Synthesis of 2-fluorobenzoic acids by nucleophilic fluorination of 1-arylbenziodoxolones

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Abstract

We report a facile, transition metal-free synthesis of fluorobenzoic acids by nucleophilic fluorination of readily available 1-arylbenziodoxolones using fluoride salts in polar aprotic solvents. This protocol was applied for the preparation of 2-[18F]-fluoro-5-nitrobenzoic acid, which is a potentially important radioligand for Positron Emission Tomography (PET).

Keywords: Hypervalent compounds, iodine, arylbenziodoxoles, fluorobenzoic acids, radiofluorination

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Introduction

Positron emission tomography (PET) is a powerful nuclear imaging technique that is used to study and visualize human physiology by the detection of positron-emitting radiopharmaceuticals (PET radiotracers).\(^1\) Fluorine-18 is the most commonly used radioisotope in PET because of its favorable physical and nuclear characteristics, such as, a short but manageable half-life (\(t_{1/2} = 109.7\) min), which allows sufficient time for multistep synthetic labeling reactions.\(^2,3\) Nucleophilic \(^{18}\)F-anion is produced with a cyclotron by the nuclear reaction from enriched \(^{18}\)O-water. The \(^{18}\)F-labeling of organic molecules is most commonly performed via nucleophilic substitution reaction using a source of \(^{18}\)F-anion under standard conditions.\(^4-6\)

The introduction of the fluorine-18 radioactive label into a peptide molecule is an important area of PET. Derivatives of fluorobenzoic acid are the most common reagents used for peptide radiolabeling via addition to the lysine amino group in the appropriate peptide fragment.\(^7\) In particular, the \(N\)-succinimidyl derivative of 4-[\(^{18}\)F]fluorobenzoic acid (SFB, 3) represents an important example of the peptide radiolabeling reagent.\(^{1-3}\) SFB 3 is prepared by a multistep reaction sequence starting from 4-formyl-\(N,N,N\)-trimethylbenzenaminium trifluoromethanesulfonate 1 or 4-ethoxycarbonyl-\(N,N,N\)-trimethylbenzenaminium trifluoromethanesulfonate 4 via 4-fluorobenzoic acid 2 (Scheme 1).\(^7-9\)

![Scheme 1. Radiosynthesis of 4-[\(^{18}\)F]fluorobenzoic acid 2 and [\(^{18}\)F]SFB 3.](image)

The overall time of these multistep procedures (Scheme 1) exceeds half-life decay of the \(^{18}\)F-isotope, which is a significant disadvantage of the approaches utilizing quaternary ammonium salts 1 or 4 as starting materials. Carroll and coworkers have demonstrated the possibility of the synthesis of [\(^{18}\)F]-fluorobenzoic acids by nucleophilic fluorination of iodonium salts.\(^10\) However, this method requires the use of an uncommon precursor, \((4-((2,5\text{-dioxopyrrolidin-1-yl})\text{carbonyl})\text{phenyl})\text{(thiophen-2-yl})\text{iodonium trifluoroacetate, which can be obtained by a multistep synthesis in a low overall yield.}\]

In the present paper, we report a convenient and fast procedure for a single-step preparation of 2-fluorobenzoic acids 6 by nucleophilic fluorination of the readily available 1-arylbenziodoxolones 5 (Scheme 2). We have investigated the role of solvent and substituents in compounds 5 on the yields of 2-fluorobenzoic acids 6 and found that the 5-nitro-substituted benziodoxole (5, \(R = \text{NO}_2, \text{Ar} = \text{Mes}\)) is the most efficient precursor to the corresponding 2-fluoro-5-nitrobenzoic acid (89% yield). Furthermore, we have demonstrated
that our protocol can be applied to the preparation of $2-[^{18}\text{F}]$-fluoro-5-nitrobenzoic acid, which is a potentially important PET-tracer for the incorporation of $^{18}\text{F}$ into peptides, proteins or antibodies.

Scheme 2. This work: preparation of 2-fluorobenzoic acids $6$ by nucleophilic fluorination of 1-arylbenziodoxolones $5$.

Results and Discussion

1-Arylbenziodoxolones $5$ were prepared by the previously reported one-pot procedure starting from commercially available substituted iodobenzoic acids.\textsuperscript{11} Previously, we have demonstrated that compounds $5$ can react with the azide anion as a nucleophile producing respective 2-azidobenzoic acids in moderate to high yields.\textsuperscript{11,12} In the present study, we investigated reactions of 1-arylbenziodoxolones $5$ with the fluoride anion in polar aprotic solvents under anhydrous conditions. In the first step of our study, we have checked the effect of the aryl group, Ar, on the reaction of unsubstituted benziodoxoles $7\text{a-c}$ with CsF. We have found that unactivated benziodoxoles $7$ do not react with CsF in dimethylformamide under reflux conditions. Activation of compounds $7$ by addition of trifluoroacetic acid improves reactivity, probably due to protonation leading to the formation of the more reactive noncyclic intermediates $8$. Reaction of the activated reagents with CsF in DMF in the presence of TEMPO (required to suppress radical side reactions) resulted in $70\%$ conversion after $4\ h$ heating at $150\ ^\circ\text{C}$ (Scheme 3). According to GC-MS data, the main product of these reactions was benzoic acid $10$, while the product of nucleophilic fluorination, 2-fluorobenzoic acid $9$, was observed in low yields with the highest yield of $8\%$ in the reaction the mesityl derivative $7\text{c}$. Therefore, reactions of unsubstituted benziodoxoles $7$ are unsuitable for efficient preparation of 2-fluorobenzoic acids because of the low reactivity of the reagents. The yields of the products of nucleophilic fluorination in these reactions are low; however, the use of the more bulky Ar groups leads to noticeable improvement.

