New Synthesis of Fluorine-18-Labeled 6-Fluoro-L-Dopa by Cleaving the Carbon-Silicon Bond with Fluorine*

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A new synthesis of 3,4-dihydroxy-6-[^{18}F]fluoro-L-phenylalanine using 6-trimethylsilyl-3,4-dimethoxy-L-dopa-ethylester as a fluorination substrate is described. The silane is prepared from the corresponding bromo compound by reacting the latter with magnesium and trimethylsilyl chloride. Reaction of the silane with [^{18}F]F_2 (0.5% F_2 in neon) in a mixture of freon-11/CCl_4 (1:1) kept in a dry ice bath, subsequent hydrolysis with concentrated HBr in a bath at 140°C, and simple chromatographic purification† yielded ^{18}F-labeled 6-fluoro-L-dopa. A radiochemical yield of about 8% was achieved at the end of the 1-hr synthesis. The specific activity at the end of the synthesis was about 680 mCi/mmol after a 30-min irradiation.

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Fluorine-18-(^{18}F) labeled 6-fluoro-L-dopa (3,4-dihydroxy-6-fluoro-L-phenylalanine) accumulates in areas of the brain that contain a large concentration of the neurotransmitter dopamine (*1*). This finding has prompted interest in developing an improved synthesis for ^{18}F-labeled 6-fluoro-L-dopa, a tracer suggested as a marker for the dopamine pool (*1–5*). Two ^{18}F-labeled fluoro-dopas (5- and 6-, substituted) have been prepared by various procedures (*2–5*); however, all syntheses reported to date involve low incorporation of fluorine, lengthy preparation times, and consequently a low yield of the ^{18}F-labeled radiopharmaceutical obtained at the end of the synthesis and available for positron emission tomography. Fluorination of L-dopa with fluorine in liquid HF has recently been reported (*5*). This procedure produces a mixture of 2-, 5-, and 6-fluorodopa; an elaborate separation is therefore required before components can be resolved (*4, 5*) and 6-[^{18}F]fluoro-L-dopa of 96% radiochemical purity can be obtained. The yield and the level of reactivity are invariably low. Since 6-[^{18}F]fluoro-L-dopa might be an important radiopharmaceutical for estimating the dopamine pool (*6, 7*) in the human brain by means of positron emission tomography (PET), a more productive, reproducible synthesis must be developed.

Recently it was shown that aryl-trimethyl silanes (*7*) and arylpentafluorosilicates (*8*) can be used as substrates for the fluorination reaction in the synthesis of simple fluorinated compounds. Encouraged by our preliminary results (*7*), we have investigated the synthesis of an ^{18}F-labeled vinyl fluoride (4-fluoroantipyrine) (*9*). We report here a synthesis of ^{18}F-labeled 6-fluoro-L-dopa which involves cleaving the carbon–silicon (C–Si) bond with molecular [^{18}F]F_2 in a nonpolar solvent at the temperature of dry ice.

EXPERIMENTAL

Materials and Methods

Fluorination reactions were done by using 5% F_2 in nitrogen ("cold" preparations) and 0.5% [^{18}F]F_2 in neon when the labeled compound was synthesized. All fluorination reactions were carried out in a freon-11/CCl_4 (1:1) mixture in a dry ice bath. The fluorine gas mixture was bubbled at a rate of about 50 ml/min in the fluorination

