Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXIX, No. 4

THE SYNTHESIS OF o- AND p-[^{18}F]FLUOROBENZYL BROMIDES AND THEIR APPLICATION TO THE PREPATATION OF LABELED NEUROLEPTICS.

Kentaro Hatano , Tatsuo Ido * and Ren Iwata

Division of Radiopharmaceutical Chemistry, CYRIC, Tohoku University, Aoba, Aramaki, Aoba-ku, Sendai, Japan, 980.
(*Author for correspondence.)

SUMMARY

The syntheses of o- and p- [^{18}F]fluorobenzyl bromides as labeled synthons were described. They were obtained from nitrobenzaldehyde *via* a three step synthesis that exhibited good yield. The preparation of [^{18}F]fluororinated analog of a benzamide neuroleptic, *cis*-N-[(2RS, 3RS)-1-[^{18}F]fluorobenzyl-2-methyl-pyrrolidin-3-yl]-5-chloro-2-methoxy-4-methylaminobenzamide, *via* N-benzylation with the synthons was also mentioned.

Key words: [^{18}F]Arylfluoride, Positron Emission Tomography, D_2-Dopamine Receptor.

INTRODUCTION

Since the nucleophilic aromatic substitution of a no-carrier-added (NCA) [^{18}F]fluoride for an activated nitro group in DMSO was reported (1,2), this method became the representative route for the preparation of radiopharmaceuticals having NCA fluorine-18 on an aromatic ring system. However, a precursor for this reaction requires a strong activating group on an o- or p-(rarely m-) position to a leaving group. Because of the structural limitation, this labeling procedure is considered to be less flexible when it is compared to the nucleophilic aliphatic fluorination. Consequently, several fluorine-18 labeled reactive building blocks, applicable to the synthesis of radiopharmaceuticals, have been prepared from [^{18}F]fluorobenzonitrile or [^{18}F]fluoronitrobenzene. 3-Chloro-p-fluorobutyrophenone (3), p-fluorophenacyl bromide (4), p-fluorobenzenesulfonyl chloride (5) and p-fluorobenzenediazonium chloride (6) were the examples. If a fluorine-18 labeled building block was applicable to the preparation of numerous radiopharmaceuticals, the derivative would bring more flexibility to the aromatic fluorination method. [^{18}F]Fluorobenzyl halide is fascinating from this point of view as it can be utilized for the synthesis of benzylester, ether, thioether, etc. as well as N-benzyl moiety. The preparation of carbon-11 labeled aromatic amino acid (phenylalanine) from [^{11}C]benzyl chloride was also reported (7).

0362–4803/91/040373–08$05.00

Received 7 June, 1990
Revised 24 October, 1990 and 17 December, 1990

We previously reported the synthesis of carbon-11 labeled YM-09151-2, a potent benzamide neuroleptic, and this compound showed highly specific binding toward D_2-dopamine receptors *in vivo* (8). While the derivative having a [^{18}F]fluoropropylamino moiety instead of a methylamino group of YM-09151-2 was also prepared in a good yield, the compound showed rather rapid clearance from rat striatum, suggesting its lower affinity (9). We regard that YM-09151-2 can be labeled using [^{18}F]fluorobenzyl bromide as it has N-benzyl structure. The effect of the fluorine incorporation to the neurochemical property of the product is expected to be smaller in this case, and the F-18 labeled analog would be potent for the D_2-dopamine receptor measurement by positron emission tomography (PET). We present here the preparations of o- and p-[^{18}F]fluorobenzyl bromides, the labeled synthons of extensive use, and their application to the synthesis of [^{18}F]fluoro-analogs of YM-09151-2.

RESULTS AND DISCUSSION

Three major routes were considered for the preparation of fluorobenzyl bromide (i.e., bromination of fluorotoluene, bromine substitution for corresponding chloride and alcohol). Among the precursors of these methods, [^{18}F]fluorobenzyl alcohol can be prepared by reduction of [^{18}F]fluorobenzaldehyde that had already been reported (10). Our synthetic scheme is given in Figure 1.

