ARYLTRIMETHYLAMMONIUM TRIFLUOROMETHANESULFONATES AS PRECURSORS TO ARYL [^{18}F]FLUORIDES: IMPROVED SYNTHESIS OF [^{18}F]GBR-13119

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SUMMARY

Aromatic nucleophilic substitution of various trimethylammonium trifluoromethanesulfonates with [^{18}F]fluoride has been evaluated. Fluorinations were studied over a temperature range of 45-165°C, with decay corrected yields ranging from 20-80%. [^{18}F]GBR 13119, 1-[2-{(4-[^{18}F]fluorophenyl)(phenyl)methoxy}ethyl]-4-(3-phenylpropyl)piperazine, a potential radiotracer for the dopamine uptake system, has been prepared in no-carrier-added form from 4-N,N,N,-trimethylaniliniumphenylmethanone trifluoromethanesulfonate. Purification by solid-phase techniques yielded the product in 20% decay corrected radiochemical yield and >98% radiochemical and chemical purity without HPLC.

KEY WORDS: Trimethylammonium trifluoromethanesulfonates, Fluorine-18, [^{18}F]GBR 13119, Aromatic nucleophilic substitution

INTRODUCTION

We recently developed and reported the synthesis of [^{18}F]GBR 13119, a presynaptic dopamine uptake antagonist (1). This synthesis involved [^{18}F]-fluorination via aromatic nucleophilic substitution of 4-nitrobenzophenone. The product, no-carrier-added (NCA) [^{18}F]GBR 13119, was obtained along with a trace amount of the corresponding nitro-substituted derivative as well as a second chemical impurity 1-(2-hydroxyethyl)-4-(3-phenylpropyl)piperazine. For human

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studies, removal of these impurities from the product is essential, and can be accomplished by HPLC. In our continuing efforts to simplify aromatic nucleophilic substitution by $^{18}F^-$ and to provide for simplified product work-up and isolation, we have investigated aryl-trimethylammonium salts as useful precursors to NCA ^{18}F-labeled aryl fluorides. Cationic precursors have been previously studied for the preparation of ^{18}F-labeled radiopharmaceuticals (2,3,4,5,6), but nitro groups (1,3,13,14) remain as the predominant leaving group in aromatic nucleophilic fluorinations. We report here the a study of trimethylammonium trifluoromethanesulfonates as simple to prepare, highly reactive precursors for aryl [^{18}F]-fluorinations, and their application to an improved synthesis of [^{18}F]GBR 13119.

EXPERIMENTAL

Materials and Methods

All reagents and N,N-dimethylamines except for the acetophenone derivative were purchased from Aldrich Chemical Co. N,N-dimethyl-aminoacetophenone was purchased from Pfaltz and Bauer, Inc. Substituted phenyltrimethylammonium perchlorates (**8-10**) were prepared according to established procedures from the corresponding aniline, methyl iodide, and silver perchlorate (3,11). Thin layer chromatography (TLC) was performed using Merck silica gel plastic backed TLC plates. 1-(2-hydroxyethyl)-4-(3-phenylpropyl)piperazine and GBR 13119 were prepared by literature methods (7). HPLC was performed using Varian SI-10 (4 mm x 30 cm) and Phenomenex Maxsil 5 μC_8 (4.6 mm x 15 cm) columns. Elemental analyses were performed by Spang Micro-analytical Laboratory, Eagle Harbor, MI. Melting points are reported uncorrected. Infrared (IR) spectra were recorded with a Beckman AccuLab 8. Nuclear magnetic resonance (^1H NMR) spectra were recorded with a Bruker WM 360; data is expressed relative to TMS as an internal standard.

Preparation of Nucleophilic [^{18}F]Fluoride Ion

[^{18}F]Fluoride ion was produced by cyclotron irradiation of oxygen-18 enriched water (86% isotopic enrichment; Mound Laboratories) held in an all-silver target (1 mL target volume).