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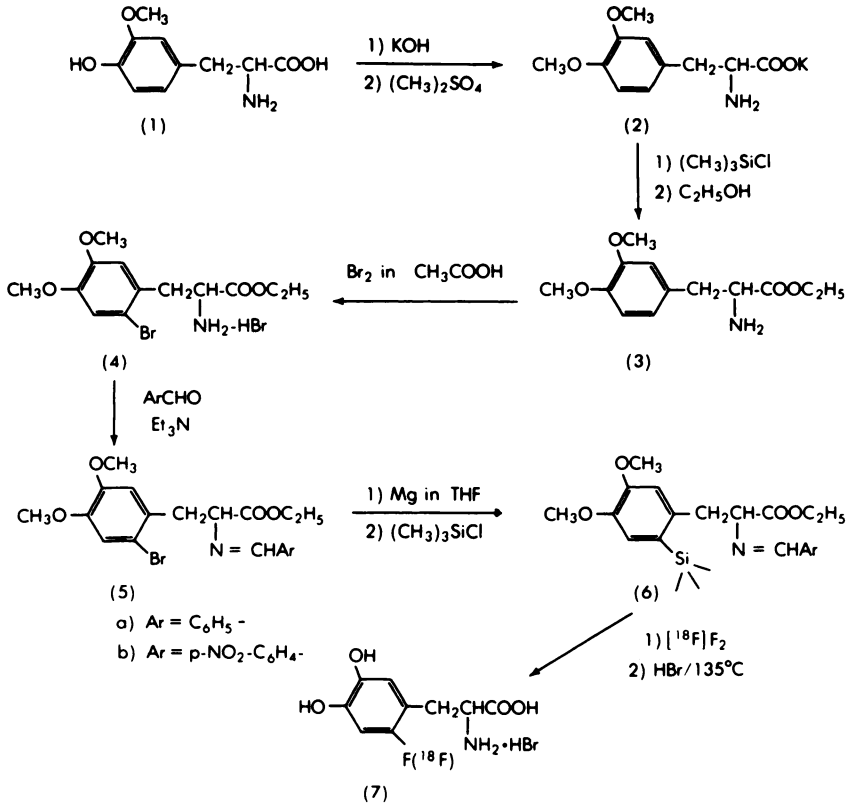

FIGURE 1
Schematics of reaction sequences used in synthesis of 6-[^{18}F]fluoro-L-dopa

with ^{18}F-labeled fluorine and gradually decreased from 60 ml/min to almost zero in the fluorination with 5% F_2 in N_2. Techniques used to control the introduction of fluorine and the production of $[^{18}F]F_2$ were described in detail elsewhere (*10*) and will not be repeated here. ^{1}H-NMR spectra were taken at 299.94 MHz using tetramethylsilane (TMS) as the internal or external standard when spectra of silanes were taken. ^{19}F-NMR spectra were taken at 75.386 MHz on a Bruker WP-80 SY and at 282.203 MHz on a Varian XL-200 spectrometer using $CFCl_3$ as the external standard. All ^{19}F chemical shifts are reported relative to $CFCl_3$ ($\emptyset = 0$) with the negative sign representing a downfield shift. Mass spectra (MS) were obtained using a HP5980A spectrometer. Melting points were determined in a capillary tube using conventional apparatus and are reported uncorrected. High performance liquid chromatography (HPLC) was done on a reverse-phase column. Both uv and radioactive detectors were used for all ^{18}F preparations. A radioactive detector with a cell of 500 or 50 μl was used. Chromatographic conditions are given later in the paper.

Thin layer chromatography (TLC) and radiochromatography (TLRC) were performed on hard layer silica gel plates developed with solvent mixtures described in the experimental part. The radiochemical yields are given at the end of the synthesis relative to the $[^{18}F]F_2$ coming from the target into the reaction mixture (equated with the total radioactivity present in the fluorination vessel at the end of bubbling).

3,4-dimethoxyphenyl-L-alanine ethyl ester (3)

3-methoxy-L-tyrosine (1, Fig. 1) (1.2 g, 5 mmol) was converted into its potassium salt (*11*) by dissolving it in 35% KOH (6 ml). The reaction mixture was stirred for 30 min at room temperature. The potassium salt was dried under vacuum for a few hours and then an excess of dimethylsulfate (2.6 ml, 30 mmol) (*11*) in 30 ml of methanol was added. The reaction mixture was refluxed for 14 hr after which time a white precipitate was filtered off and discarded. The solvent was evaporated to dryness and the residue (compound 2) dissolved in ethanol (20 ml). The esterification was done by adding chlorotrimethylsilane (2.1 ml, 16.2 mmol) into the ethanolic solution under nitrogen atmosphere (*12*). The reaction mixture was stirred at room temperature for 3 hr and the white precipitate was filtered off to collect the first crop of the product (3). An additional crop of product was isolated from the filtrate by evaporating the solvent to dryness, dissolving the resultant colorless oil in ethyl acetate, washing the ethyl acetate solution with a saturated solution of NaCl in water, and concentrating the ethyl acetate solution. The white crystals collected in the first step were also dissolved in ethyl acetate and the solution was washed and concentrated as described above. TLC plates developed in a mixture of isopropanol/ammonia (7:3) showed one spot with $R_f = 0.45$. About 4.2 mmol of ester (3) was isolated. The product was identified by ^{1}H-NMR and MS.

