Fast and Easy Drying Method for the Preparation of Activated $^{18}$F]Fluoride Using Polymer Cartridge

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An efficient nucleophilic $^{18}$F]fluorination has been studied to reduce byproducts and preparation time. Instead of conventional aqueous solution of K$_2$CO$_3$-K$_{222}$, several organic solution containing inert organic salts were used to release $^{18}$F]fluoride ion and anion bases captured in the polymer cartridge, concluding that methanol solution is the best choice. Comparing to azeotropic drying process, one min was sufficient to remove methanol completely, resulting in about 10% radioactivity saving by reducing drying time. The polymer cartridge, Chromafix® (PS-HCO$_3$) was pretreated with several anion bases to displace pre-loaded bicarbonate base. Phosphate bases showed better results than carbonate bases in terms of lower basicity. tert-Butanol solvent used as a reaction media played another critical role in nucleophilic $^{18}$F]fluorination by suppressing eliminated side product. Consequent $^{18}$F]fluorination under the present condition afforded fast preparation of reaction solution and high radiochemical yields (98% radio-TLC, 84% RCY) with 94% of precursor remained.

Key Words: $^{18}$F]Fluoride, Nucleophilic fluorination, Drying method, PET, Polymer cartridge

Introduction

Positron emission tomography (PET) is an emerging technology in the molecular imaging area because it enables biological dysfunction at a specific region of interest to be quantitatively visible, and thereby rendering reliable diagnosis of early stage diseases.1 Of numerous positron emitters, fluorine-18 is predominant in the field of PET reflecting several favorable properties such as low positron energy, ease of large scale production,2 and manageable half-life of 110 min. Proton irradiation to O-18 enriched water produces no-carrier-added $^{18}$F]fluoride with high specific activity in a highly diluted $^{18}$O]H$_2$O solution. To purify $^{18}$F]fluoride from the aqueous solution and metal impurities, solid-phase extraction (SPE) method is employed frequently with QMA (filled with quaternary ammonium chloride polymer) or Chromafix® (PS-HCO$_3$) filled with quaternary ammonium bicarbonate polymer cartridge in an anion exchange manner.3 The $^{18}$F]fluoride trapped in the cartridge is released by eluting an aqueous acetonitrile solution of kryptofix2.2.2 (K$_{222}$) and alkali metal base salt,4 in which K$_2$CO$_3$ is the most common alkali metal base in use. As a result, the eluted $^{18}$F]fluoride solution comprises a large amount of water and excess K$_2$CO$_3$ compared to a small quantity of $^{18}$F]fluoride. To obtain sufficient nucleophilicity of $^{18}$F]fluoride, water is usually then removed by an iterative azeotropic evaporation with acetonitrile solvent 3 - 5 times. Usually, this drying procedure takes 10 - 20 min, which correlates to 6 - 12% loss of radioactivity of $^{18}$F]fluoride. Although excess K$_2$CO$_3$ in the $^{18}$F]fluoride solution maintains the nucleophilicity of $^{18}$F]fluoride, it allows numerous side reactions to occur, thereby diminishing the radiochemical yield (RCY) and purity (RCP).4 Moreover, this basic environment requires the use of a large amount of precursor to compensate for side reactions. In addition, K$_{222}$ is a highly effective and expensive phase transfer catalyst.4 Unfortunately, it activates K$_2$CO$_3$ as well as $^{18}$F]fluoride, resulting in fast decomposition of the precursor.

After the typical preparation of 2-$^{18}$F]fluoro-deoxy-D-glucose ([F]FDG), radiochemists have encountered such practical disadvantages when applying this method to other $^{18}$F] radionuclide as well. In an attempt to address these problems, a pioneering investigation by Kilbourn, M. R. and coworkers demonstrated that $^{18}$F]fluoride ion can be recovered from target water by passage through a small column of microporous polymer impregnated with a lipophilic cryptand or quaternary ammonium salt, followed by elution with a small volume of acetonitrile or other organic solvent.5 Recently, this concept was revisited and advanced somewhat by using a longer alkyl chain ammonium salt.6

