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Synthesis of [^{18}F]fluoroacetaldehyde. Application to [^{18}F]fluoroethylation of benzylamine under reductive alkylation conditions

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The radiosynthesis of a new [^{18}F]fluoroalkylating agent, [^{18}F]fluoroacetaldehyde, is described. It was produced using the Kornblum method by oxidation with dimethyl sulphoxide of 2-[^{18}F]fluoroethyl *p*-toluenesulphonate ([^{18}F]FETos). In these conditions the oxidation proceeds smoothly and rapidly to the selective conversion of tosyl esters of primary alcohols to aldehydes with no carboxylic acids being produced. The chemical identity of [^{18}F]fluoroacetaldehyde was determined by comparing its chromatographic properties as well as those of its 2,4-dinitrophenylhydrazone (2,4-DNPH) derivative with those of, respectively, the standard fluoroacetaldehyde and its 2,4-DNPH derivative. Standard fluoroacetaldehyde was prepared by oxidation of fluoroethanol with pyridinium dichromate and characterized as its 2,4-DNPH derivative by mass spectrometry. To test its reactivity with amines under reductive alkylation conditions, [^{18}F]fluoroacetaldehyde was reacted with benzylamine used as model substrate. The chemical identity of the resulting radiolabelled product was determined to be [^{18}F]*N*-(2-fluoroethyl)-benzylamine by comparing its chromatographic properties with those of the synthesized standard *N*-(2-fluoroethyl)-benzylamine characterized by ^{19}F and ^{1}H NMR spectroscopy and mass spectrometry. This new fluorine-18 labelled synthon may find applications in radiolabelling peptide, protein and antibody fragments as well as in aldol condensation or in the Mannich reaction.

Keywords: [^{18}F]fluoroacetaldehyde; Kornblum oxidation; reductive alkylation; [^{18}F]*N*-(2-fluoroethyl)-benzylamine

Introduction

Radiolabelling, with fluorine-18, of amines by [^{18}F]fluoroethylation is commonly carried out using [^{18}F]FETos or 2-bromo-1-[^{18}F]fluoroethane.[1–3] A procedure involving two steps has been reported for the synthesis of [^{18}F]*N*-(2-fluoroethyl)-anilines based on direct nucleophilic substitution with [^{18}F]fluoride ion in an *N*-haloacetylaniline (halo = Cl or Br) followed by reduction of the generated [^{18}F]*N*-fluoroacetyl-aniline *in situ*.[4]

[^{18}F]fluoroethylation using [^{18}F]FETos or 2-bromo-1-[^{18}F]fluoroethane requires an intermediate purification step of the ^{18}F-fluoroethylating agents from their respective starting materials ethylene di-*p*-toluenesulphonate and 1,2-dibromoethane using high-performance liquid chromatography (HPLC) or a solid-phase extraction method. Furthermore these reactions take place in organic, anhydrous, solvents (dimethylformamide, dimethyl sulphoxide (DMSO) or acetonitrile). We have developed a synthesis route to [^{18}F]fluoroacetaldehyde as an alternative to [^{18}F]fluoroethylating agent for amines and for its possible applications in radiolabelling peptides, proteins and antibody fragments.

Aldehydes and ketones are known to react with primary or secondary amines in the presence of hydrogen or a hydrogenation catalyst to produce *N*-alkylamines.[5–7] These alkylations can be carried out in water as the reaction solvent when using high-reactivity carbonyl compounds. Small aldehydes, formaldehyde and acetaldehyde, are very effective reagents in reductive alkylation.[8–10] Electron-withdrawing substituents in acetaldehyde, e.g. trifluoroacetaldehyde or difluoroacetaldehyde, increase the chemical reactivity of the carbonyl carbon with nucleophiles when compared with non-fluorinated acetaldehyde.[11,12] For these reasons [^{18}F]fluoroacetaldehyde was expected to be a good [^{18}F]fluoroethylating agent for amines in reductive alkylation conditions.

