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Efficient synthesis of 2-bromo-1-[^{18}F]fluoroethane and its application in the automated preparation of ^{18}F-fluoroethylated compounds

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Abstract

An efficient synthesis of 2-bromo-1-[^{18}F]fluoroethane from commercially available 1,2-dibromoethane and its integration into an automated preparation device was developed for the routine synthesis of ^{18}F-fluoroethylated compounds. The 1,2-dibromoethane was reacted with the [^{18}F]fluoride/Kryptofix®2.2.2./carbonate complex in acetonitrile at 70°C for 3 min resulting in 60–70% radiochemical yields. The crude reaction mixture was diluted with water, loaded on a LiChrolute®EN-cartridge, eluted with acetonitrile and passed through an AluminaB®-cartridge. This method provides 2-bromo-1-[^{18}F]fluoroethane with 98% radiochemical purity and $<0.1\,\mu$mol of 1,2-dibromoethane within 10 min, thus avoiding a purifying distillation step. This method was easily integrated into an automated system for the routine synthesis of ^{18}F-fluoroethylated compounds. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: 2-Bromo-1-[^{18}F]fluoroethane; Fluoroethylation

1. Introduction

^{18}F-Fluoroalkylation is an effective way to introduce a no-carrier-added (nca) ^{18}F-fluorine label into molecules comprising hydroxy-, amino- or amido-moieties. In comparison to a direct ^{18}F-fluorination of relevant precursors, this method is not negatively affected by acidic groups which are often found in complex molecules.

The most common ^{18}F-fluoroalkylating agent is 2-[^{18}F]fluoroethyltosylate ([^{18}F]FETos) first introduced by Block et al. (1987). The disadvantage of this secondary labelling synthon is the suggested HPLC purification step to avoid the transfer of its educt 1,2-bistosyloxyethane which adversely affects the subsequent ^{18}F-fluoroalkylating step by decreasing the radiochemical yields of the product. Up to now there is no purification method of [^{18}F]FETos available which uses only a combination of cartridges.

Another detriment is the fact that fluoroalkylation reactions with [^{18}F]FETos often only work well in DMSO and DMF rather than in acetonitrile. However, DMF and DMSO can decrease the efficiency of the final HPLC purification step of the labelled product because of peak-tailing and peak-fronting. In comparison, 1-bromo-2-fluoroethane (BFE, [^{18}F]BFE) has slightly better alkylating properties in dipolar aprotic solvents (Bunton, 1963) than [^{18}F]FETos and might diminish purification problems by generally using acetonitrile. There are several examples in the literature for the synthesis of [^{18}F]BFE starting from different precursors (Chi et al., 1987; Mulholland et al., 1999). All methods include a final distillation of the [^{18}F]BFE from the reaction vessel into a receiving flask, which makes an integration into an automated synthetic system difficult. For that reason, [^{18}F]BFE has not often been applied as

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a secondary labelling precursor yet, although the quality of bromide as a leaving group in nucleophilic substitutions in dipolar aprotic solvents such as DMSO, DMF and acetonirile is slightly better than the tosylate leaving group (Streitwieser jun, 1956).

Suppose a rapid and effective chromatographic separation of [^{18}F]BFE from its educt can be developed, it could become an alternative to [^{18}F]FETos for the use as a ^{18}F-fluoroethylating agent in automated radioactive syntheses of defined ^{18}F-labelled pharmaceuticals.

2. Materials and methods

1,2-Dibromoethane, 4-benzylpiperidine, benzylamine and Kryptofix®2.2.2. were obtained from Merck, Germany. 1-Bromo-2-fluoroethane was purchased from Lancaster. All solvents were absolute and stored over molecular sieve.

