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

Anastasia V. Ozerskaya,[a,b] Mariia S. Larkina,[a,c] Ekaterina V. Podrezova,[a] Dmitrii Yu. Svitich,[a] Roza Ya. Yusubova,[a] Viktor V. Zhdankin,[d]* and Mekhman S. Yusubov[a,c]*

[a]*Tomsk Polytechnic University, 634050 Tomsk, Russia*
[b]*Federal Siberian Research Clinical Centre, 660037, Krasnoyarsk, Russia*
[c]*Siberian State Medical University, 634050 Tomsk, Russia*
[d]*Department of Chemistry and Biochemistry, University of Minnesota Duluth, Duluth, MN 55812, USA*
Email: vzhdanki@d.umn.edu, yusubov@tpu.ru

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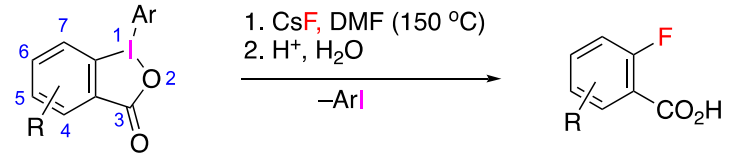
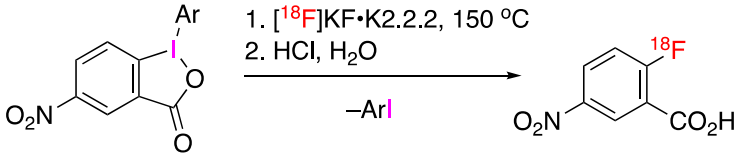
Abstract

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-[^{18}F]-fluoro-5-nitrobenzoic acid, which is a potentially important radioligand for Positron Emission Tomography (PET).



Ar = Ph, 4-$CH_3C_6H_4$, or 2,4,6-C_6H_2
R = H, 7-CH_3, or 5-NO_2



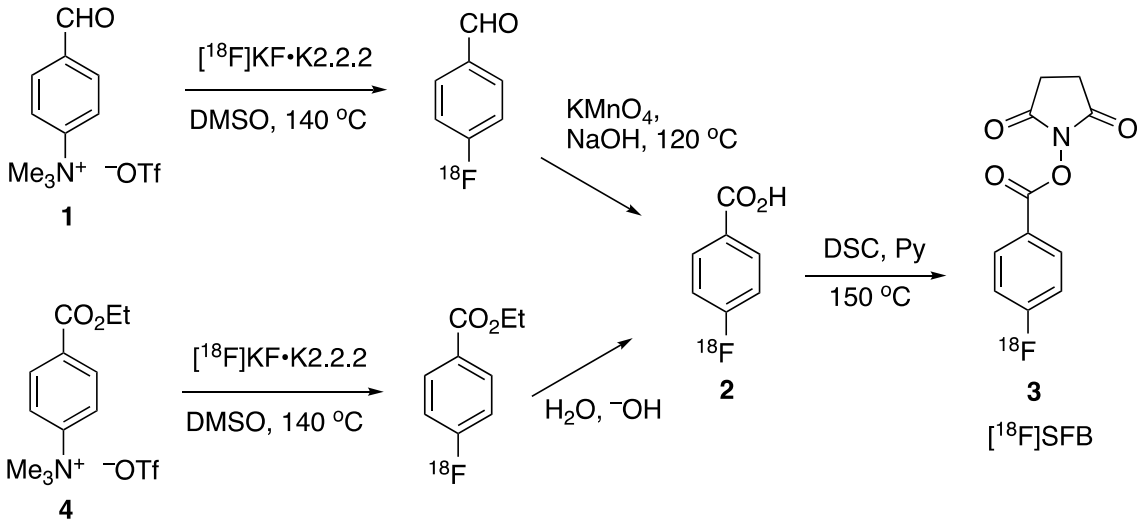
Ar = 4-*n*-BuC_6H_4 RCY 39.5%

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

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. [^{18}F]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]

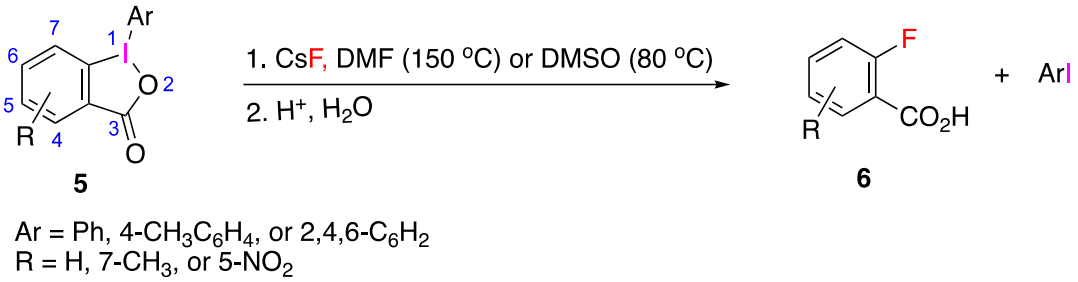


Scheme 1. Radiosynthesis of 4-[^{18}F]fluorobenzoic acid **2** and [^{18}F]SFB **3**.

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-dioxopyrrolidin-1-yloxy)carbonyl)phenyl)(thiophen-2-yl)iodonium trifluoroacetate, which can be obtained by a multistep synthesis in a low overal 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 = NO_2, Ar = 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}F]-fluoro-5-nitrobenzoic acid, which is a potentially important PET-tracer for the incorporation of ^{18}F into peptides, proteins or antibodies.



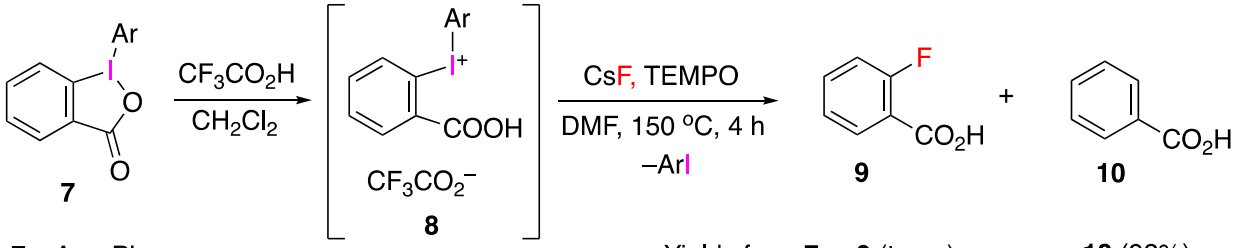
5 **6**

Ar = Ph, 4-$CH_3C_6H_4$, or 2,4,6-C_6H_2
R = H, 7-CH_3, or 5-NO_2

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.[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. [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 **7a-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 supress radical side reactions) resulted in 70% conversion after 4 h heating at 150 °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 **7c**. 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.



