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# Efficient alkali iodide promoted $^{18}$F-fluoroethylations with 2-[$^{18}$F]fluoroethyl tosylate and 1-bromo-2-[$^{18}$F]fluoroethane

Andreas Bauman, Markus Piel,* Ralf Schirrmacher and Frank Rösch

*Institute of Nuclear Chemistry, University of Mainz, Fritz-Strassmann-Weg 2, D-55128 Mainz, Germany*

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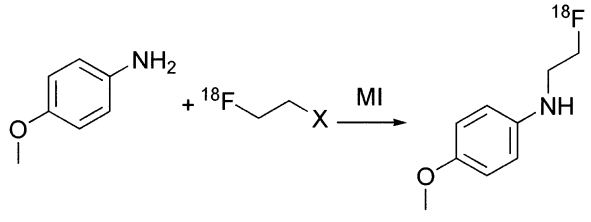
**Abstract**—Radiochemical $^{18}$F-fluorination yields of several compounds using the secondary labelling precursors 2-[$^{18}$F]fluoroethyl tosylate ([$^{18}$F]FETos) and 1-bromo-2-[$^{18}$F]fluoroethane ([$^{18}$F]BFE) could be considerably enhanced by the addition of an alkali iodide. The radiochemical yield of [$^{18}$F]fluoroethyl choline for example could be doubled with [$^{18}$F]BFE and increased from 13% to ≈80% with [$^{18}$F]FETos. By addition of alkali iodide to the precursor, the $^{18}$F-fluoroethylation yields of established radiopharmaceuticals, especially in the case of automated syntheses, could be significantly increased without major changes of the reaction conditions.


The introduction of [$^{18}$F]fluorine into molecules relevant for application in Positron Emission Tomography (PET) can be achieved by several synthetic routes. While the electrophilic method leads to carrier-added products with a maximum radiochemical yield of 50%, the nucleophilic route leads to non-carrier-added products. It has, however, the disadvantage of being negatively affected by acidic protons which are often found in complex molecules or protic solvents. Apart from these two methods, $^{18}$F-labelling can be carried out by $^{18}$F-fluoroalkylation via small prosthetic groups. The most important $^{18}$F-fluoroalkylating agent is 2-[$^{18}$F]fluoroethyl tosylate ([$^{18}$F]FETos), first introduced by Block et al.[1] [$^{18}$F]FETos can be synthesised easily in a reproduceable manner by using HPLC for product separation. In comparison 1-bromo-2-[$^{18}$F]fluoroethane ([$^{18}$F]BFE), synthesised by Chi et al.,[2] is less commonly used because the synthetic route includes a final distillation step which makes the integration into an automated system difficult. Recently, Comagic et al.[3] developed a synthetic route including a solid phase purification of [$^{18}$F]BFE. Molecules comprising hydroxy-, amino- or thio-moieties can be labelled with both precursors. In a recent study the reactivity of [$^{18}$F]BFE could be further raised by addition of NaI to the reaction solution.[4]

The aim of this work was the systematical examination of the alkali iodide promoted $^{18}$F-fluoroethylation using the secondary labelling synthons [$^{18}$F]BFE or [$^{18}$F]FETos in a Finkelstein-type reaction (Scheme 1).

For this purpose we decided to compare the properties of the established agents [$^{18}$F]BFE and [$^{18}$F]FETos with their alkali iodide promoted properties by means of labelling the weakly nucleophilic $NH_2$-function of *p*-anisidine. In the case of this model compound, no radiochemical yields could be obtained while using [$^{18}$F]BFE and [$^{18}$F]FETos with varying reaction conditions such as solvents (MeCN, DMF, DMSO) and reaction times (0–20 min) in the absence of a base.[5] Equimolar amounts of the strong bases NaH or lithium diisopropylamide (LDA) resulted in radiochemical yields of not more than 15% when using [$^{18}$F]FETos/LDA/DMF only.