Solid phase cartridges LiChrolut®EN and Alumina®B were purchased from Merck, Germany. High performance liquid chromatography (HPLC) was performed with an HPLC system from Sycam S1100, UV detection at 254 nm was obtained using a UV detector from Sycam S3200. Detection of radioactivity with radio-HPLC was performed using an NaI detector from Canberra Packard. The HPLC system was used isocratically for the detection of [^{18}F]BFE and [^{18}F]-FETos. [^{18}F]Fluoride, produced via the ^{18}O(p,n)^{18}F reaction, was purchased at several institutions. Separation of [^{18}F]FETos was accomplished using a Lichrosphere RP18-EC5, 250 × 10 mm^2 HPLC column.

2.1. Synthesis of the non-radioactive standard compounds

2.1.1. 1-(2-Fluoroethyl)-4-benzylpiperidine

4-Phenylpiperidine (1.3 g, 8 mmol), 1-bromo-2-fluoroethane (1.22 g, 9.6 mmol), potassium iodide (15 mg) and potassium carbonate (3.32 g, 24 mmol) were dissolved in dioxane (10 ml) and refluxed for 24 h. The crude reaction mixture was diluted with ethylacetate (20 ml), filtered, washed twice with water (5 ml), dried over magnesium sulfate and the solvent was removed in vacuo. Final purification of the crude product was achieved with column chromatography on silicagel Si-60 with ethylacetate/*n*-hexane as the solvent to yield the desired product as an oil (1.52 g, 91%).

- ^{1}H-NMR (200 MHz, $CDCl_3$): (5H, m, 1.2–1.7 ppm), (2H, m, 1.9–2.1 ppm), (3H, m, 2.5–2.65 ppm), (1H, t, 2.7 ppm), (2H, d, 2.9 ppm), (1H, t, 4.4 ppm), (1H, t, 4.65 ppm), (5H, m, 7.1–7.3 ppm).
- ^{13}C-NMR (400 MHz, $CDCl_3$): 32.5 (piperidine), 37.5 (piperidine), 43.2 (aryl-$\underline{C}H_2$), 54.0 (piperidine), 58.4 (N-$\underline{C}H_2$), 82.8 ($\underline{C}H_2$-F), 125.5 (aryl), 128.0 (aryl), 129.0 (aryl), 160.5 (aryl),
- ^{19}F-NMR (400 MHz, $CDCl_3$): −218.4 (tt).
- MS (FD): m/z (% rel. int.) 221.7 (100, M+]).
- Anal. ($C_{14}H_{20}FN$) C, H, N calc.: C: 75.98 H: 9.11 N: 6.33; found: C: 75.91 H: 8.99 N: 6.29.

2.1.2. Benzyl-(2-fluoroethyl) amine

The synthesis was performed in the same manner as described above to yield the desired compound as an oil (81.3% chemical yield).

- ^{1}H-NMR (200 MHz, $CDCl_3$): (1H, t, 2.8 ppm), (1H, t, 2.95 ppm), (2H, s, 3.8 ppm), (1H, t, 4.4 ppm), (1H, t, 4.65 ppm), (5H, m, 7.2–7.4 ppm).
- ^{13}C-NMR (400 MHz, $CDCl_3$): 49.0 ($\underline{C}H_2$-NH), 53.5 (aryl-$\underline{C}H_2$-NH), 82.7 ($\underline{C}H_2$-F), 127.0 (aryl), 127.8 (aryl), 128.4 (aryl), 139.9 (aryl).
- ^{19}F-NMR (400 MHz, $CDCl_3$): −224.3 (tt).
- MS (FD): m/z (% rel. int.) 153.6 (100, M+]).
- Anal. ($C_{14}H_{20}FN$) C, H, N calc.: C: 70.56, H: 7.90, N: 9.14; found: C: 70.54 H: 7.82 N: 9.07.

2.2. Synthesis of ^{18}F-compounds

2.2.1. [^{18}F]fluoride/Kryptofix®2.2.2./carbonate complex

To an aqueous [^{18}F]fluoride solution (370–740 MBq) were added Kryptofix®2.2.2. (10 mg, 25 μmol), potassium carbonate (1 N) (12.5 μl) and 1 ml acetonitrile. The mixture was dried in a stream of nitrogen at 80°C. The drying procedure was repeated three times until the reaction mixture was absolutely dry. The dried Kryptofix®2.2.2./[^{18}F]fluoride complex was then dissolved in 1 ml acetonitrile.

