Efficient alkali iodide promoted ^{18}F-fluoroethylations with 2-[^{18}F]fluoroethyltosylate and 1-bromo-2-[^{18}F]fluoroethane

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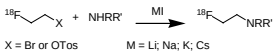
The introduction of [^{18}F]fluorine into molecules relevant for application in Positron Emission Tomography (PET) can be achieved by several synthetic routes. While the electrophilic method leads to carrier-added products with a maximum radiochemical yield of 50%, the nucleophilic route leads to non-carrier-added 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. Among these synthons, ^{18}F-fluoroethylation is most widely employed. The most important ^{18}F-fluoroethylating agent is 2-[^{18}F]fluoroethyltosylate ([^{18}F]FETos), first introduced by Block *et al.*[1] [^{18}F]FETos can be synthesized easily in a reproduceable manner using HPLC for product separation. In comparison, 1-bromo-2-[^{18}F]fluoroethane ([^{18}F]BFE), synthesized 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.* 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.[3] In a recent study the reactivity of [^{18}F]BFE could be further raised by addition of NaI.[4]

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

Here the established synthons [^{18}F]BFE and [^{18}F]FETos were compared concerning 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 or [^{18}F]FETos. In order to find the most suitable alkali cation for the Finkelstein-type reaction, different alkali iodides in mounting concentrations were examined in different solvents (DMSO, DMF, MeCN).The order of potency for increasing the radiochemical yield of this reaction was LiI > NaI > KI >> CsI. Further, DMSO or DMF as solvents led to significantly higher yields than acetonitrile. For *p*-anisidine, the radiochemical yields could be increased to ≈ 80% under optimised reaction conditions.[5]



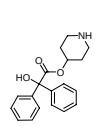
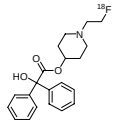
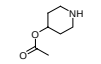
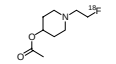
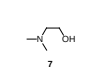
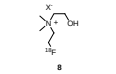
Scheme 1.

For proving the general value and feasibility of this approach, three ^{18}F-radiopharmaceuticals of clinical relevance, namely [^{18}F]fluoroethyl-piperidyl-4 benzilate ([^{18}F]FEtP-4-B), [^{18}F]fluoroethyl-piperidyl-4 acetate ([^{18}F]FEtP-4-A) and [^{18}F]fluoroethyl-cholin ([^{18}F]FEtCh) (*cf.* Table 1) were prepared according to the above mentioned reaction conditions.[6-9]

The results are shown in Table 2. Labelling of the 4-piperidyl benzilate **3** was carried out in DMSO at 120 °C.[6,7] 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**) significantly increased ([^{18}F]BFE/LiI 68 ± 0.6%; [^{18}F]FETos/LiI 80 ± 1%).

Similar results were obtained with 4-piperidyl acetate (**5**). For [^{18}F]FETos, 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%), while addition of 143 mM LiI resulted in radiochemical yields of 85 ± 0.5%.

Table 1. ^{18}F-labelled compounds with potential for nuclear medicine

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

The ^{18}F-fluoroethylation of *N,N*-dimethylethanolamine (**7**) was performed following the procedure of Hara and co-workers.[9] 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) and 95 ± 0.3% ([^{18}F]BFE/LiI) compared to 12 ± 0.8% ([^{18}F]FETos) and 54 ± 0.5% ([^{18}F]BFE) could be obtained.

*Table 2. Radiochemical yields of the ^{18}F-fluoroethylation of P4B **3**, P4A **5** and N,N-dimethylethanolamine **7** using different ^{18}F-fluoroalkylating agents*

Radioligand	Radiochemical Yield [%] with					
	[^{18}F]BFE	Ref. for [^{18}F]BFE	[^{18}F]FETos	Ref. for [^{18}F]FETos	[^{18}F]BFE / LiI	[^{18}F]FETos / LiI
[^{18}F]FEtP-4-B (**4**)	0	---	44 ± 1.0	14-24[7]	68 ± 0.6	80 ± 1.0
[^{18}F]FEtP-4-A (**6**)	49 ± 6.8	48[8]	39 ± 2.1	---	85 ± 0.5	87 ± 2.1
[^{18}F]FEtCh (**8**)	54 ± 0.5	---	12 ± 0.8	100[9]	95 ± 0.3	82 ± 2.4

In conclusion, the addition of alkali iodides to the secondary labelling precursors [^{18}F]FETos and [^{18}F]BFE leads to increased radiochemical yields for each 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 examined alkali iodides 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 scheme and in the used module. The extension of this study to other interesting ^{18}F-radiopharmaceuticals is currently under investigation.

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