An aliquot of the [^{18}O]water/[^{18}F]fluoride solution was converted to NCA Kryptofix/K_2CO_3/^{18}F (Kry/K/^{18}F) (9); prepared by addition of the [^{18}O]water/[^{18}F]fluoride solution to a mixture of the aminopolyether 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (Kryptofix 222) (10 mg, 0.027 mmole) and potassium carbonate (1.0 mg, 0.007 mmole) and evaporation of the water.

Synthesis of 4-N,N,N-Trimethylaniliniumphenylmethanone Trifluoromethanesulfonate (1)

4-Dimethylaminobenzophenone (100 mg, 0.44 mmoles) was added to an evacuated and purged (Ar) 25 mL sidearm flask with a stirring bar. This was followed by the addition of reagent grade CH_2Cl_2 (7 mL) with stirring, which produced a clear, slightly greenish-yellow solution. Methyltrifluoromethanesulfonate (53.75 µL, 0.475 mmoles) was then added, via syringe, which resulted in an immediate color change to intense yellow. After stirring overnight the crude product was obtained by addition of diethyl ether as a white powder, 0.1405g. Recrystallization from CH_2Cl_2/Et_2O produced a fine, white, crystalline product which was found to be analytically pure, 0.1302 g, 75.35% yield; mp 132-134 °C; Anal. Calcd. for $C_{17}H_{17}NF_3$: C, 52.44; H, 4.66; N, 3.59; F, 14.64. Found: C, 52.52; H,4.33; N, 3.57; F, 14.65; IR (nujol): 1665 (s, C=O), 1220-1280 cm^{-1} (br, CF_3SO_3); ^1H NMR (CD_3CN) δ 3.62 (s, 9H), 7.54-7.95 (m, 9H).

Synthesis of 4-Nitro-N,N,N-Trimethylanilinium Trifluoromethanesulfonate (2)

4-Nitroaniline (203 mg, 1.47 mmoles) and 2,6-Di-tert-butyl-4-methylpyridine (603 mg, 2.93 mmoles) were added to an evacuated and purged (Ar) 25 mL sidearm flask with a stirring bar. Addition of reagent grade CH_2Cl_2 (20 ml) produced a clear, bright yellow solution. The reaction mixture was allowed to stir 5 min before addition of $CF_3SO_3CH_3$ (332 µL, 2.94 mmoles), via syringe. After 3h of stirring, a fine, white precipitate of pyridinium triflate salt was observed, which was removed by filtration after 12h. TLC analysis of the clear, orange filtrate indicated formation of the N,N-dimethylamino intermediate, along with a small amount of the trimethylammonium derivative. Under argon, one additional equivalent of $CF_3SO_3CH_3$ was added via syringe to the reaction mixture. After 24 h, a crystalline, orange solid was obtained upon filtration which exhibited a single spot via TLC analysis; 0.42 g, 86.5%yield ; mp 172-174 °C.

Experimental data of other isolated products, with varying X, $(XC_6H_4NMe_3)^+CF_3SO_3^-$ were as follows:

(3) p-CN: 83.4% yield; mp 156-158 °C; Anal. Calcd. for $C_{11}H_{13}N_2F_3$: C, 42.59; H, 4.22; N, 9.03. Found: C, 42.45; H, 3.86; N, 8.35; IR (nujol): 2240 (s, C=N), 1220-1280 cm^{-1} (br, CF_3SO_3); ^1H NMR (CD_3CN) δ 3.59 (s, 9H); 7.9-8.1 (m, 4H).

(4) p-CHO: 72.2% yield; mp 100-102 °C; Anal. Calcd. for $C_{11}H_{14}NF_3$: C, 42.19; H, 4.50; N, 4.47; F, 18.20. Found: C, 42.59; H, 4.23; N, 4.42; F, 18.21; IR (nujol); 1667 (s, C=O),

1220-1295 cm^{-1} (br, CF_3SO_3); ^1H NMR (CD_3CN) δ 3.58 (s, 9H); 7.75-7.95 (m, 4H); 9.80 (s, 1H).

