SYNTHESES OF NO-CARRIER-ADDED (NCA) [^{18}F]FLUOROALKYL HALIDES AND THEIR APPLICATION IN THE SYNTHESES OF [^{18}F]FLUOROALKYL DERIVATIVES OF NEUROTRANSMITTER RECEPTOR ACTIVE COMPOUNDS

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SUMMARY

Nucleophilic aliphatic substitution of alkyl halides, 1, [$(CH_2)_nX_2$ (n=2,3; X=Br,I)], with NCA K[^{18}F]/Kryptofix 2.2.2 in CH_3CN gave the corresponding NCA [^{18}F]fluoroalkyl halides 2 in 30-40% yields. The factors which influence the yield of 2 were compared. N-Alkylation of several neurotransmitter receptor active amides and amines with this reagent gave the corresponding NCA N-[^{18}F]fluoroalkyl derivatives (3-6) in 20-60% yield.

KEYWORDS: NCA [^{18}F]Fluoroalkyl halides, N-(2-[^{18}F]fluoroethyl)spiroperidol, N-(3-[^{18}F]fluoropropyl)spiroperidol, (±)-N-(3-[^{18}F]fluoropropyl)-normetazocine, N-(3-[^{18}F]fluoropropyl)lorazepam, nucleophilic aliphatic substitution reaction, fluorine-18

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INTRODUCTION

Widespread interest in metabolic and receptor binding studies via positron emission tomography (PET) (1) calls for new synthetic strategies which allow rapid and efficient incorporation of short-lived radionuclides (e.g. ^{11}C and ^{18}F) into organic molecules (2). One of the most commonly used intermediates for the syntheses of N-alkyl radioligands is C-11 labelled methyl iodide (3-6) and to a lesser extent ethyl iodide (7). However, compared with ^{18}F, ^{11}C has inherent

0362-4803/87/010055-10$05.00

Received May 14, 1986

disadvantages: (a) its maximum positron energy is higher than that of ^{18}F (0.96 MeV vs. 0.635 MeV), (b) its half-life is shorter than that of ^{18}F (20.4 min vs. 109.7 min) and (c) the specific activity of ^{11}C-labeled radiotracers, especially those derived from $[^{11}C]O_2$ is usually lower than that of ^{18}F-labeled radiotracers synthesized from $[^{18}F]$fluorine. To date, only a few ^{18}F-labeled alkyl halides have been synthesized (8,9) and found to be useful for the syntheses of ^{18}F-labeled radiopharmaceuticals. For example, $[^{18}F]CH_2Br$ has been synthesized by nucleophilic aliphatic substitution reaction (8). Unfortunately, since N-methylated products, fluoromethyldialkylamines, are reported to be unstable (10), the utility of this reagent for labeling of secondary amines is limited. We report here the synthesis of a series of NCA $[^{18}F]$fluoroalkyl halides (2) by nucleophilic aliphatic substitution of alkyl halides (1) with NCA $[^{18}F]$fluoride along with their applications in the syntheses of NCA ^{18}F-labelled derivatives of neurotransmitter receptor active compounds.