2.2.2. 1-Bromo-2-[^{18}F]fluoroethane

The radiolabelling of [^{18}F]BFE for the non-automated applications was performed via the reaction of 1,2-dibromoethane and the [^{18}F]fluoride/Kryptofix®2.2.2./carbonate complex in acetonitrile (1 ml) using a 2 ml septum sealed reaction vial.

1,2-Dibromoethane (2–5 mg) was added and the mixture was stirred for 3 min at a reaction temperature of 70°C. The mixture was diluted with 20 ml water and passed through a LiChrolute®EN-cartridge. The fixed product was eluted with acetonitrile (1 ml) and immediately passed through an Alumina®B-cartridge into a receiving flask. The whole preparation time was 10 min and the overall radiochemical yield was between 60% and 70%.

2.2.3. 2-[^{18}F]fluoroethyltosylate

To the dried Kryptofix 2.2.2./[^{18}F]fluoride complex in acetonitrile (1 ml) ethylenglycol-1,2-ditosylate (8–10 mg, 20–25 μmol) was added and heated under stirring in a sealed vial for 3 min. Purification of the crude product was accomplished using HPLC (acetonitrile/water 50:50, flow rate: 5 ml/min r_t: 8 min). After diluting the HPLC

fraction containing the 2-[^{18}F]fluoroethyl tosylate with water the product is loaded on a C18-Sepac cartridge, dried with nitrogen stream and eluted with 1 ml of acetonitrile. The overall radiochemical yield was 50%.

2.2.4. ^{18}F-Fluoralkylation reactions with [^{18}F]FETos

10 mg of the labelling precursor 4-benzylpiperidine or benzylamine was dissolved in 0.5 ml acetonitrile, [^{18}F]FETos in acetonitrile (0.5 ml) was added and stirred at 70°C. Aliquots were taken during 30 min and analysed via HPLC (1:1 acetonitrile/water; 1-(2-fluoroethyl)-4-benzylpiperidine, $R_t = 4.8$ min; 40:60 acetonitrile/di-sodium hydrogenphosphate buffer (0.05 N) for benzyl-(2-[^{18}F]fluoroethyl) amine, $R_t = 7.2$ min).

2.2.5. ^{18}F-Fluoralkylation reactions with [^{18}F]BFE

As a practical example for the effective and simple application of [^{18}F]BFE we chose the synthesis of 1-(2-[^{18}F]fluoroethyl)-4-benzylpiperidine and benzyl-(2-[^{18}F]-fluorethyl)amine in acetonitrile and compared it with the syntheses via [^{18}F]FETos. 10 mg of the labelling precursor 4-benzylpiperidine or benzylamine was dissolved in 0.5 ml acetonitrile, [^{18}F]BFE in acetonitrile (0.5 ml) was added and stirred at 80°C. Aliquots were taken during 30 min and analysed via HPLC as shown above.

2.3. Automated synthesis system

Fig. 1 shows the automated system developed for the routine ^{18}F-fluoroalkylation of eligible precursors with [^{18}F]BFE, illustrated for the labelling of 4-benzylpiperidine with [^{18}F]BFE. The reaction vessel B was charged with the respective precursor. Prior to the synthesis of [^{18}F]BFE the [^{18}F]fluoride/[^{18}O] water (500 MBq) stored in vessel (1) was passed through a QMA-cartridge (3). The [^{18}O] water was collected in vessel (2) and the [^{18}F]fluoride was rinsed from the QMA into the reaction vessel A with Kryptofix®2.2.2./K_2CO_3 in acetonitrile (1 ml), stored in loop (4) (470 MBq). The mixture was dried in reaction vessel A in a stream of nitrogen at 80°C (5 min). The dried Kryptofix®2.2.2./[^{18}F]fluoride complex (420 MBq) was then dissolved by addition of 1 ml acetonitrile from vessel (5) and the temperature was adjusted to 70°C. 2 mg of 1,2-dibromoethane in acetonitrile (400 μl) was added from a charged vessel (6) and the solution was allowed to stir for 3 min. The mixture was transferred into vessel (7), quenched with 20 ml water and passed through a LiChrolute®EN-cartridge. After fixation, the cartridge was rinsed with 1 ml