(5) p-COMe: 81.2% yield; mp 80-82 °C; Anal. Calcd. for $C_{12}H_{16}NF_3$: C, 44.04; H, 4.93; N, 4.28; F, 17.41. Found: C, 44.11; H, 4.66; N, 4.30; F, 17.55; IR (nujol): 1668 (s, C=O), 1220-1295 cm^{-1} (br, CF_3SO_3); ^1H NMR (CD_3CN) δ 2.61 (s, 3H); 3.57 (s, 9H); 7.89-7.92 (d, J = 9.1 Hz 2H); 8.13-8.15 (d, J = 9.2 Hz, 2H).

(6) p-$CO_2C_2H_5$: 92.6% yield; mp 112-114 °C; Anal. Calcd. for $C_{13}H_{18}NF_3$: C, 43.71; H, 5.08; N, 3.92. Found: C, 43.86; H, 4.75; N, 4.11; IR (nujol): 1695 (s, C=O); 1220-1280 cm^{-1} (br, CF_3SO_3); ^1H NMR (CD_3CN): δ 1.35-1.39 (t, 3H); 3.61 (s, 9H); 4.3-4.4 (q, 2H); 7.91-7.94 (d, J = 9.1 Hz, 2H); 8.1-8.2 (d, J = 9.2 Hz, 2H).

Synthesis of NCA ^{18}F-Labeled Aryl Fluorides

Reactions of the aryltrimethylammonium trifluoromethanesulfonates (1-7), aryltrimethylammonium perchlorates (8-10), and the nitro-substituted aromatics (11-13) with NCA [^{18}F]fluoride ion are summarized in Table 1 and Table 2. Typically, resolubilized [^{18}F] fluoride ion (in 100 μL of anhydrous DMSO, 65-70 % yield from start of synthesis, SOS) was added to 2 mg of the substrate and heated at the designated temperature for 25 min. Immediately following, the vial was cooled to quench the reaction. The DMSO solution was then taken up into a 10 mL syringe containing 7 mL of H_2O, and the entire mixture was passed through an activated C_{18} SEP-PAK. 1-2 mL of diethyl ether was then used to elute the organic product, followed by drying with Na_2SO_4. Passage of the organic phase through a small column of silica (1 cm x 0.5 cm) afforded pure aryl [^{18}F]fluoride as indicated by TLC and HPLC.

[^{18}F]GBR 13119 (10)

A solution of Kry/K/^{18}F (1-150 mCi) in anhydrous DMSO (100-200 μL) was added to 2 mg of 4-N,N,N-trimethylaniliniumphenylmethanone trifluoromethanesulfonate (1) and the solution heated (80-165 °C) for 25 min. The DMSO solution was cooled to 0 °C and lithium aluminum hydride (300 μL , 1M solution in THF) was added. The reaction vessel was then shaken a few times and reduction terminated after 1 min with 1 mL of 6N H_2SO_4. The aqueous mixture was then transferred via N_2 gas to an activated (5 ml CH_3OH, followed by 10 ml H_2O) C_{18} SEP-PAK which