Alcohol oxidation in DMSO is widely used in synthetic organic chemistry.[13] The reaction requires a base and a hydroxyl activating agent such as *N,N′*-dicyclohexylcarbodiimide,[14] acetic

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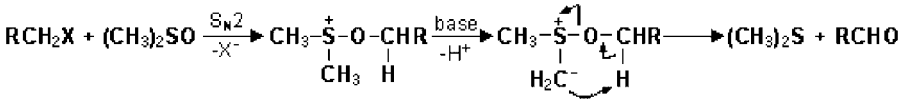

Figure 1. Alkyltosylate oxidation with DMSO (X = tosyl).

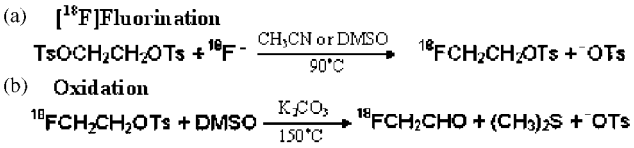

Figure 2. [^{18}F]fluoroacetaldehyde radiosynthesis steps.

anhydride[15] or a reagent for prior activation of DMSO such as oxalyl chloride.[16] In these gentle oxidation conditions primary alcohols are converted to aldehydes with no carboxylic acids being produced. In a similar way tosyl esters of primary alcohols or primary alkyl halides are oxidized to aldehydes with DMSO in conditions developed by Kornblum *et al.*[17] Alkyltosylate oxidation, using the Kornblum method, is carried out by treatment with a sodium bicarbonate–DMSO mixture at a temperature between 130 and 150°C for 3 min.[18,19] The reaction proceeds via an alkoxysulphonium ion intermediate (Figure 1).[20,21] The Kornblum method provided an attractive way to produce [^{18}F]fluoroacetaldehyde from the well-described synthon [^{18}F]FETos.[22–25]

A two-step synthesis route to [^{18}F]fluoroacetaldehyde was thus investigated (Figure 2). [^{18}F]FETos obtained, in the first step, by the reaction of ethylene di-*p*-toluenesulphonate with potassium [^{18}F]fluoride in the presence of Kryptofix® 222 was oxidized by DMSO in the second step.

[^{18}F]fluoroacetaldehyde has a lower boiling point than its heavier chlorinated analogue chloroacetaldehyde (boiling point = 85–86°C) and it was expected that it would be easily distilled. In fact [^{18}F]fluoroacetaldehyde volatility allowed for a continuous separation from the oxidation reaction by distillation. The distillate was analysed by HPLC with UV detection at 277 nm (λ_{max} of the UV absorption of the acetaldehyde carbonyl, in solution in water, due to the $n \rightarrow \pi^*$ electronic excitation). [^{18}F]fluoroacetaldehyde was characterized as the 2,4-dinitrophenylhydrazone (2,4-DNPH) derivative and reacted with benzylamine, used as model substrate, in order to test its reactivity with amines under reductive alkylation conditions using sodium cyanoborohydride[26,27] as the reducing agent. Synthesis of the resulting [^{18}F]*N*-(2-fluoroethyl)-benzylamine has already been reported by [^{18}F]fluoroethylation of benzylamine using either of the reagents [^{18}F]FETos or 2-bromo-1-[^{18}F]fluoroethane.[3]

Standard fluoroacetaldehyde was prepared following a method described by Moss *et al.*[28] by oxidation of fluoroethanol using pyridinium dichromate (PDC)[29,30] and characterized as the 2,4-DNPH derivative.