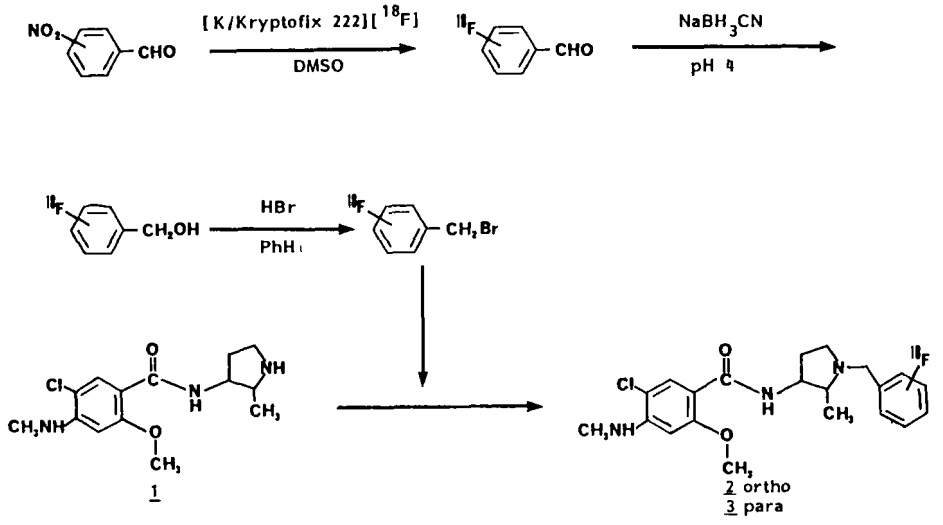

Figure. 1. Reaction Scheme

[^{18}F]Fluorination of o- or p-nitrobenzaldehyde was carried out with [K/Kryptofix 222]$^+$[^{18}F]$^-$ in DMSO according to the literature (10). To the cooled reaction mixture was added $NaBH_3CN$ and the solution was maintained approximately to pH 4 with acid. [^{18}F]Fluorobenzaldehydes were quantitatively converted to the corresponding benzylalcohols in case more than 10 mg of the reductant was used. (Typical radiochromatograms are presented in Figure 2A and 2B.) The mean radiochemical yields for o- and p- [^{18}F]fluorobenzyl alcohol were 59 % from HPLC analysis of the reaction mixtures. However, isolated yield of the products were ranged from 28 to

44 %, because the products were less ether extractable. (The extraction with SEPPAK C18 also did not show good results.)

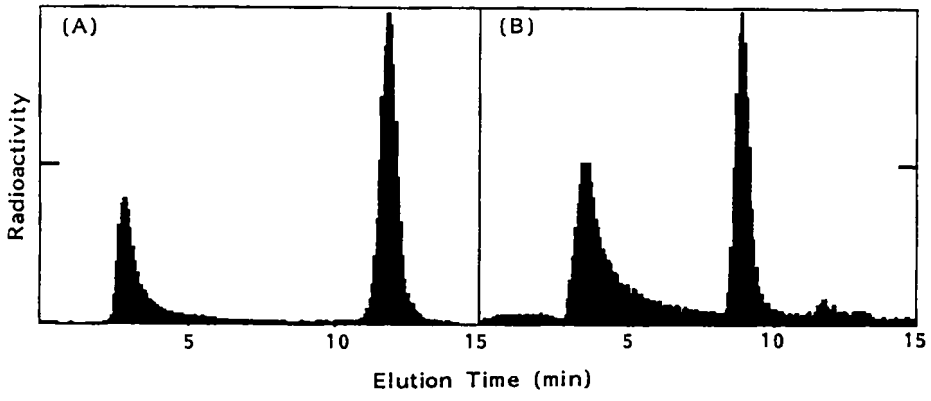

Figure 2. Radio-HPLC chromatograms of reaction mixtures of (A) [^{18}F]fluorination of p-nitrobenzaldehyde and (B) the sequential reduction with $NaBH_3CN$ in an acidic medium.

The reduction of p-[^{18}F]fluorobenzaldehyde with $LiAlH_4$ was also investigated. The ethereal extract of reaction mixture of [^{18}F]fluorobenzaldehyde, that was washed with water and applied to a silica gel column to remove DMSO, was evaporated *in vacuo*. (See experimental section for the details.). The residue was dissolved in THF and $LiAlH_4$ was added to the solution. p-[^{18}F]Fluorobenzyl alcohol was obtained with a small amount (up to 15 %) of a by-product after 5 min reaction at room temperature. No starting material was observed. The by-product had almost no retention on a reversed phase HPLC column and this might suggest that defluorination occurred. After additional 15 min reaction, only the by-product was detected. The reduction with $NaBH_3CN$ under acidic condition is concluded to be more convenient as it is not accompanied by the defluorination and as it can be achieved following fluorination in the same reaction vessel.

