Application of the Nucleophilic Substitution Reaction to the Synthesis of No-Carrier-Added [^{18}F]Fluorobenzene and Other ^{18}F-Labeled Aryl Fluorides

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SUMMARY

No-carrier-added (NCA) [^{18}F]fluorobenzene was prepared in a multistep synthesis with a radiochemical yield of 20-30%. A series of NCA and CA ^{18}F-labeled aryl fluorides which are important precursors of ^{18}F-labeled butyrophenone neuroleptics have also been synthesized in radiochemical yields of 30-50%. The direct synthesis of [^{18}F]spiroperidol and [^{18}F]benperidol from the parent compounds and/or nitro and/or chloro compound using the nucleophilic substitution reactions were also investigated.

KEY WORDS: NCA [^{18}F]Fluorobenzene, NCA Aryl ^{18}F fluorides, Nucleophilic substitution reaction, [^{18}F]Spiroperidol, [^{18}F]Benperidol

INTRODUCTION

Since fluorine-18 substituted aromatic rings are common structural components of an increasing number of ^{18}F-labeled radiopharmaceuticals (1,2), the discovery of efficient synthetic routes to these compounds has been actively pursued. Of special importance is the development of synthetic strategies which would employ ^{18}F-labeled fluoride because of its ease of production in high yield, its high specific activity and its potential incorporation with 100% efficiency.

Until very recently, only two routes to ^{18}F-labeled aryl fluorides using ^{18}F$^-$ as a fluorine source were known. These were the Schiemann reaction (3,4) and the triazene decomposition reaction (5-7). Both of these reactions have been investigated as routes to ^{18}F-labeled butyrophenones such as spiroperidol and haloperidol (8-13). Both methods however, give low yields and while the

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triazene decomposition reaction gives a no-carrier-added (NCA) product, the Schiemann reaction gives a product of low specific activity. Recently, we reported that the nucleophilic substitutions of activated nitro groups by NCA ^{18}F-labeled fluoride was an efficient general route to NCA ^{18}F-labeled aromatic compounds (14,15). This reaction is an extension of the previously reported ^{18}F-^{19}F "exchange" reaction which gave ^{18}F-labeled aryl fluoride (carrier-added, CA) in high yield (16) and can therefore be applied to the synthesis of either CA or NCA aryl fluorides depending on the leaving group. The structural requirements for this reaction are that ortho or para relationship of a nucleofugic group (F or NO_2) and an activating group ($-NO_2$, -CN, -COR) exist in the molecule. Butyrophenone neuroleptics such as benperidol and spiroperidol have the proper orientation of groups to undergo this substitution reaction and therefore this reaction should provide a simple method to prepare ^{18}F-labeled benperidol and spiroperidol. We report here the successful application of this general reaction to the synthesis of [^{18}F]fluorobenzene in a radiochemical yield of 20-30% and in addition a series of NCA and CA ^{18}F-labeled aryl fluorides in 30-50% yield. The initial attempts to effect a direct substitution on derivatives of benperidol and spiroperidol is also described.

EXPERIMENTAL

Materials.

Rubidium carbonate was purchased from Alfa Products Division, Ventron, Inc. Cesium carbonate was purchased from Johnson, Matthey and Co. Dimethylsulfoxide (DMSO) was a Gold Label reagent from Aldrich Chemical Co. It was dried over 4Å molecular sieve. p-Bromonitrobenzene, p-chloronitrobenzene, p-fluoronitrobenzene, p-fluoroaniline, fluorobenzene, p-nitrobenzonitrile, 4-chlorobenzonitrile, p-nitroacetophenone, p-fluoroacetophenone and 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one were obtained from Aldrich Chemical Co. p-Fluorobenzonitrile was purchased from ICN. Cyclopropyl 4-fluorophenyl

ketone was purchased from Trans World Chemical Co. n-Butyl nitrite was obtained from Eastman Chemical Co. and used without further purification. The other substrates which were not commercially available were synthesized and characterized by standard methods.

General Methods.

Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. NMR spectra were recorded with JEOL MH-100 spectrometer in either chloroform-d, or dimethylsulfoxide-d_6 with tetramethylsilane as an internal standard. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, New York. Gas-liquid chromatographic analyses (GLC) were carried out with a gas chromatograph equipped with a thermal conductivity detector. Radioactivity was assayed as described previously (17). HPLC analyses were carried out with a Perkin-Elmer Series 3B liquid chromatograph equipped with a radioactivity monitor (Berthold Model LB503). An IBM C18 column (4.5x250mm) was used with MeOH-0.01M$(NH_4)_2HPO_4$ as the solvent (70:30) with flow rate of 2ml/min.