MS (m/e, intensity): 253, 0.76 (M^+). ^{1}H-NMR (CD_3OD, TMS) for ester; δ = 4.18 (q, $-OCH_2-CH_3$,

2H); δ = 1.26 (t, $-OCH_2-CH_3$, 3H); δ = 3.84 (s, $-OCH_3$, 6H); δ = 2.77–2.88 (m, $-CH_2-CH(NH_2)$, 2H); δ = 2.98–3.07 (d of d,$-CH_2-CH(NH_2)-$, 1H); δ = 6.64–6.84 (m, aromatic ring, 3H).

Bromination of 3,4-dimethoxy-L-phenylalanine ethyl ester

The product (3) (1.14 g, 4.5 mmol) from the previous step was brominated with bromine in glacial acetic acid (*13*) (0.25 ml, 5 mmol) [10 ml of a solution of potassium acetate in acetic acid (0.15 *M*)], a procedure previously used for introduction of bromine to position-6 (*14*). The red-brown mixture was stirred for 30 min at room temperature and then the ester (3), dissolved in acetic acid (2 ml), was added slowly to the mixture. The color of the mixture disappeared a few minutes after the ester was added. Stirring was continued for 2 hr at the same temperature. Evaporation of the solvent gave a yellowish oil (*4*), which was generally used without further purification in the subsequent step because the integrated ^{1}H-NMR agreed with the expected structure. An indication for the introduction of bromine into the aromatic ring in position-6 was obtained from the ^{1}H-NMR (CD_3OD/TMS), which showed two sets of broad singlets at δ = 6.66 ppm and δ = 6.91 ppm, each integrated for one aromatic proton. The ultimate proof for the proper assignment was obtained from the structure of the final product and comparison with the ^{1}H-NMR of diethyl (6-bromo-4,5-dimethyl) benzylacetamideomalonate (*14*). The rest of the splitting was similar to that given above for 3,4-dimethoxyphenylalanine ethyl ester (3).

The MS-spectrum of the product, 6-bromo ethyl ester, gave a molecular peak for both Br-isomers (M^+, 331, ^{79}Br-ester and 333, ^{81}Br-ester, ratio 1:1).

Schiff's base of aminoacid ester (5)

The amino group of the 6-bromo-ethyl ester (4), prepared as described in the previous step, was protected by reacting the bromo-ester (4) with benzaldehyde (1 eq) or p-nitrobenzaldehyde (1 eq) in ethanol (15) in the presence of triethylamines. The bromo adduct (4) (1.6 g, 4.8 mmol) was dissolved in ethanol (1.5 ml) and Et_3N was added until the pH of the solution became neutral. Benzaldehyde (520 mg, 4.8 mmol) or p-nitrobenzaldehyde (725 mg, 4.8 mmol), dissolved in ethanol (1.5 ml), was added to the above solution and the mixture was kept at 50°C for 20 min and stirred for 6 hr at room temperature. In the case of p-nitrobenzaldehyde, the solution should be refluxed. After that the mixture was kept at -10°C for 14 hr. Evaporation of the solvent gave a yellow oil, which was purified by extraction with hot ethyl acetate. The yield of N-benzylidene (5a) and N-p-nitrobenzylidene (5b) was about 60%. ^{1}H-NMR for N-benzylidene adduct (5a) was (CD_3OD/TMS), δ = 6.99 (m, *Ar*-H, *CH*=N and aromatic protons of amino acid ester, 8H). ^{1}H-NMR for N-p-nitrobenzylidene adduct in $CDCl_3$/TMS showed a multiplet at δ = 7.25 ppm (NO_2-*Ar*-H, *CH*=N and aromatic protons of amino acid ester; 7H).