No halogen substitution of the [^{18}F]fluorobenzyl alcohols was found to proceed with aqueous acids like hydrochloric acid. The method using HI/LiI, reported for the preparation of p-chlorobenzyl iodide (11), was also unsuccessful. Therefore, bromination using anhydrous hydrogen bromide (12) were attempted. Into the extracted alcohol dissolved in dry benzene was introduced gaseous HBr through a $CaBr_2$ column. The solution was stirred for 20 min with and without heating. A better yield is found for p-[^{18}F]fluorobenzyl bromide at room temperature than for ortho congener in Table 1. The reaction mixture was passed through a K_2CO_3 column to remove unreacted HBr. Both o- and p-[^{18}F]fluorobenzyl bromides were obtained in good yield *via* the three step synthesis.

The preparations of [^{18}F]fluorobenzyl iodides were also undertaken. The gaseous hydrogen iodide prepared from tetrahydronaphthalene and iodine (13), was introduced to benzene. Table 1 shows that the yields of iodides, prepared with this solution, were lower than the corresponding bromides.

Table 1. Yields of Benzyl Halides from Benzyl Alcohols

Product	Temperature	Yield
o-[^{18}F]Fluorobenzyl Bromide	R.T.	53 %
	60°C	90 %
p-[^{18}F]Fluorobenzyl Bromide	R.T.	95 - 100 %
o-[^{18}F]Fluorobenzyl Iodide	R.T.	16 %
	60°C	15 %
	120°C	22 %
p-[^{18}F]Fluorobenzyl Iodide	R.T.	70 %
	60°C	89 %

Radiochemical yield was obtained by radio-TLC analysis. (See experimental section.)

Cold preparation of o- or p-fluorinated analogs of YM-09151-2 (2 and 3, respectively) were achieved with a desbenzyl derivative (1) and an excess amount of corresponding fluorobenzyl bromides prepared from corresponding fluorobenzyl alcohol. In the reaction of p-fluorobenzyl bromide and 1 in CH_3CN, a trace amount of a less polar by-product was produced besides 3 in 45% yield. The mass spectrum of this by-product had a molecular ion peak (m/e = 513) suggesting a difluorobenzyl derivative and a fragment ion peak (m/e = 306) suggesting chloro-(fluorobenzyl-methylamino)-methoxy-phenylcarbonyl structure. The o-fluoro congener was obtained in 57% yield in DMSO.

The incorporations of the obtained fluorine-18 labeled synthons into 1 were attempted in various solvents and temperatures as in Table 2. p-[^{18}F]Fluorobenzyl bromide was observed to be more reactive than the ortho congener in this synthesis. This positional effect of the substituent to the reactivity of benzyl bromide would be explained by the steric effect of fluorine atom. The purification of the products using preparative normal phase HPLC was successful. The fraction containing the product was collected (retention time of the compound [^{18}F]-2 and [^{18}F]-3 were 17 min) and eluent was evaporated *in vacuo* The residual final products were dissolved in saline. The synthesis took four hours including the each analysis. The chemical purity of the injectates was above 95 % from the same reversed phase HPLC analysis system as reported for [^{11}C]YM-09151-2 (Hatano, 1989). The specific activity was determined to be from 6.7 to 8.9 TBq/mmol (180-240 Ci/mmol) at the end of synthesis. These values were almost identical to our previous result determined for the [^{18}F]fluoropropyl analog (Hatano, 1990) when it is decay corrected to the end of the bombardment.

Table 2. Yield of [^{18}F]-2 and [^{18}F]-3 from [^{18}F]Fluorobenzyl Bromide.

Product	Solvent	Base	Temperature	Yield
[^{18}F]-2	CH_3CN	$NaHCO_3$	40°C	0 %
	DMF	NaH	40°C	Trace
	DMSO	NaH	40°C	14 %
	DMSO	*TBA-OH	60°C	36 %
[^{18}F]-3	CH_3CN	$NaHCO_3$	R.T.	28 %
	CH_3CN	$NaHCO_3$	40°C	88 %

Radiochemical yield was obtained by radio-TLC analysis. (See experimental section.) *TBA-OH = tetrabutylammonium hydroxide.

As mentioned in the present report, F-18 labeled fluorobenzyl bromides were synthesized in good yield and the preparation of p-[^{18}F]fluoro analog of YM-09151-2 was successful. The animal study, suggesting that [^{18}F]-3 was potent over the D_2-dopamine receptor measurement, will be presented separately. As fluorine is not an element that is commonly observed in pharmaceuticals and as the structures that can be labeled with NCA [^{18}F]fluoride are limited, we often have to study using a modified analog of the mother compound. In such a case, preparation of a series of labeled compounds is feasible and one can select the best derivative. [^{18}F]Fluorobenzyl bromides not only open a new synthetic possibility but also enable us to prepare two labeled ligands from one desbenzyl precursor.

