The ^{18}F-Labelled Alkylating Agent 2,2,2-Trifluoroethyl Triflate : Synthesis and Specific Activity

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Abstract

A method for synthesizing the alkylating agent 2,2,2-trifluoroethyl triflate labelled with [^{18}F]fluoride in the two position is presented. Ethyl [2-^{18}F]-trifluoroacetate was synthesized by the nucleophilic reaction of [^{18}F]F$^-$ with ethyl bromodifluoroacetate in DMSO (45-60%, 5 min, 80 °C) and subsequently converted to [2-^{18}F]-2,2,2-trifluoroethanol using alane in THF (85-95%, 2 min, 40 °C). Reaction with triflic anhydride in 2,6-lutidine produced [2-^{18}F]-2,2,2-trifluoroethyl triflate (70-80%, 1 min, 0 °C). In all three cases the product was removed from the reaction vessel by heating to distil under a stream of nitrogen. [2-^{18}F]-2,2,2-Trifluoroethyl triflate was used to label 2-oxoquazepam by *N*-alkylation in a toluene:DMF mixture (80-85%, 20 min, 120 °C). Although no-carrier-added [^{18}F]F$^-$ was used, considerable unlabelled ethyl trifluoroacetate was produced in the first reaction. Varying the conditions for the fluoro-debromination reaction did not appreciably improve the relative ratio of labelled to unlabelled ester. The specific activity of the labelled 1,4-benzodiazepine-2-one obtained from 1850 MBq [^{18}F]F$^-$ was found to be ≈37 MBq/μmol (1 mCi/μmol).

Key words: PET, fluorine-18, trifluoroethyl triflate, benzodiazepine

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Introduction

We have previously presented approaches for radiofluorinating 1,4-benzodiazepine-2-ones by nucleophilic (1,2) and electrophilic (3,4) aromatic substitution reactions, applied to the labelling of 2-oxoquazepam (7-chloro-1-(2,2,2-trifluoroethyl)-1,3-dihydro-5-(2-fluorophenyl)-2H-1,4-benzodiazepine-2-one). These methods, while differing in synthesis time and complexity, have all been designed to introduce the radionuclide in the 2'-position in the 5-aryl ring. This paper describes an investigation of a method for labelling the target molecule in the *N*-alkyl chain by use of a new radiolabelling precursor [2-^{18}F]-2,2,2-trifluoroethyl triflate (5).

The use of labelled alkyl halides or sulfonates has provided a rapid and usually efficient means of introducing a positron-emitting nuclide in radiotracers for positron emission tomography (PET)

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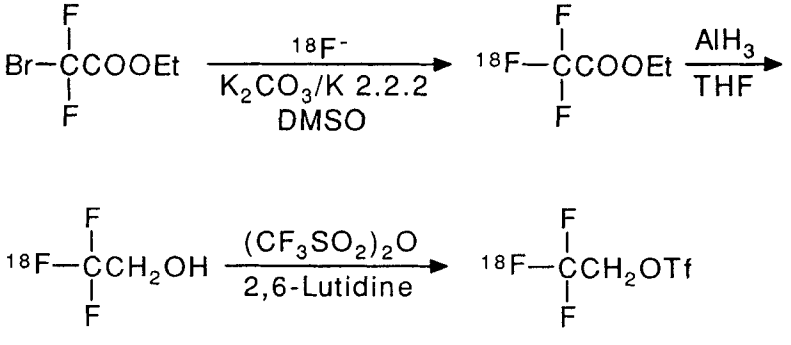
via *N*-, *O*- or *S*- alkylation reactions. In the case of fluorine-18, the synthesis of the [^{18}F]fluoroalkyl group is performed by the reaction of [^{18}F]fluoride with a bifunctional substrate, X-$(CH_2)_n$-Y (X, Y = halide and/or sulfonates) (6-9). A number of radiopharmaceutical syntheses using these alkylating agents have been reported (see references in 10). In at least two of these studies *N*-desalkyl-1,4-benzodiazepine-2-ones were alkylated by [^{18}F]fluoroethylation (11) and [^{18}F]fluoropropylation (9).