This paper furthers these investigations and describes a feasible solution to the inherent problems of conventional nucleophilic $^{18}$F]fluorination, i.e. excess K$_{222}$, alkali metal base and large amount of water in $^{18}$F]fluoride solution prepared after elution with aqueous K$_2$CO$_3$-K$_{222}$ solution. It should be noted that after presentation of our results at the 17th International Symposium on Radiopharmaceutical Science in 2007 (17th ISRS in Aachen, Germany),7 this issue has been a matter of interest.8

Figure 1 illustrates our method for efficient and fast preparation of the reaction solution comprising activated $^{18}$F]fluoride ion using an organic solution and SPE cartridge pretreated with several anionic bases. This approach consists of three points.1) For an efficient release of $^{18}$F]fluoride trapped on SPE polymer cartridge and improved faster drying time, conventional aqueous solution of K$_2$CO$_3$-K$_{222}$ would be substituted...
with volatile organic solutions containing chemically-inert quaternary ammonium salts, which would act as good phase transfer catalysts in place of K$_{222}$.

2) For less basic and milder [F]fluorination condition, conventional bicarbonate or carbonate base in SPE cartridge would be altered with several anion bases before trapping [F]fluoride.

3) For suppression of eliminated side product, tert-alcohol solvent would be used as a reaction media instead of common aprotic solvents according to our previous result.

**Experimental Section**

**General Method.** Reagents were purchased from Aldrich Company and anhydrous solvents were purchased from either Aldrich or Burdick & Jackson Company. Visualization of radioactivity on TLC was monitored by AR-2000 TLC Imaging Scanner (Bioscan, Washington DC, USA) and visualization of organic compounds on TLC was monitored by UV light. HPLC analysis for determining RCY was performed with Thermo Separation Products (pump: SpectraSYSTEM P4000, UV: SpectraSYSTEM UV3000). Analysis of mass trace and standard compounds was performed with Gilson HPLC system. [F]Fluoride was produced by the $^{18}$O(p,n)$^{18}$F reaction on [18O]water using cyclotron (IBA Cyclone 18/9, Belgium). $^1$H and $^{13}$C NMR spectra were obtained on a Varian Gemini-200 and chemical shifts were reported in δ unit (ppm) relative to tetramethylsilane. QMA cartridge and Chromafix® (PS-HCO$_3$) cartridge (product no. 731876) was purchased from Waters company and ABX company, respectively.

**Individual Procedure of [F]Fluorination of 1 in Table 1.**

**TBAOH (entry 1, Table 1):** [F]Fluoride-containing target water (0.1 mL) was directly transferred to a vial containing TBAOH (40 wt %, 10 μL, 15.4 μmol). Water was removed by azeotropic evaporation with acetonitrile (0.5 mL × 3) at 100°C with gentle stream of N$_2$ over 17 min. Mesylate precursor 1 (5.0 mg, 17.8 μmol) and acetonitrile (0.5 mL) were added to the vial. Reaction was carried out at 100°C for 20 min. Radio-TLC yield was obtained after developing with 40% EtOAc/n-Hx. Reaction mixture was filtered with a membrane filter. Residual activity inside the vial was washed with acetonitrile (0.5 mL × 2) and the wash was filtered. The resultant diluted reaction mixture (0.3 mL) was injected into HPLC (semi-prep RP-C18, 250 mm × 10 mm, 4 mL/min of acetonitrile/H$_2$O (60/40) at 254 nm) to obtain a radiochemical yield (RCY). After overnight stood in a hot cell, the reaction mixture was analyzed by an analytical HPLC (RP-C18, 250 mm × 4.6 mm, 1 mL/min of acetonitrile/H$_2$O (55/45) at 254 nm) for UV mass pattern.

**TBAHCO$_3$ (entry 2, Table 1):** [F]Fluoride trapped in a Chromafix® (PS-HCO$_3$) was released by eluting TBAHCO$_3$ solution (TBAHCO$_3$ (8 μL, 26 μmol) in acetonitrile (0.3 mL) and H$_2$O (0.3 mL)) into a vial. Excess water was removed by azeotropic evaporation with acetonitrile (1 mL × 3) at 100°C with gentle stream of N$_2$ over 17 min. Mesylate precursor 1 (6.0 mg, 21.4 μmol) and acetonitrile (0.5 mL) was added to the vial. The further experiment was performed by the same procedure as above (entry 1, Table 1).