Results and discussion

[^{18}F]fluoroacetaldehyde preparation and 2,4-DNPH derivatization

[^{18}F]FETos produced by nucleophilic substitution of ethylene di-*p*-toluenesulphonate with [^{18}F]KF/Kryptofix 2.2.2 in acetonitrile was not isolated but reacted further with DMSO at 150°C after evaporation of acetonitrile. Because of the presence of excess potassium carbonate used to convert [^{18}F]HF to [^{18}F]KF, the addition of sodium bicarbonate, as described in the Kornblum method, was not considered required for the oxidation of [^{18}F]FETos and pure DMSO was used instead. The reaction mixture was set to distil immediately after addition of DMSO and the distillate was collected into a vial containing 50 µl of water kept at room temperature. According to the reaction mechanism depicted in Figure 1, other products were expected to distil with the radiolabelled aldehyde such as dimethyl sulphide, glyoxal and DMSO vapour. Dimethyl sulphide, produced from the reduction of DMSO during the reaction, is a volatile liquid (boiling point = 38°C) only slightly soluble in water (2.0% (w/w) at 20°C)[31], only reactive with oxidizing agents and not expected to interfere in the reaction of [^{18}F]fluoroacetaldehyde with amines in the presence of a reducing agent. Glyoxal was a potential product of ethylene di-*p*-toluenesulphonate oxidation, this reagent being used in excess for the production of [^{18}F]FETos. Glyoxal is a volatile liquid (boiling point = 51°C), readily soluble in water and which reacts with amines. Its production and distillation with [^{18}F]fluoroacetaldehyde would compromise the use of the latter as an *N*-[^{18}F]fluoroethylating agent. HPLC analyses of the distillate showed no trace of glyoxal. Furthermore, reaction of [^{18}F]fluoroacetaldehyde with either 2,4-dinitrophenylhydrazine or benzylamine was not prevented. Moreover, no precipitate was observed in the homogenous DMSO mixture; thus, decomposition of glyoxal or its rearrangement to glycolic acid which boils at 100°C with decomposition[31] are possible explanations why glyoxal was not found.

To minimize the amount of distilled DMSO, the distillation was carried out at 150°C for 4 min and carried on at 130°C for another 4 min with a low flow rate of nitrogen as the carrier gas (7–8 ml/min). Efficiency of trapping the radioactivity into water was checked by connecting a second vial, containing tetrahydrofuran (THF) (0.3 ml), kept at around −10°C (ice–alcohol), to the vent of the first one. The total radioactivity distilled and trapped in the two vials accounted for 31–37% (yield based on three experiments and decay corrected) of the initial radioactivity as [^{18}F]HF and more than 97% of the distilled radioactivity was found in the water containing vial. The radioactivity extracted by distillation and efficiently trapped in a small volume of water showed that the radiolabelled, volatile product of the reaction was highly hydrophilic. Such high hydrophilicity was expected from fluoroacetaldehyde as electron-withdrawing substituents increase solvation of the aldehyde under its more hydrophilic hydrate form.

As the fraction of the distilled radioactivity trapped into THF was not analysed, we cannot exclude the fact that a hydro-tosyl elimination yielding [^{18}F]vinylfluoride occurred; but as this amount of radioactivity was low if [^{18}F]vinylfluoride was produced, it was only via a minor side reaction.