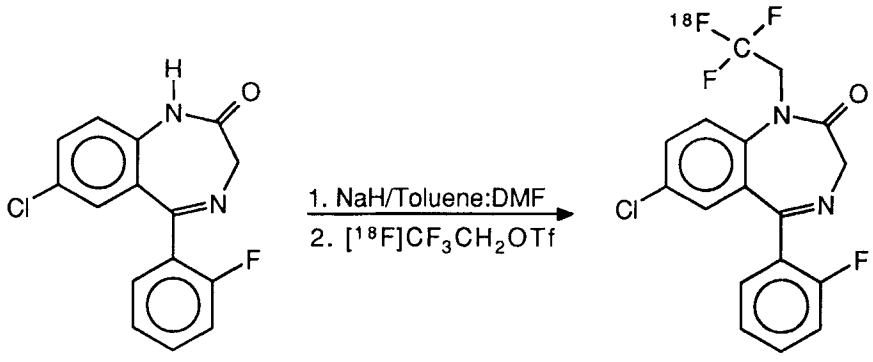
Synthesis of the desired ^{18}F-labelled trifluoroethyl alkylating agent by this method is, however, not feasible. Since the carbons in the analogous substrate (X-CF_2CH_2-Y) are not identical, two different products ($^{18}FCF_2CH_2$-Y and X-$CF_2CH_2{}^{18}F$) could potentially and would probably be obtained (12, 13). Instead, an alternative approach had to be designed using a substrate with one end activated for the nucleophilic displacement with [^{18}F]F^- and the other end with a functionality that could be used to generate the alkylating agent.

Fluorine-18 labelled esters have been previously synthesized from haloesters (14-17). Tewson and Welch (14) also demonstrated that the [^{18}F]fluoroester could easily be reduced to the corresponding alcohol, which in the present synthesis might be used to provide a route to the halide or sulfonate.

The method presented here for the synthesis of the alkylating agent, [2-^{18}F]-2,2,2-trifluoroethyl triflate ([^{18}F]CF_3CH_2OTf), is shown in Scheme 1. Ethyl bromodifluoroacetate ($BrCF_2COOEt$) was chosen as the substrate for the initial introduction of the radionuclide by an aliphatic fluorodebromination using no-carrier-added [^{18}F]F^-. The ^{18}F-labelled ester was subsequently reduced to the alcohol using alane (AlH_3). [2-^{18}F]-2,2,2-Trifluoroethanol ([^{18}F]CF_3CH_2OH) was then converted to the triflate rather than the iodide since the former is a more reactive alkylating group (18-21) and has reportedly given higher alkylation yields with the *N*-desalkyl-1,4-benzodiazepine-2-one (22). Additionally, a literature precedent indicated that trifluoroethyl iodide is difficultly prepared from the trifluoroethanol (23). The [^{18}F]CF_3CH_2OTf was used to label 2-oxoquazepam in the side chain by alkylation of the sodium salt of the *N*-desalkyl precursor (Scheme 2).



Scheme 1: Three-step method for synthesizing 2,2,2-trifluoroethyl triflate labelled in the 2-position with [^{18}F]F^-



Scheme 2: *N*-alkylation performed with $[^{18}F]CF_3CH_2OTf$ to label a 1,4-benzodiazepine-2-one producing [*N*-[2-^{18}F]-2,2,2-trifluoroethyl]-2-oxoquazepam

Materials and Methods

General

All solvents used were of analytical grade, were purified according to standard procedures (24) and, where appropriate, stored over activated molecular sieves (4Å). Potassium carbonate and bicarbonate (K_2CO_3, $KHCO_3$), potassium oxalate, Kryptofix 2.2.2 and lithium aluminium hydride ($LiAlH_4$) were obtained from Merck. Trifluoromethanesulfonic anhydride (triflic anhydride, $(CF_3SO_2)_2O$), cesium carbonate (Cs_2CO_3), rubidium carbonate (Rb_2CO_3), 2,6-lutidine and CF_3CH_2OH were obtained from Aldrich. $BrCF_2COOEt$, 2,2-difluoroethanol (CHF_2CH_2OH) and 2-fluoroethanol (CH_2FCH_2OH) were obtained from Lancaster. Ethyl trifluoroacetate (CF_3COOEt) was obtained from Sigma, potassium phosphate from BDH Chemicals, potassium acetate from Riedel-de Haën and tetrabutylammonium hydroxide ($Bu_4N^+OH^-$, 25% in methanol) and sodium hydride (NaH) from Fluka. Reference CF_3CH_2OTf was synthesized according to the method of Gassman and Harrington (25). Reference 2-oxoquazepam and the corresponding *N*-desalkyl compound were supplied by Schering Plough Corporation. AlH_3 was prepared by the method of Yoon and Brown (26) by adding H_2SO_4 (100%, 5.5 µL) (24) dissolved in THF (0.5 mL) to a solution of $LiAlH_4$ (0.2 mmol) in THF (≈1.3 mL) at 0 °C.