Syntheses of Substrates.

Cyclopropyl p-aminophenyl ketone (7). A solution of 2.4 g of p-acetamido-γ-chlorobutyrophenone (6) (10) in a mixture of 80 ml of EtOH and 20 ml of 16% aq. NaOH was refluxed for 1 hr. After removal of EtOH, the residue was diluted with H_2O. The crystals were collected and recrystallized from EtOH-H_2O to give 1.29 g (90%) of pale brown needles of 7, mp 122-123°. NMR ($CDCl_3$)δ: 7.8 (2H, d,J = 8 Hz, aromat. H), 6.6 (2H, d, J = 8 Hz, aromat. H), 4.2 (2H, b, NH_2), 2.6 (1H, m, COCH), 1.1-0.9 (4H, m, CH_2). Anal. Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.58; H, 6.98; N, 8.49.

Cyclopropyl p-nitrophenyl ketone (8). To a well stirred suspension of 1.7 g (0.01 mol) of 7 in 12 ml of fluoboric acid solution,a cold solution of 0.72 g (0.01 mol) of $NaNO_2$ in 2 ml of H_2O was added. The mixture was stirred in an ice-bath for 10 min., the precipitates were filtered, washed with cold

fluoboric acid solution, EtOH and Et_2O, to give the diazonium fluoborate of 7. The suspension of diazonium fluoborate in 4 ml of H_2O was then added slowly to a mixture of 8.4 g of $NaNO_2$ and 1.79 g of copper powder in 10 ml of H_2O. The reaction mixture was stirred at room temperature for 2 hr, extracted with Et_2O, washed with H_2O and dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in $CHCl_3$, passed through a silica gel column and eluted with the same solvent. The eluant was evaporated and the resulting crystals were recrystallized from Et_2O to yield pale yellow needles of 8, 1.39 g (69%), mp 102-103°. NMR ($CDCl_3$)δ: 8.2 (2H, d, J = 8 Hz, aromat. H), 8.0 (2H, d, J = 8 Hz, aromat. H), 2.6 (1H, m, COCH), 1.2 (4H, m, CH_2). Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 63.09; H, 4.92; N, 7.30.

γ-Chloro p-nitrobutyrophenone (9). A solution of 100 mg of 8 in 8 ml of MeOH and 2 ml of conc. HCl was refluxed for 30 min. After cooling, the mixture was extracted with hexane. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give 69 mg (58%) of pale yellow oil of 9. NMR ($CDCl_3$)δ: 8.3 (2H, d, J = 8 Hz, aromat. H), 8.1 (2H, d, J = 8 Hz, aromat. H), 3.7 (2H, t, J = 6 Hz, CH_2Cl), 3.3 (2H, t, J = 6 Hz, $COCH_2$), 2.3 (2H, q, J = 6 Hz, CH_2).

8-[4-Oxo-4-(p-nitrophenyl)butyl]-1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one "nitrospiroperidol" (10) (18). A mixture of 498 mg (2.2 mmol) of γ-chloro p-nitrobutyrophenone (9), 925 mg (2 mmol) of 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one and 20 mg of KI in 5 ml of THF and 0.5 ml of DMF was heated at 95-100° under a stream of N_2 for 40 min. The reaction mixture was dissolved in $CHCl_3$, washed with H_2O, dried over Na_2SO_4 and loaded on a silica gel column. The column was first eluted with $CHCl_3$ and then with 4% EtOH-$CHCl_3$. The fraction of 4% EtOH-$CHCl_3$ was evaporated and the residue was recrystallized from $CHCl_3$ to yield yellow needles of 10, 270 mg (29%), mp 232-236° (decomp.). HPLC showed compound 10 to have a retention time of

4.9 min. Anal. Calcd. for $C_{23}H_{26}N_4O_4$: C, 65.38; H, 6.20; N, 13.26. Found: C, 65.06; H, 6.09; N, 13.08.