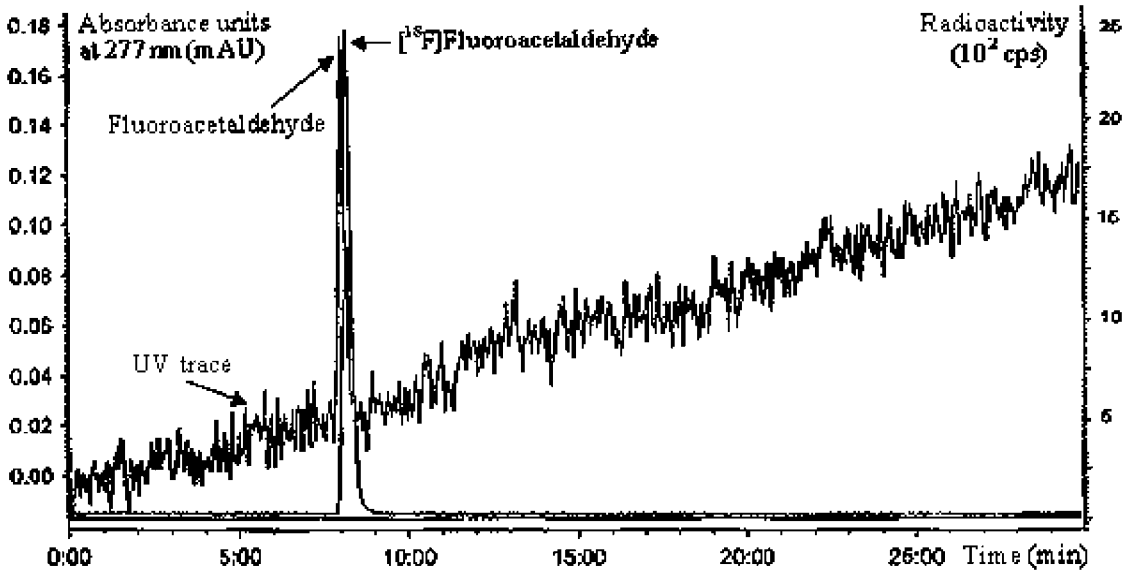

Figure 3. HPLC analysis of the distillate from the [^{18}F]FETos oxidation reaction with DMSO, co-injection with standard fluoroacetaldehyde.

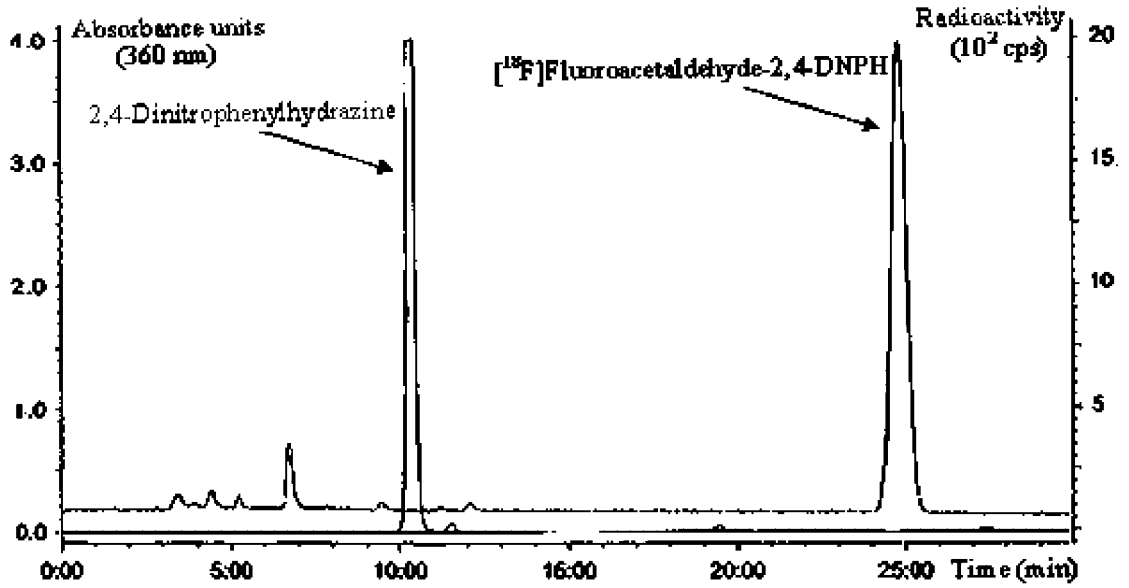

Figure 4. HPLC analysis of the reaction with 2,4-dinitrophenylhydrazine of the distillate from the [^{18}F]FETos oxidation with DMSO.

A sample from the distillate trapped into water was analysed by HPLC under reverse-phase conditions. No UV detection was observed at 277 nm. The radio-HPLC trace showed a single peak with a retention time of 8.2 min that was identified as [^{18}F]fluoroacetaldehyde on the basis of both retention time and coelution with standard fluoroacetaldehyde (Figure 3). Under these HPLC conditions, glyoxal and DMSO had 6.1 and 10.2 min retention times, respectively.