In order to find the most suitable alkali cation for this reaction, different alkali iodides in increasing concentrations were examined. The Finkelstein-type reactions were carried out by adding 22–143 μmol alkali iodide to




**1** X= Br, OTos; M= Na; K; Cs **2**

**Scheme 1.**

*Keywords*: positron emission tomography; $^{18}$F-fluoroethylation; 2-[$^{18}$F]fluoroethyl tosylate; 1-bromo-2-[$^{18}$F]fluoroethane.
* Corresponding author. Tel.: +49-6131-3926038; fax: +49-6131-3925253; e-mail: piel@mail.kernchemie.uni-mainz.de

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a solution of 17–23 μmol precursor in DMSO (800 μL) and starting the reaction by the addition of 40–50 MBq of the secondary labelling agent in 200 μl DMSO.[6] For *p*-anisidine, the radiochemical yields could be increased to ≈80% under optimised reaction conditions (cf. Tables 1 and 2).

Therefore in contradiction to Zhang et al.[4] our results indicate that the amount of alkali iodide affects the efficiency of the $^{18}$F-fluoroethylation. This discrepancy may be due to the higher reaction temperature Zhang et al. examined which results in a not negligible amount of [$^{18}$F]BFE in the gas phase,[7] which may also change the kinetics of this iodide promoted $^{18}$F-fluoroethylation.

In further experiments phase-transfer catalysts were added to the reaction mixture, in order to complex the cation and to increase the nucleophilicity of the iodide. The commercially available phase-transfer catalysts 18-crown-6 (for sodium) and Kryptofix®2.2.2 (for potassium) were added in equimolar concentrations to the alkali iodide (Table 2), while the other experimental conditions were identical to those described above. No improvements were obtained using the above mentioned 18-crown-6 and Kryptofix®2.2.2. Thus their use is obviously not required.

For proving the dependence of the radiochemical yield on the alkali iodides (LiI, NaI, KI, CsI) used and solvent system, the reactions were carried out under identical conditions (143 mM iodide, 85°C, no base). The order of potency for increasing the radiochemical yield of this reaction was LiI>NaI>KI≫CsI which could possibly be attributed to a decrease of salt-solubility in dipolar aprotic solvents.[8] Therefore DMSO or DMF as solvents led to significantly higher yields than acetonitrile (Table 3). In addition to its slightly higher radiochemical yields compared to NaI, another advantage of LiI is the formation of less by-products, which simplifies the purification of the product via HPLC. Thus further investigations of these Finkelstein-type reactions were carried out with DMSO or DMF as solvents and LiI as alkali iodide.

For proving the general value and feasibility of this approach, three $^{18}$F-radiopharmaceuticals of clinical relevance, namely [$^{18}$F]fluoroethyl-4-piperidyl benzilate ([$^{18}$F]FEtP-4-B), [$^{18}$F]fluoroethyl-4-piperidyl acetate ([$^{18}$F]FEtP-4-A) and [$^{18}$F]fluoroethyl choline ([$^{18}$F]FEtCh) (cf. Table 4) were prepared according to the above reaction conditions.[9–12]

The results of these experiments are shown in Table 5. The labelling of the 4-piperidyl benzilate (**3**) was carried out in DMSO at 120°C.[9,10] In the absence of iodine salts, radiochemical yields were only obtained with [$^{18}$F]FETos (44±1%). By adding LiI to the precursor, the yields of [$^{18}$F]FEtP-4-B (**4**) were significantly increased ([$^{18}$F]BFE/LiI 68±0.6%; [$^{18}$F]FETos/LiI 80±1%).

