JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2005; **48**: 557–568.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.949

Research Article

Improved synthesis of [^{18}F]fluoromethyl tosylate, a convenient reagent for radiofluoromethylations

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Summary

The utility of [^{18}F]fluoromethyl tosylate as an [^{18}F]fluoromethylation reagent has been reexamined. The preparation of this potentially useful compound from the reaction of *bis*(tosyloxy) methane with ^{18}F- was reported several years ago, but it had not found use as a labeling reagent. When the reported reaction of *bis*(tosyloxy) methane with ^{18}F- was carried out, [^{18}F]fluoromethyl tosylate was formed along with [^{18}F]tosyl fluoride. The product ratio depended upon reaction conditions, with the yield of [^{18}F]fluoromethyl tosylate usually in the range of 25–40%. Addition of a small amount of water to the reaction mixture resulted in a significant increase in the yield of [^{18}F]fluoromethyl tosylate. Reaction conditions were defined that produced a yield of $71 \pm 6\%$ of [^{18}F]fluoromethyl tosylate (decay corrected). The product was conveniently purified by alumina chromatography. Reaction of [^{18}F]fluoromethyl tosylate with the (des-fluoromethyl) fluticasone propionate thioacid precursor produced [^{18}F]fluticasone propionate in improved yield (16%, from fluoride in production-scale runs) over other synthesis methods. Similarly, formation of [^{18}F]choline, [^{18}F]fluoromethionine and *N*-([^{18}F]fluoromethyl)spiperone from the reaction of [^{18}F]fluoromethyl tosylate with corresponding precursors was examined. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: fluorine-18; fluoromethylation; [^{18}F]fluoromethyl tosylate; fluticasone propionate

Introduction

In conjunction with other work, the preparation [^{18}F]fluticasone propionate ([^{18}F]FP) was desired. The synthesis of [^{18}F]FP by the reaction shown in

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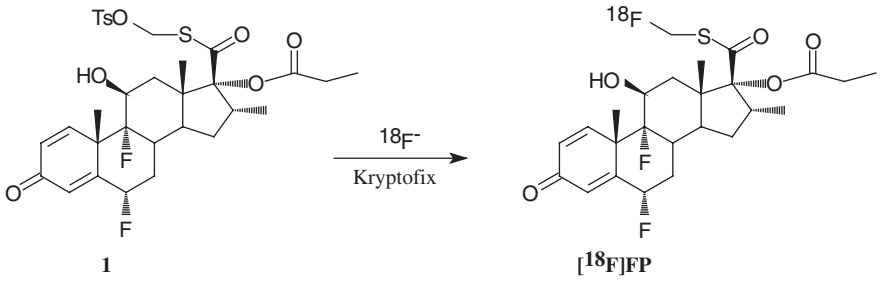
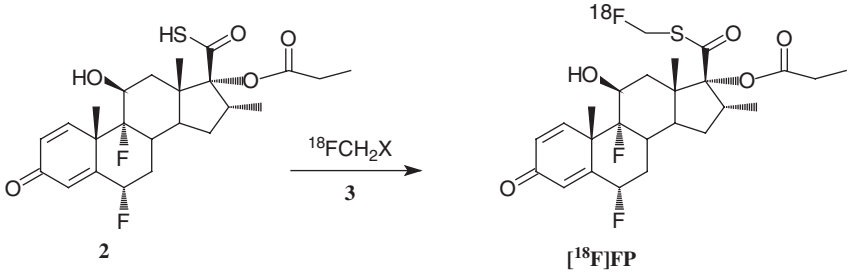
Contract/grant sponsor: GlaxoSmithKline

Received 10 September 2004
Revised 22 September 2004
Accepted 10 March 2005



1 [18F]FP

Scheme 1. Published route of Aigbirhio *et al.* for the preparation of [18F]FP



2 [18F]FP

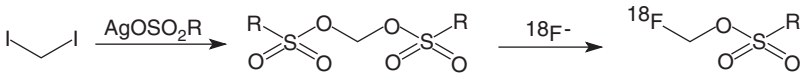
Scheme 2. Possible alternate route for the preparation of [18F]FP