Synthesis of 6-trimethylsilyl-3,4-dimethoxy-L-dopa ethyl ester (6)

The benzylidene (5a, Fig. 1) or p-nitro-benzylidene (5b, Fig. 1) adduct of aminoacid ester (4 mmol) was reacted with magnesium turnings (120 mg, 5 mmol) in anhydrous tetrahydrofuran (*15*) at reflux for 7 hr in the presence of a crystal of iodine. Trimethylsilyl chloride (1 ml, 10 mmol) was then added and the reaction was refluxed overnight. After filtering off the magnesium salts, the filtrate was evaporated to a brown oil, which was dissolved in chloroform and washed with water. After evaporation of the solvent, the yellowish oil was extracted with carbon tetrachloride giving the silane (6, Fig. 1) in a 5% yield (0.4 mmol) relative to 3-methoxy-L-tyrosine (*1*). ^{1}H-NMR of the products (CCl_4) showed a peak at δ = 0.02 ppm for the trimethylsilyl group which corresponded to nine protons. The other resonances were not greatly different from the compounds described above. Integration agreed with the expected structure.

Preparation of 6-^{18}F-fluoro-L-dopa (7)

The carbon tetrachloride/freon-11 (1:1) (10 ml) solution of 6-trimethylsilyl 3,4-dimethoxy-L-dopa ethyl ester (6) (0.2 mmol) obtained in the previous reaction step was first cooled in a dry ice bath for 10 min and [^{18}F]-F_2 (0.07 mmol) (*9*) was bubbled for 10 min at the temperature of dry ice. Evaporation of the solvent gave a solid residue which was dissolved in chloroform (3 ml) and treated with CaO. After the CaO was filtered off and the solvent evaporated under vacuum, the residue was dissolved in 5 ml HBr (*2, 3*) (48%) and transferred in a vial. The vial was closed and heated in a bath kept at 135°C for 35 min. Hydrobromic acid was evaporated to dryness under reduced pressure and the excess acid removed by redissolving the residue in 12 ml of water and re-evaporating it. To remove HBr completely, the previous procedure was repeated twice. The product was decolorized by redissolving it in H_2O (10 ml) and heating it with charcoal at 120°C for 3 min.

TLRC of the colorless solution in isopropanol-NH_4OH (6.5:3.5) showed 6-[^{18}F]fluoro-L-,dopa with a R_f = 0.45. Purification of a buffered solution (pH 4.5) by filtration through a reverse Sep-Pak[§] (two in series) and sterilization by filtration through a 0.2 μm Millipore yielded 6-[^{18}F]fluoro-L-dopa with a radiochemical yield of 5–10% (average 8%). The radiochemical purity of the final product was about 95%. The product, 6-[^{18}F]fluoro-L-dopa (7, Fig. 1), was identified by its ^{19}F-NMR, which was compared to an authentic sample[‡] using D_2O plus a few drops of CD_3COOD as a solvent, by HPLC comparing the elution volume, and by R_f values. ^{19}F-NMR (D_2O and a few drops of CD_3COOD) ϕ = -126.91 ppm ($^3J_{HF}$ = 9.8 Hz, $^4J_{HF}$ = 7.3 Hz); ^{1}H-NMR (D_2O + MeOD -d_4 + DMSO-

d_6) appeared as two AB parts of the two ABX systems corresponding to protons on carbon-2 and carbon-5, respectively. The lines appeared between 6.72 and 6.75 ppm for hydrogen in position-2 (J_{HH} (para) = 1.7 Hz, $^4J_{HF}$ = 8 Hz, 1H) and between 6.91 and 6.95 ppm for hydrogen in position-5 (J_{HH} (ortho) = 1.7 Hz, $^3J_{HF}$ = 10 Hz, 1H). The protons of the side chain appear as an ABX system with the X part at δ = 3.77 ppm ($^3J_{HxHb}$ = 4.4 Hz, -*CH*(NH_2)-, 1H) and AB parts between 2.92 and 3.0 ppm ($^2J_{HaHb}$ = 14.6 Hz, $^3J_{HaHx}$ = 8.3 Hz, -CH_2-, 1H) and 3.16 and 3.23 ppm ($^2J_{HbHa}$ = 14.4 Hz, $^3J_{HbHx}$ = 4.4 Hz, -CH_2-, 1H).

