Synthesis of $^{18}$F-difluoromethylenes using aryl boronic acids, ethyl bromofluoroacetate and $[^{18}$F]$^+$ fluoride†

Jeroen B. I. Sap, a Thomas C. Wilson, a Choon Wee Kee, a,b Natan J. W. Straathof, a Christopher W. am Ende, b Paramita Mukherjee, b Lei Zhang, b Christophe Genicot, b and Véronique Gouverneur *a

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

Introduction

Positron emission tomography (PET) is a molecular imaging technique that requires molecules labelled with a positron-emitting 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-$[^{18}$F]$^+$fluoro-D-glucose, a radiopharmaceutical prepared from $[^{18}$F]$^+$fluoride. While radiochemists have in recent years focused their efforts on methods enabling $^{18}$F-fluorination and $^{18}$F-trifluoromethylation of (hetero)arenes, $^{11}$ $^{18}$F-difluoromethylation reaction have been less studied despite the importance of the CF$_2$H motif in radiogold design for drug discovery programmes. In 2013, we reported a Ag(i)-mediated $^{18}$F-fluorodecarboxylation of 2-fluoro-2-arylacetic acids with $[^{18}$F]$^+$Selectfluor (bis)triflate leading to $[^{18}$F]$^+$ArCF$_2$H. $^5$ Subsequently, we disclosed a Ag(i)-mediated halogen exchange reaction using $[^{18}$F]$^+$fluoride. $^6$ In 2016, a multi-step method to label $[^{18}$F]$^+$ArCF$_2$H 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 $[^{18}$F]$^+$fluoride followed by oxidative benzyl C–H fluorination with Selectfluor afforded $[^{18}$F]$^+$ArCF$_2$H with improved molar activity. $^8$ Despite these advances, $^{18}$F-difluoromethylation remains a challenging problem, especially for structurally complex targets. We initially considered adapting difluoromethylation reactions operating via C–H functionalisation. $^9$ Whilst this strategy is ideal for (hetero)arenes with innate reactivity leading to site-selective $^{18}$F-difluoromethylation, substrates that are not reactive or too reactive would be unsuitable, thereby limiting applicability for radiogold synthesis. We therefore opted to develop a method using pre-functionalised aryl boron reagents; these are amenable to $^{18}$F-fluorination and $^{18}$F-trifluoromethylation, $^{10}$ so extension to $^{18}$F-difluoromethylation was viewed as a valuable development. Building on our Ag(i)-mediated $^{18}$F-fluorodecarboxylation towards $[^{18}$F]$^+$ArCF$_2$H, $^3$ a reaction requiring $[^{18}$F]$^+$Selectfluor (bis)triflate (Scheme 1A), $^{11}$ and on the Mn-mediated fluorodecarboxylation reported by Groves and co-workers, a reaction using $[^{18}$F]$^+$fluoride (Scheme 1B), $^{12,13}$ we envisaged that the $^{18}$F-fluorodecarboxylation of 2-fluoro-2-arylacetic acids with $[^{18}$F]$^+$fluoride could afford $[^{18}$F]$^+$ArCF$_2$H. The beneficial effect of fluorine substitution on radical stabilisation would be favorable for this process. $^{12,14}$ This approach would require a robust method to cross-couple the aryl boron reagent with ethyl bromofluoroacetate followed by hydrolysis to...
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 bromofluorooacetate, and [18F]fluoride (Scheme 1C).16

Results and discussion

Preliminary experiments demonstrated that the model fluorosubstituted carboxylic acid 1a is amenable to fluorodecarboxylation 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 fluoro-substituted precursor 1a is more reactive than non-fluorinated 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. Yields of isolated products.

The proposed strategy therefore relies on three substoichiometric fluoride. (C) Reaction of iodine(ii) complex 5a with substoichiometric fluoride. Yields of isolated products. Mn(tmp)Cl = Mn(ii) meso-tetra(2,4,6-trimethylphenyl)porphyrin chloride.18

Scheme 2 (A) Competition studies evaluating the effect of fluorine substitution on fluorodecarboxylation. (B) Reaction with sub-stoichiometric fluoride. (C) Reaction of iodine(ii) complex 5a with substoichiometric fluoride. Yields of isolated products. Mn(tmp)Cl = Mn(ii) meso-tetra(2,4,6-trimethylphenyl)porphyrin chloride.18