Scheme 1 has been reported by Aigbirhio *et al.*,[1] and Constantinou *et al.*,[2,3] but the precursor **1** has limited stability in the reaction solution, resulting in low and variable yields of [18F]FP. Therefore, the feasibility of producing [18F]FP from the reaction of the FP thioacid precursor **2** with a suitable [18F]fluoromethyl derivative **3** was explored, as shown in Scheme 2.

At the time this work was begun, [18F]fluoromethyl bromide[4–9] (**3**, $X = \mathrm{Br}$) and [18F]fluoromethyl iodide[5,8,10,11] (**3**, $X = \mathrm{I}$), had been reported as reagents for introduction of the [18F]fluoromethyl group. These reagents suffer from relatively low reactivity and are somewhat inconvenient to prepare. The preparation of [18F]fluoromethyl triflate (**3**, $X = \mathrm{OTf}$) has recently been reported.[12,13] Although this precursor is highly reactive, its preparation involves two steps and requires a specialized synthesis system. It was hoped some of the disadvantages of these labeling reagents could be circumvented.

The mesylate and tosylate analogs of **3** ($X = \mathrm{OMs}$ and OTs) were first prepared by Coenen and Block several years ago,[14,15] but no additional literature references for these compounds were found. The preparation of these reagents is depicted in Scheme 3.

Coenen and Block reported that the reaction of diiodomethane with the silver salt of the appropriate sulfonic acid in refluxing acetonitrile yielded the corresponding *bis*(sulfonyloxy) methane derivative.[14–16] Reaction of



Scheme 3. Preparation of [^{18}F]fluoromethyl mesylate and tosylate (R = methyl and *p*-tolyl, respectively)

bis(mesyloxy) methane and *bis*(tosyloxy) methane with ^{18}F- resulted in the formation of [^{18}F]fluoromethyl mesylate and [^{18}F]fluoromethyl tosylate in approximately 80 and 40% yield, respectively.[14,15] (chloromethyl-, bromomethyl- and iodomethyl tosylate have been reported)[17]. The yield of [^{18}F]fluoromethyl sulfonate was found to increase dramatically as the concentration of *bis*(sulfonyloxy) methane was increased over the range of 0.02–0.3 M.[14,15] It was stated that the limited solubility of *bis*(tosyloxy) methane (maximum 0.25 M) is responsible for the lower yield of the tosyl derivative.[14,15] Reaction of [^{18}F]fluoromethyl mesylate and [^{18}F]fluoromethyl tosylate with *p*-chlorophenol was reported to produce *p*-chloroanisole in 1 and 23% yield, respectively.[15] No other reactions of these reagents were reported; however the results appeared promising for applications involving the labeling of molecules of interest with ^{18}F. Therefore [^{18}F]fluoromethyl mesylate and [^{18}F]fluoromethyl tosylate were reexamined in this work as potential [^{18}F]fluoromethylation reagents.[†]

Results and discussion

Reaction of *bis*(mesyloxy) methane with ^{18}F- resulted in the formation of [^{18}F]fluoromethyl mesylate in good yield. Reaction with **2** produced only a trace of [^{18}F]FP, consistent with the result of the reported reaction with *p*-chlorophenol.[15] Consequently, subsequent experiments utilized [^{18}F]fluoromethyl tosylate.

Coenen and Block examined the effect of solvent, reaction time and substrate concentration on the reaction of *bis*(tosyloxy) methane with ^{18}F-.[14,15] Based upon their observations, some modifications were made to determine the affect on yield. In the present work, the reaction was carried out in acetonitrile, dimethylformamide and acetone, using ^{18}F- solubilized with tetrabutylammonium bicarbonate (TBABC), Kryptofix® 2.2.2(Kryptofix)/K_2CO_3, and Kryptofix/$KHCO_3$, and with varying amounts of complexing agent and *bis*(tosyloxy) methane. None of the modifications made in the present work resulted in an improvement in yield.

