimed at developing TRPV1 antagonists[9a] and TRPV1 inhibitors.[9b] We noted that there is no methodology available to date for the ^{18}F-labeling of such a motif.

In this work, we opted for an ^{18}F-labeling route leading to the $ArOCF_2$ motif with a diversity-oriented methodology in mind. The carboxylic acid group is incredibly versatile for functionalization; hence, we reasoned that [^{18}F]α,α-difluoro-α-(aryloxy)acetic acids ([^{18}F]**3**) could serve as divergent intermediates for the radiosynthesis of a range of ^{18}F-labeled difluoro-containing targets via post-^{18}F-fluorination functionalization (Scheme 1b).

Scheme 1. ^{18}F-Labeling of $ArOCF_2$ Motif



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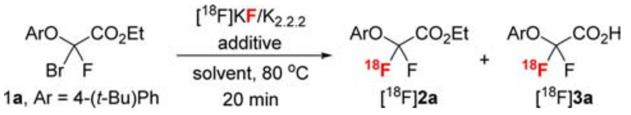
In order to prepare [^{18}F]**3**, we considered a two-step procedure involving halogen exchange of ethyl *α*-bromo-*α*-fluoro-*α*-(aryloxy)acetate (**1**) with cyclotron-produced [^{18}F]-fluoride to afford ^{18}F-labeled ethyl *α*,*α*-difluoro-*α*-(aryloxy)-acetates [^{18}F]**2**. Hydrolysis of [^{18}F]**2** would then lead to [^{18}F]**3**. The 4-*tert*-butyl aryl substituted ester **1a** was chosen as a model substrate to validate this strategy and optimize the reaction conditions (Table 1).

Table 1. Optimization for the ^{18}F-Fluorination of the Brominated Precursor 1a[a]



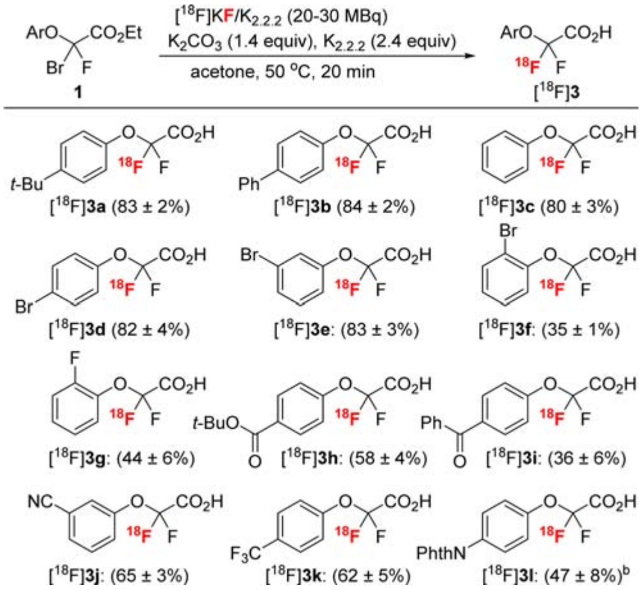
entry	solvent	additive (equiv)	[^{18}F]**2a** RCC[b] (%)	[^{18}F]**3a** RCC[b] (%)
1[c,d]	MeCN		<1	0
2[c,d,e]	DMF		<1	0
3[d,f]	MeCN		28 ± 2	0
4[d]	MeCN		57 ± 15	0
5	MeCN		70 ± 6	0
6	MeCN	1 M HNO_3 (10.0)[g]	19 ± 18	22 ± 14
7	MeCN	1 M NaOH (5.0)[g]	0	26 ± 0
8	MeCN	Bu_4NOH (1.4)	20 ± 0	1 ± 0
9	MeCN	LiOH (1.4)	9 ± 4	21 ± 1
10	MeCN	$CsOH{\cdot}H_2O$ (1.4)	31 ± 21	16 ± 5
11	MeCN	Cs_2CO_3 (1.4)	15 ± 1	36 ± 0
12	MeCN	K_2CO_3 (1.4)	24 ± 21	40 ± 18
13	MeCN	K_2CO_3 (2.8)	22 ± 6	14 ± 2
14[h]	MeCN	K_2CO_3 (1.4)	34 ± 13	38 ± 18
15[i]	MeCN	K_2CO_3 (1.4)	<1	80 ± 4
16[i]	DMSO	K_2CO_3 (1.4)	<1	2 ± 1
17[i]	DMF	K_2CO_3 (1.4)	<1	60 ± 11
18[i]	*t*-BuOH	K_2CO_3 (1.4)	<1	45 ± 10
19[i,j]	acetone	K_2CO_3 (1.4)	<1	83 ± 2