Scheme 3. Reactions of unsubstituted benziodoxoles $7\text{a-c}$ with CsF after activation with CF$_3$CO$_2$H.
Our previous study of the reactions of 1-arylbenziodoxolones with the azide anion as a nucleophile has demonstrated that compounds 5 bearing methyl substituent in the benziodoxole ring ortho to the iodine atom have a significantly higher reactivity than unsubstituted benziodoxoles.\textsuperscript{11,12} The dramatic enhancement of reactivity observed in the reactions of 1-aryl-7-methylbenziodoxolones with nucleophiles is explained by steric effect of the bulky methyl substituent on the structure of the reaction intermediate.\textsuperscript{11} At the next step, we have investigated reactions of 7-methyl-substituted 1-arylbenziodoxolones 11 with CsF in DMF without activation by trifluoroacetic acid (Scheme 4). As expected, reagents 11 were more reactive and 100% conversion was achieved without pre-activation by addition of trifluoroacetic acid. However, the yields of the desired fluorobenzoic acid 12 remained low (6-18% after aqueous work-up) and the main product of these reactions was 3-methylbenzoic acid 13. Same as in the reaction of unsubstituted benziodoxoles 7, the use of the more bulky Ar groups resulted in noticeable improvement of the yield up to 18%.

**Scheme 4.** Reactions of 1-aryl-7-methylbenziodoxolones 11a-c with CsF.

Pre-activation of reagents 11 by trifluoroacetic acid via the formation of the more reactive noncyclic intermediates 14 led to further improvement of the yield (Scheme 5). The yield of 2-fluoro-3-methylbenzoic acid 12 in the reaction of 1-mesityl-7-methylbenziodoxolone 11c has reached 78% (\textsuperscript{1}H NMR data); however, the formation of 3-methylbenzoic acid 13 (the product of radical decomposition of benziodoxolones 11) was not completely suppressed under these conditions. Because of the difficult separation of fluorobenzoic acids (9 and 12) from benzoic acids (10 and 13) it was important to find more selective reaction conditions for nucleophilic fluorination.

**Scheme 5.** Reactions of 1-aryl-7-methylbenziodoxolones 11a-c with CsF after activation with CF\textsubscript{3}CO\textsubscript{2}H.
In a search for optimized reaction conditions for the nucleophilic fluorination of 1-mesityl-7-methylbenziodoxolone 11c, we have investigated reactions of different sources of fluoride anions in different solvents. In particular, NMR experiments have demonstrated that the reactions of 11c with tetramethylammonium fluoride in acetonitrile, benzene, toluene, or DMF resulted in low yields (under 23%) of 2-fluoro-3-methylbenzoic acid 12 with 3-methylbenzoic acid 13 as major product. Therefore, we came to a conclusion that 1-mesityl-7-methylbenziodoxolone 11c is not the optimal reagent for selective nucleophilic fluorination that can be utilized in PET.

Previously, we have reported that 5-nitro-substituted 1-arylbenezidoxolones have increased reactivity in reactions with nucleophiles due to the electron-withdrawing effect of the nitro group.\textsuperscript{11} Also, the presence of the highly polar nitro-group suppresses radical decomposition of benziodoxole preventing formation of the non-fluorinated benzoic acids. Therefore, we decided to investigate the reactions of 1-aryl-5-nitrobenziodoxolones 14 with different sources of fluoride anion in different solvents. We have found that the greatest selectivity and highest isolated yields of the products of nucleophilic fluorination could be achieved in the reactions of reagents 14 with CsF in anhydrous DMSO (Scheme 6).

![Scheme 6. Reactions of 1-aryl-5-nitrobenziodoxolones 14a-c with CsF.](image)

These reactions (Scheme 6) selectively afforded 2-fluoro-5-nitrobenzoic acid 16 in excellent preparative yields after aqueous workup. Additional $^{19}\text{F}$ NMR study of this reaction in NMR tube indicated that the interaction of benziodoxole 14 with fluoride anion proceeds via initial formation of diarylidoonium fluoride 15 ($^{19}\text{F}$ NMR signal at -12.96 ppm), which is in agreement with literature data on nucleophilic fluorination of iodonium salts.\textsuperscript{13} The final product 16 can be conveniently separated from iodoarene (ArI) by treatment with NaHCO$_3$ followed by extraction and acidification of the aqueous solution. Therefore, the study using nonradioactive fluoride anion indicates that 1-aryl-5-nitrobenziodoxolones 14 are better substrates than 1-aryl-7-methylbenziodoxolones 11 for the selective nucleophilic fluorination with fluoride anion.