Analytical radio-HPLC was performed using an LDC Constametric III pump, a Shimadzu SPD-6A UV-spectrophotometer or a Shimadzu RDI-6A refractive index detector and a Beckman model 170 β-flow radiodetector were used to monitor the UV-absorption or the refractive index and the radioactivity, respectively. A Shimadzu C-R4A integrator was used for peak processing. The HPLC systems were:

A: μBondapak C18 column (Waters 300 x 7.8 mm, 10 μm); CH_3CN/H_3PO_4 (0.01 M) 45:55; flow 4 mL/min; retention times: 3.7 min (CF_3CH_2OH), 6.8 min (CF_3COOEt), 8.2 min ($BrCF_2COOEt$), 10.0 min (CF_3CH_2OTf) and 12.7 min (2-oxoquazepam).

B: Hamilton PRP-1 column (305 x 7 mm, 10 μm); CH_3OH/H_3PO_4 (0.01 M) 30:70; flow 3 mL/min; retention times: 2.8 min (CH_2FCH_2OH), 3.9 min (CHF_2CH_2OH) and 7.0 min (CF_3CH_2OH).

Radio-TLC was performed using Merck 60 F_{254} silica plates. A Bioscan imaging scanner, system 200, was used to scan the TLC plates for radioactivity. The eluent was toluene: ethyl acetate 2:1; R_f = 0.48 (2-oxoquazepam).

Radionuclide production

No-carrier-added $[^{18}F]F^-$ was produced via the $^{18}O(p,n)^{18}F$ reaction using the Scanditronix MC 16 cyclotron at the Karolinska Hospital. [^{18}O]Water (95-98% enrichment, Isotec, obtained from Campro Scientific, Veenendaal, Netherlands) was diluted to 10-50% enrichment using 18 MΩ water produced from a Milli-Q water system. A total volume of 1.7-1.8 mL was irradiated in a high-purity silver target (27) with 17 MeV protons (15 μA) for 30-45 min. After waiting for the decay of ^{13}N also produced during the irradiation, the contents of the target were emptied through silicon tubing into a sterile injection vial for transportation to the radiochemistry laboratory. Although the amount of carrier $^{19}F^-$ present in the target water after bombardment has not been determined, the no-carrier-added $[^{18}F]F^-$ obtained with this system has been used (1, 2, 28, 29) to prepare radiolabelled compounds with specific activities of 74 - 148 GBq/μmol (2000 - 4000 mCi/μmol) at end-of-synthesis.

Ethyl [2-^{18}F]trifluoroacetate

The aqueous solution was added to Kryptofix 2.2.2 (20 mg; 0.053 mmol) and K_2CO_3 (3.7 mg; 0.027 mmol) and the water was azeotropically evaporated with CH_3CN (4 x 1 mL) at 120 °C under a stream of N_2. $BrCF_2COOEt$ (25 μL; 0.195 mmol) dissolved in DMSO (0.5 mL) was added and the mixture was allowed to react for 5 min at 80 °C. The resulting $[^{18}F]CF_3COOEt$ was isolated by distillation with a stream of N_2 at 80 °C.

[2-^{18}F]-2,2,2-Trifluoroethanol

For reduction the $[^{18}F]CF_3COOEt$ was trapped in an AlH_3/THF solution (see preparation under general) at 0 °C. The solution was stirred at 40 °C for 2 min, THF was evaporated with a stream of N_2 at 120 °C before hydrolysis with water (2 mL) at 0 °C. The $[^{18}F]CF_3CH_2OH$ was isolated by distillation with a stream of N_2 at 120 °C.