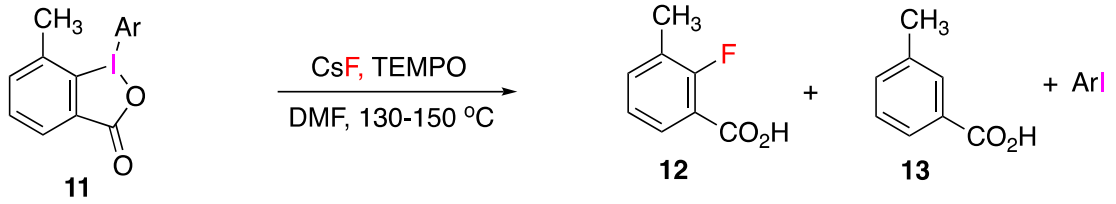
7 **8** **9** **10**

7a, Ar = Ph
7b, Ar = 4-$CH_3C_6H_4$
7c, Ar = 2,4,6-C_6H_2

Yields from **7a**: **9** (trace) **10** (92%)
from **7b**: **9** (5%) **10** (88%)
from **7c**: **9** (8%) **10** (84%)

Scheme 3. Reactions of unsubstituted benziodoxoles **7a-c** with CsF after activation with CF_3CO_2H.

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.[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.[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%.

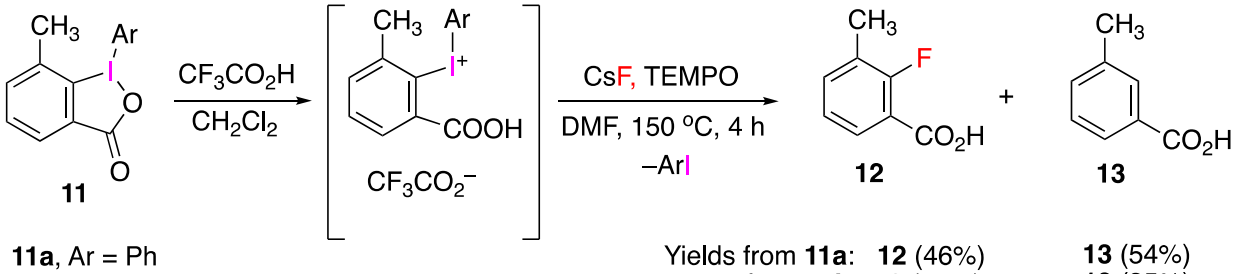


11a, Ar = Ph
11b, Ar = 4-$CH_3C_6H_4$
11c, Ar = 2,4,6-C_6H_2

Yields from **11a**: **12** (6%) **13** (86%)
from **11b**: **12** (10%) **13** (80%)
from **11c**: **12** (18%) **13** (78%)

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-mesytyl-7-methylbenziodoxolone **11c** has reached 78% (^{1}H NMR data); however, the formation of 3-methylbenzoic acid **13** (the product of radical decomposition of benziodoxolones **11**) was not completely supressed 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.



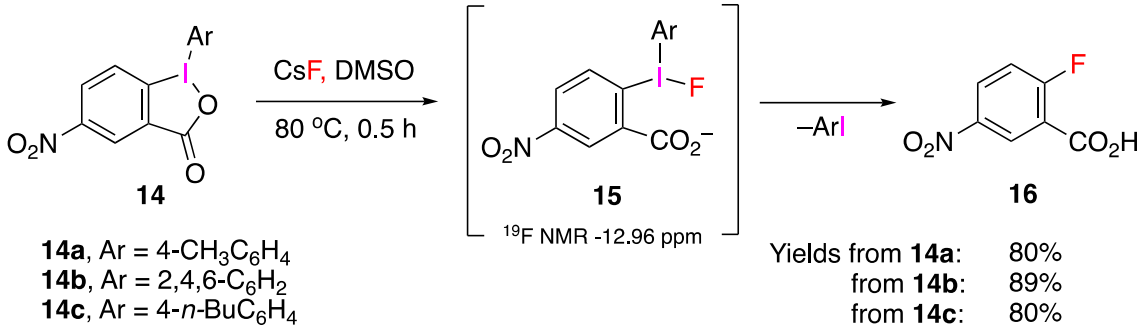
11a, Ar = Ph
11b, Ar = 4-$CH_3C_6H_4$
11c, Ar = 2,4,6-C_6H_2

Yields from **11a**: **12** (46%) **13** (54%)
from **11b**: **12** (65%) **13** (35%)
from **11c**: **12** (78%) **13** (22%)

Scheme 5. Reactions of 1-aryl-7-methylbenziodoxolones **11a-c** with CsF after activation with CF_3CO_2H.

In a search for optimized reaction conditions for the nucleophilic fluorination of 1-mesytyl-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 yelds (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-mesytyl-7-methylbenziodoxolone **11c** is not the optimal reagent for selective nucleophilic fluorination that can be utilized in PET.

