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Synthesis of ¹⁸F-difluoromethylarenes using aryl boronic acids, ethyl bromofluoroacetate and [¹⁸F] fluoride†

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Herein, we report the radiosynthesis of ¹⁸F-difluoromethylarenes *via* the assembly of three components, a boron reagent, ethyl bromofluoroacetate, and cyclotron-produced non-carrier added [¹⁸F]fluoride. The two key steps are a copper-catalysed cross-coupling reaction, and a Mn-mediated ¹⁸F-fluorodecarboxylation.

Introduction

Positron emission tomography (PET) is a molecular imaging technique that requires molecules labelled with a positronemitting radionuclide. Fluorine-18 is a widely used positron emitting radionuclide in part due to its favourable decay properties, and the numerous clinical applications of 2-deoxy-2-[18F] fluoro-p-glucose, a radiopharmaceutical prepared from [18F]fluoride.1 While radiochemists have in recent years focused their efforts on methods enabling 18F-fluorination2 and trifluoromethylation of (hetero)arenes, 2,3 18F-difluoromethylation reactions have been less studied despite the importance of the CF2H motif4 in radioligand design for drug discovery programmes. In 2013, we reported a Ag(1)-mediated ¹⁸Ffluorodecarboxylation of 2-fluoro-2-arylacetic acids with [18F] Selectfluor (bis)triflate leading to [18F]ArCF₂H.⁵ Subsequently, we disclosed a Ag(1)-mediated halogen exchange reaction using [18F] fluoride.6 In 2016, a multi-step method to label [18F]ArCF₂H from aryl (pseudo)halides was disclosed by Ritter and co-workers.7 Later, Liang and co-workers demonstrated that halogen exchange of benzyl (pseudo)halides with [18F]fluoride followed by oxidative benzylic C-H fluorination with Selectfluor afforded [18F]ArCF₂H with improved molar activity.8 Despite these advances, ¹⁸F-difluoromethylation remains a challenging problem, especially for structurally complex targets. We initially considered adapting difluoromethylation reactions operating via C-H

Scheme 1 (A) Ag(i)-mediated ^{18}F -fluorodecarboxylation with [^{18}F] Selectfluor (bis)triflate. (B) Mn(iii)-mediated ^{18}F -fluorodecarboxylation with [^{18}F]fluoride towards [^{18}F]ArCH $_2F$. (C) Synthetic plan towards [^{18}F] ArCF $_2H$ from boron reagents and [^{18}F]fluoride.

functionalisation.9 Whilst this strategy is ideal for (hetero)arenes with innate reactivity leading to site-selective 18F-difluoromethylation, substrates that are not reactive or too reactive would be unsuitable, thereby limiting applicability for radioligand synthesis. We therefore opted to develop a method using prefunctionalised aryl boron reagents; these are amenable to 18Ffluorination and ¹⁸F-trifluoromethylation, ¹⁰ so extension to ¹⁸Fdifluoromethylation was viewed as a valuable development. Building on our Ag(1)-mediated ¹⁸F-fluorodecarboxylation towards [18F]ArCF₂H,⁵ a reaction requiring [18F]Selectfluor (bis)triflate (Scheme 1A),11 and on the Mn-mediated fluorodecarboxylation reported by Groves and co-workers, a reaction using [18F]fluoride (Scheme 1B), 12,13 we envisaged that the 18F-fluorodecarboxylation of 2-fluoro-2-arylacetic acids with [18F]fluoride could afford [18F] ArCF₂H. The beneficial effect of fluorine substitution on radical stabilisation would be favorable for this process. 5,14 This approach would require a robust method to cross-couple the aryl boron reagent with ethyl bromofluoroacetate followed by hydrolysis to

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access the carboxylic acid precursor; we gave preference to a coupling methodology applying Cu-catalysis instead of Pd or Ni, a decision driven by guidelines for residual metals in (radio) pharmaceuticals.¹⁵ The proposed strategy therefore relies on three readily available components, the boron reagent, ethyl bromofluoroacetate, and [18F]fluoride (Scheme 1C).16