**K$_2$CO$_3$/K$_{222}$ (entry 3, Table 1):** [F]Fluoride trapped in a Chromafix® (PS-HCO$_3$) was released by eluting K$_2$CO$_3$ solution (K$_2$CO$_3$ (12 mg, 86.8 μmol) in H$_2$O (0.3 mL)) into a vial, and K$_{222}$ solution (K$_{222}$ (22 mg, 58.4 μmol) in acetonitrile (0.3 mL)) was added. Excess water was removed by azeotropic evaporation with acetonitrile (1 mL × 3) at 100°C with gentle stream of N$_2$ over 20 min. Mesylate precursor 1 (4.6 mg, 16.4 μmol) and acetonitrile (0.5 mL) was added. The further experiment was performed by the same procedure as above (entry 1, Table 1).

**Cs$_2$CO$_3$/K$_{222}$ (entry 4, Table 1):** [F]Fluoride trapped in a Chromafix® (PS-HCO$_3$) was released by eluting Cs$_2$CO$_3$ solution (Cs$_2$CO$_3$ (12 mg, 36.8 μmol) in H$_2$O (0.3 mL)) into a vial, and K$_{222}$ solution (K$_{222}$ (22 mg, 58.4 μmol) in acetonitrile (0.3 mL)) was added. Excess water was removed by azeotropic evaporation with acetonitrile (1 mL × 3) at 100°C with gentle stream of N$_2$ over 20 min. Mesylate precursor 1 (5.1 mg, 18.2 μmol) and acetonitrile (0.5 mL) was added. Reaction was carried out at 100°C for 20 min. The further experiment was performed by the same procedure as above (entry 1, Table 1).

**[bmim][OTf] (entry 5, Table 1):** A Chromafix® cartridge containing [F]fluoride was washed with anhydrous methanol (2 mL), and then eluted with 0.2 M [bmim][OTf] solution in methanol (0.5 mL, 29 mg (101 μmol) of [bmim][OTf]) into a vial. The methanol solution was stirred and heated at 100°C with gentle stream of N$_2$ until methanol solvent was removed entirely. Mesylate precursor 1 (5.0 mg, 17.8 μmol) and acetonitrile (0.5 mL) were added to the reaction vessel (2 min was sufficient for the preparation of the reaction solution after releasing [F]fluoride). The further experiment was performed by the same procedure as above (entry 1, Table 1).

**Individual procedure of [F]Fluorination of 1 in Table 2.**

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**Figure 1.** Conventional method vs our method.
A preliminary study was carried out to determine how much base exists in the SPE cartridge. For this study, both anions pre-loaded in QMA and Chromafix® (PS-HCO₃⁻) cartridge were displaced with bicarbonate ion by eluting 20 mL of 0.4 M NaHCO₃ aqueous solution and 5 mL of distilled water. The quantities of bicarbonate ion in cartridges were measured by acid-base titration with 0.01 M HCl aqueous solution after releasing them with 0.2 M NaCl solution (20 mL). Both were found to contain 13.2 ± 0.5 μmol (n = 2, for QMA) and 31.0 ± 0.1 μmol (n = 2, for Chromafix® (PS-HCO₃⁻)) of bicarbonate anion. Elemental analysis of the packing polymer in Chromafix® (PS-HCO₃⁻) exhibited 42 μmol of bicarbonate on the basis of nitrogen content (see supplementary materials). The quantities of bicarbonate base in both cartridges were considered to be sufficient to maintain the nucleophilicity of [¹⁸F]fluoride with no need of additional base. For further study, we used Chromafix® (PS-HCO₃⁻) cartridge.

A series of inert ionic solutions in various organic solvents were prepared to release [¹⁸F]fluoride trapped in the cartridge. We chose two ionic compounds, tetrabutylammonium methanesulfonate (TBAOMs) and 1-ethyl-3-methylimidazolium triflate ([bmim][OTf]),. Aqueous solutions of 0.2 M TBAOMs and [bmim][OTf] were almost neutral with pH 7.8 and 6.4, respectively.