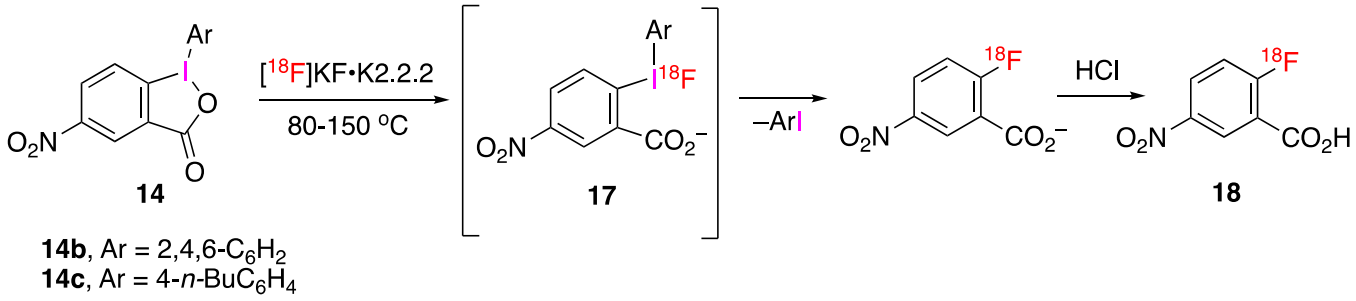
Previously, we have reported that 5-nitro-substituted 1-arylbenziodoxolones have increased reactivity in reactions with nucleophiles due to the electron-withdrawing effect of the nitro group.[11] Also, the presence of the highly polar nitro-group suppresses radical decomposition of benziodoxole preventing 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.

These reactions (Scheme 6) selectively afforded 2-fluoro-5-nitrobenzoic acid **16** in excellent preparative yields after aqueous workup. Additional ^{19}F NMR study of this reaction in NMR tube indicated that the interaction of benziodoxole **14** with fluoride anion proceeds via initial formation of diaryliodonium fluoride **15** (^{19}F NMR signal at -12.96 ppm), which is in agreement with literature data on nucleophilic fluorination of iodonium salts.[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}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}F-anion was produced with a cyclotron from enriched [^{18}O]-water by the standard ^{18}O(p,n)^{18}F nuclear reaction. The produced [^{18}F]F$^-$ was eluted by a mixture of solutions of Kriptofix 2.2.2 in acetonitrile and K_2CO_3 in water for conversion into [^{18}F]KF•K2.2.2. Solutions of benziodoxoles **14b** and **14c** in anhydrous acetonitrile or DMSO were added to [^{18}F]KF•K2.2.2 after azeotropic 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}F]-fluoro-5-nitrobenzoic acid **18** with 2 mL of acetonitrile.



Scheme 7. Radiofluorination of 1-aryl-5-nitrobenziodoxolones **14**.

We have investigated the influence of solvent, temperature, and reaction time on the isolated radiochemical yield (RCY) of 2-[^{18}F]-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[a,b]

Precursor	Radiochemical yield (RCY), %	
	DMSO	Acetonitrile
14b	12.4±0.3	17.1±0.4
14c	39.0±0.5	39.5±0.4

[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.

[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-[^{18}F]-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[a,b]

Precursor	Radiochemical yield (RCY), %			
	80 °C	100 °C	150 °C	200 °C
14b	7.1±0.3	11.3±0.1	17.1±0.4	16.8±0.2
14c	11.8±0.4	24.2±0.1	39.5±0.4	36.5±0.4

[a]The reaction was carried out using 10 mg of **14b** or **14c** in acetonitrile (1.0 mL) for 30 min in a closed reaction vessel.

[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[a,b]

Precursor	Radiochemical yield (RCY), %				
	15 min	20 min	25 min	30 min	45 min
14b	8.3±0.2	13.1±0.3	15.7±0.2	17.1±0.4	16.8±0.3
14c	18.7±0.3	24.0±0.5	31.1±0.4	39.5±0.4	37.4±0.3

[a]The reaction was carried out using 10 mg of **14b** or **14c** in acetonitrile (1.0 mL) at 150 °C in a closed reaction vessel.

[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 [^{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 **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 [^{18}F]fluoride **17**. The formation of the analogous fluoride intermediates has been reported in the literature on nucleophilic fluorination of iodonium salts.[13] After purification, RCP of 2-[^{18}F]-fluoro-5-nitrobenzoic acid increases from 67% to 75%; however, we were unable to achieve the higher levels of RCP required for PET.