Results and discussion

Preliminary experiments demonstrated that the model fluorosubstituted carboxylic acid 1a is amenable to fluorodecarboxvlation with fluoride. When an equimolar mixture of 1a and 2a was treated with Mn(tmp)Cl (2.5 mol%), Et₃N·3HF (1.2 equiv.) and PhIO (3.3 equiv.) in MeCN at 50 °C, 3a and 4a were obtained in 44% and 20% yield, respectively. This result indicates that the fluorine-substituted precursor 1a is more reactive than nonfluorinated 2a towards fluorodecarboxylation (Scheme 2A). We verified that product 4a did not undergo fluorination via C-H functionalisation under these conditions.17 When an excess of 1a (1 equiv.) was treated with TBAF (0.1 equiv.), PhIO (0.5 equiv.) and Mn(tmp)Cl (0.2 equiv.) in MeCN, 3a was obtained in 50% yield (determined by 19F NMR based on TBAF consumption) (Scheme 2B). Notably, quantitative fluoride incorporation was observed applying similar reaction conditions to the preformed hypervalent iodine complex 5a (Scheme 2C). These preliminary data boded well for 18F-labeling with [18F]fluoride as the limiting reagent, and prompted the development of a robust protocol to convert aryl boron reagents into 2-fluoro-2-arylacetic acids.

The cross-coupling of arylboronic acids and ethyl bromofluoroacetate has been reported using an excess of boron reagent under Ni or Pd catalysis, but has not been accomplished under Cu catalysis. 18-22 Initial studies reacting [1,1'-biphenyl]-4-

Et₃N·3HF (1.2 equiv.) Mn(tmp)Cl (2.5 mol %) MeCN (0.1M) 1a (0.1 mmol) 2a (0.1 mmol) Ar = 1,1'-biphenyl PhIO (0.5 equiv.) n(tmp)Cl (0.2 equiv TBAF (0.1 equiv.) MeCN (0.1M) 50 °C, 20 min 1a (0.1 mmol) Ar = 1,1'-biphenyl Mn(tmp)CI PhIO (0.5 equiv.) CO₂F MeCN (0.1M) 50 °C. 10 min. 1a (0.1 mmol) За Ar = 1,1'-biphenyl

Scheme 2 (A) Competition studies evaluating the effect of fluorine substitution on fluorodecarboxylation. (B) Reaction with sub-stoichiometric fluoride. (C) Reaction of iodine(III) complex 5a with substoichiometric fluoride. Yields of isolated products. Mn(tmp)Cl = Mn(III) meso-tetra(2,4,6-trimethylphenyl)porphyrin chloride. aYield determined by ¹⁹F NMR using $\alpha_{i}\alpha_{i}\alpha_{r}$ a-trifluorotoluene as internal standard.

ylboronic acid 6a (2 equiv.) with ethyl bromofluoroacetate (1 equiv.) in the presence of 1,10-phenanthroline (L1, 20 mol%), CuI (20 mol%) and Cs₂CO₃ (2 equiv.) in dioxane (0.2 M) under N2 at 100 °C afforded 7a in 7% yield (Table 1, entry 1). When 2,2':6',2"-terpyridine (L2) was used as the ligand, the yield was significantly improved to 58% yield (Table 1, entry 2). When the stoichiometry was altered to 1 equivalent of 6a and 2 equivalents of ethyl bromofluoroacetate in the presence of 4,4',4"-tritert-butyl-2,2':6',2"-terpyridine (L3) in toluene instead of dioxane 7a was obtained in 63% yield (Table 1, entry 3). Further optimisation increasing the concentration led to the optimal protocol consisting of treating 6a (0.1 mmol) with ethyl bromofluoroacetate (0.2 mmol), Cs₂CO₃ (0.2 mmol), CuI (20 mol%) and L3 (20 mol%) in toluene (0.4 M) at 100 °C. Under these reaction conditions, 7a was isolated in 82% yield (Table 1, entry 4). A one-pot sequence involving cross-coupling followed by hydrolysis with MeOH and aqueous K₂CO₃ afforded 8a isolated in 75% yield (Table 1, entry 5). In the absence of ligand and/or copper source (Table 1, entries 6, 7), no product formation was observed. Furthermore, no reaction was observed with CuCl₂ (Table 1, entry 8), or when the reaction solvent was DMF or DMSO (Table 1, entry 9).

These optimised conditions gave access to a range of 2fluoro-2-arylacetic acids (Scheme 3). The reaction is broad in scope and tolerates various functional groups, for example alkyl 8c-8e and 8s-8u, alkoxy 8f, 8g, trifluoromethyl 8h, bromo 8p, 8q, iodo 8r, and aldehyde 8i all performed well. Substrates featuring heterocycles such as dibenzofuran 8j, pyridine 8k,

Table 1 Optimisation of the Cu-catalysed cross-coupling of aryl boronic acid 6a with ethyl bromofluoroacetate towards ester 7a and the corresponding carboxylic acid 8aa