[2-^{18}F]-2,2,2-Trifluoroethyl triflate

The $[^{18}F]CF_3CH_2OH$ was trapped in 2,6-lutidine (1 mL) at 0 °C. Triflic anhydride (100 μL; 0.59 mmol) was added and the solution was stirred for 1 min before the formed $[^{18}F]CF_3CH_2OTf$ was distilled by a stream of N_2 at 120 °C. The triflate was trapped in toluene (0.3 mL) at -10 °C (ethylene glycol/CO_2).

[N-[2-^{18}F]-2,2,2-Trifluoroethyl]-2-oxoquazepam

Toluene (0.5 mL) was added to *N*-desalkyl-2-oxoquazepam (5 mg; 0.018 mmol) and DMF (≈5%) was added to achieve complete dissolution. A suspension of NaH in toluene (0.15 mL; ≈0.027 mmol) was added and the mixture was stirred for 15 min. The [^{18}F]CF_3CH_2OTf in toluene was added to the sodium salt of the *N*-desalkyl precursor and the solution was heated (120 °C) for 20 min. The reaction mixture was quenched with ethanol (0.1 mL), hexane (2 mL) was added and the mixture was eluted on a SepPak Si cartridge (pretreated with hexane (5 mL)). The SepPak was washed with additional hexane (2 mL) prior to elution of the fluorine-18 labelled products with CH_3CN (2 mL).

Results and Discussion

Incorporation of [^{18}F]F^-

A previous study of α-mono-halo esters (Block et al. (17)) indicated that competion by reaction at the acyl carbon was less for ethyl esters and that fluoro-dehalogenation yields varied with the halogen leaving group, with Br > Cl >> I. Investigations performed here with the difluorinated analogs also indicated that yields decreased with Br > Cl. Therefore, $BrCF_2COOEt$ was used for the subsequent optimizations. It was found that higher radiochemical yields of the trifluoro product, [^{18}F]CF_3COOEt, could be obtained by performing the reaction in DMSO or DMF rather than in CH_3CN used for the mono-halo esters (17). The high boiling solvents offered an additional advantage in that the product (b.p.= 60-62 °C) could be isolated by simple distillation from the reaction medium. DMSO was selected as the solvent since, in DMF, increasing amounts of an unidentified volatile byproduct (#2 below) were also produced with increased time of heating (Table 1).

Table 1: Comparative study [a] of the effect of solvent on the product distribution obtained in the fluoro-debromination of $BrCF_2COOEt$.

Solvent	Time (min)	Byproduct #1 [b] (%)	Byproduct #2 [c] (%)	[^{18}F]CF_3COOEt (%)
CH_3CN	5	6	39	55
DMSO	5	15	5	80
	20	15	5	80
DMF	5	15	15	70
	20	11	40	49

[a] Reaction conditions as described in the experimental. The distributions are for the radiolabelled products detected in the HPLC analysis (see Figure 1 below). Unreacted [^{18}F]F^-, which does not elute from the column, was determined to be 20-30% for all three solvents by eluting an aliquot through a silica column.

[b] Unidentified byproduct with elution time corresponding to that of the hydrolyzed esters.

[c] Unidentified byproduct eluting between the halo-acids and the halo-esters.

Radiochemical conversions to [^{18}F]CF_3COOEt did not increase with reaction times longer than 5 min in any of the three solvents tested. Direct ^{18}F-^{19}F exchange on $BrCF_2COOEt$ (yielding radiolabelled $BrCF_2COOEt$) was not observed for any of the reaction conditions used.

[^{18}F]CF_3COOEt was distilled by continued heating at 80 °C with a N_2 flush and was trapped in ethanol (0 °C) for the HPLC analysis or in the next reaction mixture for conversion to the trifluoroethanol. After distillation for 5-6 min, HPLC analysis of the residue indicated that only byproduct #1 remained in the first vessel. [^{18}F]CF3COOEt was efficiently (>95%) trapped in the cooled reagent solution used for the reduction.