8-[4-Oxo-4-(p-chlorophenyl)butyl]-1-phenyl-1,3,8-triazspiro[4.5] decan-4-one "chlorospiroperidol" (12) (19). A mixture of 217 mg (1 mmol) of 4,4'-dichlorobutyrophenone, 323 mg (1.4 mmol) of 1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one and 20 mg of KI in 5 ml of DMF was refluxed for 20 min. The solvent was evaporated in vacuo, the residue was dissolved in H_2O, extracted with $CHCl_3$ and dried over Na_2SO_4. The solution was concentrated, passed through a silica gel column and fractionated. The column was eluted with $CHCl_3$, 1% EtOH in $CHCl_3$ and then with 2% EtOH in $CHCl_3$. The fraction of 2% EtOH in $CHCl_3$ was evaporated to dryness. The residue was recrystallized from EtOAc to give 95 mg of product. Concentration of the mother liquor gave an additional 32 mg of product. Total yield of 12 is ~127 mg (31%), mp 203-206°C (Lit. (19) 202-203.8°C). HPLC showed compound 12 had retention time of 7.8 min. Anal. Calcd. for $C_{23}H_{26}ClN_3O_2$: C, 67.06; H, 6.36; N, 10.20; Cl, 8.61. Found: C, 66.81; H, 6.32; N, 9.96; Cl, 8.56.

Preparation of $Rb^{18}F$. NCA $Rb^{18}F$ was prepared by dissolving 3 mg of Rb_2CO_3 in ~1 ml of aqueous $H^{18}F$ solution, prepared from the $^{18}O(p,n)^{18}F$ reaction (20). The aqueous solution was evaporated in a platinum crucible at ~150°C while a slow stream of nitrogen was bubbling through and then coevaporated to dryness with acetonitrile. The $Rb^{18}F$ thus obtained was used for the next step without further purification. NCA $Cs^{18}F$ was prepared in the same manner.

General procedure for the nucleophilic substitution. Except as indicated, the substitution reactions were carried out in DMSO solution at 160-165°C for 15 minutes. The solution was cooled to room temperature and then H_2O was added. The product was isolated either by extraction of the reaction mixture with pentane or using a C18 Sep-pak column.

Synthesis of p-[^{18}F]fluoronitrobenzene (2). A solution of p-chloronitrobenzene (1) (10.5 mg, 6.6 μmole) in 3 ml of dry DMSO was added to the

dried $Rb^{18}F$. The mixture was stirred at 160-165°C for 15 minutes, cooled to room temperature, and then water was added. The mixture was extracted with ether (3 x 1 ml), the ether solution dried over Na_2SO_4 and evaporated to give p-[^{18}F]fluoronitrobenzene (2) in a radiochemical yield of 35-50% at (EOB). Radiogas chromatography (10% DC-710, 12ft x 1/8in; flow 30 ml/min, 150°) of the product showed the only radioactivity peak to be congruent with the mass peak corresponding to p-fluoronitrobenzene, R_T = 7.8 min. The reaction product also contained p-chloronitrobenzene, R_T = 19.5 min., as a chemical impurity. However, the reaction mixture was used for the next step without further purification. The other ^{18}F-labeled aryl fluorides were synthesized by the same procedures and the results are listed in Table 1.

Synthesis of No-Carrier-Added [^{18}F]Fluorobenzene (4).

NCA [^{18}F]fluorobenzene was synthesized by a multistep synthesis starting with p-chloronitrobenzene (1). The experimental details for isolation of intermediates or for a one pot synthesis are given below.

Synthesis of NCA p-[^{18}F]fluoroaniline (3). A solution of p-[^{18}F]fluoronitrobenzene (0.3 mCi) in 1 ml of THF was added to a mixture of 10% Pd/C (10 mg) and 50% H_3PO_2 (0.1 ml) (21), a solution of p-[^{18}F]fluoronitrobenzene (0.3 mCi) in 1 ml of THF was added. The mixture was stirred at 65° for 5 min., diluted with 2 ml of H_2O, made basic with 6 N NaOH and extracted with ether (2 x 2 ml). The ether layer was dried (Na_2SO_4) to give p-[^{18}F]fluoroaniline (3) (0.17 mCi EOS, radiochemical yield 56.7% EOS based on starting compound 2). Radiogas chromatograph of the product showed the only radioactivity peak to be p-[^{18}F]fluoroaniline (3), R_T = 5.5 min. p-Chloroaniline was the other chemical impurity, R_T = 16.5 min.