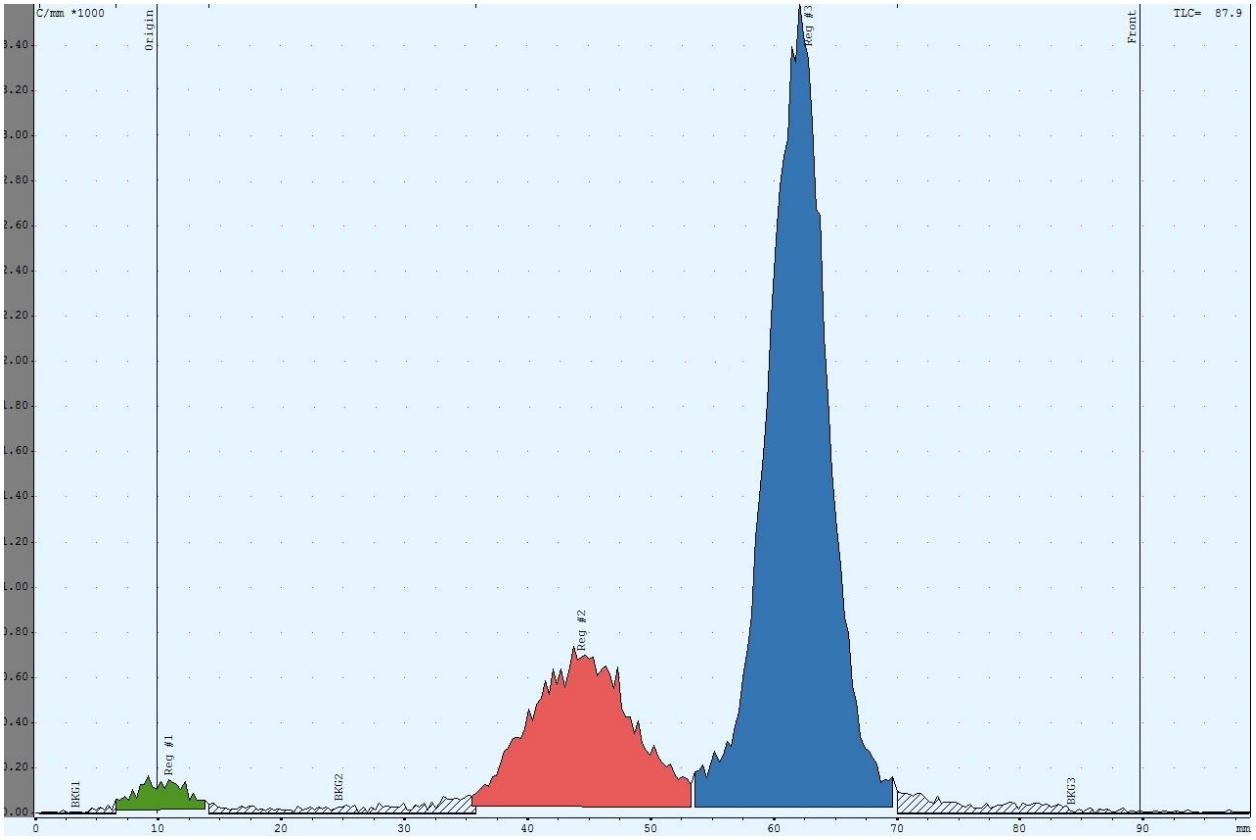


Figure 1. Radio-TLC chromatogram of the radiofluorination products of precursor **14b** (CH_3CN-H_2O, 95:5) after purification. First peak from the left: impurity [^{18}F]KF•K2.2.2, second peak: benziodoxole [^{18}F]fluoride **17**, third peak: 2-[^{18}F]-fluoro-5-nitrobenzoic acid **18** (RCP 75%).

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.

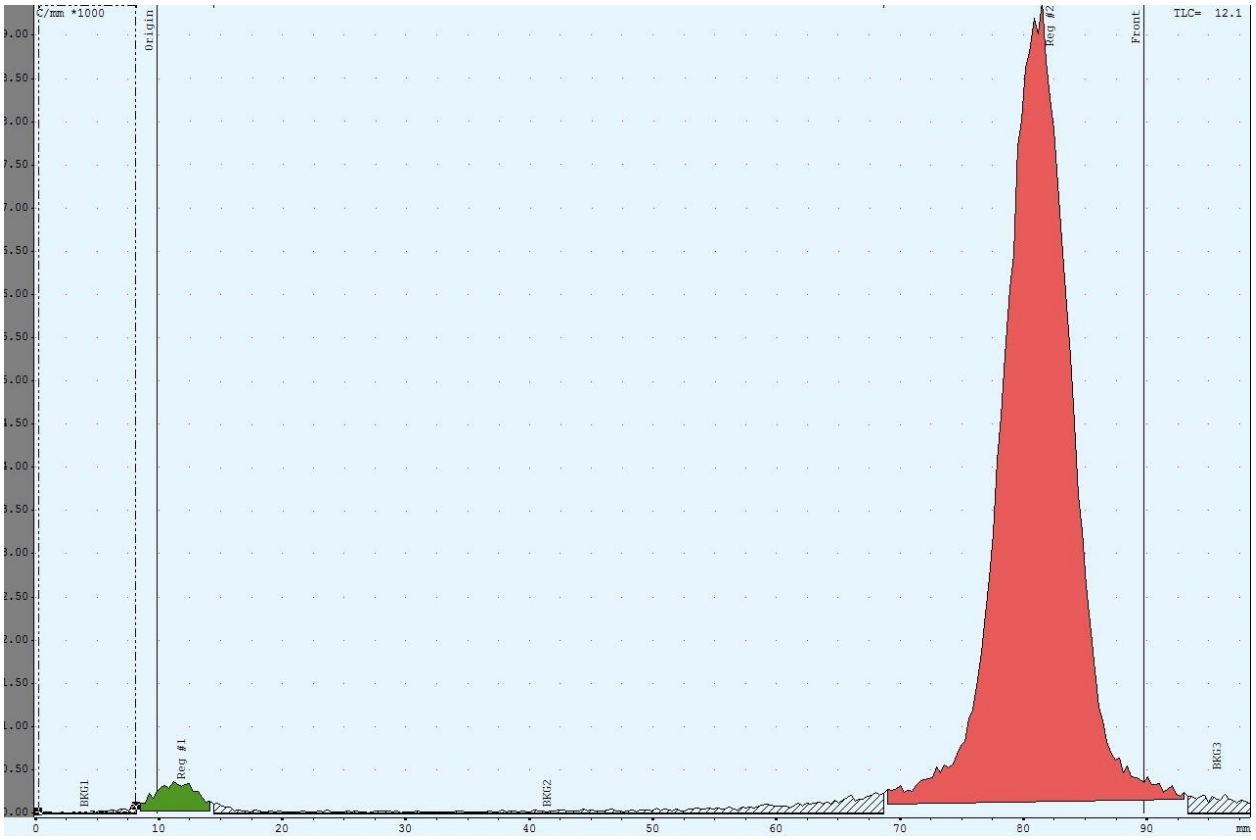


Figure 2. Radio-TLC chromatogram of the radiofluorination products of precursor **14c** (CH_3CN-H_2O, 95:5) after purification. First peak from the left: impurity [^{18}F]KF•K2.2.2, second peak: 2-[^{18}F]-fluoro-5-nitrobenzoic acid **18** (RCP 98.4%).

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 radiofuorination 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 ^{o}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).[11] 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_2SO_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_2SO_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_2SO_4 was added, the magnetic stirring was continued for 30 min at room temperature, the mixture was cooled to 5 °C, and CH_2Cl_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_2Cl_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_2Cl_2 (5 mL). The organic extracts were combined and dried with Na_2SO_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-1*H*-1λ^3-benzo[e][1,2]iodaoxin-4(3H)-one (**7a**):[12] The reaction of 2-iodobenzoic acid (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), H_2SO_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.[12] 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, 1H), 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)-1*H*-1λ^3-benzo[e][1,2]iodaoxin-4(3*H*)-one (**7b**).[12] The reaction of 2-iodobenzoic acid (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), H_2SO_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.[12] 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-1*H*-1λ^3-benzo[e][1,2]iodaoxin-4(3*H*)-one (**7c**).[12] The reaction of 2-iodobenzoic acid (248 mg, 1.0 mmol), Oxone (400 mg, 0.65 mmol), H2SO4 (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.[12] mp 213−214 °C). ^{1}H NMR (CD_3OD, 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_3OD, 125 MHz): δ= 170.2, 145.7, 144.9, 135.7, 135.4, 133.8, 132.1, 131.0, 127.5, 120.4, 114.3, 26.6, 21.4 ppm.