In the first stage, we tried to elute [¹⁸F]fluoride existing in the Chromafix® (PS-HCO₃⁻) cartridge with TBAOMs or [bmim][OTf] solution in protic (H₂O, MeOH, and tert-butanol) and aprotic (CH₃CN, DMF, and DMSO) solvents, which are all water-miscible. Before elution, the [¹⁸F]fluoride-trapped cartridge was washed with 2.0 mL of the corresponding pure organic solvent as the eluting solution to remove water residue in the cartridge. As illustrated in Figure 2, releasing abilities were determined in terms of counting the radio activity released from the cartridge. The volume vs. activity curves indicate that two protic solutions, water and methanol enable to quantitati-
solution dissolved in various solvents. most bicarbonate base is also eluted along with $[^{18}F]$fluoride less than 0.3 mL volume. It is noteworthy that in both cases, vely release $[^{18}F]$fluorides trapped in the cartridge by eluting in various solvents.

**Figure 2.** Volume vs. released radioactivity from Chromafix® (PS-HCO$_3$) cartridge after elution by (a) TBAOMs and (b) [bmim][OTf] solution dissolved in various solvents.

**Table 1.** $[^{18}F]$Fluorination of 1 by conventional method (entry 1 - 4) vs. new method (entry 5)

<table>
<thead>
<tr>
<th>entry</th>
<th>base or additive$^a$</th>
<th>amount$^b$ (mg)</th>
<th>anion in cartridge</th>
<th>% area of 1$^c$</th>
<th>TLC$^d$ (%)</th>
<th>RCY$^e$ (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>TBAOH</td>
<td>4</td>
<td>-</td>
<td>15</td>
<td>83</td>
<td>66</td>
</tr>
<tr>
<td>2</td>
<td>TBAHCO$_3$</td>
<td>8</td>
<td>HCO$_3^-$</td>
<td>4</td>
<td>96</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>K$_2$CO$<em>3$/K$</em>{222}$</td>
<td>12/22</td>
<td>HCO$_3^-$</td>
<td>7</td>
<td>79</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>Cs$_2$CO$<em>3$/K$</em>{222}$</td>
<td>12/22</td>
<td>HCO$_3^-$</td>
<td>81</td>
<td>88</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>[bmim][OTf]</td>
<td>29</td>
<td>HCO$_3^-$</td>
<td>63</td>
<td>99</td>
<td>70</td>
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</table>

$^a$TBAOH was added directly while the others were eluted through the cartridge. $^b$The numbers indicate the amount of additional base or additives in the eluting solution. $^c$The relative integration of 1 in HPLC at 254 nm. $^d$Radio-TLC yield. $^e$Decay-corrected radioactivity after HPLC purification.

82% and 89% of the activity were released out with 1.0 mL of TBAOMs and [bmim][OTf] solution, respectively. In contrast, the aprotic solutions i.e., acetoniitrile, DMF, and DMSO could not release $[^{18}F]$fluoride at all. The use of methanol eluting solution is therefore quite promising because it takes about 1 min to evaporate methanol solvent. Eventually, the residue consists of $[^{18}F]$TBAF, TBAHCO$_3$, and TBAOMs without any inorganic components when using the methanol solution of TBAOMs.

Our method (entry 5) was evaluated by comparison with four common procedures (entries 1 - 4) as shown in Table 1. Nucleophilic $[^{18}F]$fluorination of a simple primary mesylate precursor 1 (5 mg) was performed for 20 min at 100°C. All reactions were analyzed by radio-TLC and high performance liquid chromatography (HPLC). Some analogues produced during the reaction were identified by HPLC retention time with pre-synthesized plausible byproducts such as 2-naphthol (3), hydroxylated compound 4, carbonate dimer 5, ether dimer 6, and eliminated compound 7 (see supplementary materials). We considered the percentage area of 1 in HPLC as the criterion of reaction mildness and selectiveness. In entry 1, the $[^{18}F]$fluoride cocktail was prepared by combining $[^{18}F]$fluoride aqueous solution and tetra-n-butylamonium hydroxide (TBAOH, 10 µL, 40 wt % in H$_2$O), followed by removing water by iterative azeotropic evaporation with acetoniitrile (0.5 mL × 3). This procedure took about 10 min, resulting in 6% loss of initial radioactivity before reaction. Radio-TLC yield was 83% after reaction for 20 min at 100°C. HPLC analysis, however, showed that only 15% of the precursor remained intact, giving many complicated analogues, including 2-naphthol (3), hydroxylation product 4, small amount of ether dimer 6, elimination product 7, along with several unidentified compounds appeared in small peaks.