Synthesis of NCA [^{18}F]fluorobenzene (4). A solution of n-butyl nitrite (0.1 ml) in DMF (1 ml) (22) was added to the solution of p-[^{18}F]-fluoroaniline (0.32 mCi) in 1 ml of DMF. The solution was stirred at 60° for 15 min., cooled to room temperature and diluted with H_2O (1 ml). The solution was extracted with pentane (3 x 2 ml), dried (Na_2SO_4) and concentrated to give

p-[^{18}F]fluorobenzene (4) (0.17 mCi at EOS, radiochemical yield 53.1% EOS based on starting compound 3). Radiogas chromatography (10% DC-710, 12ft x 1/8in; flow 30 ml/min., 90°) of the product showed the only radioactivty peak to be [^{18}F]fluorobenzene (4), R_T = 3.1 min, chlorobenzene has R_T = 9.8 min. Compound 4 also can be separated from chlorobenzene by HPLC (IBM C18 column, 4.5 x 250 mm, MeOH:H_2O (1:1), 1 ml/min.). Fluorobenzene has R_T = 15 min. while chlorobenzene has R_T = 28 min.

"One-pot" synthesis of NCA [^{18}F]fluorobenzene (4) from NCA p-[^{18}F]Fluoronitrobenzene (2). A solution of p-[^{18}F]fluoronitrobenzene (0.78 mCi) in 1 ml of THF was added to a mixture of 10% Pd/C (10 mg) and 50% H_3PO_2 (0.1 ml). The mixture was stirred at 65°C for 10 minutes and THF was evaporated by a stream of N_2. The mixture was suspended in 0.5 ml of DMF and 50 µl of n-butyl nitrite was then added. The mixture was stirred at 65°C for 15 min. and work-up as described above to give NCA [^{18}F]fluorobenzene (4) (0.26 mCi at EOS, radiochemical yield 33.3% EOS based on starting compound 2).

Synthesis of NCA γ-Chloro-p-[^{18}F]fluorobutyrophenone (5). Compound 5 was synthesized by two different methods: (a) via [^{18}F]fluorobenzene (4), and (b) via cyclopropyl p-nitrophenyl ketone (8).

Method A. In a typical experiment, 0.2 ml of 1,2-dichloroethane was added to a pentane solution of [^{18}F]fluorobenzene (4) synthesized from p-chloronitrobenzene (1) (347 µCi in 10 ml of pentane), and a slow stream of nitrogen was then bubbled through to remove pentane. A solution of $AlCl_3/Cl(CH_2)_3\overset{O}{\overset{\|}{C}}-Cl$ complex in 1,2-dichloroethane (0.5 ml) prepared from chlorobutyryl chloride (0.4 ml) and aluminum chloride (480 mg) in 10 ml of 1,2-dichloroethane, was added and the solution was stirred at 60°C for 10 min. The reaction mixture was cooled to room temperature, diluted with 1N HCl and extracted with ether (2 ml). The ether solution was washed successively with 1N HCl, sat. $NaHCO_3$ solution, dried over Na_2SO_4 and evaporated to give 128 µCi of mixture in a synthesis time of 33 min. Radio-HPLC analysis (C18 column, MeOH:H_2O (3:2): flow 1.0 ml/min) of the mixture showed peaks at R_T 8.4 min, 14 min and 16.8 min. These corresponded to cyclopropyl

p-[^{18}F]fluorophenyl ketone, [^{18}F]fluorobenzene (4) and γ-chloro-p-[^{18}F]fluorobutyrophenone (5) in a ratio of 19:4:77.

Method B. A solution of cyclopropyl p-nitrophenyl ketone (8) (2 mg) in 0.2 ml of DMSO was added into the dried Rb^{18}F. The mixture was stirred at 155°C for 20 min, cooled to room temperature and 2 ml of HCl (conc):MeOH (1:1) was added. The mixture was stirred at 105-110°C for 10 min, cooled to room temperature and work-up as described above to give γ-chloro-p-[^{18}F]fluorobutyrophenone (5). In a typical experiment, from 4.42 mCi of ^{18}F, 1 mCi of γ-chloro-p-[^{18}F]fluorobutyrophenone was obtained calc to EOB. Thus the radiochemical yield of 5 is 22.5% (EOB).