The reaction of ^{18}F- with *bis*(tosyloxy) methane resulted in the formation of [^{18}F]fluoromethyl tosylate and a moderately volatile and less polar product,

[†] We[18] and Lim and coworkers[19] have presented preliminary results using [^{18}F]fluoromethyl tosylate as a [^{18}F]fluoromethylation reagent. Unlabelled fluoromethyl tosylate has been recently reported.[13,20]

based upon analysis by TLC and HPLC.[18] The reaction of *bis*(tosyloxy) methane with unlabeled KF produced fluoromethyl tosylate[14,15] and the same byproduct. When ^{18}F- was solubilized with TBABC or low levels of Kryptofix /K_2CO_3, the byproduct predominated. By using a larger amount of Kryptofix/K_2CO_3, [^{18}F]fluoromethyl tosylate was the major labeled product. The effect of solubilization agent upon product distribution is presented in Table 1.

The yield of [^{18}F]fluoromethyl tosylate was usually in the 25–40% range, consistent with the reported results.[14,15] Although the yield of [^{18}F]fluoromethyl tosylate was relatively reproducible, the yield of byproduct was highly variable. Total consumption of fluoride ion could be raised significantly higher than 40%, but the increase was due only to increased formation of the byproduct.

The exclusive formation of the byproduct from this reaction has recently been reported, and its identity as [^{18}F]difluoromethane was suggested.[19] However, in this work the byproduct was identified as [^{18}F]tosyl fluoride. The reactions of both ^{18}F- and KF with *bis*(tosyloxy) methane produced material which had the same R_f (normal-phase TLC) and retention time (reversed-phase HPLC) as authentic unlabeled tosyl fluoride. De Kleijn and coworkers have reported that [^{18}F]tosyl fluoride is formed from reaction of ^{18}F- with tosyl chloride.[21,22] The product of a separate reaction of tosyl chloride with high specific activity ^{18}F- also coeluted on TLC and HPLC with the reaction byproduct. Further, there was no evidence that [^{18}F]difluoromethane was formed in the reaction, as previously suggested.[19] Production of [^{18}F]difluoromethane would require that two fluoride ions react with a single precursor in a no-carrier-added reaction. This is a highly unlikely event. No other labeled products were observed in any experiments and typically $\geqslant$95% of the initial radioactivity was accounted for by the observed products and unreacted fluoride. Thus, at most a trace of [^{18}F]difluoromethane could have been produced.

Table 1. Effect of TBABC and amount of Kryptofix on product ratio of ^{18}F-CH_2-OTs and [^{18}F]tosyl fluoride[a]

Kryptofix[b] (mg)	Product distribution ^{18}F-CH_2-OTs: [^{18}F]tosyl fluoride
1.5	9:91
9	26:74
12	36:64
15	62:38
18	68:32
TBABC[c]	15:85 $\pm$ 6, $n = 15$

[a] Data from selected experiments demonstrating a trend.
[b] Reaction conditions: 10 mg *bis*(tosyloxy) methane, 100 µl ACN, Kryptofix/K_2CO_3 = 3.8, 110°C, 10 min, $n = 1$.
[c] Reaction conditions: 5–10 mg *bis*(tosyloxy) methane, 5–10 mg TBABC, 100 µl ACN, 110°C, 10 min.