[a] **1a** (0.01 mmol), solvent (600 μL). [b] Radiochemical conversions determined by radio-TLC and radio-HPLC ($n = 2$). [c] [^{18}F](Et_4N)F was used. [d] **1a** (0.03 mmol), MeCN (300 μL). [e] Temperature = 150 °C. [f] Reaction time = 10 min. [g] The additive was added after the reaction and then stirred at 80 °C for another 20 min. [h] The reaction was performed in the presence of 2.4 equiv of 18-crown-6. [i] The reaction was performed in the presence of 2.4 equiv of Kryptofix-2.2.2. [j] Acetone (200 μL), 50 °C.

Preliminary optimization investigating the source of ^{18}F-fluoride revealed that [^{18}F]Et_4NF was not efficient for this transformation even with a reaction temperature as high as 150 °C (Table 1, entries 1 and 2). However, [^{18}F]**2a** was detected in 28% radiochemical conversion (RCC) when **1a** was treated with [^{18}F]KF/$K_{2.2.2}$ in MeCN at 80 °C for 10 min (Table 1, entry 3). The reaction finished in 20 min with the RCC of [^{18}F]**2a** increasing to 57% (Table 1, entry 4). After the amount of precursor and solvent was optimized, the RCC was further improved to 70% (Table 1, entry 5) (see Table S1). The subsequent hydrolysis of [^{18}F]**2a** was examined by addition of 1 M HNO_3 or 1 M NaOH to the crude mixture of the optimized conditions then stirred at 80 °C for 20 min (Table 1, entries 6 and 7). Under acidic conditions, a mixture of [^{18}F]**2a** and [^{18}F]**3a** was obtained. The labeled ester [^{18}F]**2a** was fully consumed under basic conditions, but the desired carboxylic acid [^{18}F]**3a** was obtained in 26% RCC only. Therefore, we considered instead a protocol involving in situ hydrolysis by introducing the base as an additive in the ^{18}F-fluorination step. A mixture of [^{18}F]**2a** and [^{18}F]**3a** was obtained when the reaction was performed in the presence of various bases with the best result observed with K_2CO_3 (Table 1, entries 8–12). A decrease in RCC of [^{18}F]**3a** was observed when the amount of K_2CO_3 was doubled (Table 1, entry 13). It is known that certain crown ethers and cryptands can serve as a chelator for potassium ion, hence enhancing the solubility of the base.[10] Although the addition of 18-crown-6 (2.4 equiv) did not lead to a significant improvement (Table 1, entry 14), the RCC of [^{18}F]**3a** was dramatically increased to 80% when the reaction was performed in the presence of Kryptofix-2.2.2 ($K_{2.2.2}$) (2.4 equiv) as an additional additive (Table 1, entry 15). A solvent screen (Table 1, entries 16–19) revealed that the reaction was most efficient in acetone at 50 °C, affording [^{18}F]**3a** in 83% RCC (Table 1, entry 19) (see Table S2 for full data).

With the optimized reaction conditions in hand, the scope of ^{18}F-fluorination with in situ hydrolysis was investigated with a range of brominated precursors containing various functional groups on the arene (Scheme 2). Substrates containing electron neutral and bromine substituents gave the desired ^{18}F-fluorinated acids [^{18}F]**3a–f** in RCCs ranging from 35% to 84%. The lower RCC of the *o*-bromo substrate ([^{18}F]**3f**) could be accounted for by evoking steric hindrance. The reaction tolerates a wide range of functional groups such as fluoro, ester, ketone, nitrile, trifluoromethyl, and protected amine ([^{18}F]**3g-l**); for these functionalized products, the RCCs ranged from 36% to 65%.[11]

Scheme 2. Substrate Scope for the ^{18}F-Labeling of *α*,*α*-Difluoro-*α*-(aryloxy)acetic Acids [^{18}F]3[a]



[a] **1** (0.01 mmol), K_2CO_3 (0.014 mmol), $K_{2.2.2}$ (0.024 mmol), acetone (200 μL), 50 °C, 20 min; RCCs determined by radio-TLC and radio-HPLC ($n = 4$). [b] Along with 28 ± 8% of radiolabeled byproduct resulting from the partial hydrolysis of the phthalimide group. Phth = phthalimide.