Next, we have investigated the radiofluorination of nitro-substituted benziodoxoles 14 using $^{18}\text{F}$KF•K2.2.2 in the Synthra RN Plus synthesizer (Synthra GmbH, Germany) adapted to the reaction conditions (Scheme 7). We used benziodoxoles 14b and 14c as the precursors based of the high yields of the products of fluorination and high solubility in DMSO and acetonitrile. Nucleophilic $^{18}\text{F}$-anion was produced with a cyclotron from enriched $^{18}\text{O}$-water by the standard $^{18}\text{O}(p,\text{n})$F$^-$ nuclear reaction. The produced $^{18}\text{F}$F$^-$ was eluted by a mixture of solutions of Kriptofix 2.2.2 in acetonitrile and K$_2$CO$_3$ in water for conversion into $^{18}\text{F}$KF•K2.2.2. Solutions of benziodoxoles 14b and 14c in anhydrous acetonitrile or DMSO were added to $^{18}\text{F}$KF•K2.2.2 after azotropic drying. The reaction mixture was heated at 150 °C for 30 min, then cooled, acidified with 0.01 M HCl, and purified using Sep-Pak C18 cartridge washing with water and finally eluting 2-$^{18}\text{F}$-fluoro-5-nitrobenzoic acid 18 with 2 mL of acetonitrile.

We have investigated the influence of solvent, temperature, and reaction time on the isolated radiochemical yield (RCY) of 2-[18F]-fluoro-5-nitrobenzoic acid 18 in the reactions of benziodoxoles 14b and 14c (Scheme 7). We have used the most common solvents for radiofluorination, acetonitrile and DMSO. In order to identify the optimal solvent, we have performed reactions of 14b and 14c in these two solvents under standard conditions (Table 1).

Table 1. Effect of solvent on radiochemical yield\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Radiochemical yield (RCY), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DMSO</td>
</tr>
<tr>
<td>14b</td>
<td>12.4±0.3</td>
</tr>
<tr>
<td>14c</td>
<td>39.0±0.5</td>
</tr>
</tbody>
</table>

\textsuperscript{a} The reaction was carried out using 10 mg of 14b or 14c in solvent (1.0 mL) at 150 °C for 30 min in a closed reaction vessel.

\textsuperscript{b} All statistical data were obtained in three parallel experiments.

The results shown in Table 1 indicate that RCY of 18 was significantly higher in the reaction of precursor 14b when acetonitrile was used as a solvent. Lower yield of 18 in DMSO can be explained by lower solubility of 14b in DMSO compared to acetonitrile. A potentially important factor could be the excessive pressure developed at 150 °C the closed reaction vessel, resulting in even better solubility of benziodoxole 14b. In the case of precursor 14c, the RCY of 18 is practically independent on solvent because of the excellent solubility of the n-butyl derivative 14c in acetonitrile and DMSO.

The effect of temperature on RCY of 2-[18F]-fluoro-5-nitrobenzoic acid 18 was investigated in the range from 80 to 200 °C in acetonitrile (Table 2). The best yields of product 18 were achieved at 150 °C. The lower RCY at 200 °C can be explained by side processes via benzyne intermediates.
Table 2. Effect of temperature on radiochemical yield\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Radiochemical yield (RCY), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80 °C</td>
</tr>
<tr>
<td>\textit{14b}</td>
<td>7.1±0.3</td>
</tr>
<tr>
<td>\textit{14c}</td>
<td>11.8±0.4</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The reaction was carried out using 10 mg of \textit{14b} or \textit{14c} in acetonitrile (1.0 mL) for 30 min in a closed reaction vessel.

\textsuperscript{b}All statistical data were obtained in three parallel experiments.

A study of the reaction time on RCY has demonstrated that 30 min is the optimal time (Table 3). Increased reaction time did not lead to improved yields.

Table 3. Effect of reaction time on radiochemical yield\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Radiochemical yield (RCY), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
</tr>
<tr>
<td>\textit{14b}</td>
<td>8.3±0.2</td>
</tr>
<tr>
<td>\textit{14c}</td>
<td>18.7±0.3</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The reaction was carried out using 10 mg of \textit{14b} or \textit{14c} in acetonitrile (1.0 mL) at 150 °C in a closed reaction vessel.

\textsuperscript{b}All statistical data were obtained in three parallel experiments.

In order to achieve high levels of radiochemical purity (RCP) of product 18, it is required to remove the unreacted [\textsuperscript{18}F]KF•K2.2.2 by washing with no less than 40 mL of water followed by elution of product 18 with 2 mL of acetonitrile. Using smaller volumes of water and acetonitrile results in lower RCP and RCY. In the reaction of precursor \textit{14b}, we observed the presence of two products in the radio-TLC chromatogram (Figure 1). Based on the studies with the non-radioactive fluorine derivatives (Scheme 6), we suggest that the second peak belongs to the intermediate benziodoxole [\textsuperscript{18}F]fluoride 17. The formation of the analogous fluoride intermediates has been reported in the literature on nucleophilic fluorination of iodonium salts.\textsuperscript{13} After purification, RCP of 2-[\textsuperscript{18}F]-fluor-5-nitrobenzoic acid increases from 67% to 75%; however, we were unable to achieve the higher levels of RCP required for PET.
Figure 1. Radio-TLC chromatogram of the radiofluorination products of precursor 14b (CH$_3$CN-H$_2$O, 95:5) after purification. First peak from the left: impurity [$^{18}$F]KF•K2.2.2, second peak: benziodoxole [$^{18}$F]fluoride 17, third peak: 2-[$^{18}$F]-fluoro-5-nitrobenzoic acid 18 (RCP 75%).