Table 2. Results of varying the amount of water, *bis*(tosyloxy) methane, and K-Fix of the yield of ^{18}F-CH_2-OTs

Run[a]	H_2O (μl)	*bis*(tosyloxy) methane (mg)	Kryptofix (mg)	Radiochemical yield[b] (%)
1	0	10	15	42
2[c]	0	10	15	29
3	0	7.5	15	55
4	0	5	10	38
5	2.5	5	10	74
6	2.5	5	10[d]	75
7	2.5	5	10	62
8	5	5	10	71
9	5	5	10	65
10	5	7.5	15	83
11	5	7.5	12	69
12	5	7.5	10	67
13	5	7.5	7.5	62
14	5	10	15	76
15[c]	5	10	15	76
16[c]	7.5	10	15	74
17[c]	10	10	15	72

[a] Reaction conditions: 100 μl ACN, 110°C, Kryptofix/K_2CO_3 = 5, 10 min.
[b] Decay corrected.
[c] 150 μl ACN.
[d] Kryptofix/K_2CO_3 = 2.5.

During attempts to selectively decompose [^{18}F]tosyl fluoride, it was discovered that addition of a small amount of water to the reaction resulted in a significant increase in the yield of [^{18}F]fluoromethyl tosylate. Various conditions were examined to optimize the yield of [^{18}F]fluoromethyl tosylate. The results of 17 syntheses are summarized in Table 2. In reactions 1–4 no water was added, with an average yield of $41 \pm 11\%$. Reactions 5–17 contained various amounts of water (2.5–10 μl), *bis*(tosyloxy) methane (5–10 mg) and Kryptofix (7.5–15 mg). The average yield for these reactions was significantly higher at $71 \pm 6\%$.

Upon completion of the reaction, the solvent was evaporated, the residue was dissolved in a 9:1 mixture of hexanes:dichloromethane and passed over a short column of alumina. Most of the [^{18}F]tosyl fluoride was eluted in this fraction. The product was obtained by elution with a 95:5 mixture of hexanes:ethyl acetate. By using 4 ml of 95:5 hexanes:ethyl acetate, excess *bis*(tosyloxy) methane, ^{18}F- and Kryptofix are strongly retained on the column and [^{18}F]fluoromethyl tosylate was completely eluted. Evaporation of solvent afforded [^{18}F]fluoromethyl tosylate ready for reaction with the appropriate precursor. Figure 1 shows the TLC analysis of a typical crude reaction mixture, the activity eluted with 9:1 hexanes:dichloromethane and the activity eluted with 95:5 hexanes:ethyl acetate.

Two factors to explain the affect of water on the reaction were considered. One possibility was that the fluoride liberated from the selective hydrolysis of

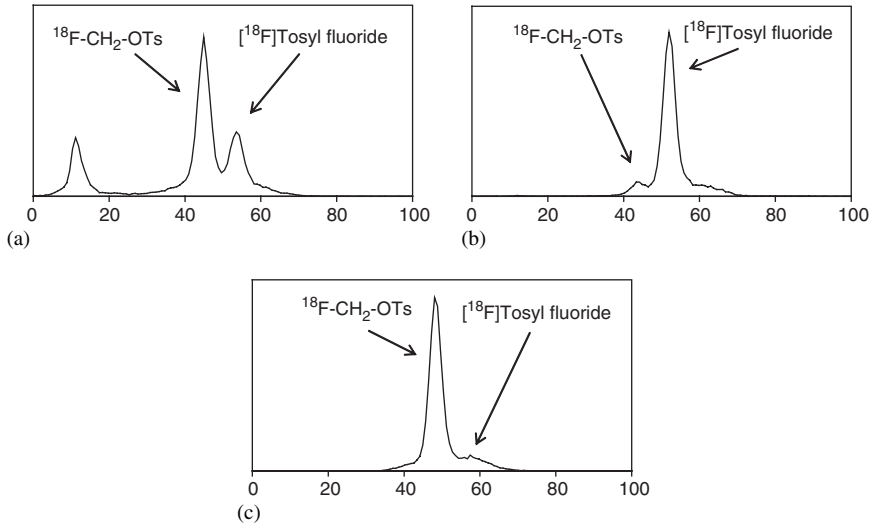


Figure 1. TLC analysis of (a) crude reaction mixture, (b) activity eluted with 9:1, hexanes:dichloromethane, (c) activity eluted with 95:5, hexanes:ethyl acetate (see Experimental Section for details)

[^{18}F]tosyl fluoride would be available to react with precursor, thus driving the reaction toward the formation of [^{18}F]fluoromethyl tosylate. The other possibility was that the water affected the reactivity of the fluoride. Briard and Pike have recently reported a significant increase in fluorination yield upon addition of a small amount of water to the reaction mixture.[23] They attributed the higher yield to increased solubility of the hydrated fluoride ion complex.