The distillate was reacted with 2,4-dinitrophenylhydrazine and a sample was analysed by HPLC with UV detection at 360 nm (Figure 4). The UV trace showed only one peak at 10.3 min, which was the retention time of 2,4-dinitrophenylhydrazine. Radio-HPLC trace showed a single peak that was identified as [^{18}F]fluoroacetaldehyde-2,4-DNPH on the basis of both retention time and coelution with standard fluoroacetaldehyde-2,4-DNPH. These HPLC analyses showed that [^{18}F]fluoroacetaldehyde was the main component of the radioactivity distilled from the oxidation reaction.

Radiosynthesis conditions for [^{18}F]FETos production are described using acetonitrile as the reaction solvent.[23–25] To simplify the [^{18}F]fluoroacetaldehyde synthesis procedure, we tried using DMSO for both [^{18}F]FETos production and oxidation steps by heating the reaction mixture at 90°C, 8 min, for the first step and then at 150°C for the second step. We checked, previously, using a Merck aldehyde colorimetric test kit, that no oxidation of ethylene di-*p*-toluenesulphonate with DMSO occurred below 100°C. Nevertheless, in our hands, the first-step reaction of [^{18}F]fluoride with ethylene di-*p*-toluenesulphonate to

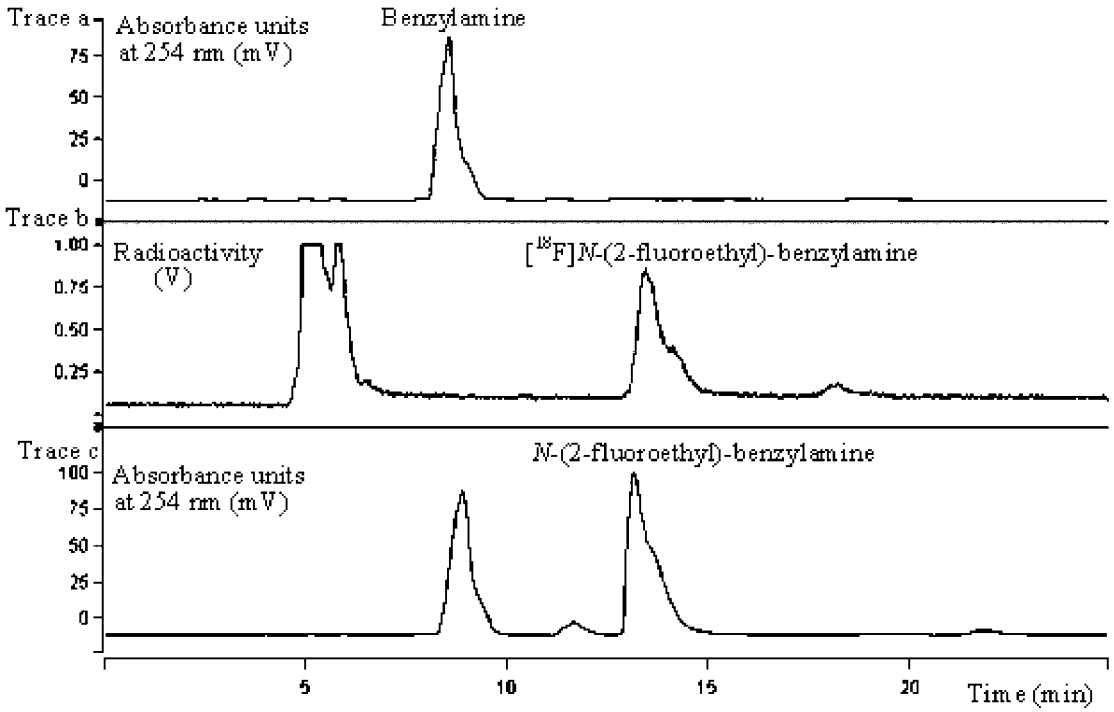

Figure 5. HPLC analysis of the reaction mixture of [^{18}F]fluoroacetaldehyde with benzylamine (traces a and b) Trace c: co-injection of *N*-(2-fluoroethyl)-benzylamine standard with the reaction mixture.

produce [^{18}F]FETos generated a slightly higher yield in acetonitrile, 75–88%, than in DMSO, 69–75%, for 8 min reaction time (based on four experiments, analyses carried out by radio-thin layer chromatography (radio-TLC)).