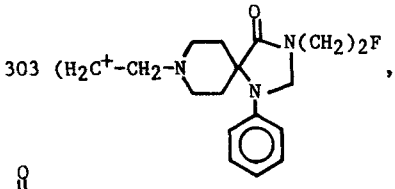
MATERIALS AND METHODS

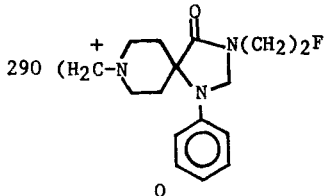
Acetonitrile was an HPLC grade reagent from Fischer Scientific Co. Kryptofix 2.2.2 was purchased from MCB Chemical Co. 1,3-Dibromopropane and 1,3-diiodopropane were purchased from Eastman Kodak Co. and used without further purification. 1,2-Dibromoethane and 1,2-diiodoethane were purchased from Fischer Scientific Co. and Aldrich Chemical Co. respectively. 1-Bromo-2-fluoroethane was purchased from Fairfield Chemical Co. 1-Bromo-3-fluoropropane was synthesized by the known method (11). Tetrabutylammonium hydroxide (0.4 M in H_2O) was purchased from Eastman Kodak Co. The melting points were determined on a Fischer-Johns melting point apparatus and were uncorrected. NMR spectra were recorded with a Varian CFT-20 spectrometer or Bruker BZH 300/52 spectrometer with TMS as an internal standard. The mass spectra were measured with a Finnigan MAT 5100 GC/MS/DS spectrometer. High-pressure liquid chromatographic (HPLC) analyses were carried out with a Perkin-Elmer Series 2 or 3B liquid chromatograph equipped with a radioactivity monitor (Berthold Model LB503). An analytical reversed-phase C18 column (4.5 x 250 mm) was used with either $CH_3OH:H_2O:(i\text{-}Pr)_2NH$ (70:30:0.1) or CH_3OH:0.02N NH_4CO_2H (75:25) as the solvent with a flow rate of 1.5 ml/min. For the preparative separation a semi-preparative C18 column (10 x 250 mm,

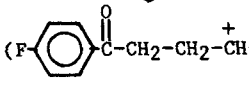
Phenomenex, ODS-1) was used and eluted with appropriate solvents. The C18 Sep-Pak cartridges were obtained from Waters Associates.

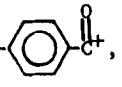
Syntheses of 8-[4-(4-Fluorophenyl)-4-oxobutyl]-3-(2-fluoroethyl)-1-phenyl-1,3,8-triazaspiro[4.5] decan-4-one [N-(2-fluoroethyl)spiroperidol]: Spiroperidol (57.23 mg, 0.15 mmol) was dissolved in 3.5 ml of dimethylforamide (DMF) and then tetrabutylammonium hydroxide (200 µl, 0.31 mmol, 40% aq. solution) and 1-bromo-2-fluoroethane (190 µl, 2.3 mmol) were added. The mixture was stirred at 80°C for 15 min. The progress of the reaction was monitored by taking an aliquot of the reaction mixture and analyzed by HPLC. At the end of the reaction (15 min), the mixture was cooled to room temperature. The crude product was dissolved in CH_3OH (~ 2 ml) and injected into semi-preparative HPLC (C18 column, 10 x 250 mm; CH_3OH: H_2O: $(i\text{-}Pr)_2NH$, 70:30:0.1 as the solvent with a flow rate of 4 ml/min). The fractions containing N-(2-fluoroethyl)spiroperidol (retention time = ~ 19 min) were collected and evaporated to give 36 mg (57%) of product, m.p. 115-118°C. NMR ($CDCl_3$)δ: 1.0-3.3 (series of overlapping multiplets), 4.64 (dd, J_{HH} = 4.5 Hz, J_{HF} = 48 Hz, CH_2F); 4.79 (s, 2H); 6.9 - 7.4 (m, 7H); 8.0 - 8.05 (q, J = 5.5 Hz, 2H).

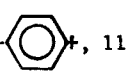
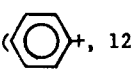
Mass spectrum: m/e (relative intensity) = 441 (M^+, 0.7%); 423 (M-18, 8.1%);

303  , 9.3%);

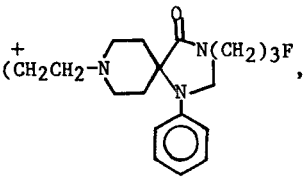
290  , 43.6%);

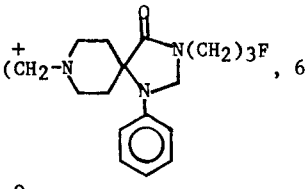
165  , 22.0%);

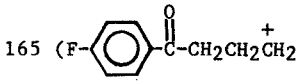
142 (100%); 123  , 34.6%); 100 (50.1%);

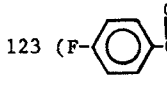
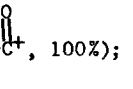
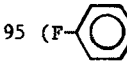
95  , 11.7%); 77  , 12.7%).