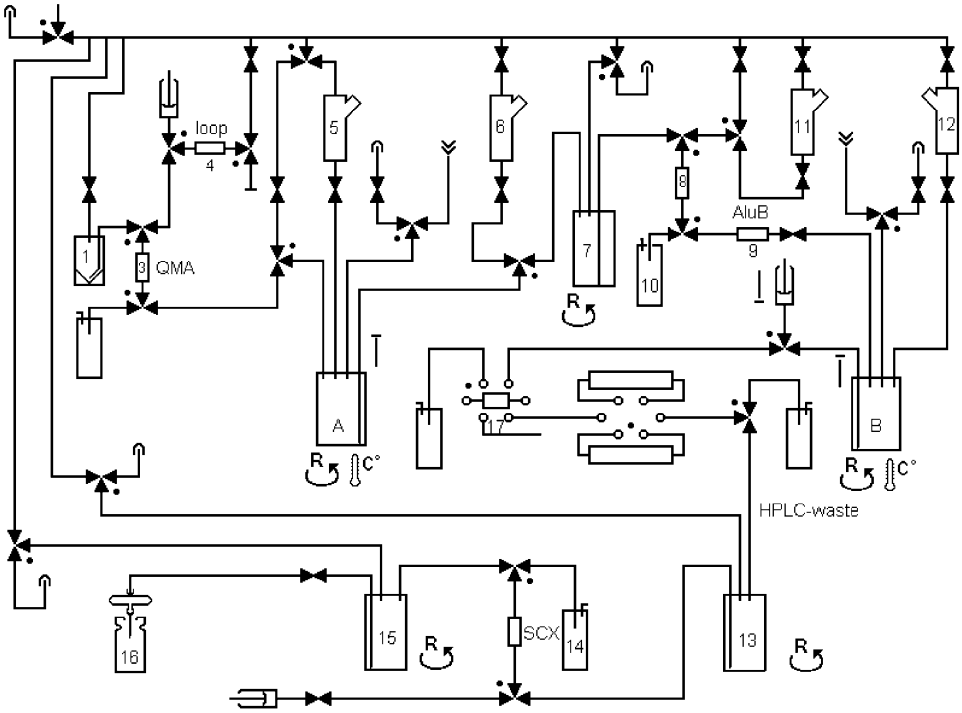

Fig. 1. Automated system for routine ^{18}F-fluoroalkylation of eligible precursors illustrated for the synthesis of 1-(2-[^{18}F]fluoroethyl)-4-phenylpiperazine with [^{18}F]BFE.

acetonitrile from (11) and [^{18}F]BFE was passed through an Alumina®B-cartridge into the second reaction vessel B (240 MBq), charged with the labelling precursor (4-benzylpiperidin or benzylamine) in acetonitrile (300 μl). The mixture was heated for 2 min at 80°C, cooled down to ambient temperature and injected directly into a 6-way HPLC injector valve (17).

Purification of the final product was achieved using a HPLC solvent as described above. The isolated product peak was collected in vessel (13), which had previously been filled with water, and was subsequently passed through a C18-cartridge (14). The loaded cartridge was eluted with 1 ml ethanol and mixed with 5 ml isotonic sodium chloride solution in vessel (15). The solution was passed through a sterile filter (18) into the final receiving vessel (16) (150 MBq).

The whole procedure was controlled with a personal computer. In order to achieve feedback control, the automated system was equipped with radiation and temperature sensors at the two reaction vessels A and B.