retained the 4-[^{18}F]fluorobenzhydrol. Yields averaged 60% uncorrected, calculated from resolubilized [^{18}F]fluoride. Removal of residual H_2O on the C_{18} SEP-PAK was achieved via passage of a steady stream of N_2 through the solid-phase support for 10 min. Following this drying period, a mixture of gaseous $SOCl_2$ and N_2 gas was passed through the C_{18} SEP-PAK for 10-15 min. Formation of 4-[^{18}F]fluorobenzhydryl chloride was essentially quantitative and the product was eluted from the C_{18} SEP-PAK with 1-2 mL of diethyl ether. Removal of the organic solvent was accomplished by N_2 flow above the solution with gentle heating. 1-(2-Hydroxyethyl)-4-(3-phenylpropyl)piperazine (10 mg) in 50 µL of toluene was then added and the condensation was run for 20 min at 160 °C. After completion of the reaction, 150 µL of CH_3OH was added to the brown residue, vortexed for one min, and then diluted with 1 mL of H_2O. The mixture was agitated and transferred to an activated C_{18} SEP-PAK. Another 150 µL of CH_3OH was then used to rinse the reaction vial, followed by vortexing and transfer to the C_{18} SEP-PAK. The desired product, [^{18}F]GBR 13119, (R_f = 0.1; silica gel TLC, 97:3 chloroform: methanol), along with two radioactive impurities identified as unreacted 4-[^{18}F]fluorobenzhydryl chloride (R_f= 0.62) and 4-[^{18}F]fluorobenzhydrol (R_f= 0.45) were then eluted off the C_{18} SEP-PAK with 20 mL of pentane and deposited onto an activated (10 mL CH_2Cl_2, followed by 10 mL pentane) silica SEP-PAK. Presence of 4-[^{18}F]-fluorobenzhydrol at this stage of the synthesis was probably due to hydrolysis of 4-[^{18}F]fluorobenzhydryl chloride from trace amounts of H_2O. Both 4-[^{18}F]fluorobenzhydryl chloride and 4-[^{18}F]fluorobenz-hydrol are then removed with 20 mL of a 50/50 pentane/CH_2Cl_2 solution. Pure [^{18}F]GBR 13119 (20% decay-corrected radiochemical yield) was then eluted off the silica SEP-PAK with 20 mL of a 5% CH_3OH/CH_2Cl_2 solution leaving the unreacted 1-(2-hydroxyethyl)-4-(3-phenylpropyl)piperazine retained on the silica SEP-PAK. HPLC analysis (C_8, 70/25/5 CH_3CN/H_2O/140 mM $HClO_4$) exhibited a single radioactive product (R_t= 4.00 min), which co-eluted with authentic GBR 13119. Specific activity measurements of the organic solution (2 1/2 hours SOS) typically were well above 2000 Ci/mmole. This was the limit of detectibility for our present system with the accompanying UV trace featureless. Removal of the solvent was achieved by rotary evaporation, without heating. For biological studies [18F]GBR 13119 was then formulated in 2% ethanol in saline (pH 6).

RESULTS AND DISCUSSION

This investigation stems from our successful synthesis of 1-[2-{(4-[^{18}F]fluorophenyl)-(phenyl)methoxy}ethyl]-4-(3-phenylpropyl)-piperazine (**13**), ([^{18}F]GBR 13119 , Figure

1); utilizing 4-N,N,N-trimethylaniliniumphenylmethanone trifluoromethanesulfonate (1) as the precursor. We and others have found that the formation of high specific activity aryl [^{18}F]fluorides can be achieved via nucleophilic displacement of NMe_3 groups by [^{18}F]fluoride ion (2-6). The cationic nature of these precursors greatly facilitates the purification of the desired neutral product. With the successful synthesis of [^{18}F]GBR 13119 via such a species, we thought it reasonable to further examine these trifluoromethanesulfonate salts as general precursors for aryl [18F]fluoride syntheses.

Most syntheses of aryl [^{18}F]fluorides utilize the corresponding nitro-substituted precursor (1,3,13,14). HPLC is usually performed to separate the desired product from the precursor, a time consuming and sometimes difficult procedure. Aryltrimethylammonium salts (2-5) and aryldimethylsulfonium salts (6) have seen less application in fluorine-18 labeling despite their superior leaving abilities in aromatic nucleophilic substitutions (2,3,10). Previous experiences with aryltrimethylammonium perchlorates exhibited facile substitution with [^{18}F]fluoride ion, but possible decomposition at elevated temperatures, and in one case, unacceptable chemical purity of the product, [^{18}F]N-methylspiperone (3). Although not identified as [^{19}F]N-methylspiperone, the impurity nevertheless lowered the effective specific activity of the final product, and better overall results were obtained using the corresponding nitro precursor. In addition, the synthesis of trimethylammonium perchlorates is lengthy, involving first reaction of silver perchlorate with methyl iodide, followed by alkylation of the dimethylamino group, and requires the use of potentially explosive perchlorate salts (2,3,11). Kevill and Shen reported that reaction times to produce these perchlorate salts were typically two weeks, but ranged up to three months in the presence of strongly electron-withdrawing substituents within the aniline (11).