Synthesis of 8-[4(4-Fluorophenyl)-4-oxobutyl]-3-(3-fluoropropyl)-1-phenyl-1,3,8-triazaspiro[4.5] decan-4-one [N-(3-fluoropropyl)spiroperidol]: The method used for the synthesis of N-(2-fluoroethyl)spiroperidol was adapted for the synthesis of N-(3-fluoropropyl)spiroperidol. NMR ($CDCl_3$)δ: 1.0 - 3.6 (series of overlapping multiplets); 4.62 (dd, J_{HH} = 5.6 Hz, J_{HF} = 48 Hz, CH_2F); 4.71 (s, 2H); 6.8 - 7.4 (m, 7H); 8.0 - 8.05 (q, J = 5.5 Hz, 2H). Mass spectrum: m/e (relative intensity) = 455 (M^+, 0.5%);

437 (M-18, 15.1%) 317  ,

19.0%); 304  , 62.7%);

165  , 45.9%); 142 (12.0%);

123  , 100%); 95  , 30%); 77  , 31.1%).

It is interesting to note that the retention times of N-methylspiroperidol, N-(2-fluoroethyl)spiroperidol and N-(3-fluoropropyl)spiroperidol in a C18 column (4.5 x 250 mm eluted with CH_3OH:H_2O:$(i\text{-}Pr)_2NH$, 70:30:0.1 at 1.5 ml/min) are very similar (9.90 min, 10.00 min, and 10.63 min respectively) indicating that these three compounds have similar lipophilicity.

A General Synthesis of NCA 1-[^{18}F]Fluoroalkyl Halides (2) by Nucleophilic Aliphatic Substitution of Alkyl Halides (1) with NCA [^{18}F]Fluoride: No-carrier-added aqueous[^{18}F]fluoride (~ 1 ml) prepared by the $^{18}O(p,n)^{18}F$ reaction (12) on a small volumn enriched water (95-99% ^{18}O) target (13,14), was added to a solution of 10 mg (26.6 μmol) of Kryptofix 2.2.2 and 2.5 mg (18 μmol) of K_2CO_3 in 0.2 ml of CH_3CN in an open Pyrex vessel. The water was removed using a stream of nitrogen at 115°C and coevaporated to dryness with CH_3CN (3 x 0.5 ml). To the dried K[^{18}F] was added 23 μmol of alkyl halide (1) in 0.5 ml of CH_3CN and the

vessel was covered. This solution was heated at 75°C for 10 min, cooled to room temperature and then 3 ml of water was added. The mixture was transferred onto a C18 Sep-Pak cartridge which had been prewashed with 3 ml of CH_3OH followed by 4 ml of water. The Sep-Pak cartridge was washed with 4 ml of water and the washing was discarded. The product, NCA 1-[^{18}F]fluoroalkyl halide, was eluted with 5 ml of pentane which was filtered through an anhydrous K_2CO_3 tube. The identities of the products were confirmed by comparison of their HPLC retention times with authentic samples. The results are listed in Table 1.

Optimization of ^{18}F Substitution in (1): K[^{18}F] was prepared as described above and the yield of the substitution reaction was measured by carrying out the reaction as described above. The identities of the products were confirmed by comparison of their HPLC retention times with authentic samples. Variables were solvent, substrate, substrate concentration and reaction temperature (Tables 2 and 3).

Table 1. Radiochemical yield of NCA ^{18}F-labeled fluoroalkyl halides from the nucleophilic aliphatic substitution of alkyl halides with NCA [^{18}F]fluoride in CH_3CN at 65-75°C[a]

$(CH_2)_nX_2$	Radiochemical Yield (%)[b] $^{18}F(CH_2)_nX$	
	With Kryptofix 2.2.2	Without Kryptofix 2.2.2
a; n=2, X=I	~ 5	---
b; n=2, X=Br	30-40	---
c; n=3, X=I	30-40	< 5
d; n=3, X=Br	30-40	---

a. Reaction time = 10-15 min; Substrate Concentration: ca. 20 μmole, K[^{18}F] (NCA); pyrex vessel.

b. Products were isolated by C18 Sep Pak cartridge extraction (H_2O/pentane) and were identified using a radio HPLC [Perkin-Elmer Series 2 or 3B Liquid Chromatograph equipped with a UV detector and connected to a Berthold Model LB 503 radioactivity detector. C18 column with MeOH:H_2O:$(i\text{-Pr})_2NH$ (70:30:0.1) as elution solvent] and comparison of retention times with those of authentic samples. The yield has been decay corrected.