Synthesis of [^{18}F]spiroperidol (11) by isotopic exchange method. A solution of Cs^{18}F in 0.2 ml of DMSO was added to spiroperidol (~ 2 mg). The solution was kept at 145-150°C for 20 min, and then 3 ml of H_2O were added. The solution was passed through a C18 Sep-pak cartridge (Waters Associates). The C18 Sep-pak was washed with an additional 3 ml of H_2O and then eluted with CH_3CN (2 x 2 ml). The CH_3CN solution was concentrated, the residue was dissolved in 1 ml of $CHCl_3$ and applied to a silica gel column (0.75 x 10 cm). The column was eluted with 35 ml of CH_3CN-MeOH (v/v 4:1) and the eluate discarded. The product was eluted with 25 ml of CH_3CN-MeOH (v/v 2:1) and the eluate evaporated to dryness. HPLC gave a retention time of 5.2 min for compound 11.

In a typical experiment, 6.8 mCi of Cs^{18}F yielded 0.35 mCi of [^{18}F]spiroperidol in a synthesis time of 40 min from EOB. Thus the radiochemical yield of 11 was 5.1% (EOB). The radiochemical purity of [^{18}F]spiroperidol was > 95% as determined by radio TLC and radio HPLC.

Fluorine-18 labeled benperidol (13) has also been synthesized in the same manner in ~ 5% radiochemical yield. HPLC showed compound 13 to have a retention time of 4.6 min.

The reaction of nitrospiroperidol or chlorospiroperidol with Cs^{18}F was carried out in the same manner.

RESULTS AND DISCUSSION

The nucleophilic aromatic substitution reaction has been used to produce a number of NCA ^{18}F-labeled aryl fluorides in moderate to high yield using ^{18}F-labeled fluoride from a water target (see Table 1). Reactions are rapid and conversion of aqueous ^{18}F-labeled fluoride to anhydrous H^{18}F is not required.

Based on yield determinations of a large number of substrates, the following generalizations on substituent effects can be made.

1. The activating effect of the substituent groups X in the nucleophilic aromatic substitution on C_6H_4XY in DMSO decreased in the order

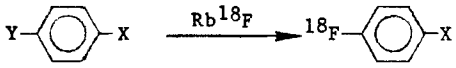
$$\underline{p}\text{-}NO_2 > \underline{p}\text{-}CN > -\overset{O}{\overset{\|}{C}}-\langle \cong -\overset{O}{\overset{\|}{C}}-CH_3$$

2. The nucleofugality of Y in the nucleophilic aromatic substitutions of C_6H_4XY in DMSO decreased in the order $NO_2 \gg F > Cl > Br$

This method thus provides an efficient labeling technique for the syntheses of a number of ^{18}F-labeled aryl fluorides which can be useful intermediates in preparing labeled radiopharmaceuticals. For example, a rapid conversion of $\underline{p}$-[^{18}F]fluoronitrobenzene and cyclopropyl p-[^{18}F]fluorophenyl ketone to γ-chloro-$\underline{p}$-[^{18}F]fluorobutyrophenone, a useful intermediate in ^{18}F-labeled butyrophenone neuroleptic synthesis has been developed. In addition, one of the products, p-[^{18}F]fluoronitrobenzene has been converted to NCA [^{18}F]fluorobenzene, a potential myelin marker (23) in an overall yield of 20-30% (Fig. 1). This sequence can be carried out in "one-pot" without isolation of the intermediates (p-[^{18}F]fluoronitrobenzene and p-[^{18}F]fluoroaniline) using $^{18}F^-$ from a water target as a source of fluoride. Other routes to [^{18}F]fluorobenzene are the Schiemann reaction (4), electrophilic substitution of tributylphenyltin with [^{18}F]F_2 (24) (both giving products of low specific activity), halogen exchange (25) and triazene decomposition (5) (both potential routes to NCA products). Although the triazene method has been reported to give high yields of NCA

Table 1

Application of the Nucleophilic Aromatic Substitution Reaction to the Synthesis of [^{18}F] Aryl Fluorides[a]