Methyl trifluromethanesulfonate is an easy to handle, highly reactive methylating agent which rapidly converts N,N-dimethylanilines to the corresponding N,N,N-trimethylammonium trifluoromethanesulfonate salts. Yields of isolated pure products were, in this work, consistently above 70%. The methylation reaction is tolerant of a wide range of substituents on the aromatic ring (nitriles, ketones, aldehydes, esters). The use of the trifluoromethanesulfonate (triflate) salts appear entirely compatible with nucleophilic displacement of the cationic group by NCA [^{18}F]fluoride ion (Table 2). The triflate counterion should, therefore, be considered a suitable replacement for the perchlorate ion, which was originally chosen for it's high nucleofugality and low nucleophilicity (11,12). Mechanistically, the formation of the Meisenheimer complex by [^{18}F]fluoride ion progresses rapidly and competitively with decomposition of the

trimethylammonium salt. It has been reported that high temperatures increase the proportion of this decomposition, resulting in a decrease in the radiochemical yield (5). For example, when

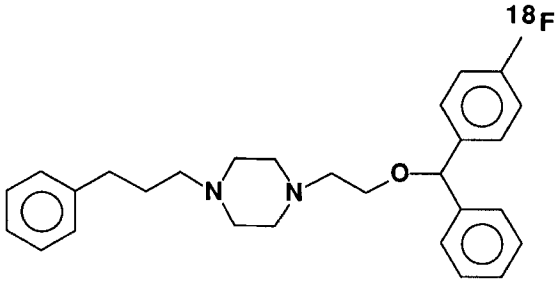
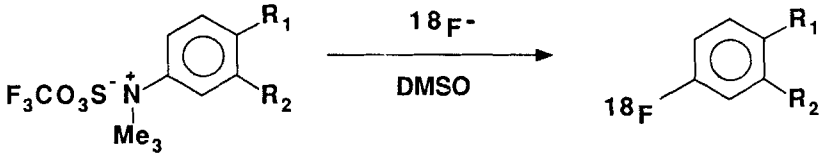


Figure 1. [^{18}F]GBR 13119 (13)

trimethylpurin-6-ylammonium chloride was used as the precursor to 6-[^{18}F]fluoro-ß-D-ribofuranosylpurine, temperatures above 80°C were detrimental to the reaction (5). It has also been reported that temperatures exceeding 150 °C were not conducive to nucleophilic substitution of trimethylammonium perchlorates by [^{18}F]fluoride ion, presumably due to decomposition of the salt (2). In this latter study radiochemical yields were also sharply reduced at temperatures below 80°C. We have found that with the use of trimethylammonium trifluoromethanesulfonates, it may be possible to overcome this temperature dependence. As one can see from Table 1 the radiochemical yields of [^{18}F]fluorination with strongly activated aromatic rings (X=NO_2, CN) do not seem to be temperature dependent over a large temperature range (45-165 °C). The base-sensitive compounds (X= CHO, COMe, CO_2Et) also produced reasonable results at all temperatures, except for the acetophenone derivative where decreased yields were observed below 80 °C. A limited comparison of our triflate salts (1-7) with the corresponding perchlorate salts or nitroaromatic precursors is shown in Table 2. In our hands the synthesis of the perchlorates (8-10) using literature procedures appeared successful, but assurances of chemical purity (m.p., elemental analyses) were questionable. Therefore, a strict comparison of the yields in subsequent [^{18}F]fluorinations is not possible. Yields of aryl [^{18}F]fluorides using either ammonium salt are comparable (this work and 2,3). It is clear that the trimethylammonium triflates produce better yields of aryl [^{18}F]fluorides at lower temperatures than can be obtained with the corresponding nitroaromatic precursors. In comparing the results obtained in this work with the literature on nucleophilic substitutions with [18F]fluoride ion, one should recognize the

Table 1. Decay-Corrected Radiochemical Yields on Fluorination of Activated Aromatic Ammonium Salts with [^{18}F]Fluoride Ion.