Table 2. Effects of Solvent and Temperature on Yield of 1-[^{18}F]Fluoro-3-Iodopropane from 1c[a]

Run	Solvent	Temperature (°C)	Yield(%)[b]
1	CH_3CN	70	33
2	CH_3CN	75	45
3	CH_3CN	80	35
4	CH_3CN	90	43
5	DMSO	70	6
6	DMSO	80	4
7	DMSO	90	4
8	DMSO	100	3
9	DMSO	120	2
10	DMSO	140	2

a. Reactions were carried out in a Pyrex vessel.

b. The yield has been decay corrected.

Table 3. The Influence of Substrate and Substrate Concentration on Yield of 1-[^{18}F]Fluoropropyl Halides (2c,d)[a]

Substrate	Substrate Concentration (μm)	Yield(%)[b]
1c	4.5	28
1c	24.8	36
1c	45	28
1d	4.5	25
1d	25	24
1d	45	28

a. All reactions were carried out at 75°C in a Pyrex vessel.

b. Percentage of activity isolated in the product, corrected for decay.

A General Synthesis of NCA N-[^{18}F]Fluoroalkyl Radioligands (3-6): The substrate (~ 5 mg) and base (40 μl of 0.4M tetrabutylammonium hydroxide in H_2O for spiroperidol and ~ 4 mg of K_2CO_3 for normetazocine and lorazepam) were added to NCA 1-[^{18}F]fluoro-3-iodopropane or 1-bromo-2-[^{18}F]fluoroethane, prepared as described above, in 5 ml of pentane in an open test tube. The solution was heated (110°C) and when the volume of the pentane solution was reduced to ~ 0.2 ml, 0.5 ml of a 1:10 solution of DMF-THF was added and the mixture was heated for 10 min after THF had evaporated. The crude product was dissolved in

1.5 ml of HPLC solvent for preparative HPLC purification. Preparative HPLC purification of the crude product was accomplished using a 10 x 250 mm reversed-phase column (Phenomenex, ODS-1) and eluted with appropriate solvents. The effluent of the HPLC column is passed through a UV detector at 254 nm and into a fraction collector set up in an ionization chamber. The product fraction is taken at the appropriate time when the UV trace has returned to base line and when radioactivity elutes from the column. Collection is continued for 2-3 minutes. The eluate from HPLC was evaporated and coevaporated with 5 ml of ethanol and then with 1 ml of 2% HCl-ethanol to dryness. A stream of dry N_2 was applied to the residue for ~ 1 minute to ensure removal of all traces of solvent. To the residue was added 3 ml of saline and the resulting solution was filtered through a 0.22 μm millipore filter into a multiinjection vial. The results are listed in Table 4.

RESULTS AND DISCUSSION

Reactions of compounds 1a-d with K[^{18}F]/Kryptofix 2.2.2 (8) in CH_3CN at 65-75°C for 10 min followed by purification gave the corresponding NCA [^{18}F]fluoroalkyl halides (2a-d) in 30-40% yield [(equation 1), Table 1].

$$\underset{1}{(CH_2)_nX_2} \xrightarrow[CH_3CN]{K[^{18}F]/Kryptofix\ 2.2.2} \underset{2}{^{18}F(CH_2)_nX} \qquad (1)$$

Since the synthesis of 3-6 from [^{18}F]fluoride is a two-step process, the optimization of the radiochemical yield in each step is necessary to increase the overall radiochemical yield of 3-6. As shown in Table 2, the solvent has a significant effect while the reaction temperature has only a slight effect on the yield of 2. That the radiochemical yield of 2c is lower in DMSO than that in CH_3CN suggests that compound 1c may have been oxidized by DMSO to give the corresponding aldehyde (15). The nature of the substrates (X = Br or I) and the concentration of the substrate have little effect on the yield of 2 (Table 3). This makes it possible to use less substrate in the synthesis and results in a more easily purified product mixture. However, Kryptofix 2.2.2 has a significant effect on the yield of 2 as reported by Coenen (8).