In contrast to benziodoxole 14b, the reaction of precursor 14c results in the formation of a single product of radiofluorination. A similar purification of crude product obtained from the reaction of 14c affords 2-[$^{18}$F]-fluoro-5-nitrobenzoic acid 18 with RCP above 98% (Figure 2). Therefore, we have achieved the goal of efficient preparation of a substituted [$^{18}$F]-fluorobenzoic acid, which is a potentially important PET-tracer for the incorporation of $^{18}$F into peptides, proteins, or antibodies.
Figure 2. Radio-TLC chromatogram of the radiofluorination products of precursor 14c (CH$_3$CN-H$_2$O, 95:5) after purification. First peak from the left: impurity [${}^{18}$F]KF•K2.2.2, second peak: 2-[${}^{18}$F]-fluoro-5-nitrobenzoic acid 18 (RCP 98.4%).

Conclusions

In conclusion, we have demonstrated the possibility of using 1-arylbenziodoxoles as efficient precursors for the synthesis of fluorobenzoic acids via nucleophilic fluorination using fluoride salts in polar aprotic solvents. 5-nitro-substituted benziodoxole 14c was found to be an excellent reagent for the radiofluorination leading to [${}^{18}$F]-fluorobenzoic acids in up to 39% radiochemical yield with excellent radiochemical purity above 98%. This protocol under optimized reaction conditions (30 min at 150 °C in acetonitrile) was applied for the preparation of 2-[${}^{18}$F]-fluoro-5-nitrobenzoic acid 18, which is a potentially important radioligand for Positron Emission Tomography (PET).

Experimental Section

General. 2-Iodobenzoic acid, all aromatic precursors, and other reagents and solvents were from commercial sources and used without further purification from freshly opened containers. NMR spectra were recorded at 300, 400 and 500 MHz ($^1$H NMR) and 75, 100, 125 MHz ($^{13}$C NMR) and 376 and 470 MHz ($^{19}$F NMR). Chemical shifts (δ) are reported in parts per million.
General procedure for preparation of 1-arylbenziodoxolones (7a-c, 11a-c). The finely crushed, solid 2-iodobenzoic acid (2.0 mmol) was mixed with powdered Oxone (0.75–0.8 g, 1.2–1.3 mmol) in a 50 mL round-bottom flask and stirred without solvent for 5 min using a magnetic stirrer until a homogeneous reaction mass was formed. Then the reaction mixture was cooled with ice to 5 °C and, under magnetic stirring, and H$_2$SO$_4$ (total 1.6 mL, precooled to 5 °C) was added via syringe by 0.2 mL portions to the center of the reaction mixture. After addition of each portion of H$_2$SO$_4$, the reaction mass was mechanically shaken to achieve better mixing; the color of the resulting mass can vary from pale yellow to brown depending on the intensity of mixing. After all H$_2$SO$_4$ was added, the magnetic stirring was continued for 30 min at room temperature, the mixture was cooled to 5 °C, and CH$_2$Cl$_2$ (3 mL) and ArH (2.0–4.0 mmol) were added. The magnetic stirring of the resulting mixture was continued at 5 °C for 1 h and then at room temperature for 2 h. The reaction mixture was recooled to 5 °C and CH$_2$Cl$_2$ (10mL), and then a saturated aqueous solution of NaHCO$_3$ were added in small portions until pH 8.0. The organic layer was separated, and the aqueous layer was additionally extracted with CH$_2$Cl$_2$ (5 mL). The organic extracts were combined and dried with Na$_2$SO$_4$, the solvent was evaporated, and the crystalline product was dried in vacuum. Additional purification of the products can be performed by crystallization from water.

1-Phenyl-1H-1λ³-benzo[e][1,2]iodoxin-4(3H)-one (7a). The reaction of 2-iodobenzoic acid (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), H$_2$SO$_4$ (total 0.8 mL) and benzene (0.2 mL) according to the general procedure afforded 288 mg (88%) of product 7a monohydrate, isolated as off-white crystals; mp 221–222°C (from water) (lit. mp 221–222 °C). $^1$H NMR (500 MHz, CDCl$_3$): δ = 8.33 (dd, J = 1.5, 2.0 Hz, 1H), 7.96 (dd, J = 1.0, 1.5 Hz, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.69 (t, J = 7.5 Hz, 2H), 7.54 (t, J = 7.5 Hz, 2H), 7.39 (m, 1H), 6.69 (d, J = 8.5 Hz, 1H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 166.8, 137.2, 133.5, 133.4, 132.5, 132.4, 131.7, 130.4, 126.4, 115.7, 115.4 ppm.

1-(Methylphenyl)-1H-1λ³-benzo[e][1,2]iodoxin-4(3H)-one (7b). The reaction of 2-iodobenzoic acid (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), H$_2$SO$_4$ (total 0.8 mL), and toluene (0.2 mL) according to the general procedure afforded 288 mg (81%) of product 7b monohydrate, isolated as off-white crystals: mp 217–219°C (from water) (lit. mp 217–219 °C). $^1$H NMR (CDCl$_3$, 500 MHz): δ = 8.37 (dd, J = 1.5, 7.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 2H), 7.53 (m, 1H), 7.37 (m, 3H), 6.76 (d, J = 8.5 Hz, 1H), 2.50 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ = 166.7, 143.6, 137.2, 133.5, 133.4, 132.7, 132.6, 130.6, 126.1, 115.6, 111.1, 21.8 ppm.