1-Phenyl-7-methyl-1*H*-1λ^3-benzo[e][1,2]iodaoxin-4(*3H*)-one (**11a**).[12] 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 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.[12] mp 170−172°C). ^{1}H NMR (CD_3OD, 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_3OD, 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-1*H*-1λ^3-benzo[e][1,2]iodaoxin-4(3*H*)-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. ^{1}H NMR (D_2O, 500 MHz): δ = 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. ^{1}H NMR (CD_3OD, 500 MHz): δ = 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-1λ^3-benzo[b]iodo-3(2*H*)-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). ^{1}H NMR (CD_3OD, 500 MHz): δ = 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_3OD, 125 MHz): δ= 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-(1*H*)-ones (14a-c).[11] Suspension of 5-nitro-2-iodosobenzoic 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_2SO_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-(1*H*)-one (**14a**).[11] The reaction of 5-nitro-2-iodosobenzoic 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; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.99 (s, J 2.7 Hz, 1 H), 8.13 (dd, J 2.7, 9.0 Hz, 1 H), 7.93 (d, J 8.1 Hz, 2 H), 7.43 (d, J 7.8 Hz, 2 H), 6.95 (d, J 9.0 Hz, 1 H), 2.54 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/CD_3OD, 2:1): δ = 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-(1*H*)-one (**14b**).[11] The reaction of 5-nitro-2-iodosobenzoic 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). ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD, 2:1): δ = 9.02 (d, *J* 2.7 Hz, 1 H), 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, 6 H), 2.44 (s, 3 H) ppm.^{13}C NMR (100 MHz, $CDCl_3$/CD_3OD, 2:1): δ= 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-(1*H*)-one (14c).[11] The reaction of 5-nitro-2-iodosobenzoic acid (309 mg, 1.0 mmol), 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. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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}C NMR (100 MHz, $CDCl_3$): δ= 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), CH_2Cl_2 (1 mL) and CF_3COOH (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% $NaHCO_3$) and CH_2Cl_2 (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 CH_2Cl_2 (3 mL). The mixture was shacked for a minute and then the organic layer was separated, dried with Na_2SO_4, the solvent was evaporated and the residue was analyzed by GC-MS and NMR (Figure 3). **2-Fluoro-3-methylbenzoic acid (12):**[14] ^{1}H NMR (500 MHz, CD_3OD): 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_3OD, $CFCl_3$ as standard), δ, ppm: -114.82. **3-Methylbenzoic acid (13):**[15] ^{1}H NMR (500 MHz, CD_3OD): 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).

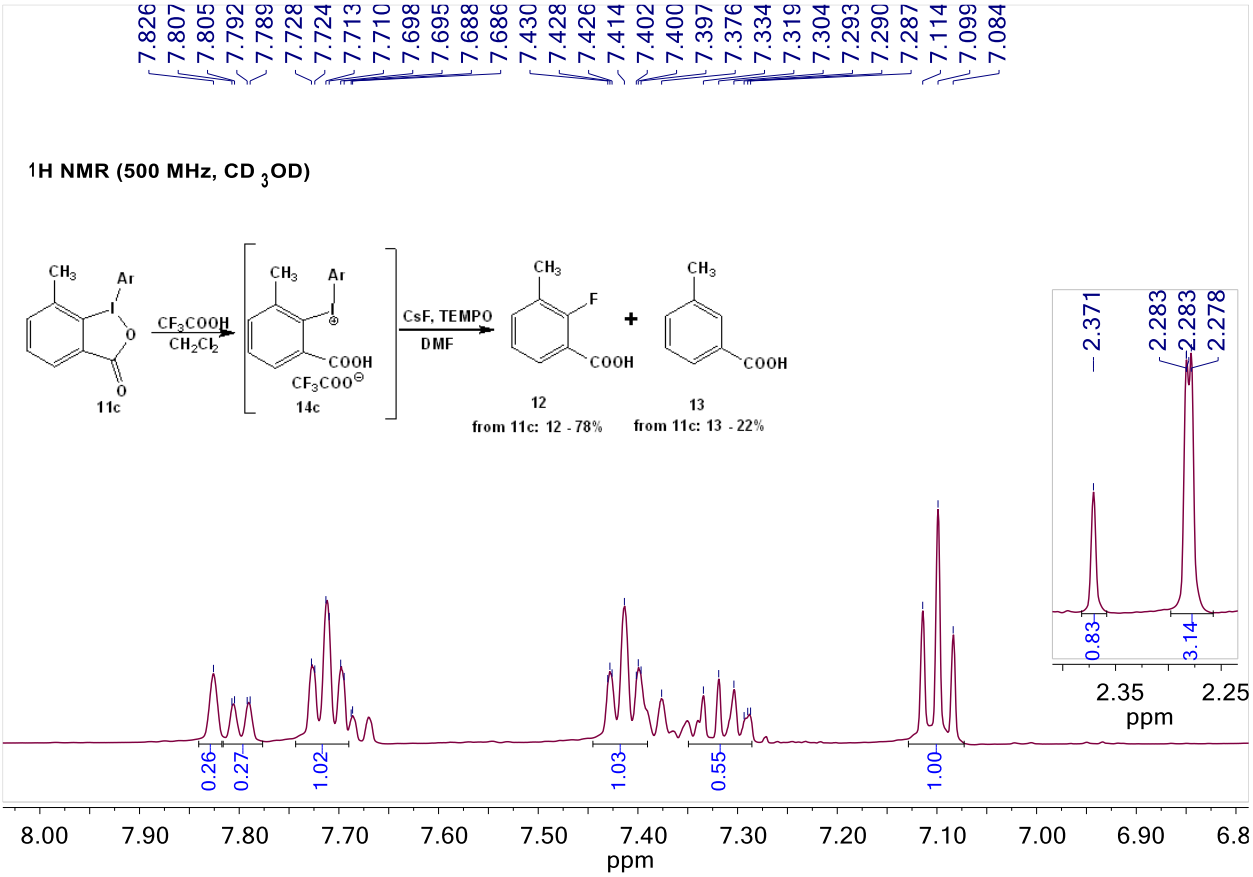


Figure 3. ^{1}H NMR spectrum of the reaction of 1-arylbenziodoxolone **11c** with CsF (Method A).