In conclusion, [^{18}F]fluorobenzaldehydes obtained by the reported method were quantitatively reduced with $NaBH_3CN$ in acidic condition. [^{18}F]Fluorobenzyl alcohols thus produced were converted to [^{18}F]fluorobenzyl bromides using gaseous HBr. These labeled synthons of extensive use were obtained in three synthetic steps from [^{18}F]fluoride. In the N-benzylation reaction of 1 using these synthons, p-[^{18}F]fluorobenzyl bromide was more reactive than ortho congener. Because of their synthetic usefulness and the deduced good biochemical characteristics of the products they give, o- and p-[^{18}F]fluorobenzyl bromide will increase the possibility of nucleophilic aromatic fluorination method.

EXPERIMENTAL

General

The desbenzyl derivative of YM-09151-2 (1) was a gift from Yamanouchi Pharmaceutical Co.,Ltd.(Japan). Kryptofix 222 and gaseous hydrogen bromide were purchased from Merck (West Germany) and Matheson (USA), respectively. DMSO, DMF and CH_3CN were used after distillation.

Hundred MHz ^{1}H-NMR spectra were recorded using a JNM FX100 spectrometer (JEOL, Japan) in $CDCl_3$, and chemical shifts δ (ppm) were referred to an internal TMS standard. Mass spectra were obtained with M-52 mass spectrometer (Hitachi, Japan). HPLC was carried out on a model 600A solvent delivery system, and a model 440 UV detector (Waters, USA). UV absorbance was recorded on 280 nm wavelength and radioactivity was also detected with a NaI radioactivity monitor. Columns and solvent system used were as follows: (A) RadialPAK NVC18 column (8 × 100 mm, Waters, USA) with CH_3OH : H_2O (4 : 6) as an eluent at flow rate of 1 mL/min, (B) RadialPAK NVC18 column with 3% $(C_2H_5)_3N$-H_3PO_4 (pH 2) aqueous solution : CH_3CN (7 : 3) at 1.5 mL/min, and (C) A-024 SIL (10 × 300 mm, Yamamura Chemical Laboratory, Japan) with n-C_6H_{14}: $CHCl_3$: $(C_2H_5)_3N$ (60 : 40 : 0.1) at 5 mL/min. TLC was performed with a Kieselgel 60 F_{254} plate (Merck, West Germany). Silica gel column chromatography was achieved with Wakogel C-200 (Wako pure chemical, Japan).

cis-N-[(2RS,3RS)-1-(2-fluorobenzyl)-2-methoxy-pyrrolidin-3-yl]-5-chloro-2-methoxy-4-methylaminobenzamide (2).

Into the benzene solution (3mL) of o-fluorobenzyl alcohol (100 mg) in reaction vessel with gas inlet and outlet tubes was introduced gaseous HBr through a $CaBr_2$ column at moderate flow rate for 10 min. The stop valves on both tubes were then closed and the solution was stirred for 30 min at room temperature. This mixture was washed with 10mL of 1N NaOH and evaporated to

dryness . To the residue was added 1 (22mg, 74μmol) in 3mL of DMSO and 10% aqueous solution of $(n\text{-}C_4H_9)_4NOH$ (0.1mL). The solution was stirred for 2 hours at room temperature. After 10 mL each of water and $CHCl_3$ was added, the organic layer was separated and was washed several times with water. (About 100mL of water was used totally.) The product was further purified with silica gel column chromatography. Seventeen mg (42μmol, 57%) of 2 (colorless oil, Rf=0.49 (5% MeOH/$CHCl_3$)) was eluted with 2% MeOH/CH_2Cl_2.
NMR($CDCl_3$) δ : 1.14 (d, J=6.3Hz, 3H, $C\underline{H_3}CH$), 1.59 (m, 1H), 2.18 (m, 3H), 2.63 (m, 1H), 2.94 (d, J=5.4Hz, 3H, $C\underline{H_3}NH$), 3.33 (d, J=13.6Hz, 1H), 3.97 (s, 3H, $OC\underline{H_3}$), 4.64 (br, 2H), 6.09 (s, 1H), 6.86-7.47 (m, 5H), 8.05 (s, 1H). Mass m/e: 405 (M+), 198 (CH_3NH(Cl-, CH_3O-)C_6H_2, 192 ($CH_3\underline{CH(C_6H_4FCH_2}$-)$\underline{NCH_2CH_2}CH$).

cis-N-[(2RS,3RS)-1-(4-fluorobenzyl)-2-methyl-pyrrolidin-3-yl]-5-chloro-2-methoxy-4-methylaminobenzamide (3).