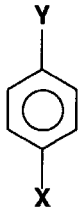
Trimethylammonium salts			Temperature (°C)							
	R_1	R_2	45	60	80	100	120	140	150	160
(1)	-COPh	-H	36	60	72 [2]	62 [2]	80 [3]	78	79	75 [30]
(2)	-CN	-H	77	62	77	77	83	69	*65	86 [2]
(3)	-CHO	-H	8	35	50	62	70	50 [3]	45 [3]	74
(4)	$-NO_2$	-H	65	58	70	84	87	68 [2]	75 [2]	77
(5)	-COMe	-H	0	0	10 [2]	43 [2]	42	28 [2]	26 [2]	41
(6)	$-CO_2Et$	-H	32	49	60	59	59	52 [2]	59	46
(7)	-H	$-NO_2$	10	20	20 [2]	26	20	19 [2]	34	20

[ ] represents number of runs

* Reaction time= 10 min.

Substrate concentration range= 5.0×10^{-2} - 0.1 mole/liter

Table 2. Decay-corrected yields of ^{18}F Aryl Fluorides. Effects of Various Leaving Groups on F-18 Incorporation.



	Substrate X	Y	Temp	Product	Yield%
(1)	COPh	$CF_3SO_3^-$	60	4-[^{18}F]Ph_2=O	60
			120		80 [3]
			160		75 [30]
(8)	COPh	ClO_4^-	60	4-[^{18}F]Ph_2=O	20
			120		52 [2]
			160		50
(11)	COPh	NO_2	60	4-[^{18}F]Ph_2=O	24
			120		63
			160		66
(2)	CN	$CF_3SO_3^-$	60	4-[^{18}F]C_6H_4CN	62
			120		83
			160		86
(9)	CN	ClO_4^-	60	4-[^{18}F]C_6H_4CN	11
			120		42
			160		42
(12)	CN	NO_2	60	4-[^{18}F]C_6H_4CN	30
			120		62
			160		70
(3)	CHO	$CF_3SO_3^-$	60	4-[^{18}F]C_6H_4CHO	35
			120		70
			160		74
(10)	CHO	ClO_4^-	60	4-[^{18}F]C_6H_4CN	7
			120		34 [2]
			160		33
(13)	CHO	NO_2	60	4-[^{18}F]C_6H_4CN	8
			120		28
			160		19

[ ] represents number of runs

variability in the reactivity of [18F]fluoride ion due to different cyclotron targets and varying methods of preparation for reaction (counterion, drying procedure).

In all of our syntheses, we did not observe unlabeled products (aryl [19F]fluorides or trimethylammonium salts) upon TLC or HPLC analysis of the final aryl [^{18}F]fluoride preparations. The [18F]GBR 13119 prepared from (1) has been repeatedly and carefully examined by HPLC, and has shown a consistent final specific activity in excess of 2000 Ci/mmol (limit of detection). This value is consistent with the use of high specific activity, NCA [^{18}F]fluoride (15), and furthermore indicates there is little (if any) dilution of the specific activity by [^{19}F]fluoride ion in the reagents or precursors, nor exchange of the fluorines between the [^{18}F]fluoride ion and the trifluoromethyl group of the triflate counterion. This is also consistent with the previous use of triflates as leaving groups in aliphatic nucleophilic substitutions (14).

CONCLUSIONS

Use of aryltrimethylammonium trifluoromethanesulfonates would thus appear advantageous in the synthesis of high specific activity fluorine-18 labeled radiopharmaceuticals. Preparation of the precursors is simple and efficient, and reaction with [^{18}F]fluoride proceeds in high yields and can be performed at low temperatures (50-100 °C). Products can be simply separated from unreacted salt by liquid-liquid extraction or solid phase methods, and are obtained in NCA form with no apparent dilution of specific activity by adventitious fluoride ion. Substrate volatility and decomposition of precursors or products due to high temperatures are two parameters which can now be controlled through use of these trimethylammonium triflate salts and lower reaction temperatures. The potential advantages of these precursors is exemplified in our improved synthesis of [^{18}F]GBR 13119, where the product can be obtained in > 98% radiochemical and chemical purity without application of HPLC.

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