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% $NaHCO_3$) and CH_2Cl_2 (3 mL) were added. The organic layer was discarded and to the water layer were added HCl (100 μL, 37%) and CH_2Cl_2 (3 mL). The mixture was shacked for a minute and then the organic layer

was separated, dried with Na_2SO_4, the solvent was evaporated and the residue was analyzed by GC-MS and NMR (Figure 4). **2-Fluoro-3-methylbenzoic acid (12):**[14] ^{1}H NMR (500 MHz, CD_3OD): 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_3OD, $CFCl_3$ as standard), δ, ppm: -114.82. **3-Methylbenzoic acid (13):**[15] ^{1}H NMR (500 MHz, CD_3OD): 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).

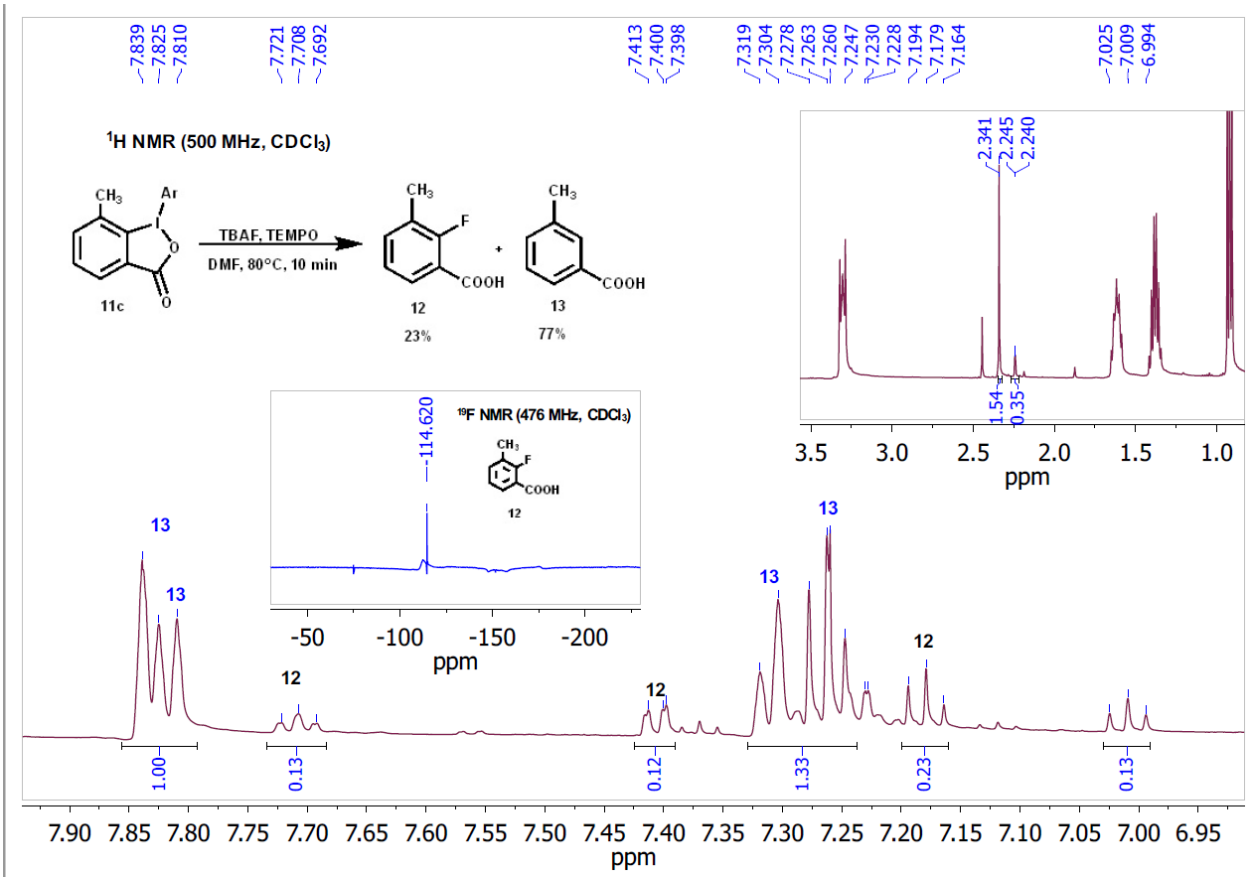


Figure 4. ^{1}H NMR spectrum of the reaction of 1-arylbenziodoxolone **11c** with TBAF (Method B).

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_2Cl_2 (3 mL) were added. The organic layer was discarded and to the water layer were added HCl (100 μL, 37%) and CH_2Cl_2 (3 mL). The mixture was shacked for a minute and then the organic layer was separated, dried with Na_2SO_4, the solvent was evaporated and the residue was analyzed by GC-MS and NMR (Figure 5). **2-Fluoro-3-methylbenzoic acid (12):**[14] ^{1}H NMR (500 MHz, CD_3OD): 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_3OD, $CFCl_3$ as standard), δ, ppm: -114.82. **3-Methylbenzoic acid (13):**[15] ^{1}H NMR (500 MHz, CD_3OD): 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).