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Cu-source</th>
<th>Ligand</th>
<th>Product</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Dioxane (0.2 M)</td>
<td>CuI</td>
<td>L1</td>
<td>7a</td>
<td>7%</td>
</tr>
<tr>
<td>2a</td>
<td>Dioxane (0.2 M)</td>
<td>CuI</td>
<td>L1</td>
<td>7a</td>
<td>7%</td>
</tr>
<tr>
<td>3</td>
<td>Toluene (0.2 M)</td>
<td>CuI</td>
<td>L3</td>
<td>7a</td>
<td>63%</td>
</tr>
<tr>
<td>4a</td>
<td>Toluene (0.4 M)</td>
<td>CuI</td>
<td>L3</td>
<td>7a</td>
<td>82%</td>
</tr>
<tr>
<td>5a</td>
<td>Toluene (0.4 M)</td>
<td>CuI</td>
<td>L3</td>
<td>8a</td>
<td>75%</td>
</tr>
<tr>
<td>6a</td>
<td>Toluene (0.4 M)</td>
<td>CuI</td>
<td>—</td>
<td>7a</td>
<td>0%</td>
</tr>
<tr>
<td>7a</td>
<td>Toluene (0.4 M)</td>
<td>CuI</td>
<td>—</td>
<td>7a</td>
<td>0%</td>
</tr>
<tr>
<td>8a</td>
<td>DMSO (0.2 M)</td>
<td>CuCl2</td>
<td>L2</td>
<td>7a</td>
<td>0%</td>
</tr>
<tr>
<td>9a</td>
<td>DMF or DMSO (0.2 M)</td>
<td>CuI</td>
<td>L3</td>
<td>7a</td>
<td>0%</td>
</tr>
</tbody>
</table>

a Screening reactions performed on 0.1 mmol scale.1a Yield determined by 19F-NMR using 2,2,6,2′,6′-terfluorotoluene as internal standard.1b 2 equiv. of 6a and 1 equiv. of ethyl bromofluorooacetate. c 1 equiv. of 6a, and 2 equiv. of ethyl bromofluorooacetate. d Yield of isolated product. e One-pot procedure towards 8a.
triazole 8l, and pyrazoles 8m, 8n, are also suitable coupling partners applying our optimised protocol according the desired products in 40% to 70% yield. Additionally, this cross-coupling chemistry afforded 8o, 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 μL) was reduced, [18F]3b was obtained in 6% 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%–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) (Scheme 4).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material (mmol)</th>
<th>Protocol</th>
<th>Solvent</th>
<th>PhIO (mmol)</th>
<th>RCCa,b (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8b (0.11)</td>
<td>A</td>
<td>MeCN</td>
<td>0.33</td>
<td>3% ± 1%</td>
</tr>
<tr>
<td>2</td>
<td>8b (0.11)</td>
<td>A</td>
<td>MeCN</td>
<td>0.02</td>
<td>6% ± 1%</td>
</tr>
<tr>
<td>3</td>
<td>8b (0.11)</td>
<td>A</td>
<td>DMF</td>
<td>0.02</td>
<td>7% ± 2%</td>
</tr>
<tr>
<td>4</td>
<td>8b (0.055)</td>
<td>A</td>
<td>DMF</td>
<td>0.02</td>
<td>22% ± 7%</td>
</tr>
<tr>
<td>5</td>
<td>5b (0.014)</td>
<td>B</td>
<td>—</td>
<td>—</td>
<td>40% ± 10%</td>
</tr>
<tr>
<td>6</td>
<td>5b (0.014)</td>
<td>B</td>
<td>—</td>
<td>—</td>
<td>0% ± 0%</td>
</tr>
<tr>
<td>7</td>
<td>8b (0.014)</td>
<td>A</td>
<td>MeCN</td>
<td>0.02</td>
<td>0% ± 0%</td>
</tr>
<tr>
<td>8</td>
<td>5b (0.014)</td>
<td>B</td>
<td>DMF</td>
<td>—</td>
<td>0% ± 0%</td>
</tr>
</tbody>
</table>

a Radiochemical conversion. b n = number of reactions. c 600 μL of MeCN. d 300 μL 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. i No Mn Catalyst.
and DMF (300 μL), a drastic improvement was observed, and [18F]3b was obtained in 40% ± 10% RCC (n = 10) (Table 2, entry 5). When the reaction was run at 100 ºC, 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).

The fluorine substitutent is advantageous for 18F-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 ºC in DMF. Difluoromethanamine [18F]3a was the only product observed in the crude reaction mixture (Scheme 4A). Furthermore, an additional competition experiment showed that the iodine(m) 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, alky, aldehyde, ketone, pyridine, triazole, pyrazole, dibenzofuran motifs were all tolerated. The highest RCCs were obtained for electron rich arenes. [18F]3a derived from a boronic acid analogue of fenofibrate was successfully labelled in 23% ± 4% (n = 4). The boronic acid derivative of the COX-II inhibitor ZA140 6a was transformed into the labelled difluoromethylated product [18F]3z in 15% ± 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 RCC of 12% and a molar activity of 3.0 GBq μmol⁻¹ in a total synthesis time of 30 minutes.

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 boronic acids to [18F]ArCF2H. Prior to labelling, the cross-coupling 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/Me2O afforded the precursor required for fluorodecarboxylation. 18F-labelling applying protocol B afforded [18F]11a in 21% ± 6% RCC (n = 3).

**Conclusions**

In summary, a novel method was developed to transform aryl boronic acids to [18F]ArCF2H. Prior to labelling, the cross-coupling 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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References


16. Our attempts to assemble one-pot the aryl boron reagent, ethyl bromofluoroacetate and [18F]fluoride were not fruitful. Details in ESI†.

17. See the ESI†.


23. All radiochemical yields (RCYs) are decay corrected.