Unlike, TBAOH, other experiments in Table 1 (entries 2 - 5) were conducted with Chromafix® (PS-HCO$_3$) cartridge. When TBAHCO$_3$ (entry 2) or K$_2$CO$_3$/K$_{222}$ (entry 3) were used as additional base and eluting solution, 15-20 min was required to dry the resultant aqueous solutions by azeotropic evaporation with acetoniitrile (1 mL × 3), resulting in 9 - 11% loss of radioactivity. HPLC showed that precursor 1 was almost decom-
posed to hydroxylated compound 4 with only 4% and 7% of 1 for entries 2 and 3, respectively. Treatment with Cs$_2$CO$_3$/K$_{222}$ (entry 4) conserved 81% of 1 on HPLC profile, whereas the radiochemical yield (RCY) was unusually low in spite of 88% conversion on radio-TLC. Low yield was most likely because $[^{18}\text{F}]$CsF is not quite soluble in acetonitrile solvent, and K$_{222}$ is ineffective for Cs cation, resulting in the reaction proceeding very slowly, and most $[^{18}\text{F}]$fluoride (91%) remaining unreacted on the reaction vessel. In contrast, our novel method (entry 5) using 0.2 M [bmim][OTf] in methanol as the eluting solution afforded 99% conversion on radio-TLC and 70% RCY (decay-corrected) after HPLC purification. More importantly, it showed simpler HPLC pattern, in which 63% of 1 remained. Moreover, the evaporation of methanol used for releasing the $[^{18}\text{F}]$fluoride trapped in the cartridge was easier and faster than that of aqueous solution used in other experiment (entries 1 - 4). It took only 1 min to remove the methanol completely with no iterative azotropic evaporation. This rapid drying resulted in remarkable saving of radioactivity by reducing the total synthesis time.

Despite the promising result of our new method, the 29 mg of [bmim][OTf] used in entry 5 of Table 1 was too large for the successful HPLC purification. Therefore, 0.2 M of [bmim][OTf] methanol solution was diluted to 0.1, 0.05, and 0.025 M of [bmim][OTf] and TBAOMs in methanol. Releasing ability of these solutions was examined in the same manner as Figure 2 to determine the minimum volume and concentration. Figure 4 indicates that 0.6 mL of 0.05 M solution is sufficient to release almost all $[^{18}\text{F}]$fluoride in both cases. Consequently, the quantities of organic salts could be reduced to almost a quarter in Figure 2.

Further optimization was accomplished using 0.05 M [bmim][OTf] or TBAOMs in methanol (Table 2). The reaction solvent, acetonitrile used in Table 1 was displaced by tert-butanol based on our recent report, which described that tert-alcohol solvents suppress various base-catalyzed side reactions by hydrogen bond formation between the proton of alcohols and the $[^{18}\text{F}]$fluoride or basic anion. The combination of [bmim][OTf] and bicarbonate in tert-butanol showed only 67% radio-TLC yield and 30% RCY (entry 1, Table 2). In contrast, when TBAOMs salt was used instead of [bmim][OTf] (entry 3), radio TLC yield reached 94% and RCY was also increased to be 81%. However, the formation of hydroxylated compound 4 and ether compound 6 was increased yielding only 12% of the precursor (entry 3, Figure 5).