1,2,4,6-Trimethylphenyl-1H-1λ³-benzo[e][1,2]iodoxin-4(3H)-one (7c). The reaction of 2-iodobenzoic acid (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), H$_2$SO$_4$ (total 0.8 mL), and 1,3,5-trimethylbenzene (0.15 mL, 1.1 mmol) according to the general procedure afforded 300 mg (78%) of product 7c monohydrate, isolated as off-white crystals: mp 223–223.5°C (from water) (lit. mp 213–214 °C). $^1$H NMR (CD$_2$OD, 500 MHz): δ = 8.31 (m, 1 H), 7.66 (m, 1 H), 7.49 (m, 1 H), 7.29 (s, 2H), 6.80 (d, J = 8.5 Hz, 1H), 2.53 (s, 6H), 2.43 (s, 3H) ppm. $^{13}$C NMR (CD$_2$OD, 125 MHz): δ = 170.2, 145.7, 144.9, 135.7, 135.7, 133.5, 133.8, 132.1, 131.0, 127.5, 120.4, 114.3, 26.6, 21.4 ppm.

1-Phenyl-7-methyl-1H-1λ³-benzo[e][1,2]iodoxin-4(3H)-one (11a). The reaction of 2-iodo-3-methylbenzoic acid (262 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), H$_2$SO$_4$ (total 0.8 mL), and benzene (0.4 mL) according to the general procedure afforded 270 mg of product 11a as dark brown solid. Treatment of this solid with activated carbon in boiling water afforded 185 mg (52%) of product 11a monohydrate, isolated as off-white crystals: mp 170–172°C (from water) (lit. mp 170–172 °C). $^1$H NMR (CD$_2$OD, 500 MHz): δ = 8.10 (dd, J = 1.5, 7.5 Hz, 2H), 7.98 (dd, J = 1.5, 7.5 Hz, 1H), 7.68 (t, J = 2.5 Hz, 1H), 7.52 (m, 3H), 7.42 (dd, J = 1.5, 7.5 Hz, 1H), 2.03 (s, 3H) ppm. $^{13}$C NMR (CD$_2$OD, 125 MHz): δ = 171.5, 142.4, 140.7, 137.3, 136.9, 133.3, 132.8, 132.5, 130. 9, 119.6, 118.0, 25.4 ppm.
1-(p-Methylphenyl)-  7-methyl-1H-1λ3-benzo[e][1,2]jiodoxin-4(3H)-one (11b).11 The reaction of 2-iodo-3-methylbenzoic acid (262 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), $H_2SO_4$ (total 0.8 mL), and toluene (0.4 mL) according to the general procedure afforded 258 mg of product 11b as dark brown solid. Treatment of this solid with activated carbon in boiling water afforded 180 mg (51%) of product 11b monohydrate, isolated as off-white crystals. $^1H$ NMR (D$_2$O, 500 MHz): $\delta$ = 7.74 (d, J 8.5 Hz, 2H), 7.65 (d, J 7.5 Hz, 1H), 7.44 (t, J 7.5 Hz, 1H), 7.32 (dd, J 1.5, 7.5 Hz, 1H), 7.19 (d, J 8.5 Hz, 2H), 2.41 (s, 3H), 2.03 (s, 3H) ppm. $^1H$ NMR (CD$_3$OD, 500 MHz): $\delta$ = 7.96 (m, 3H), 7.51 (t, J 7.5 Hz, 1H), 7.41 (m, 1H), 7.34 (m, 2H), 2.43 (s, 3H), 2.04 (s, 3H) ppm.

1-(2,4,6-Trimethylphenyl)-7-methyl-1H-1λ3-benzo[b]jiodo-3(2H)-one (11c).12 The reaction of 2-iodo-3-methylbenzoic acid 7 (314 mg, 1.2 mmol), Oxone (412 mg, 0.67 mmol), $H_2SO_4$ (total 0.85 mL), and 1,3,5-trimethylbenzene (0.2 mL, 1.44 mmol) according to the general procedure afforded 360 mg of product 11c as a dark brown solid. Treatment of this solid with activated carbon in boiling water afforded 282 mg (62%) of 11c, isolated after crystallization from water as off-white crystals: mp 148.5–150.5°C (from water/methanol) (lit.12 mp 148.5–150.5°C). $^1H$ NMR (CD$_3$OD, 500 MHz): $\delta$ = 8.05 (d, J 1.5 Hz, 1H), 7.52 (t, J 7.5 Hz, 1H), 7.41 (d, J 7.5 Hz, 1H), 7.18 (s, 2H), 2.50 (s, 6H), 2.45 (s, 3H), 1.65 (s, 3H) ppm. $^{13}$CNMR (CD$_3$OD, 125 MHz): $\delta$ = 171.2, 145.2, 144.0, 142.1, 140.1, 137.5, 132.1, 131.7, 131.1, 122.6, 118.3, 26.7, 23.5, 21.2 ppm.

General procedure for the synthesis of 5-nitro-1-aryl-1,2-benziodoxol-3(1H)-ones (14a-c).11 Suspension of 5-nitro-2-idosobenzoic acid (309 mg, 1 mmol) in DCM (8 mL) was added to trifluoromethanesulfonic acid (2 equiv., 0.18 mL) at –30 °C. Reaction mixture was stirred for 10 min, then arene (0.3 mL) was added. Magnetic stirring of the resulting mixture was continued overnight at room temperature. Then reaction mixture was washed with water (3x5 mL). The organic layer was separated, the organic extracts were combined, dried with Na$_2$SO$_4$, the solvent was evaporated, and the crystalline product was dried in vacuo. Additional purification of products 14a,b can be performed by crystallization from water.