Table 4. Radiochemical Yield of NCA ^{18}F-Labeled N-[^{18}F]Fluoroalkyl Radioligands[a]

Substrate	Product	Radiochemical Yield (%)[b]
Spiroperidol	N-(2-[^{18}F]fluoroethyl)-spiroperidol (3)[c]	10-20
Spiroperidol	N-(3-[^{18}F]fluoropropyl)-spiroperidol (4)[c]	30-50
(±)Normetazocine	(±)N-(3-[^{18}F]fluoropropyl)-normetazocine (5)[d] (19)	50-60
Lorazepam	N-(3-[^{18}F]fluoropropyl)-lorazepam (6)[e]	50-60

a. Reaction time: 10 min; reaction temperature: 110°C; substrate concentration: 10-15 μmole in DMF.

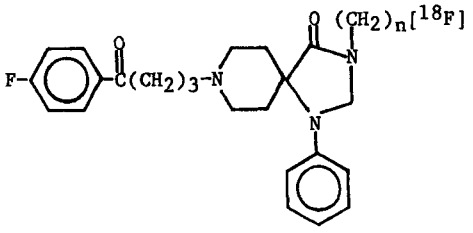
b. Products were isolated by a semi-preparative C_{18} column (10 x 250 mm) eluted with various solvents and were identified by comparison of retention times with those of authentic samples. The yield has been decay corrected.

c. The product was eluted with MeOH:H_2O:$(i\text{-pr})_2NH$ (70:30:0.1), 4 ml/min.

d. The product was eluted with MeOH:0.05N NH_4CO_2H (65:35), 4 ml/min.

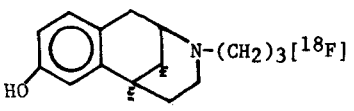
e. The product was eluted with MeOH:H_2O:$(i\text{-pr})_2NH$ (60:40:0.1), 4 ml/min.

These results indicate that NCA ^{18}F-labelled fluoroalkyl halides can be rapidly prepared under very mild conditions and in moderate yields. Since ^{18}F has several advantages over ^{11}C, ^{18}F-labelled fluoroalkyl halides may be superior to $^{11}CH_3I$ for the synthesis of a number of different classes of radiotracers. An obvious application of this reagent would be the syntheses of ^{18}F-labelled neurotransmitter receptor active compounds (16-18) by N-[^{18}F]fluoroalkylation of the appropriate precursors. Thus, a series of NCA N-[^{18}F]fluoroalkyl radioligands (3-6) have been prepared in 20-60% yield by N-[^{18}F]fluoroalkylation of the corresponding amides and/or amines (Table 4). The application of this reagent for the syntheses of other radioligands for PET studies and the study of the influence of the fluoropropyl group on receptor binding properties of the parent molecule as well as the metabolic stability of these tracers are continuing.



3 n=2

4 n=3



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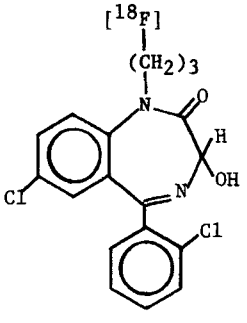

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ACKNOWLEDGEMENT

This research was carried out at Brookhaven National Laboratory under contract DE-AC02-76CH00016 with the U. S. Department of Energy and supported by its Office of Health and Environmental Research and also supported by the National Institute of Health Grant NS-15380. The authors thank Dr. A. L. Feliu for the sample of 1-bromo-3-fluoropropane, Janssen Pharmaceutica, Inc. for the sample of spiroperidol, Mr. Albert Soria, Sterling Winthrop Research Institute, Rensselaer, NY, and also the Research Triangle Institute, Research Triangle Park, NC for the sample of racemic N-normetazocine, and Wyesh Laboratories, Inc. for the sample of lorazepam.

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