Entry	Solvent	Cu-source	Ligand	Product	$Yield^b$
	-: ()			_	
1^c	Dioxane (0.2 M)	CuI	L1	7a	7%
2^c	Dioxane (0.2 M)	CuI	L2	7a	58%
3	Toluene (0.2 M)	CuI	L3	7a	63%
4^d	Toluene (0.4 M)	CuI	L3	7a	$82\%^e$
5^d	Toluene (0.4 M)	CuI	L3	8a	75% ^{e,f}
6^d	Toluene (0.4 M)	CuI	_	7a	0%
7^d	Toluene (0.4 M)	_	_	7a	0%
8^d	Toluene (0.4 M)	$CuCl_2$	L2	7a	0%
9^d	DMF or DMSO (0.2 M)	CuI	L3	7a	0%

^a Screening reactions performed on 0.1 mmol scale. ^b Yield determined by ¹⁹F-NMR using α,α,α -trifluorotoluene as internal standard. ^c 2 equiv. of 6a and 1 equiv. of ethyl bromofluoroacetate. d 1 equiv. of 6a, and 2 equiv. of ethyl bromofluoroacetate. e Yield of isolated product. f Onepot procedure towards 8a.

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Scheme 3 Scope of Cu-catalysed cross-coupling. The reactions were performed on a 0.3 mmol scale. Conditions: Cul (20 mol%), L3 (20 mol%), aryl boronic acid (1 equiv.), ethyl bromofluoroacetate (2 equiv.), Cs_2CO_3 (2 equiv.), toluene (0.4 M) at 100 °C for 18 h then onepot hydrolysis with $\rm K_2CO_3$ (10 equiv.), MeOH/H₂O (1 : 1), 5 h. $^{\rm a}$ Hydrolysis performed as a subsequent step with K2CO3 (5 equiv.). ^bReaction run on 5 mmol scale. All yields are of isolated products.

triazole 81, and pyrazoles 8m, 8n are also suitable coupling partners applying our optimised protocol affording the desired products in 40% to 70% yield. Additionally, this cross-coupling

Scheme 4 (A) Competition experiment subjecting equimolar amount of 9a and 5a to [18F] fluorodecarboxylation. (B) Competition experiment reacting equimolar amount of 1a and 3a with PIDA

chemistry afforded 80, a derivative of fenofibrate, in 72% yield. Finally, the reaction was amenable to scale-up to 5 mmol (Scheme 3, 8m).

The key 18F-fluorodecarboxylation step was studied next (Table 2). We started our investigation applying protocol A that consists of reacting in one-pot 8b (0.11 mmol) with PhIO (0.33 mmol), Mn(tmp)Cl (2 mg) and [18F]TEAF (20-30 MBq) in MeCN (600 μL) at 50 °C; this protocol led to only traces of [18F]3b (Table 2, entry 1). When the loading of PhIO (0.02 mmol) and MeCN (300 μ L) was reduced, [18F]3b was obtained in 6% \pm 1% radiochemical conversion (RCC) (Table 2, entry 2). Similar results were obtained in DMF (Table 2, entry 3). Reducing the stoichiometry of **8b** led to a significant increase in RCC (22% \pm 7%) (Table 2, entry 4). When applying protocol B which consists of mixing 8b with PhIO, a process generating complex 5b, prior to the addition of Mn(tmp)Cl (2 mg) and [18F]TEAF (20-30 MBq)

Table 2 Optimisation studies for the [18F]fluorodecarboxylation of 8b

Entry	Starting material (mmol)	Protocol	Solvent	PhIO (mmol)	$RCC^{a,b}$ $(n=2)$
1	8b (0.11)	A	$MeCN^c$	0.33	$3\%\pm1\%$
2	8b (0.11)	A	$MeCN^d$	0.02	$6\%\pm1\%$
3	8b (0.11)	A	DMF^d	0.02	$7\% \pm 2\%$
4	8b (0.055)	A	$\mathrm{DMF}^{d,e}$	0.02	$22\% \pm 7\%$
5	5b (0.014)	В	$\mathbf{DMF}^{d,e}$	_	$\mathbf{40\%} \pm \mathbf{10\%}^{f}$
6	5b (0.014)	В	$\mathrm{DMF}^{d,e}$	_	$0\% \pm 0\%^g$
7	8b (0.014)	A	$MeCN^d$	0.02	$0\% \pm 0\%^h$
8	5b (0.014)	В	$\mathrm{DMF}^{d,e}$	_	$0\% \pm 0\%^i$

^a Radiochemical conversion. ^b n = number of reactions. ^c 600 μ L of MeCN. ^d 300 μ L of MeCN. ^e MeCN removed at 100 °C after dispensing [¹⁸F]TEAF. f(n = 10). g Reaction temperature = 100 °C. h Catalyst is Mn(tmp)OTs. No Mn Catalyst.