The radiosyntheses of [^{18}F]**3a** and [^{18}F]**3k** were performed using a higher amount of [^{18}F]fluoride (~4 GBq) (Scheme 3, eq 1). In these processes, the addition of K_2CO_3 and $K_{2.2.2}$ as additives was not necessary since they were used in the eluent

Scheme 3. Isolation of [^{18}F]3a and [^{18}F]3k and the Preparation of TRPV1 Antagonist [^{18}F]4 and TRPV1 Inhibitor [^{18}F]5

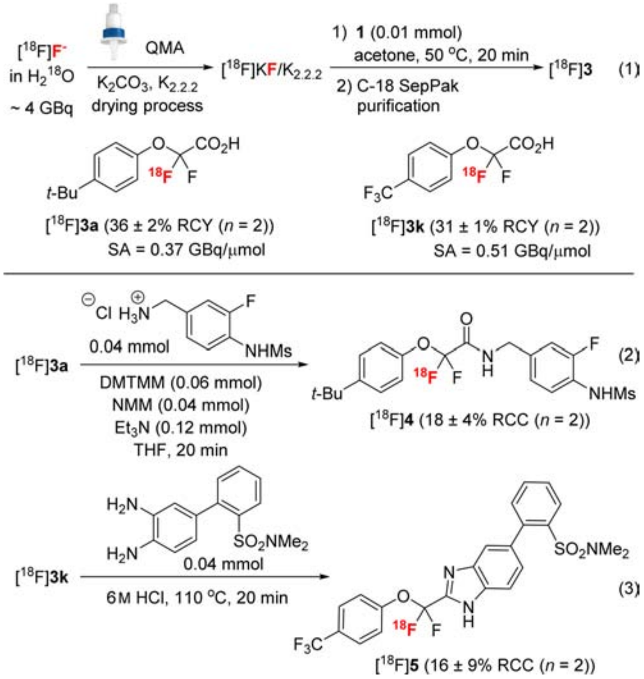
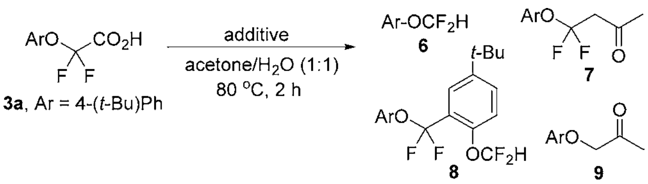
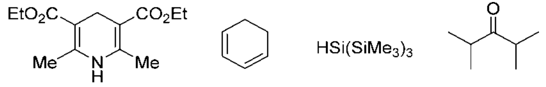


Table 2. Optimization of Conditions for the Decarboxylation of 3a[a]



entry	additive (equiv)	conv of **3a**[b] (%)	yield of **6**[b] (%)
1[c]	KOH (1.5)	0	0
2	$AgNO_3$ (1.0), $K_2S_2O_8$ (2.0)	91	30
3	$AgNO_3$ (1.0), $K_2S_2O_8$ (4.0)	>99	53 (50)[d]
4[e]	$AgNO_3$ (1.0), $K_2S_2O_8$ (4.0)	82	47
5[f]	$AgNO_3$ (1.0), $K_2S_2O_8$ (4.0)	96	4[g]
6	$AgNO_3$ (1.0), $K_2S_2O_8$ (4.0), **A** (1.0)	62	25
7	$AgNO_3$ (1.0), $K_2S_2O_8$ (4.0), **B** (1.0)	9	8
8	$AgNO_3$ (1.0), $K_2S_2O_8$ (4.0), **C** (1.0)	34	1
9	$AgNO_3$ (1.0), $K_2S_2O_8$ (4.0), **D** (1.0)	84	53
10[h]	$AgNO_3$ (1.0), $K_2S_2O_8$ (4.0)	22	4
11	$AgNO_3$ (1.0), $(NH_4)_2S_2O_8$ (4.0)	>99	41
12	Ag(II) picolinate (1.0)	55	0



A **B** **C** **D**

[a] **3a** (0.1 mmol), acetone/H_2O (1:1) (400 μL). [b] Yields determined by ^{19}F NMR using Ph−CF_3 as an internal standard; isolated yield of a 2.0 mmol scale reaction in parentheses. [c] In diglyme at 200 °C. [d] Compounds **6**, **7**, **8**, and **9** were separated and isolated in 50%, 3%, 4%, and 4% yield, respectively. [e] In acetone/D_2O (1:1). [f] In acetone-d_6/H_2O. [g] 5% of deuterated **6** observed. [h] The reaction was performed at room temperature.