Reaction of [^{18}F]fluoroacetaldehyde with benzylamine, synthesis of [^{18}F]*N*-(2-fluoroethyl)-benzylamine

The oxidation of [^{18}F]FETos with DMSO is very fast and the oxidation reaction mixture was distilled, as the reaction proceeded as mentioned above, into a vial containing a solution of benzylamine and sodium cyanoborohydride in a mixture of phosphate-buffered saline (PBS) and acetonitrile. Acetonitrile was used to increase the solubility of benzylamine in the mixture. Radioactivity trapped into the benzylamine solution was monitored and started to be detected and increased less than 1 min after the temperature of the reactor had reached 150°C and was at its maximum after 7–8 min.

The alkylation reaction mixture was analysed by reverse-phase HPLC after a 10 min reaction at 50°C. The UV trace (Figure 5, trace a) showed only benzylamine eluting at 8.5 min. The radioactivity trace (Figure 5, trace b) showed three main radioactive peaks: a first one at 5.0 min that was decreasing in intensity as the [^{18}F]fluoroethylation reaction proceeded and was inferred to be unreacted [^{18}F]fluoroacetaldehyde, a second one at 5.8 min that was not identified and the third one at 13.5 min that coeluted with stable *N*-(2-fluoroethyl)-benzylamine (Figure 5, trace c) and was thereby identified as [^{18}F]*N*-(2-fluoroethyl)-benzylamine. The radioactive fractions were collected and the radioactivity measured. [^{18}F]*N*-(2-fluoroethyl)-benzylamine was produced with an overall radiochemical yield of 17% (decay corrected).

Experimental

Materials

Chemicals and solvents were purchased from Sigma-Aldrich Company Ltd. (Gillingham, UK) and were used without further purification. The aldehyde colorimetric test kit (formaldehyde test) was purchased from Merck Chemicals Ltd. (Nottingham, UK). HPLC solvents and a ready-to-use commercial cyanoborohydride PBS solution (cyanoborohydride coupling buffer) were obtained from Sigma. The coupling solution is made up of 0.02 M sodium phosphate, pH 7.5, containing 0.2 M sodium chloride and 3.0 g/l sodium cyanoborohydride.

[^{18}F]fluoride was produced via the ^{18}O(p,n)^{18}F nuclear reaction by 16.4 MeV proton bombardment of an isotopically enriched [^{18}O] water target (95–97% $H_2^{18}O$ water enrichment) using a GE PETtrace cyclotron at the Wolfson Molecular Imaging Centre, Manchester, UK, or provided by the Douglas Cyclotron Unit of the Clatterbridge Centre for Oncology, UK.

Wheaton borosilicate screw-top V-vials, capacity 3.0 and 1 ml, with open-top cap and PTFE-faced silicon septum from Aldrich were used for the radiosyntheses.

TLC was performed on Fluka silica gel plates (20 × 20 cm, 250 μm thickness). Radio-TLC plates were analysed with an instant phosphor imager (Packard).

Radioactivity was monitored using a Ratemeter Mini 900 from Thermo Electron Corporation.

HPLC analyses of *N*-(2-fluoroethyl)-benzylamine and [^{18}F]*N*-(2-fluoroethyl)-benzylamine were carried out on a Varian ProStar 210 solvent delivery system equipped with a semi-preparative C18 column (μBondapak™, 10 μm particle size; 300 × 7.8 mm i.d.; Waters Ltd., Elstree, UK). The eluate was monitored for

absorbance (254 nm; model 325; Varian) and simultaneously for radioactivity with a Bioscan PM Flow-count detector. Collected radioactive peaks were measured on a Capintec CRC-15R.