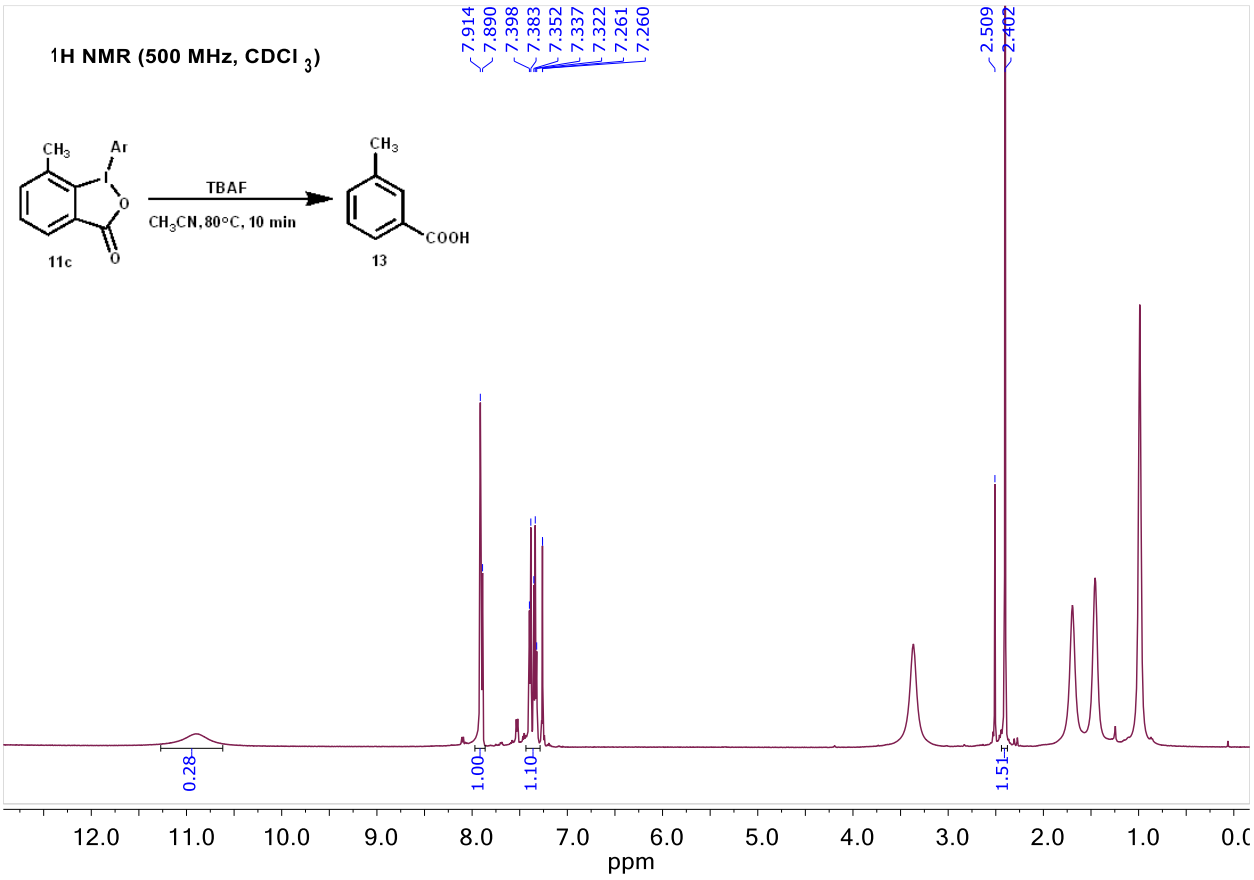


Figure 5. ^{1}H NMR spectrum of the reaction of 1-arylbenziodoxolone **11c** with TBAF without TEMPO (Method C).

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_2Cl_2 (3 mL) were added. The organic layer was discarded and to the water layer were added HCl (100 mL, 37%) and CH_2Cl_2 (3 mL). The mixture was shacked for a minute and then the organic layer was separated, dried with Na_2SO_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.[16] mp 144-146 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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): δ 8.86 (dd, *J* 6.4, 2.8 Hz, 1H), 8.38 (dt, *J* 6.8 Hz, 2,8 Hz, 1H), 7.28 (t, *J* 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$-DMSO-TMS): δ = 164.5(d, C_2, $^{1}J_{C\text{-}F}$ = 270.4 Hz), 163.6 (d, COOH, $^{3}J_{C\text{-}F}$ = 5.4 Hz), 142.8 (C_5), 128.9 (d, C_4, $^{3}J_{C\text{-}F}$ = 11.0 Hz), 127.7 (d, C_6 $^{3}J_{C\text{-}F}$ = 2.7 Hz), 118.5 (d, Ci, $^{2}J_{C\text{-}F}$ = 11.4 Hz), 117.5 (d, C_3, $^{2}J_{C\text{-}F}$ = 24.7Hz). ^{19}F NMR ($CDCl_3$, 476 MHz): δ = -97.73 ppm.

General radiochemistry: source, equipment and analytical methods

[^{18}F]-Fluoride was produced in an IBA Cyclon 18/9 cyclotron using the ^{18}O(p,n)^{18}F nuclear reaction. ^{18}O-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 K_2CO_3. 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 CH_3CN-H_2O, 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-[^{18}F]fluoro-5-nitrobenzoic acid (18) in CH_3CN. The starting substrate aryliodoxole **14b** or **14c** (10 mg) in MeCN (1 mL) was added to the activated [^{18}F]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-[^{18}F]-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 CH_3CN 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-[^{18}F]-fluoro-5-nitrobenzoic acid (**18**) was eluted from the Sep-Pak C18 using CH_3CN (2 mL) into the product vial. RCY of 2-[^{18}F]-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-[^{18}F]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 [^{18}F]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-[^{18}F]-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 CH_3CN 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-[^{18}F]- fluorobenzoic acid (18) was eluted from the Sep-Pak C18 using CH_3CN (2 mL) into the product vial. RCY of 2-[^{18}F]-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).