**Table 1.** $^{18}$F-Fluoroethylation yields (mean±SE, $n=3$) of *p*-anisidine in DMSO ($t=20$ min, $T=85$°C, varying alkali iodide concentration)

| *c*(Iodide) (mM) | Radiochemical yield (%) with | |
|---|---|---|
| | [$^{18}$F]BFE/NaI | [$^{18}$F]BFE/KI |
| 22 | 22±0.7 | 18±1.2 |
| 69 | 35±0.9 | 43±0.6 |
| 143 | 82±0.1 | 73±0.4 |

**Table 2.** $^{18}$F-Fluoroethylation yields (mean±SE, $n=3$) of *p*-anisidine ($t=20$ min, $T=85$°C, varying type of alkali iodide ($c=143$ mM), phase-transfer catalysts and solvents)

| Labelling system | Radiochemical yield (%) in | | |
|---|---|---|---|
| | MeCN | DMF | DMSO |
| [$^{18}$F]BFE/NaI | 57±0.7 | 80±0.3 | 82±0.1 |
| [$^{18}$F]BFE/NaI/18-crown-6 | 31±0.9 | 75±1.2 | 80±0.8 |
| [$^{18}$F]BFE/KI | 43±0.6 | 68±0.3 | 73±0.4 |
| [$^{18}$F]BFE/KI/K2.2.2 | 60±1.1 | 51±1.3 | 76±0.7 |

**Table 3.** $^{18}$F-Fluoroethylation yields (mean±SE, $n=3$) of *p*-anisidine ($t=20$ min, $T=85$°C, varying alkali iodide ($c=143$ mM) and solvents)

| Labelling system | Radiochemical yield (%) in | | |
|---|---|---|---|
| | MeCN | DMF | DMSO |
| [$^{18}$F]BFE/no Iodide | 0 | 0 | 0 |
| [$^{18}$F]BFE/LiI | 64±1.0 | 87±1.7 | 84±1.2 |
| [$^{18}$F]BFE/NaI | 57±0.7 | 80±0.3 | 82±0.1 |
| [$^{18}$F]BFE/KI | 43±0.6 | 68±0.3 | 73±0.4 |
| [$^{18}$F]BFE/CsI | 16±0.4 | 67±0.4 | 78±0.8 |

**Table 4.** $^{18}$F-Labelled compounds with nuclear medicine relevance

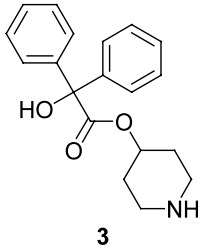
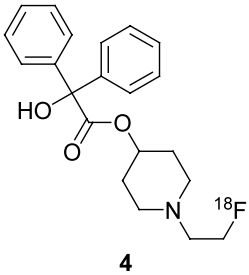
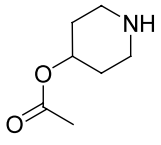
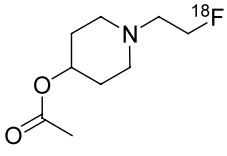
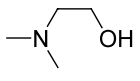
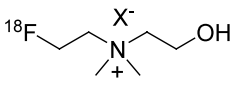
| Starting materials | Product |
|---|---|
|  |  |
| **3** | **4** |
|  |  |
| **5** | **6** |
|  |  |
| **7** | **8** |

**Table 5.** Radiochemical yields (mean±SE, $n=3$) of the $^{18}$F-fluoroethylation of P4B **3**, P4A **5** and *N*,*N*-dimethylethanolamine **7** using different labelling agents

| Radioligand | Radiochemical yield (%) with | | | | | |
|---|---|---|---|---|---|---|
| | [$^{18}$F]BFE[a] | Ref. for [$^{18}$F]BFE[b] | [$^{18}$F]FETos[a] | Ref. for [$^{18}$F]FETos[b] | [$^{18}$F]BFE/LiI[a] | [$^{18}$F]FETos/LiI[a] |
| [$^{18}$F]FEtP-4-B (**4**) | 0 | – | 44±1.0 | 14–24[10] | 68±0.6 | 80±1.0 |
| [$^{18}$F]FEtP-4-A (**6**) | 49±6.8 | 48[11] | 39±2.1 | – | 85±0.5 | 87±2.1 |
| [$^{18}$F]FEtCh (**8**) | 54±0.5 | – | 12±0.8 | 100[12] | 95±0.3 | 82±2.4 |

[a] *Experimental conditions*: $t=20$ min; $T=85$°C; DMSO; c(precursor)=12 mM; (for iodide-catalyzed reactions: c(LiI)=143 mM).
[b] For experimental conditions see references.