HPLC analyses of fluoroacetaldehyde, fluoroacetaldehyde-2,4-DNPH, [^{18}F]fluoroacetaldehyde and [^{18}F]fluoroacetaldehyde-2,4-DNPH were carried out on a Shimadzu prominence system operated using a LabLogic software Laura 3 and configured with a CBM-20A controller, an LC-20AB solvent delivery system and a SPD-20A absorbance detector. The system was equipped with a Luna C18, 5 μm particle size, 250 × 10 mm Phenomenex column. Radioactivity was monitored with a radio-HPLC Bioscan Flow-count B-FC 3100 detector.

^{1}H NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer Tetramethylsilane was used as internal reference. ^{19}F NMR spectra were recorded on a Bruker DPX 200 MHz spectrometer.

Mass spectra (electrospray) of *N*-(2-fluoroethyl)-benzylamine were acquired on a Micromass Quattro II LC/MS.

Mass spectra of fluoroacetaldehyde-2,4-DNPH were recorded on a Shimadzu-Biotech Axima TOF-TOF MALDI instrument.

Synthesis of the standard compounds

Synthesis of fluoroacetaldehyde

Fluoroethanol (62 μl, 1 mmol) was added in one portion to the magnetically stirred solution of PDC (576 mg, 1.5 mmol) in anhydrous dichloromethane (1.5 ml). The mixture was left, under stirring, at room temperature for 24 h. After removal of the precipitate by filtration (syringe filter with PTFE membrane, Acrodisc®), the reaction mixture was heated at 80°C and the volatiles were distilled into 1 ml of water. The aqueous phase was then extracted from the distillate, presence of aldehyde was checked using the Merck aldehyde colorimetric test kit and a sample was analysed by HPLC (eluent: water, flow rate: 2 ml/min) with UV detection at 277 nm. The HPLC trace showed a single peak with a retention time of 8.0 min.

Synthesis of fluoroacetaldehyde-2,4-DNPH

To 0.5 ml of the aqueous fluoroacetaldehyde solution were added 0.8 ml of 2,4-dinitrophenylhydrazine and phosphoric acid solution (~0.2 M) and the mixture was left for 15 min at 90°C. Purification of the crude product was accomplished using HPLC (eluent: acetonitrile/water 50:50, flow rate: 3 ml/min) with UV detection at 360 nm. HPLC trace showed two main peaks at 10.4 min, retention time of 2,4-dinitrophenylhydrazine, and 24.5 min, the last one was collected and analysed by MALDI mass spectrometry. A sample (1 μl) of the HPLC fraction was pipetted onto the target plate and analysed without additional matrix in both positive and negative mode: $[M+1]^+ = 243.00$ and $[M-1]^- = 241.23$ (lit.[28] $M^+ = 242.0451$).

Synthesis of N-(2-fluoroethyl)-benzylamine

A solution of 1 g (10 mmol) of 2-fluoroethylamine hydrochloride in 6 ml of methanol was prepared in a 25 ml round-bottom flask. Potassium hydroxide (160 mg) was added in one portion to the magnetically stirred solution. When it was completely dissolved, 0.92 ml (9 mmol) of benzaldehyde was added in one portion. The resulting mixture was stirred at room temperature for 15 min before a solution of 200 mg (3.18 mmol) of sodium cyanoborohydride in 2 ml methanol was added dropwise. After the addition was complete, stirring was continued for 30 min. Potassium hydroxide (600 mg) was then added, and stirring was continued until it was completely dissolved. The reaction mixture was filtered through a PTFE membrane syringe filter, Acrodisc®, and the methanol evaporated with a rotary evaporator at 50°. The resulting oil was dissolved in chloroform and purified on a silica column. Elution with chloroform–2% methanol–0.5% triethylamine followed by evaporation of the collected fraction afforded 0.743 g, 54% yield, of *N*-(2-fluoroethyl)-benzylamine as an oil. HPLC: water/acetonitrile (70:30 v/v) with 0.1% triethylamine, flow rate: 6 ml/min, $R_t = 13.2$ min. ESI-MS: $m/z = 154.18$ $[M+H]^+$. ^{1}H NMR (CD_3COCD_3) δ: 2.81 (dt, 2H, $J = 25.7$, 4.6 Hz), 3.71 (s, 2H, $ArCH_2NH$), 4.55 (dt, 2H, $J = 47.1$, 4.7 Hz), 7.25 (t, 1H, $J = 6.8$ Hz), 7.33 (t, 1H, $J = 7.1$ Hz), 7.43 (d, 2H, $J = 7.3$ Hz). ^{19}F-NMR (CD_3COCD_3) δ: −144.84.