The specific activity of the final product agreed well with the specific activity measurements of [^{18}F]F_2 (*10*). After a 30-min irradiation the specific activity was about 680 mCi/mmol expressed at the end of synthesis. In a typical preparation, from about 60 mCi of [^{18}F]F_2 we obtained about 4.8 mCi of 6-[^{18}F] fluoro-L-dopa after a 1-hr synthesis. There is no need to remove L-dopa from the final product because the concentration of L-dopa in human plasma is about 8 μM.

RESULTS AND DISCUSSION

All syntheses of ^{18}F-labeled 6-fluoro-L-dopa (7) reported to date have a low radiochemical yield (*2–5*) barely amounting to that required for PET studies in humans. The time required to complete these syntheses was generally very long (2–4 hr), especially when the synthesis was done with a 110-min radioisotope. Four hours were required when fluorination was done with [^{18}F]XeF_2 and 3 hr when it was done with acetylyhypofluorite reaching yields of up to 1.3% (*4*). However, the synthesis reported very recently (*5*) is shorter: it takes about 2 hr, reaching a radiochemical yield of 3%. The major shortcoming of even the best of these syntheses is a long, elaborate purification procedure which itself takes almost 110 min (*5*). In contrast, the synthesis reported here gives only 6-[^{18}F]fluoro-L-dopa in a radiochemical yield at least twice that of any synthesis ever reported. Having only one radioactively labeled fluoro-dopa greatly simplifies purification, reducing the synthesis time to less than 1 hr.

^{19}F-NMR analysis of the final product revealed the presence of only one 6-[^{18}F]-fluoro-L-dopa, giving doublet of doublets with coupling constants ($^3J_{HF}$ = 9.8 Hz, $^4J_{HF}$ = 7.3 Hz) and chemical shift (-126.91 ppm). The chemical shift is in good agreement with that reported by Firnau et al. (*4, 5*); our coupling constants only approximate theirs. (The chemical shift assigned to 6-fluoro-dopa in the most recent paper (*5*) has probably been confused with that of 5-fluoro-dopa). The coupling constants and chemical shift obtained in this work are close to those observed for commercially available 6-fluoro-dopamine. A possible explanation for the difference in coupling constants is that the peaks in the ^{19}F-NMR spectra are not very narrow. The broadening of the peaks might influence the determination of the coupling constants.

Another set of difficulties derives from the influence of the concentration on the shape of the spectra and therefore on the determination of the coupling constants. We have observed the splitting in the ^{19}F-NMR spectra to be a function of the 6-fluoro-L-dopa concentrations. When the amount of this compound was below about 1.0 mg the peaks of doublet of doublets were not well resolved. ^{19}F-NMR (D_2O + TMS) of 6-fluoro-dopamine showed doublet of doublets centered at ϕ = -127.85 ppm with $^3J_{HF}$ = 9.8 Hz and $^4J_{HF}$ = 7.3 Hz, the same as those observed for 6-fluoro-L-dopa. However, ^{1}H-NMR (D_2O + TMS) of 6-fluoro-dopamine gave $^3J_{HF}$ = 11.3 Hz and $^4J_{HF}$ = 7.3 Hz with corresponding chemical shifts of 6.75 ppm. The H-F coupling constants of the 6-fluoro-dopamine ($^3J_{HF}$ = 10 Hz, $^4J_{HF}$ = 8 Hz), are similar to those obtained from ^{1}H-NMR and ^{19}F-NMR spectra of 6-fluoro-dopa ($^3J_{HF}$ = 9.8 Hz, $^4J_{HF}$ = 7.3 Hz). H-F coupling constants for 6-fluoro-L-dopa obtained from the ^{1}H-NMR spectra are somewhat greater than those obtained from the ^{19}F-NMR spectra. We do not have a clear explanation for this. It may be that the solvent and the concentration affect the resolution.