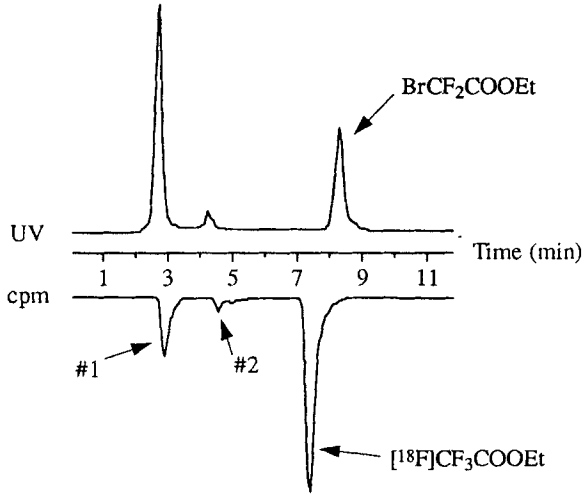


Figure 1:
Radiochromatogram of the reaction mixture from the fluoro-debromination of $BrCF_2COOEt$ performed in DMSO with the Kryptofix/K^+ complex of [^{18}F]F^- (reaction and analysis conditions are described in experimental. Note: at this detector sensitivity the UV peak of CF_3COOEt was not visible).

Reduction

One of the reagents most commonly used to reduce carbonyls to alcohols, $LiAlH_4$, is less appropriate for use in the reduction of α-halo esters since halo-hydrogenolyzation may occur even when the halide is fluorine (30). Such side-reactions could thus produce labelled CF_3-, HCF_2- and H_2CF- alcohols, which in turn would yield a mixture of labelled fluoroalkylated products difficult to separate. Instead AlH_3 prepared *in situ* in THF from $LiAlH_4$ with H_2SO_4 was selected as the reagent since it has been shown to reduce halogen-containing carboxylic esters without significant attack on the halogen (26). Good conversions of [^{18}F]CF_3COOEt to [^{18}F]CF_3CH_2OH were found to require 10 min at 0 °C or 2 min at 40 °C. Under the conditions described in the experimental section, no other ^{18}F-labelled alcohols than [^{18}F]CF_3CH_2OH were observed by radio-HPLC analysis (Figure 2). For isolation, the volatility of CF_3CH_2OH (b.p.=77-80 °C) was utilized. After evaporation of the THF, the metal complex was hydrolyzed and [^{18}F]CF_3CH_2OH distilled with N_2-flow by heating at 120 °C for 5-6 min (<5% remaining in the reaction mixture and essentially complete trapping in the reaction media chosen for the triflate formation).

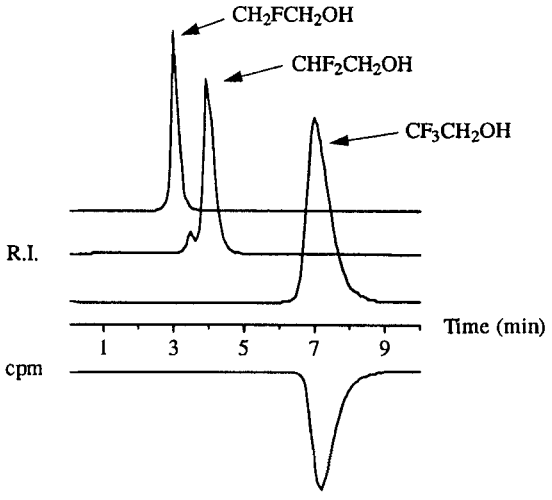


Figure 2:
HPLC analysis of the ^{18}F-labelled alcohol produced in the reduction of $[^{18}F]CF_3COOEt$ to $[^{18}F]CF_3CH_2OH$. The analysis indicates that no labelled alcohols from halo-hydrogenolysis are detectable when AlH_3 was used as the reducing agent.