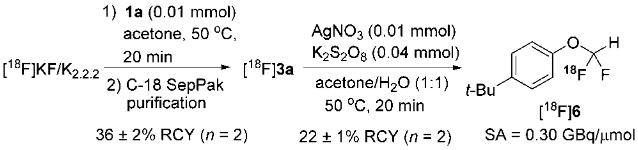
system during the drying process of [^{18}F]fluoride. After the reactions, the products were isolated by solid-phase extraction (C-18 SepPak), affording [^{18}F]**3a** and [^{18}F]**3k** in 36% and 31% radiochemical yields (RCYs) with specific activities (SA) of 0.37 GBq/μmol and 0.51 GBq/μmol, respectively.

The isolated ^{18}F-labeled carboxylic acids can be used as starting materials for subsequent radiochemical reactions. The amide coupling of [^{18}F]**3a** with the corresponding amine using 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholinium chloride (DMTMM) as a coupling reagent led to the formation of [^{18}F]**4**, an ^{18}F-labeled TRPV1 antagonist,[9a] in 18% RCC (Scheme 3, eq 2) (see Table S3 for the results of other coupling reagents). In addition, we demonstrated that the reaction of [^{18}F]**3k** with 3′,4′-diamino-*N*,*N*-dimethyl[1,1′-biphenyl]-2-sulfonamide in 6 M HCl at 110 °C gave 16% RCC of benzimidazole [^{18}F]**5**, a known TRPV1 inhibitor (Scheme 3, eq 3).[9b]

Next, we envisaged that [^{18}F]**3** could serve as a precursor for ^{18}F-labeled ArOCF_2H [^{18}F]**6** via protodecarboxylation. Since this transformation has never been reported in the literature on this motif,[12] we first investigated this process using nonlabeled **3a** as a model substrate (Table 2). No reaction was observed when **3a** was treated with KOH even at 200 °C (Table 2, entry 1).[13] Pleasingly, **3a** underwent silver-mediated oxidative decarboxylation at 50 °C using $K_2S_2O_8$ to give **6** in 30% yield (Table 2, entry 2).[14] The yield was improved to 53% with full conversion of **3a** using 4 equiv of $K_2S_2O_8$ (Table 2, entry 3). When the reaction was performed on a 2.0 mmol scale, **3a** was isolated in 50% yield along with three minor side products identified as **7**−**9**. Deuterium-labeling experiments revealed that acetone is the source of hydrogen in this process (Table 2, entries 4 and 5). The yield was not improved upon addition of hydrogen sources such as Hantzsch ester **A**, 1,3-cyclohexadiene **B**, silane **C**, or 2,4-dimethyl-3-pentanone **D** (Table 2, entries 6−9) (see Table S4 for full data). The reaction was inefficient at room temperature (Table 2, entry 10), and the yield was not improved by using either an alternative oxidant or silver(II) salt (Table 2, entries 11 and 12).

Next, radiolabeled [^{18}F]**3a** was subjected to protodecarboxylation using $AgNO_3$ (1 equiv) and $K_2S_2O_8$ (4 equiv) in acetone/H_2O (1:1) at 50 °C for 20 min. After purification by semipreparative HPLC, [^{18}F]**6** was successfully isolated in 22% RCY with a SA of 0.30 GBq/μmol (Scheme 4).

Scheme 4. Radiosynthesis and Isolation of [^{18}F]6



In summary, we have successfully developed a mild and efficient protocol for the preparation of ^{18}F-labeled α,α-difluoro-α-(aryloxy)acetic acids applying a halogen-exchange ^{18}F-fluorination of the brominated ester precursors with in situ hydrolysis. The reaction tolerates a wide range of substituents, and the subsequent postfunctionalization of the acid was demonstrated with the preparation of an amide-containing TRPV1 antagonist and a benzimidazole-containing TRPV1 inhibitor. Moreover, the protodecarboxylation to form the arylOCF_2H [^{18}F]**6** was also successfully implemented.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03730.

> Experimental procedures, characterization data, and ^{1}H, ^{19}F, and ^{13}C NMR spectra for all new compounds and optimization tables (PDF)

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Notes

The authors declare no competing financial interest.

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(12) The formation of the protodecarboxylated product ($ArOCF_2H$) was reported as a side reaction in the fluorodecarboxylation of $ArOCF_2CO_2H$; see: Zhou, M.; Ni, C.; He, Z.; Hu, J. *Org. Lett.* **2016**, *18*, 3754−3757.

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