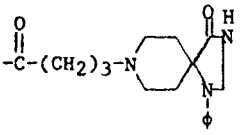
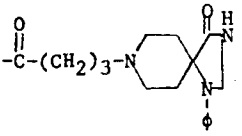
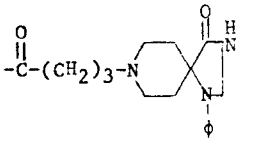
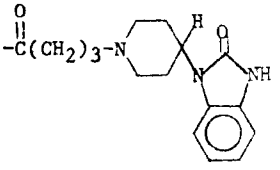
Y	X	Radiochemical Yield (%)[b]
Cl	$-NO_2$	35-50
Br	$-NO_2$	8-10
Cl	-CN	30
NO_2	-CN	50
F	$-\overset{O}{\overset{\|}{C}}-CH_3$	34
NO_2	$-\overset{O}{\overset{\|}{C}}-CH_3$	31
NO_2	$-\overset{O}{\overset{\|}{C}}-\triangleleft$	35-50
F	$-\overset{O}{\overset{\|}{C}}-\triangleleft$	50-60
Cl	$-\overset{O}{\overset{\|}{C}}-\triangleleft$	1-2
NO_2	$-\overset{O}{\overset{\|}{C}}-(CH_2)_3Cl$	0
NO_2		1-2
Cl		1-2

Table 1 (continued)

F		2-7
F		~5
Cl	NO_2	20-30[c,d]

a. Identified by comparison of their retention times on glc and/or hplc columns with those of authentic samples.

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

c. [^{18}F]fluorobenzene was prepared through a multistep synthesis. See experimental section for details.

d. X=H.

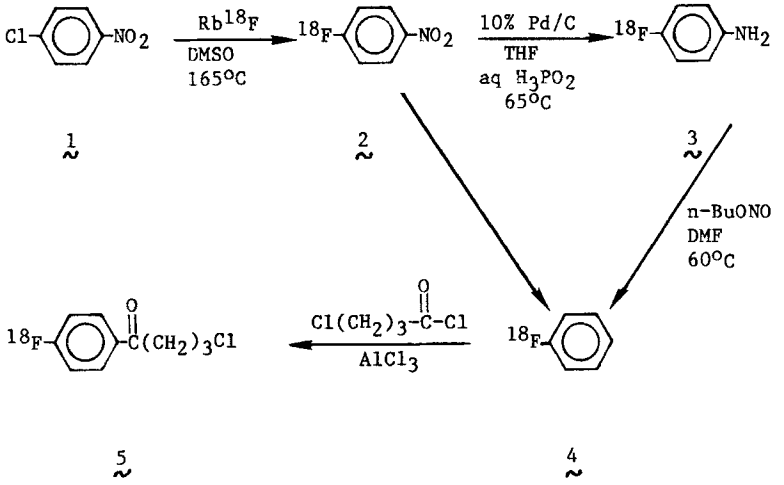


Fig. 1

Synthesis of No-carrier-added [^{18}F]fluorobenzene

[^{18}F]fluorobenzene using anhydrous H^{18}F as a source of fluoride (5), we have only been able to obtain a trace of [^{18}F]fluorobenzene via the triazene method using $^{18}F^-$ from a water target. Thus it appears that the nucleophilic substitution reaction is less sensitive to trace moisture than the triazene reaction.

The ^{18}F for ^{19}F substitution reactions on benperidol and spiroperidol do occur at 145-150°C to give [^{18}F]benperidol and [^{18}F]spiroperidol in 2-7% yield. Nonetheless, the ^{18}F for ^{19}F substitution reaction leads to a product of low specific activity and although this route has been used to produce ^{18}F-labeled spiroperidol for PETT studies of the dopamine receptor in baboons (13), its use to produce radiotracers in humans is precluded by the requirement for subpharmacological doses.

Although [^{18}F]spiroperidol has been prepared in practical yields in a multistep synthesis from p-[^{18}F]fluorobenzonitrile (26), and this general synthesis has also been applied to the synthesis of ^{18}F-labeled haloperidol and benperidol (27), a far simpler synthesis of NCA [^{18}F]spiroperidol would be a direct substitution reaction on a derivative of spiroperidol as was suggested earlier (14). Therefore both "chloro" and "nitro" spiroperidol were prepared as shown in Fig. 2 and their substitution reaction with ^{18}F-fluoride studied. The reaction of nitrospiroperidol with Cs^{18}F in DMSO at 160°C results in extensive decomposition of the substrate. At 130°C, ~ 1-2% of [^{18}F]spiroperidol was formed. Similarly, chlorospiroperidol was found to exchange with $^{18}F^-$ to give [^{18}F]spiroperidol in 1-2% yield. However, this approach remains an attractive one in view of its simplicity and ability to give no-carrier-added [^{18}F]spiroperidol in a single step. Practical yields of such a reaction may be achieved by choosing other leaving groups which require milder displacement conditions and produce reaction mixtures which are more amenable to rapid purification (27).