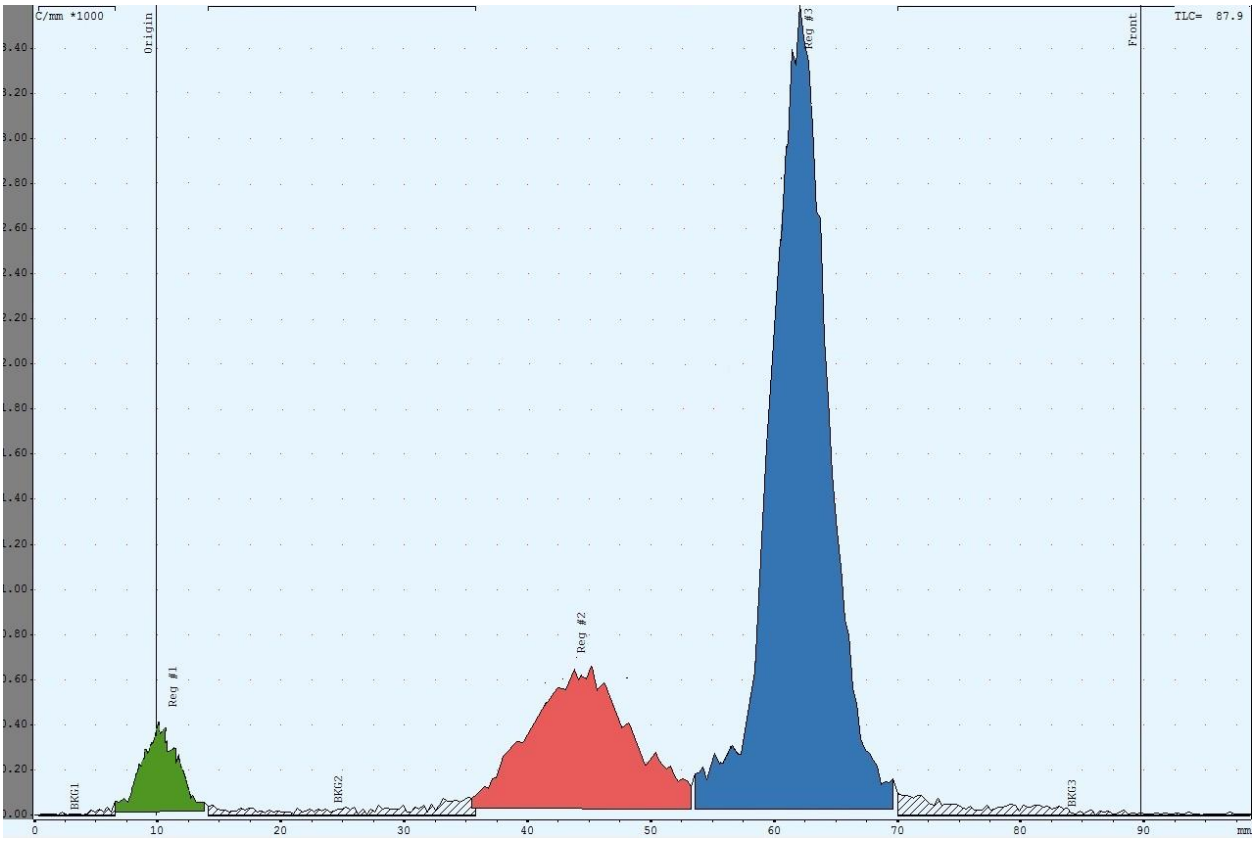


Figure 6. Radio-TLC chromatogram of the radiofluorination products of precursor **14b** (CH_3CN-H_2O, 95:5) after purification. First peak from the left: impurity [^{18}F]KF•K2.2.2, second peak: benziodoxole [^{18}F]fluoride **17**, third peak: 2-[^{18}F]-fluoro-5-nitrobenzoic acid **18** (RCP 67%).

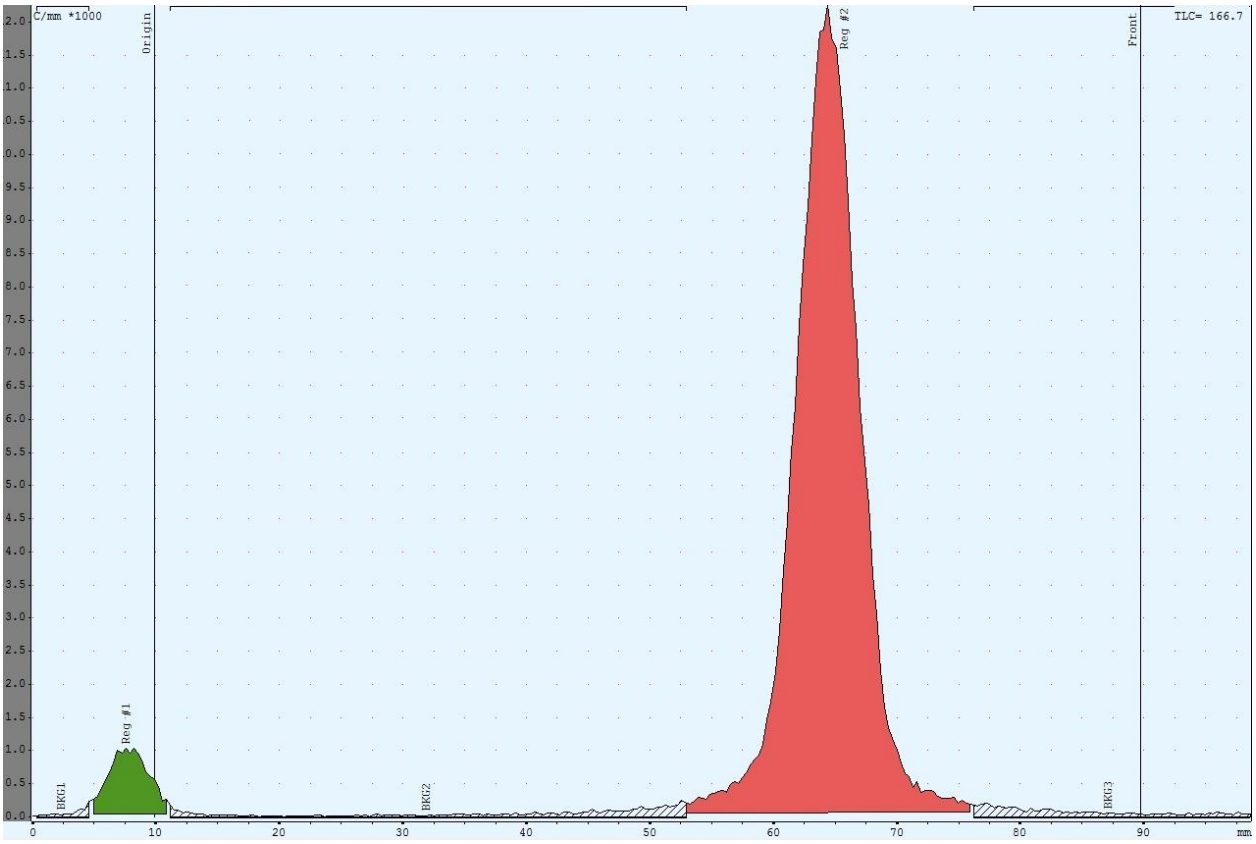


Figure 7. Radio-TLC chromatogram of the radiofluorination products of precursor **14c** (CH_3CN-H_2O, 95:5) after purification. First peak from the left: impurity [^{18}F]KF•K2.2.2, second peak: 2-[^{18}F]-fluoro-5-nitrobenzoic acid **18** (RCP 98.0%).

Acknowledgements

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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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