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and DMF (300 µL), a drastic improvement was observed, and [18 F]3b was obtained in 40% \pm 10% RCC (n = 10) (Table 2, entry 5). When the reaction was run at 100 °C, the formation of [18F] 3b was not observed (Table 2, entry 6). No ¹⁸F-labelled product was obtained when Mn(tmp)OTs was used as catalyst, or in the absence of Mn(tmp)Cl (Table 2, entries 7 and 8).

fluorine substituent is advantageous fluorodecarboxylation as demonstrated with a competition experiment subjecting equimolar amount of pre-formed hypervalent iodine(III) complexes **9a** and **5a** to ¹⁸F-fluorination with [¹⁸F] TEAF, Mn(tmp)Cl at 50 °C in DMF. Difluoromethylarene [18F]3a was the only product observed in the crude reaction mixture (Scheme 4A). Furthermore, an additional competition experiment

Scheme 5 Scope of [18F]fluorodecarboxylation applying protocol B ^aArCHFCO₂H (0.028 mmol), PhIO (0.5 equiv.), MeCN (1 mL), 50 °C, 10 min then addition of [18F]TEAF (20-30 MBq) Mn(tmp)Cl (2 mg), DMF (300 μL), 50 °C, 20 min. bArCHFCO₂H (0.014 mmol), PhIO (0.5 equiv.), MeCN (1 mL), 50 °C, 10 min then addition of [18F]Mn(tmp)F (841 MBq) DCE (300 µL), 60 °C, 20 min.

showed that the iodine(III) complex 5a is formed preferentially to 9a (Scheme 4B). Fluorine substitution therefore facilitates the two steps of the process leading to fluorodecarboxylation.

Protocol B was applied to a selection of arenes using 20-30 MBq of [18F]fluoride (Scheme 5). Ether, alkyl, aldehyde, ketone, pyridine, triazole, pyrazole, dibenzofuran motifs were all tolerated. The highest RCCs were obtained for electron rich arenes. [18F]30 derived from a boronic acid analogue of fenofibrate was successfully labelled in 23% \pm 4% (n=4). The boronic acid derivative of the COX-II inhibitor ZA140 6z was transformed into the labelled difluoromethylated product $[^{18}F]3z$ in 15% \pm 2% RCC (n = 3).

The ¹⁸F-fluorodecarboxylation of **5b** performed with 841 MBq of [18F]fluoride required further optimisation. For this experiment, [18F]fluoride was captured on an anion exchange cartridge then eluted using a solution of Mn(tmp)Cl in methanol, resulting in 85% ¹⁸F-recovery. Lowering the starting material stoichiometry to 0.007 mmol of 5b and changing the solvent from DMF to DCE afforded the cartridge-purified [18F]3b in a decay corrected RCY of 12% and a molar activity of 3.0 GBq μ mol⁻¹ in a total synthesis time of 30 minutes.23

Pleasingly, ¹⁸F-fluorodecarboxylation also enabled access to the [18F]ArOCF₂H motif. The only known route to label this motif was reported by our group, and required a multi-step synthesis of the ArOCHFCl precursors which were themselves prepared from ArOCHFCO₂H.²⁴ The reaction of estrone (1.0 equiv.) with ethyl bromofluoroacetate (1.5 equiv.) and K₂CO₃ (2.5 equiv.) in DMF (2 mL) at room temperature followed by a subsequent hydrolysis with aqueous NaOH (2.5 equiv.) in 1:1 H2O/Et2O afforded the precursor required for fluorodecarboxylation. 18F-labelling applying protocol B afforded [18F]11a in 21% \pm 6% RCC (n=3).

Conclusions

In summary, a novel method was developed to transform aryl boronic acids to [18F]ArCF₂H. Prior to labelling, the crosscoupling with ethyl bromofluoroacetate was accomplished under Cu catalysis followed by in situ hydrolysis. The radioisotope ¹⁸F is then introduced in the last step applying a Mn-mediated fluorodecarboxylation with readily available [18F]fluoride. This study has unveiled three key features for this last transformation. Firstly, the fluorine substituent on the carboxylic acid precursor is advantageous for fluorodecarboxylation; secondly, the benefit of preforming the hypervalent iodine complex prior to ¹⁸F-fluorination; and thirdly, we have established that Mn-mediated fluorodecarboxylation enables access to [18F]ArOCF2H in addition to [18F]ArCF₂H.

Conflicts of interest

There are no conflicts to declare.

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