5-Nitro-1-(4-methylphenyl)-1,2-benziodoxol-3(1H)-one (14a).11 The reaction of 5-nitro-2-idosobenzoic acid 310 mg, 1.0 mmol), triflic acid (0.18 mL), toluene (0.3 mL) according to the general procedure afforded 214 mg (56%) of product 14a, isolated as white crystals; mp 213-215°C; $^1H$ NMR (300 MHz, CDCl$_3$): $\delta$ 8.99 (s, J 2.7 Hz, 1H), 8.13 (dd, J 2.7, 9.0 Hz, 1H), 7.93 (d, J 8.1 Hz, 2H), 7.43 (d, J 7.8 Hz, 2H), 6.95 (d, J 9.0 Hz, 1H), 2.54 (s, 3H) ppm. $^{13}$CNMR (75 MHz, CDCl$_3$/CD$_3$OD, 2:1): $\delta$ = 165.8, 150.0, 144.4, 136.8, 135.4, 133.0, 128.4, 127.4, 126.4, 121.0, 110.3, 21.4 ppm.

5-Nitro-1-(2,4,6-trimethylphenyl)-1,2-benziodoxol-3(1H)-one (14b).11 The reaction of 5-nitro-2-idosobenzoic acid 309 mg, 1.0 mmol), triflic acid (0.18 mL), n-butylbenzene (0.3 mL) according to the general procedure afforded 312 mg (76%) of product 14b, isolated as white crystals; mp 227–228°C (lit. mp 227–228°C). $^1H$ NMR (300 MHz, CDCl$_3$/CD$_3$OD, 2:1): $\delta$ = 9.02 (d, J 2.7 Hz, 1H), 8.25 (dd, J 2.7, 8.7 Hz, 1H), 7.27 (s, 2H), 6.97 (d, J 8.7 Hz, 1H), 2.54 (s, 6H), 2.44 (s, 3H) ppm.$^{13}$CNMR (100 MHz, CDCl$_3$/CD$_3$OD, 2:1): $\delta$ = 167.2, 151.0, 145.4, 144.1, 137.2, 130.9, 130.7, 128.6, 127.4, 120.0, 120.0, 26.6, 21.5 ppm.

5-Nitro-1-(4-butyl)-1,2-benziodoxol-3(1H)-one (14c).11 The reaction of 5-nitro-2-idosobenzoic acid (309 mg, 1 mol), triflic acid (0.18 mL), 1,3,5-trimethylbenzene (0.15 mL, 1.1 mmol) according to the general procedure afforded 238 mg (56%) of product 14c, isolated as white crystals; mp 215-217 °C. $^1H$ NMR (400 MHz, CDCl$_3$): $\delta$ = 9.01 (d, J 2.8 Hz, 1H), 8.14 (dd, J 1.4, 9.9 Hz, 1H), 7.93 (d, J 8.0 Hz, 2H), 7.44 (d, J 8.0 Hz, 2H), 6.94 (d, J 8.8 Hz, 1H), 2.76 (m, 2H), 1.68 (m, 4H), 1.43 (m, 2H), 0.99 (d, J 7.6 Hz, 3H) ppm. $^{13}$CNMR (100 MHz, CDCl$_3$): $\delta$ = 165.5, 150.2, 149.1, 137.1, 136.1, 132.5, 128.2, 127.3, 126.9, 122.4, 111.9, 35.9, 33.3, 22.6, 14.1 ppm.
General procedure for the reaction of 1-arylbenziodoxolones (7a-c and 11a-c) with CsF.

Method A. 1-Arylbenziodoxolones (7a-c and 11a-c) (0.1 mmol), CH₂Cl₂ (1 mL) and CF₃COOH (100 µL) were placed in a Schlenk flask. The reaction mixture was stirred for 1 min at room temperature and then solvent was evaporated, and the residue was dried under vacuum. To the residue were added CsF (0.3 mmol, 0.1 mmol), TEMPO (0.1 mmol) and dry DMF (500 µL) under argon atmosphere. Reaction mixture was stirred for 20-30 min at 130-150 °C. Then water (3 mL or 5% NaHCO₃) and CH₂Cl₂ (3 mL) were added to the reaction mixture. The organic layer was discarded and to the water layer were added HCl (100 µL, 37%) and CH₂Cl₂ (3 mL). The mixture was shacked for a minute and then the organic layer was separated, dried with Na₂SO₄, the solvent was evaporated and the residue was analyzed by GC-MS and NMR (Figure 3). 2-Fluoro-3-methylbenzoic acid (12):¹⁴ ¹H NMR (500 MHz, CD₃OD): δ = 7.71 (td, J 7.5 Hz, J 1.5 Hz, 1H), 7.41 (t, J 6.0 Hz, 1H), 7.11 (t, J 7.5 Hz, 1H), 2.28 (d, J 2.5 Hz, 3H). ¹⁹F NMR (476 MHz, CD₃OD, CFCl₃ as standard), δ, ppm: -114.82. 3-Methylbenzoic acid (13):¹⁵ ¹H NMR (500 MHz, CD₃OD): δ = 7.83 (s, 1H), 7.80 (dd, J 7.5 Hz, J 1.5 Hz 1H), 7.34 – 7.29 (m, 2H), 2.37 (s, 3H).