The couplings in the ABX system of the side chain of 6-fluoro-L-dopa reported here do not agree well with those reported by Firnau et al. (*5*) and Auhoury et al. (*14*) in 5-fluoro-dopa and 6-bromo-dopa, respectively. The reason for this discrepancy is not obvious but it could result from mistaken assignment of the lines in the ABX system. We have not determined the sign of the AB coupling constants. However, from its absolute magnitude we could conclude that it has a negative sign (*17*). The chirality of the final product was confirmed by HPLC, using a chiral reverse-phase column prepared as described by Gil-Av et al. (*18*). As measured by the HPLC of the final radiopharmaceutical, only one radioactive species was present and eluted with the same elution volume as 6-fluoro-L-dopa.

Halogenation of the aromatic silanes has been investigated in the past (*19*) but not fluorination, possibly because fluorine was considered to be too reactive to allow controlled cleavage of the C—Si bond and an aryl compound. We have recently shown that cleavage can be done with relative ease and that a simple purification yields fluorinated compounds (*7*). In contrast to a recent report that the fluorination of the C—Si bond with F_2 yields a mixture of all possible substituents (*8*), the cleaving of the C-Si bond in the case reported here yielded only one fluorinated compound.

The formation of several regional isomers is similar to that reported in the bromination of substituted aryl silanes (*19*). However, in the experiments of Shiue et al. (*8*) the silane/fluorine ratio was only about 1.5–2, in contrast to the ratio of about 3:1 used in our work. The silane used in this work cannot be considered a typical representative of aryl silanes because position-6 in our compound is the most nucleophilic (*14*). Having the silane in that position would reinforce the direction of the electrophile to that position and would result in a clean cleavage of the C—Si

bond. A similar result was observed in the bromination of substituted aryl silanes (*19*) where the substituent directs the electrophile to the C—Si bond. The purification of the silane is a critical step: if a silane is not properly purified from a nonbrominated compound (3) all three isomers of fluoro-dopa will be produced, complicating the purification of the final radiopharmaceutical.

A comparison of ^{1}H-NMR spectra of 3,4-O-dimethyl-bromophenylalanine ethyl ester and diethyl (6-bromo-4,5-dimethoxy) benzylacetamide malonate, prepared as described earlier (*14*), revealed the presence of bromine in position-6. Our observations on the bromination of methoxy-L-dopa agree well with results reported earlier (*14*) to the effect that position-6 is one of the most nucleophilic- position and that bromination yields only a 6-bromo-compound. The yields of different steps during synthesis of the silane were generally good. The new synthetic routes for silane preparation have been investigated in an attempt to increase the yield.

After fluorination, hydrolysis, and Sep-Pak (C-18) purification, 6-[^{18}F]fluoro-L-dopa was analyzed by HPLC using a reverse-phase column[§] and H_2O with the addition of 0.1% AcOH and 0.01% NH_4OAC as an elution solvent. The elution volume of 11.9 ml was identical to that of an authentic sample[‡] and showed only one symmetric peak. No other radioactivity was present in the final radiopharmaceutical. The other compound carrying the ^{18}F-label, trimethylsilyl fluoride, was lost during evaporation under reduced pressure. As confirmed by elution from a chiral column, there was no racemization during the synthesis.

The specific activity obtained in our work is about twice that reported by Firnau et al. (*5*) which was claimed to be sufficiently high for the application of tracer kinetics.

A major shortcoming of the synthesis reported here is the preparation of the silane. Two different Schiff's bases were investigated but no difference in the silane yield was observed. The silane used as the fluorination substrate is difficult to prepare and at present the yield is only about 5% relative to the 3-methoxy-L-tyrosine, the synthesis starting material.

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FOOTNOTES

[†]Sep-Pak (C-18), C-18 Cartride, Waters Associates, Inc., Milford, MA.

[‡]An authentic sample was kindly provided to us by Dr. K.L. Kirk, NIH, Bethesda, MD.

[§]Whatman M9 ODS-2 column (2.5 × 50 cm), Clifton, NJ.

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