3. Results and discussions

The labelling synthon [^{18}F]BFE could be synthesised from 1,2-dibromoethane and [^{18}F]fluoride/Kryptofix®2.2.2./carbonate complex in acetonitrile with an overall radiochemical yield (RCY) of 60–70%. After the purification step using the Alumina®B-cartridge, the radiochemical purity of [^{18}F]BFE was 98%. To analyse its chemical purity, the concentration of 1,2-dibromoethane after purification of the crude radioactive reaction product with the combined EN- and AluminaB®-cartridges was determined. An HPLC calibration curve (UV at 254 nm) for 1,2-dibromoethane was measured within concentrations of 1,2-dibromoethane ranging from 0 to 127 mmol/l. However, the UV chromatogram of [^{18}F]BFE after the purification using the AluminaB®-cartridge demonstrated an absence of 1,2-dibromoethane, at least below our minimum detectable limit of <0.1 mmol/l (Fig. 2).

To study the whereabouts of 1,2-dibromoethane after passing it through the Alumina®B-cartridge, 2 mg of the precursor was diluted with acetonitrile (1 ml) and 10 mg Kryptofix®2.2.2./carbonate complex was added. The mixture was stirred at 70°C for 3 min. The mixture was passed through the Alumina®B-cartridge and the eluate was investigated using HPLC. The eluate contained only 0.05% of the precursor. We assume that either vinyl bromide with a boiling point of 16°C was formed under the basic reaction conditions within the basic column material, or the 1,2-dibromoethane was hydrolysed and retained on the cartridge. The elimination rate (E2) of 1,2-dibromoethane is significantly higher than that of