In one experiment, an anhydrous reaction mixture was heated for 10 min, the product distribution was determined (unreacted fluoride, [^{18}F]fluoromethyl tosylate and [^{18}F]tosyl fluoride), water was added and heating was continued for an additional 10 min. The yield of [^{18}F]fluoromethyl tosylate increased from 42 to 51% and the yield of [^{18}F]tosyl fluoride decreased from 25 to 14% after the addition of water. This demonstrates that [^{18}F]tosyl fluoride was selectively hydrolyzed under these conditions. However, the yield of [^{18}F]fluoromethyl tosylate was significantly lower than when water was added at the beginning of the reaction ($71 \pm 6\%$, Table 2), indicating this was not the only factor involved. When the reaction was carried out under anhydrous conditions or the water was added after heating for 10 min, at least 35% of unreacted fluoride remained; much of this was retained on the walls of the reaction vial. When water was added at the beginning (runs 5–17, Table 2), $<20\%$ of unreacted fluoride remained. Thus, an increased initial activity and/or solubility of fluoride may also be a factor, possibly as suggested by Briard and Pike.[23]

With a convenient and reproducible procedure for production of [^{18}F]fluoromethyl tosylate in hand, the preparation of [^{18}F]FP was explored. It was found that reaction of [^{18}F]fluoromethyl tosylate with **2** in acetonitrile at 110°C for 1 h using K_2CO_3 as base lead to the formation of [^{18}F]FP in an average of 76 ± 11% yield (decay corrected, $n = 5$), based upon TLC analysis of the reaction mixture. After evaporation of the solvent, the residue was purified by normal-phase HPLC.

For production runs carried out remotely in a hot cell, [^{18}F]FP was obtained in ~15% chemical yield (decay corrected radiochemical yield, based upon starting ^{18}F-) with a radiochemical purity of >95% and a specific activity of about 1000 mCi/mol 1.75–2 h after EOB. In these runs, the [^{18}F]tosyl fluoride was not separated, but carried on and the reaction of [^{18}F]fluoromethyl tosylate with **2** was carried out for 20 min (vs 1 h for the method development runs). The presence of [^{18}F]tosyl fluoride did not interfere with the coupling reaction nor purification of [^{18}F]FP and the reduction in yield from the shorted reaction was considered an acceptable compromise in order to reduce the total synthesis time. The remote process has not been optimized; doing so should result in a significant improvement in the overall radiochemical yield.

The reactions of *N*,*N*-dimethylamino ethanol, homocysteine thiolactone and spiperone with [^{18}F]fluoromethyl tosylate to produce [^{18}F]choline, [^{18}F]fluoromethionine and *N*-([^{18}F]fluoromethyl)spiperone, respectively, were briefly examined. The reaction conditions employed were the same as those typically used for the published reactions of [^{11}C]CH_3I with each precursor to produce the corresponding [^{11}C]methyl derivative, and were not optimized. The products were not thoroughly characterized, but in each case the ^{18}F-labeled product eluted from HPLC with a very similar retention time to the corresponding [^{11}C]methyl derivative.