Similar results were obtained with 4-piperidyl acetate (**5**). For [$^{18}$F]FETos the moderate yields of 39±2.1% in the absence of iodine salts could be increased to 87±2.1% by adding 143 mM LiI. The use of [$^{18}$F]BFE gave similar yields to those described by Zhang et al. in the absence of iodine salts (49±6.8%),[11] while addition of 143 mM LiI resulted in radiochemical yields of 85±0.5%.

The $^{18}$F-fluoroethylation of *N*,*N*-dimethylethanolamine (**7**) was performed following the procedure of Hara and co-workers.[12] However, it was not possible to reproduce the reported radiochemical yields (100% for [$^{18}$F]FETos). Using 143 mM LiI, radiochemical yields of 82±2.4% ([$^{18}$F]FETos/LiI) or 95±0.3% ([$^{18}$F]BFE/LiI) could be obtained.

In conclusion, we have demonstrated that the addition of alkali iodides to the secondary labelling precursors [$^{18}$F]FETos and [$^{18}$F]BFE leads to increased radiochemical yields for every investigated reaction. This is most probably due to the in situ formation of 2-iodo-1-[$^{18}$F]fluoroethane which is a much stronger fluoroethylating agent. From the alkali iodides examined LiI is the most potent, while producing the smallest amount of by-products. This improvement is especially important in the case of automated syntheses, because by addition of alkali iodides to the precursor it is possible to raise the radiochemical yields without significant changes in the synthesis and in the module used. The extension of this study to other interesting $^{18}$F-radiopharmaceuticals is currently under investigation.

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5. Radiochemical yields were determined by radio-HPLC while using [$^{18}$F]BFE as labelling agent and by radio-TLC (Instant Imager; Packard Canberra) while using [$^{18}$F]FETos.
6. *Synthesis of [$^{18}$F]BFE*: To an aqueous [$^{18}$F]fluoride solution ($\approx$ 400 MBq) were added Kryptofix®2.2.2. (10 mg, 25 μmol), potassium carbonate (1N, 12.5 μl) and 1 mL acetonitrile. The mixture was dried in a stream of nitrogen at 80°C and this drying procedure was repeated three times. To the dried Kryptofix®2.2.2./[$^{18}$F]fluoride complex 6 mg 1,2-dibromoethane in 1 mL acetonitrile was added and the mixture was stirred for 3 min at a reaction temperature of 80°C. The mixture was diluted with 20 ml of water and passed through a LiChrolute®EN-cartridge. The fixed product was eluted with DMF, DMSO or MeCN (1.2 mL) and immediately passed through an Alumina®B-cartridge into receiving flask. The whole preparation time was about 25 min and the overall radiochemical yield was between 50 and 60%.
   *Synthesis of [$^{18}$F]FETos*: To a dried Kryptofix®2.2.2./[$^{18}$F]fluoride complex, which was prepared as described above, 4 mg ethyleneglycol-1,2-ditosylate in 1 mL acetonitrile was added and heated under stirring in a sealed vial for 3 min. Purification of the crude product was accomplished using HPLC (Lichrosphere RP18-EC5, 250×10 mm, acetonitrile/water 50:50, flow rate: 5 mL/min, $t_R$: 8 min). After diluting the HPLC fraction containing the 2-[$^{18}$F]fluoroethyl tosylate with water the product was loaded on a C18-Sepac cartridge, dried with a nitrogen stream and eluted with 1.2 mL of DMF, DMSO or MeCN. The whole preparation time was about 40 min and the overall radiochemical yield was between 60 and 80%.
7. In previous experiments (data not shown) we examined the temperature-dependent behaviour of [$^{18}$F]BFE. While at reaction temperatures of 85°C the amount of [$^{18}$F]BFE (bp 73°C) in the gas phase is negligible, about 15–20% of the [$^{18}$F]BFE were found in the gas phase at temperatures of 100°C.

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