![Figure 3](image-url) ¹H NMR spectrum of the reaction of 1-arylbenziodoxolone 11c with CsF (Method A).

Method B. 1-Arylbenziodoxolones (7a-c and 11a-c) (0.1 mmol), TEMPO (0.1 mmol), DMF (500 µL) and TBAF (120 µL of 1M solution in THF, CAS Number 429-41-4, Sigma-Aldrich) were placed in a Schlenk flask under argon atmosphere. The reaction mixture was stirred for 8 min at 90 °C and then cooled to rt and water (3 mL or 5% NaHCO₃) and CH₂Cl₂ (3 mL) were added. The organic layer was discarded and to the water layer were added HCl (100 µL, 37%) and CH₂Cl₂ (3 mL). The mixture was shacked for a minute and then the organic layer...
was separated, dried with Na$_2$SO$_4$, the solvent was evaporated and the residue was analyzed by GC-MS and NMR (Figure 4). **2-Fluoro-3-methylbenzoic acid (12):** $^1$H NMR (500 MHz, CD$_3$OD): δ = 7.71 (td, J 7.5 Hz, J 1.5 Hz, 1H), 7.41 (t, J 6.0 Hz, 1H), 7.11 (t, J 7.5 Hz, 1H), 2.28 (d, J 2.5 Hz, 3H). $^{19}$F NMR (476 MHz, CD$_3$OD, CFCl$_3$ as standard), δ, ppm: -114.82. **3-Methylbenzoic acid (13):** $^1$H NMR (500 MHz, CD$_3$OD): δ = 7.83 (s, 1H), 7.80 (dd, J 7.5 Hz, J 1.5 Hz 1H), 7.34 – 7.29 (m, 2H), 2.37 (s, 3H).

**Figure 4.** $^1$H NMR spectrum of the reaction of 1-arylbenziodoxolone 11c with TBAF (Method B).

**Method C.** 1-Arylbenziodoxolones (7a-c and 11a-c) (0.1 mmol), TEMPO (0.1 mmol), acetonitrile (500 μL) and TBAF (120 μL of 1M solution in THF, CAS Number 429-41-4, Sigma-Aldrich) were placed in a Schlenk flask under argon atmosphere. The reaction mixture was stirred for 8 min at 90 °C and then cooled to rt and water (3 mL or 5% NaHCO$_3$) and CH$_2$Cl$_2$ (3 mL) were added. The organic layer was discarded and to the water layer were added HCl (100 μL, 37%) and CH$_2$Cl$_2$ (3 mL). The mixture was shacked for a minute and then the organic layer was separated, dried with Na$_2$SO$_4$, the solvent was evaporated and the residue was analyzed by GC-MS and NMR (Figure 5). **2-Fluoro-3-methylbenzoic acid (12):** $^1$H NMR (500 MHz, CD$_3$OD): δ = 7.71 (td, J 7.5 Hz, J 1.5 Hz, 1H), 7.41 (t, J 6.0 Hz, 1H), 7.11 (t, J 7.5 Hz, 1H), 2.28 (d, J 2.5 Hz, 3H). $^{19}$F NMR (476 MHz, CD$_3$OD, CFCl$_3$ as standard), δ, ppm: -114.82. **3-Methylbenzoic acid (13):** $^1$H NMR (500 MHz, CD$_3$OD): δ = 7.83 (s, 1H), 7.80 (dd, J 7.5 Hz, J 1.5 Hz 1H), 7.34 – 7.29 (m, 2H), 2.37 (s, 3H).
Figure 5. $^1$H NMR spectrum of the reaction of 1-arylbenziodoxolone 11c with TBAF without TEMPO (Method C).

General procedure for the reaction of 1-arylbenziodoxolones (14a-c) with CsF. CsF (0.3 mmol) was placed in a Schlenk flask and stirred for 6 h at 150 °C. After cooling to rt, 1-arylbenziodoxolones (14a-c) (0.2 mmol) and dry DMSO (500 µL) were added to the flask under argon atmosphere. The reaction mixture was stirred for 15 min at 80 °C and then cooled to rt and water (3 mL or 5% NaHCO$_3$) and CH$_2$Cl$_2$ (3 mL) were added. The organic layer was discarded and to the water layer were added HCl (100 mL, 37%) and CH$_2$Cl$_2$ (3 mL). The mixture was shaken for a minute and then the organic layer was separated, dried with Na$_2$SO$_4$, the solvent was evaporated, and the residue was dried under high vacuum.