Triflate formation

To convert the ^{18}F-labelled alcohol to the triflate and isolate the product by distillation, a reaction media was sought with a boiling point considerably higher than that of $[^{18}F]CF_3CH_2OTf$ (b.p. = 89-91 °C (25)). When the reaction of $[^{18}F]CF_3CH_2OH$ with triflic anhydride was performed using 2,6-lutidine (b.p. = 143-145 °C) as both solvent and base, radiochemical yields ≈70-80% (by radioanalytical HPLC) were obtained after 1 min at 0 °C. $[^{18}F]CF_3CH_2OTf$ was easily distilled from the reaction mixture with a stream of N_2 at 120 °C for 5-6 min and could be readily trapped in the solvents tested for the alkylation.

Alkylation

Triflates are often used for the alkylations of particularly unreactive substrates. Product distributions may, however, sometimes be affected by competing reactions with other more reactive components in the media (base, water, solvents, etc.), which has recently been demonstrated for radiolabellings with $[^{11}C]CH_3OTf$ (21). The results obtained here were similar to those reported for the ^{11}C-labelled triflate. When the alkylation was attempted in aprotic, dipolar solvents at high temperatures, polar byproducts were exclusively formed which presumably arose from the hydrolysis of $[^{18}F]CF_3CH_2OTf$ or from its reaction with the solvent. Best radiolabelling results were obtained when dry toluene was used as the solvent with a minimum amount of DMF (≈5%) added to dissolve the *N*-desalkyl-2-oxoquazepam. The conversion of $[^{18}F]CF_3CH_2OTf$ to [*N*-[2-^{18}F]-2,2,2-trifluoroethyl]-2-oxoquazepam was 80-85% after 20 min at 120 °C.

The reaction mixture containing labelled 2-oxoquazepam was eluted through a SepPak Si, primarily to remove toluene which interfered with the HPLC determination of the specific activity. If isolation of the product is desired, such a pre-cleaning could also be used for changing solvents prior to a reversed-phase semi-preparative separation.

Specific activity

The specific activity of the ^{18}F-labelled 2-oxoquazepam synthesized by this method was found to be very low (≈37 MBq/μmol when starting with 1850 MBq [^{18}F]F^-). Using UV-detection to estimate the mass produced, it was found that an isotopic dilution of this order of magnitude had occurred in the first step of the radiolabelling procedure. Additionally it was found that CF_3COOEt was formed even when $BrCF_2COOEt$ was subjected to the conditions used in the fluoro-debromination reaction without [^{18}F]F^- present, but not when the K_2CO_3 was also removed. These observations are similar to results previously reported with α-bromo-α,α-difluorotoluenes (31, 32).

All our attempts to alter reaction parameters to minimize carrier fluorine met with limited success. The probable source, $BrCF_2COOEt$, could not of course be eliminated but the amounts used were decreased. However, at low concentrations, little $BrCF_2COOEt$ remained at the end of reaction and product(s) with the elution characteristics of byproduct #1 were primarily formed. Thus, consistent with the results of Block et al. (17), the radiolabelling yields decreased considerably and the specific activity was therefore essentially unchanged. Decreasing the reaction temperature from 80 °C to 30-40 °C did reduce the relative amounts of unlabelled CF_3COOEt formed. However, the specific activity would have increased only by a factor of ≈5 and would have necessitated finding a new means of isolation since higher temperatures were required to distil the product from the reaction mixture. To reduce the degree of solvation (and thereby the dissociation of halogen from $BrCF_2COOEt$), the fluoro-debromination was also performed in dichloromethane, 1,2-dichloroethane, THF, dioxane, 1,2-dichlorobenzene and toluene. No net effect was observed since the [^{18}F]F^- was generally less solubilized in these solvents and, although the mass produced was lower, the radiolabelling yields also decreased. Other solubilizing agents ($Bu_4N^+OH^-$, Cs_2CO_3, Rb_2CO_3) or potassium salts (bicarbonate, phosphate, oxalate and acetate) did not significantly improve the specific activity. Microwave treatment to reduce the time of heating also gave comparable results.

Direct ^{18}F-^{19}F exchange has been deliberately utilized many times as a means of introducing fluorine-18 into organic molecules (see references in 33) and may, in fact, be the preferred exchange reaction for many aromatic substrates (34). Activated mono- and/or polyhalogenated alkyl groups have also been used as substrates for radiofluorinations. An increasing number of such studies indicate that when one of the halogens is fluorine, the radiolabelled product may contain a large amount of unlabelled product which is not in proportion to the amount of carrier normally present in the radionuclide preparation.