The yield of [^{18}F]choline (92 ± 12% decay corrected, $n = 5$, range 70–98%) is comparable to the yields reported from the reaction of *N*,*N*-dimethylamino ethanol with [^{18}F]fluoromethyl bromide[6] and [^{18}F]fluoromethyl triflate.[12] Although the yield of [^{18}F]fluoromethionine was only 14 ± 5% (decay corrected, $n = 5$, range 10–21%), it is most likely that the low yield was due to the non-optimized reaction conditions rather than an unexpected lack of reactivity of [^{18}F]fluoromethyl tosylate. The synthesis of *N*-([^{18}F]fluoromethyl)spiperone was carried out twice, resulting in yields of 37 and 69%. It is noteworthy that in previous attempts to produce *N*-([^{18}F]fluoromethyl)spiperone from the reaction of spiperone with [^{18}F]fluoromethyl iodide, no reaction was observed.[24] The yields from the reactions with homocysteine thiolactone and spiperone are similar to those obtained from the reaction of [^{11}C]methyl iodide using the same reaction conditions.

Experimental

Reagents and solvents were obtained from Aldrich Chemical Co. and Fisher Scientific and used without further purification unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under argon prior to use. Acetonitrile was freshly distilled from calcium hydride prior to use. Flash column chromatography was performed on 230 mesh silica gel. Thin layer chromatography (TLC) was carried out on E. Merck silica gel 60 F254 analytical plates. Radiation detection was performed with a Bioscan model AR-2000 thin layer plate reader using WinScan Version 3.07 software, and mass detection by UV light. High-performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1090 system with a photodiode array detector and a Beckman model 170 radiation detector. Elution conditions for TLC and HPLC varied and are specified individually for each compound below. *Bis*(tosyloxy) methane was prepared as previously reported from diiodomethane and an excess of silver tosylate,[16] and purification was accomplished by flash chromatography on silica gel, eluting with a 4:1 mixture of hexanes:ethyl acetate.

[^{18}F]fluoromethyl tosylate

^{18}F- (obtained by 17 MeV proton bombardment of [^{18}O]H_2O[25]) was passed through anion exchange resin and [^{18}O]H_2O was recovered. ^{18}F- was eluted with aqueous potassium carbonate and added to 10–15 mg (26.6–39.8 μmol) 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8,8,8]hexacosane (Kryptofix). If necessary, aqueous potassium carbonate solution was added in order to achieve the desired Kryptofix/K_2CO_3 ratio (usually 2.5–5.0). The water was evaporated under reduced pressure at 110°C and dried by coevaporation with acetonitrile. A solution of 5–10 mg (14.0–28.1 μmol) *bis*(tosyloxy)methane dissolved in 100–200 μl anhydrous acetonitrile containing 0–10 μl of water was added and heated for 10 min at 110°C. The reaction mixture was cooled and the solvent evaporated under reduced pressure. The residue was thoroughly mixed with 200 μl of dichloromethane, after which 1.3 ml of hexanes was added and the mixture was passed over a small (ca. 150 mg) column of neutral alumina. The column was eluted with 3 ml of 95:5 hexanes:ethyl acetate. The combined organic fraction was concentrated under reduced pressure and the residue was used as such for the coupling reaction.

The reaction mixture was analyzed by TLC (plate developed twice with 4:1 hexanes:ethyl acetate, R_f 0.45, [^{18}F]fluoromethyl tosylate; 0.55 [^{18}F]tosyl fluoride), and by HPLC (4.6 × 250 mm Alltech Econosphere 5μ C_{18}). HPLC was eluted at 1 ml/min with a linear gradient of water:methanol (each 25 mM NH_4OAc) 55:45 to 40:60 over 25 min (R_T: 10.9 min, [^{18}F]fluoromethyl tosylate; 14.1 min, [^{18}F]tosyl fluoride).