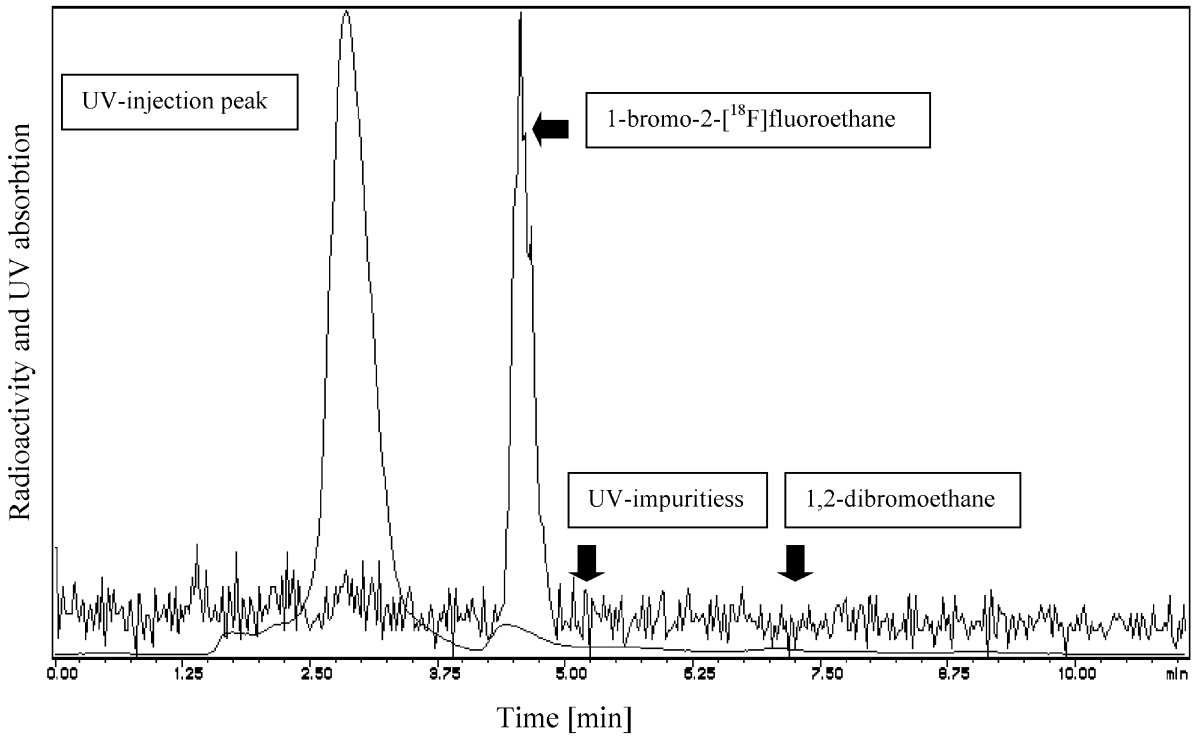

Fig. 2. Radioactivity- and UV-chromatogram of [^{18}F]BFE after purification with the LiChrolut®EN- and Alu mina®B-cartridge.

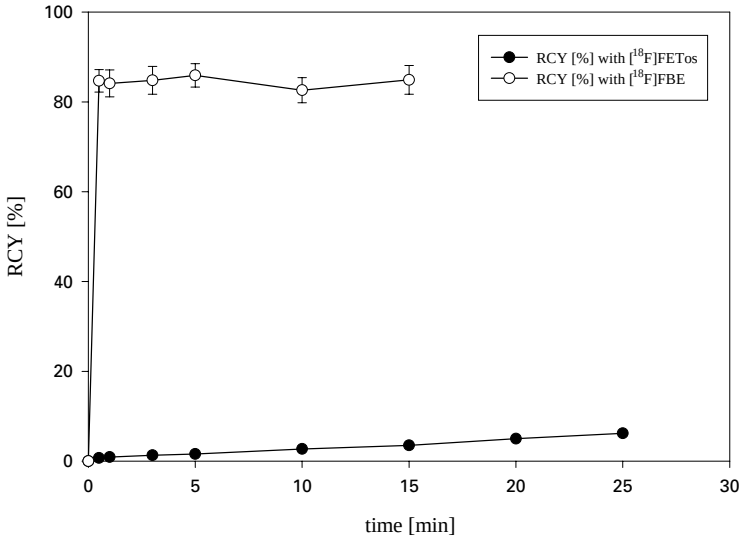

Fig. 3. Radiochemical yield of 1-(2-[^{18}F]fluoroethyl)-4-benzylpiperidine in acetonitrile using [^{18}F]BFE and [^{18}F]FETos.

1-bromo-2-fluoroethane under basic conditions (Hine and Langford, 1956), which supports our assumption. Thus, [^{18}F]BFE can be used for further labelling reactions directly and on line, i.e. without distillation or purifications using HPLC. This might be a significant advantage compared to the purification recommended for [^{18}F]-FETos.

The reaction of [^{18}F]BFE with 4-benzylpiperidine in acetonitrile at a reaction temperature of 80°C yielded the desired compound 1-(2-[^{18}F]fluoroethyl)-4-benzylpiperidine in an RCY of 80% (Fig. 3). The same reaction with [^{18}F]FETos gave the same product only in 5% RCY after 25 min (Fig. 3).

The primary amine benzylamine could be labelled with [^{18}F]BFE in the same manner to yield benzyl-(2-[^{18}F]fluoroethyl) amine with an RCY of 96% in acetonitrile within 2 min. Using [^{18}F]FETos, the product was obtained with only 10% RCY after 25 min under the same conditions. These reactions demonstrate the advantage of using [^{18}F]BFE in acetonitrile as a labelling synthon for the *N*-alkylation of neutral precursors such as amines provided that the precursor is soluble in acetonitrile. The potential of [^{18}F]BFE compared to [^{18}F]FETos for the *N*-alkylation of various other precursors or for *O*-alkylations for example needs further and systematic investigation.

The integration of the described synthesis of [^{18}F]-BFE and its purification via different cartridges into an automated system was easily achieved. Within a total preparation time of 10 min this automated system could provide a solution of [^{18}F]BFE in acetonitrile for the subsequent use in ^{18}F-fluoroalkylation reactions of eligible precursors. Thus [^{18}F]BFE is suitable for routine radiopharmaceutical synthesis if the limitations described above are taken into consideration.

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