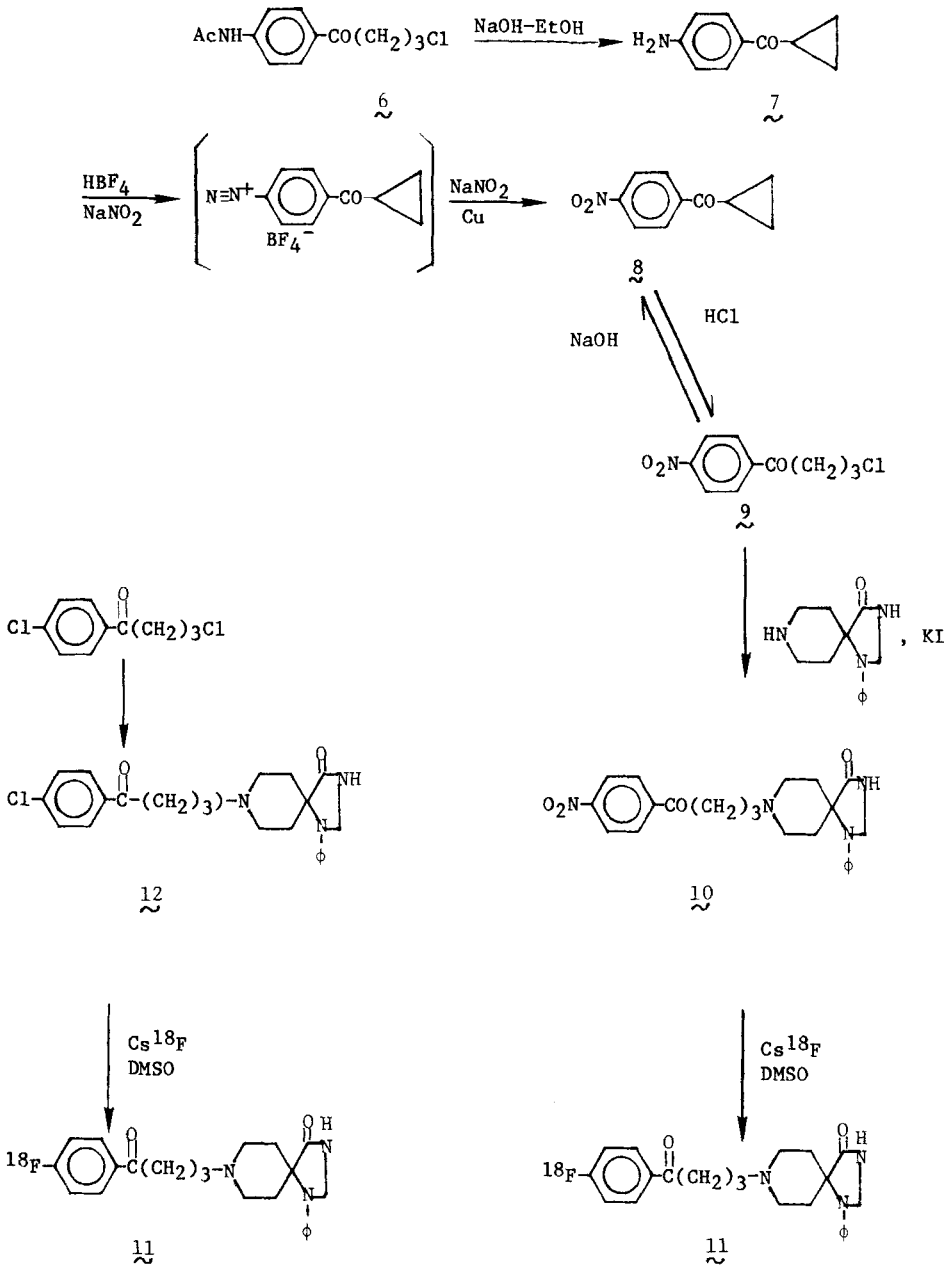


Fig. 2

Syntheses of nitrospiroperidol, chlorospiroperidol and their precursors

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