To p-fluorobenzyl bromide, obtained according to the same procedure as previously mentioned, was added the solution of 1 in CH_3CN (3mL) as well as $(n\text{-}C_4H_9)_4NOH$ solution. The mixture was stirred for 1 hour at room temperature. Following extraction, silica gel column chromatography gave 12 mg (30 μmol, 45 %) of 3 (colorless oil, Rf=0.51 (5 % MeOH/$CHCl_3$)).
NMR($CDCl_3$) δ : 1.11 (d, J=6.3Hz, 3H, $C\underline{H_3}CH$), 1.66 (m, 1H), 2.11 (m, 3H), 2.62 (m, 1H), 2.94 (d, J=5.4Hz, 3H, $C\underline{H_3}NH$), 3.14 (d, J=13.1Hz, 1H), 3.97 (s, 3H, $OC\underline{H_3}$), 4.63 (br, 2H), 6.09 (s, 1H), 6.80-7.39 (m, 4H), 8.06 (s, 1H). Mass m/e: 405 (M^+), 198 (CH_3NH(Cl-, CH_3O-, CO-)C_6H_2), 192 ($CH_3\underline{CH(C_6H_4FCH_2}$-)$\underline{NCH_2CH_2}CH$).

Preparation of o- and p-[^{18}F]fluorobenzyl alcohols.

The [^{18}F]fluorinating agent was prepared from Kryptrofix 222 (7.5 mg, 20 μmol), K_2CO_3 (0.7 mg, 5 μmol), and [^{18}F]fluoride/$H_2{}^{18}O$ solution (14) according to the usual manner. The solution of o- or p-nitrobenzaldehyde (2 mg, 13 μmol) in DMSO (0.5 mL) was added to the dried [^{18}F]fluorinating agent and the mixture was stirred at 110°C for 20 min. After cooling, $NaBH_3CN$ (10 mg, 160 μmol) and trace amount of bromocresolgreen was added to the solution. The mixture was made acidic with 0.1M HCl/CH_3OH to produce a pale green color under vigorous stirring. Small portion of the mixture was removed and was analyzed with HPLC system (A). Three mLs of diethylether and salt brine was added to the reaction mixture and the separated organic layer was washed once with water. The extract was dried by passing it through a K_2CO_3 column.

The reduction with $LiAlH_4$ were carried out after the following treatments. To the reaction mixture of [^{18}F]fluorination was added 3 mL each of water and $n\text{-}C_6H_{14}$. The organic layer was separated and washed twice with water. The extract was dried and then applied to silicagel column to remove remaining DMSO. The ethereal eluent containing [^{18}F]fluorobenzaldehyde was evaporated *in vacuo*, and the residue was dissolved in THF.

Preparation of o- or p-[^{18}F]fluorobenzyl bromide.

Into the benzene solution of o- or p- [^{18}F]fluorobenzyl alcohol in a vessel connected with gas-inlet and outlet tubes was introduced gaseous HBr through a $CaBr_2$ column. The stop valves on both tubes were closed and the solution was stirred for 20 min with or without heating. The [^{18}F]Fluorobenzyl bromides were analyzed with radio-TLC developed in 30% $CH_3COOC_2H_5$/n-

C_6H_{14}. The unreacted HBr was removed with passing the mixture through a K_2CO_3 column.

Preparation of o- or p- [^{18}F]fluorobenzyl iodide.

A solution of anhydrous hydrogen iodide was prepared by the introduction of gaseous HI generated by the method using tetrahydronaphthalene and iodine (13), into benzene. The solution was added to o- or p-[^{18}F]fluorobenzyl alcohol, and the mixture was stirred with and without heating. The yield of the products, [^{18}F]fluorobenzyl iodides, were measured by radio-TLC analysis as mentioned for bromides.

Synthesis and purification of [^{18}F]-2 and [^{18}F]-3

To o- or p-[^{18}F]fluorobenzyl bromide was added 1 (1 mg, 3.4μmol) in 0.5 mL of the reaction solvent (CH_3CN, DMF or DMSO). An appropriate base was also added. The mixtures were stirred at the temperature indicated in Table 2 for 30 min. The products were extracted in $CHCl_3$ and purified with HPLC system (C). Small portion of the extract was analyzed by radio-TLC developed in 5% MeOH/$CHCl_3$. The purified free bases were converted to hydrochloride and dissolved in saline for injection. The purity and specific activity of the obtained injectates were analyzed with HPLC system (B).

ACKNOWLEDGEMENTS

The authors are grateful to Yamanouchi Pharmaceutical Co., Ltd. (Tokyo, Japan) for giving us a desbenzyl derivative of YM-09151-2. The authors thank Kumiko Ogawa for manuscript preparation. The members of CYRIC, Tohoku University are also acknowledged for their cooperations.

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