On the next attempt, other anionic bases such as Na$_2$CO$_3$, K$_2$HPO$_4$, and K$_3$PO$_4$ were examined instead of bicarbonate ion. For this study, Chromafix® cartridge was eluted with 0.2 M Na$_2$CO$_3$, K$_2$HPO$_4$ (dibasic), and K$_3$PO$_4$ (tribasic) aqueous solution to displace bicarbonate ion with respective bases before use. Although $[^{18}\text{F}]$fluorination of precursor 1 using carbonate (entry 6) showed better result than that using bicarbonate (entry 1) giving satisfactory radio-TLC yield (99%) and RCY (76%), only 26% of precursor 1 remained with a significant amount of hydroxylated compound 3 and ether 6. Gratifyingly, when using dibasic and tribasic phosphate cartridges (entries 4 and 5), 84% and 94% of precursor 1 still remained along with excellent radio-TLC yields (97% and 98%) and RCYs (92% and 83%). These results are better than the best condition (entry 5) of Table 1 that showed 63% of precursor 1. The use of [bmim][OTf] solution and tribasic phosphate gave a slightly worse result (entry 2), showing 73% of 1 and 76% of radio-TLC. As a result of that, TBAOMs/tert-BuOH combination (entries 3 - 6, Table 2) showed dramatic improvement in radio-

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**Figure 4. Volume vs. released radioactivity from Chromafix® (PS-HCO$_3$) cartridge after elution by (a) TBAOMs and (b) [bmim][OTf] solutions dissolved in MeOH.**

**Table 2. $[^{18}\text{F}]$Fluorination of 1 with various anions in tert-butanol**

<table>
<thead>
<tr>
<th>entry</th>
<th>additive amount$^a$ (mg)</th>
<th>anion in cartridge$^b$</th>
<th>% area of 1 on TLC$^c$ (%)</th>
<th>RCY$^d$ (%)</th>
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<tr>
<td>1</td>
<td>[bmim][OTf] 8.6</td>
<td>HCO$_3^-$</td>
<td>67</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>[bmim][OTf] 8.6</td>
<td>K$_2$PO$_4^-$</td>
<td>73</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>TBAOMs 10</td>
<td>HCO$_3^-$</td>
<td>12</td>
<td>94</td>
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<tr>
<td>4</td>
<td>TBAOMs 10</td>
<td>KHPO$_4^-$</td>
<td>84</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>TBAOMs 10</td>
<td>K$_3$PO$_4^-$</td>
<td>94</td>
<td>83</td>
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<tr>
<td>6</td>
<td>TBAOMs 10</td>
<td>NaCO$_3^-$</td>
<td>26</td>
<td>99</td>
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</table>

$^a$The numbers indicate the amount of each additive. $^b$Anionic base in the cartridge. $^c$Percentage area of 1 in HPLC at 254 nm. $^d$Radio TLC yield. $^e$The decay-corrected radiochemical yield (RCY) after HPLC purification. $^f$Not determined.
TLC yield (94 - 99%) and RCY (76 - 92%) compared with [bmim][OTf] and/or acetonitrile solvent. Moreover, in contrast to carbonate-based anions (HCO₃⁻ and K₂CO₃⁻), phosphate-based anions (KHPO₄⁻ and K₂PO₄⁻) gave a great contribution to reaction mildness, remaining precursor 1 almost intact.

Conclusively, we described a novel [¹⁸F]fluorination method, in which the conventionally-used aqueous solution of K₂CO₃-based anions (KHPO₄ and K₂PO₄) was displaced with methanol solution dissolving inert quaternary ammonium salts such as [bmim][OTf] and TBAOMs. Thereby, 1) drying time was reduced remarkably to 1 min, resulting in about 10% radioactivity saving and 2) subsequent [¹⁸F] fluorination with this mild F-18 solution afforded a high radio-labeling yield with minimum byproducts. When phosphate bases were used instead of carbonate bases, the reaction proceeded more cleanly to give simpler HPLC peaks patterns, retaining a high radio-TLC yield and RCY. In addition, the tert-butanol solvent suppressed the eliminated side product. We expect that our proposed [¹⁸F]fluorination method could be adopted not only for the automated preparation of well-known radiopharmaceuticals, but also applied for the specific research purposes including microfluidic reactor¹³ and HPLC-free purification.

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