[^{18}F]tosyl fluoride

A solution of 9.4 mg (25.0 μmol) Kryptofix® 2.2.2(Kryptofix) and 2.5 mg (18.1 μmol) K_2CO_3 dissolved in 150 μl of water was mixed with 115 μl of an aqueous solution containing 3.7 mCi of ^{18}F-. The resulting solution was dried under reduced pressure at 110°C and then by coevaporation with anhydrous acetonitrile. A solution of 3.4 mg (17.8 μmol) of tosyl chloride in 100 μl of acetonitrile was added. The mixture was heated at 110°C for 10 min, cooled and passed over a short column (ca. 150 mg) of neutral alumina. The vial was rinsed with 4 × 200 μl acetonitrile; each rinse was passed over the alumina. The solution was analyzed by TLC as described for [^{18}F]fluoromethyl tosylate. Part of the solution was combined with the product obtained from the reaction of ^{18}F- and *bis*(tosyloxy) methane, and this mixture was analyzed by TLC (as above, R_f 0.55) and by HPLC (as above, R_T 14.1 min).

[^{19}F]fluoromethyl tosylate

A mixture of 15 mg (39.8 μmol) Kryptofix, 2.6 mg (44.8 μmol) KF and 11 mg (30.9 μmol) *bis*(tosyloxy) methane in 250 μl of acetonitrile was heated at 110°C for 2 h. The reaction mixture was cooled and 5 μl was diluted with 1 ml of acetonitrile. This solution was analyzed by TLC (as above), and HPLC (as above). An authentic sample of tosyl fluoride was mixed with the solution and it was reanalyzed. The tosyl fluoride comigrated with the R_f 0.55 product upon TLC analysis and coeluted with the R_T 14.1 min product upon HPLC analysis.

[^{18}F]fluticasone propionate

Approximately 500 mCi of ^{18}F- was obtained by elution from the ion exchange resin with 0.8 ml of an aqueous solution of potassium carbonate (containing 3 mg K_2CO_3). The solution was heated under reduced pressure at 110°C and dried by coevaporation with acetonitrile. During the drying process, a solution of 15.3 mg (40.6 μmol) of Kryptofix dissolved in 100 μl of acetonitrile was added. When dry, a solution of 10.4 mg (29.2 μmol) *bis*(tosyloxy)methane dissolved in 200 μl of anhydrous acetonitrile containing 10 μl of water was added. After heating at 110°C for 10 min, the reaction mixture was concentrated under reduced pressure. The residue was thoroughly mixed with 200 μl of dichloromethane, after which 1.3 ml of hexanes was added and the mixture was passed over a small (ca. 150 mg) column of neutral alumina into a vial containing 2.0 mg (14.5 μmol) of K_2CO_3. The column was eluted with 3 ml of 95:5 hexanes:ethyl acetate. The combined organic fraction was concentrated under reduced pressure at about 50°C. When most of the solvent had been removed, 2.3 mg (4.9 μmol) of the *des*-fluoromethyl fluticasone thioacid **2** dissolved in 0.4 ml of ethyl acetate was added. The remaining solvent was carefully evaporated. The residue was dissolved in 150 μl of acetonitrile and

the mixture was heated at 110°C for 20 min. The reaction mixture was cooled and evaporated under reduced pressure. The residue was dissolved in 1 ml of 3:1 hexanes:ethyl acetate and purified by HPLC (4.6 × 250 mm Alltech Econosil 10μ silica column eluted with 70:30:1 hexanes:ethyl acetate:acetonitrile at 2.5 ml/min). Thirty-six millicurie was obtained (16%, decay corrected, based on ^{18}F-) 120 min after EOB. The purified product was analyzed by TLC using a 1:1 mixture of hexanes:ethyl acetate ($R_f = 0.40$) and by HPLC using a 4.6 × 250 mm Alltech Econosphere 5μ C_{18} column eluted with a mixture of 30:70 water:acetonitrile (each 25 mM ammonium acetate) at 1 ml/min (retention time = 8.1 min).