Two thorough investigations were recently reported of the effect of reaction parameters on isotopic dilution observed in the radiofluorinations of 4-chloro-α-bromo-α,α-difluorotoluene (32) and 4-nitro-α-bromo-α,α-difluorotoluene (31). Both studies indicated that the specific activity could be increased by lowering the reaction temperature and the amount of substrate. Das and Mukherjee (31) also reported that the unlabelled product was not synthesized in the absence of K_2CO_3, although an alternative base was not used. With optimal radiolabelling conditions, specific activities of 1850 (32) and 2590 MBq/μmol (31) starting with 888 and 3700 MBq [^{18}F]F^-, respectively, were obtained. The specific activities obtained in the present study were, at best, 1-2 orders of magnitude lower, primarily because an analogous reduction in the amount of substrate used resulted in such a dramatic reduction in the radiolabelling yields.

Hammadi and Crouzel (32) proposed that the isotopic dilution originated from superconjugation of the aromatic substrate, releasing fluoride at elevated temperatures. A similar mechanism had been previously proposed by Ido and collaborators (35) to explain ^{18}F-^{19}F exchange on benzotrifluoride at elevated temperatures. On the other hand, facile radiofluorination of α-bromo-α,α-difluoromethylbenzophenones reportedly yielded high specific activity trifluoromethylbenzophenone, but the effective specific activity was only 37 MBq/μmol due to chemical contamination by the starting material (36). Angelini et al. (37) proposed that the radiofluorinating agent $[^{18}F]HF/Sb_2O_3$, could be used in no-carrier-added and carrier-added routes to the trifluoromethylaromatics, but unfortunately has only reported specific activities with a carrier-added approach (38).

Fluorine-containing aliphatic compounds have also been proposed to drop $^{19}F^-$ enabling fluoride ions to exchange in the solvent. Inhalation anesthetics were successfully labelled by a net ^{18}F-^{19}F exchange (12), which was proposed to involve a carbanion intermediate that subsequently lost $^{19}F^-$ to form an alkene before $[^{18}F]F^-$ added. In the reaction of $[^{18}F]F^-$ with 1,1,2-trifluoroethene to produce [1-^{18}F]1,1,1,2-tetrafluoroethane, coproduction of unlabelled product was also observed due to generation of $^{19}F^-$ during the radiolabelling reaction (13). In nucleophilic displacements attempted with $[^{18}F]F^-$ on the 2,2,2-trifluoroethanesulfonate (tresylate) of 2-pyrrolidinol, isotopic dilution was also reported (39). The carrier was proposed to come from extraction of the acidic proton in the trifluoroethyl group by a base in the system generating a carbanion which loses $^{19}F^-$ from the adjacent carbon to form the ethene.

In polar media $BrCF_2COOEt$ may presumably undergo solvolysis releasing halogens for exchange in the solvent. Our attempts to reduce this solvolysis have unfortunately been accompanied by corresponding reductions in the radiolabelling yields and therefore no net improvements in the specific activity. In drug design the CF_3 group is an important structural unit for increasing the lipophilicity of a lead molecule and it is a bioisotere of halogens and nitriles (40). A means of generating this unit radiolabelled with high specific activity would therefore increase radiochemists' means of manipulating radiotracer structure to alter biodistribution. Alternative routes for the production of this unit are thus being investigated.

Conclusions

A three-step method for the production of 2,2,2-trifluoroethyl triflate labelled in the two position with $[^{18}F]F^-$ is presented. The total synthesis time, including three distillations, was 25-30 min, starting from the dried Kryptofix/K^+ salt of $[^{18}F]F^-$. The successful reaction of $[^{18}F]CF_3CH_2OTf$ with the sodium salt of an *N*-desalkyl-1,4-benzodiazepin-2-one in toluene (80-85% yields in 20 min) demonstrated its potential capability as an alkylating agent. Isotopic dilution occurring during the fluoro-debromination reaction, however, necessitates the investigation of an alternative route for introducing $[^{18}F]F^-$ for reactions requiring high specific activity radiolabelling precursors.

Acknowledgements

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