Radiochemistry

[^{18}F]potassium fluoride

The aqueous [^{18}F]fluoride solution (0.3–0.5 ml, 100–150 MBq) was added to an open 3 ml conical vial containing potassium carbonate (1.1 mg, 8 μmol) and Kryptofix® 222 (10 mg, 26.5 μmol). After addition of 1 ml of acetonitrile, the mixture was dried under argon at 110°C. This drying step was repeated twice with 1 ml of acetonitrile.

2-[^{18}F]fluoroethyltosylate

To the dried Kryptofix/[^{18}F]fluoride complex was added a solution of ethylene di-*p*-toluenesulphonate, 5 mg (13.5 μmol) in 0.3 ml acetonitrile, the vial was sealed and the mixture was heated 8 min at 90°C. [^{18}F]fluoride was incorporated into 2-[^{18}F]fluoroethyltosylate with 75–88% yield (radio-TLC: chloroform–methanol, 96:4, $R_f = 0.82$).

[^{18}F]fluoroacetaldehyde

The evaporation of the acetonitrile at 60°C, under nitrogen, was followed by addition of 0.2 ml of anhydrous DMSO and [^{18}F]fluoroacetaldehyde was distilled at 150°C for 4 min, carried on at 130°C for another 4 min and conveyed by nitrogen (7–8 ml/min) into water (50 μl) in a second reaction vial. A sample was analysed by HPLC with UV detection at 277 nm (eluent: water, flow rate: 2 ml/min, $R_t = 8.2$ min).

[^{18}F]fluoroacetaldehyde-2,4-DNPH

A fraction of the distillate (30 μl) was added to a solution of 2,4-dinitrophenylhydrazine (25 μl, ~5 μmol) in ethanol (60 μl) and the mixture was heated at 90°C for 15 min. A sample was analysed by HPLC with UV detection at 360 nm (eluent: acetonitrile/water 50:50, flow rate: 3 ml/min, $R_t = 24.8$ min).

[^{18}F]N-(2-fluoroethyl)-benzylamine

[^{18}F]fluoroacetaldehyde was trapped at room temperature in 80 μl of cyanoborohydride coupling buffer (sodium cyanoborohydride content 3.8 μmol) to which 20 μl of a benzylamine solution in acetonitrile (0.5 M) was added. The reaction mixture was then heated for 10 min at 50°C before being analysed by HPLC (eluent: water/acetonitrile 70:30 with 0.1% triethylamine, flow rate: 6 ml/min, $R_t = 13.5$ min).

Conclusion

We have described a fast and simple procedure to produce [^{18}F]fluoroacetaldehyde in a two-step, one-pot reaction using oxidation with DMSO of [^{18}F]FETos. The [^{18}F]labelled aldehyde was extracted continuously by distillation from the reaction mixture. The distilled radioactivity accounted for 31–37% (yield based on three experiments and decay corrected) of the initial radioactivity as aqueous [^{18}F]HF and [^{18}F]fluoroacetaldehyde was inferred from HPLC analyses to be the main component of the radioactivity distilled. It was characterized as the 2,4-DNPH derivative as well as the product of the reaction with benzylamine used as the model substrate to test [^{18}F]fluoroacetaldehyde reactivity with primary amines under reductive alkylation conditions. This new [^{18}F]fluoroethylating agent may be useful for the generation of labelled peptides, proteins and antibody fragments as it reacts in mild conditions, PBS and at a low temperature. In addition to its use as a [^{18}F]fluoroethylating agent of amines [^{18}F]fluoroacetaldehyde may find applications in the Mannich reaction as well as in aldol condensations.

Acknowledgement

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