2-Fluoro-3-nitrobenzoic acid (16) from 14b. The reaction of 5-nitro-1-(2,4,6-trimethylphenyl)-1,2-benziodoxol-3-(1H)-one 14a (82 mg, 0.2 mmol) and CsF (45 mg, 0.3 mmol) in dry DMSO (500 µL) under argon atmosphere yielded 33 mg (89%) of 14a as white solid; mp 140-142 °C (lit.$^{15}$ mp 144-146 °C). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.96 (dd, $J$ 6.0, 2.8 Hz, 1H), 8.49 (m, 1H), 7.39 (t, $J$ 9.2 Hz, 1H); $^1$H NMR (100 MHz, CDCl$_3$-DMSO-TMS): $\delta$ 8.86 (dd, $J$ 6.6, 2.8 Hz, 1H), 8.38 (dt, $J$ 6.8 Hz, 2.8 Hz, 1H), 7.39 (t, $J$ 9.2 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$-DMSO-TMS): $\delta$ = 164.5 (d, C$_2$, $^1$J$_{C-F}$ = 270.4 Hz), 163.6 (d, COOH, $^3$J$_{C-F}$ = 5.4 Hz), 142.8 (C$_5$), 128.9 (d, C$_4$, $^3$J$_{C-F}$ = 11.0 Hz), 127.7 (d, C$_6$, $^3$J$_{C-F}$ = 2.7 Hz), 118.5 (d, Cl, $^2$J$_{C-F}$ = 11.4 Hz), 117.5 (d, C$_3$, $^2$J$_{C-F}$ = 24.7 Hz). $^{19}$F NMR (CDCl$_3$, 476 MHz): $\delta$ = -97.73 ppm.
General radiochemistry: source, equipment and analytical methods

[18F]-Fluoride was produced in an IBA Cyclon 18/9 cyclotron using the 18O(p,n)18F nuclear reaction. 18O-Enriched water (enrichment grade 98%, 2.2 mL, CMR, Russia) was irradiated with 18 MeV protons. Radiofluorinations were performed on an Synthra RN Plus module system. Kryptofix 2.2.2 (K2.2.2) and acetonitrile were obtained from ABX (Germany). Solid-phase extraction (SPE) cartridges (Sep-Pak QMA Light, Sep-Pak C18) were obtained from Waters (Milford, MA, USA). The QMA cartridge was converted to the carbonate form by treatment with an aqueous solution of 0.5 M K2CO3. Analytical TLC for all radioproducts was performed using a mini Gita starbeta TLC-scanner (Raytest, Germany). Products were analyzed using silica gel plate by the mixed solvents CH3CN-H2O, 95:5 (v/v) and hexane-ethyl acetate, 50:50 (v/v) as mobile phase; sample size: 1 µL, analysis was repeated 3 times.

Radiosynthesis of 2-[18F]fluoro-5-nitrobenzoic acid (18) in CH3CN. The starting substrate aryliodoxole 14b or 14c (10 mg) in MeCN (1 mL) was added to the activated [18F]KF•K2.2.2, prepared as described in the general procedure. The mixture was heated at 80 °C for 30 min in the closed reaction vessel to give the 2-[18F]-fluoro-5-nitrobenzoate salt. Then the reaction mixture was cooled to room temperature, mixed with 8 mL of 0.01 M HCl, and passed through the cartridge Sep-Pak C18 (360 mg) previously activated with 10 mL CH3CN and 10 mL water and purged with inert gas. After passing the reaction mixture, the cartridge was washed with water (4x10 mL). The purified 2-[18F]-fluoro-5-nitrobenzoic acid (18) was eluted from the Sep-Pak C18 using CH3CN (2 mL) into the product vial. RCY of 2-[18F]-fluoro-5-nitrobenzoic acid (18) in case of 14b was 17.1±0.4 and in case of 14c 39.5±0.4 (Figures 1 and 2).

Radiosynthesis of 2-[18F]fluoro-5-nitrobenzoic acid (18) in DMSO. The starting substrate aryliodoxole 14b or 14c (10 mg) in DMSO (1 mL) was added to the activated [18F]KF•K2.2.2, prepared as described in the general procedure. The mixture was heated at 150 °C for 30 min in the closed reaction vessel to give 2-[18F]-fluoro-5-nitrobenzoate. Then the reaction mixture was cooled to room temperature, mixed with 8 mL of 0.01M HCl, and passed through the cartridge Sep-Pak C18 (360 mg) previously activated with 10 mL CH3CN and 10 mL water and purged with inert gas. After passing the reaction mixture, the cartridge was washed with water (4x10 mL). The purified 5-nitro-2-[18F]-fluorobenzoic acid (18) was eluted from the Sep-Pak C18 using CH3CN (2 mL) into the product vial. RCY of 2-[18F]-fluoro-5-nitrobenzoic acid (18) in case of 14b was 12.4±0.3% and in case of 14c 39.5±0.5 (Figures 6 and 7).
Figure 6. Radio-TLC chromatogram of the radiofluorination products of precursor 14b (CH₃CN-H₂O, 95:5) after purification. First peak from the left: impurity [¹⁸F]KF•K₂.₂.₂, second peak: benziodoxole [¹⁸F]fluoride 17, third peak: 2-[¹⁸F]-fluoro-5-nitrobenzoic acid 18 (RCP 67%).
Figure 7. Radio-TLC chromatogram of the radiofluorination products of precursor 14c (CH$_3$CN-H$_2$O, 95:5) after purification. First peak from the left: impurity $[^{18}\text{F}]$KF•K2.2, second peak: 2-$[^{18}\text{F}]$-fluoro-5-nitrobenzoic acid 18 (RCP 98.0%).

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Supplementary Material

Copies of $^1$H and $^{13}$C NMR spectra of products 7a-c, 8, 11a-c, 14a-c and $^1$H and $^{19}$F NMR of 12, 15b, and 16 have been submitted along with the manuscript.

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