[^{18}F]fluorocholine

The reaction of ^{18}F- with *bis*(tosyloxy)methane was carried out as described above. After elution from the neutral alumina column and evaporation of the solvent, the residue was dissolved in anhydrous THF and a 50 μl aliquot of this solution was added to a vessel containing 150 μl (133 mg, 1.5 mmol) of *N*,*N*-dimethylethanolamine and 2 μl of 0.1 M potassium carbonate. The vessel was heated at 120°C for 5 min. The solvent was evaporated under reduced pressure at 120°C. The reaction mixture was analyzed by HPLC using a 4.6 × 250 mm Alltech Econosil 10μ C_{18} column eluting with an 85:15 mixture of 20 mM aqueous ammonium acetate:acetonitrile at 2 ml/min (retention time = 3.9 min, retention time of [^{11}C]choline = 3.6 min). The average yield was 92 ± 12% (decay corrected radiochemical yield, $n = 5$), based upon [^{18}F]fluoromethyl tosylate.

[^{18}F]fluoromethionine

The reaction of ^{18}F- with *bis*(tosyloxy)methane was carried out as described above. After elution from the neutral alumina column and evaporation of the solvent, the residue was dissolved in anhydrous THF and a 50 μl aliquot of this solution was added to a vessel containing 1 mg (6.5 μmol) of L-homocysteine thiolactone HCl, 100 μl of water, 250 μl of THF, and 15 μl of 1 M NaOH. After heating at 70°C for 10 min, 10 μl of 1 M HCl was added and the solvent was evaporated under reduced pressure at 150°C. The reaction mixture was analyzed by HPLC using a 4.6 × 250 mm Alltech Econosil 10μ C_{18} column, eluting with 1 mM aqueous NaH_2PO_4 at 2 ml/min (retention time = 5.3 min, retention time of [^{11}C]methionine = 3.5 min). The average yield was 14 ± 5% (decay corrected radiochemical yield, $n = 5$), based upon [^{18}F]fluoromethyl tosylate.

N-([^{18}F]fluoromethyl)spiperone

The reaction of ^{18}F- with *bis*(tosyloxy)methane was carried out as described above. After elution from the neutral alumina column and evaporation of the

solvent, the residue was dissolved in anhydrous THF and a 50 µl aliquot of this solution was added to a vessel containing 1 mg (2.5 µmol) of spiperone, 150 µl of THF and 2 µl of 0.4 M tetrabutylammonium hydroxide. After heating at 85°C for 2 min, the solvent was evaporated under reduced pressure at 100°C. The reaction mixture was analyzed by HPLC using a 4.6×250 mm Alltech Econosphere 10µ silica column, eluting with a 95:4.8:0.2 mixture of chloroform:ethanol:acetic acid at 2 ml/min (retention time = 4.4 min, retention time of [^{11}C]*N*-methylspiperone = 4.6 min). The synthesis was carried out twice, resulting in yields of 37 and 69% (decay corrected radiochemical yield), based upon [^{18}F]fluoromethyl tosylate.

Conclusion

The preparation of [^{18}F]fluoromethyl tosylate was reexamined. Reaction of *bis*(tosyloxy)methane with ^{18}F- carried out using previously reported conditions[14,15] led to the formation of [^{18}F]fluoromethyl tosylate and [^{18}F]tosyl fluoride. Labeled tosyl fluoride was identified by chromatographic comparison with authentic material and with [^{18}F]tosyl fluoride prepared from the reaction of tosyl chloride and ^{18}F-. Inclusion of a small amount of water in the reaction mixture significantly increased the yield of [^{18}F]fluoromethyl tosylate. The reaction of [^{18}F]fluoromethyl tosylate with FP thioacid precursor **2** lead to the formation of [^{18}F]FP in $76 \pm 11\%$ yield (decay corrected, $n = 5$). Reaction of [^{18}F]fluoromethyl tosylate with *N*,*N*-dimethylamino ethanol, homocysteine thiolactone, and spiperone resulted on the formation of [^{18}F]choline, [^{18}F]fluoromethionine and *N*-([^{18}F]fluoromethyl)spiperone, respectively.

Acknowledgements

Financial support of this work by GlaxoSmithKline is gratefully acknowledged.

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