Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 1236–1242.
Published online 1 October 2007 in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1454

JLCR

Research Article

Trifluoromethanesulfonic acid, an alternative solvent medium for the direct electrophilic fluorination of DOPA: new syntheses of 6-[^{18}F]fluoro-L-DOPA and 6-[^{18}F]fluoro-D-DOPA

BABAK BEHNAM AZAD[1,2], RAMAN CHIRAKAL[1,2,*] and GARY J. SCHROBILGEN[2,*]

[1] Nuclear Medicine, McMaster University Medical Centre, Hamilton Health Sciences, Hamilton, ON L8N 3Z5, Canada
[2] Department of Chemistry, McMaster University, Hamilton, ON L8S 4M1, Canada

Received 13 June 2007; Revised 6 July 2007; Accepted 7 August 2007

Abstract: Previous work from this laboratory has shown that the direct fluorination of 3, 4-dihydroxy-phenyl-L-alanine (L-DOPA) in anhydrous HF (aHF) or BF_3/HF with F_2 is an efficient method for the synthesis of 6-fluoro-L-DOPA. Since then, ^{18}F-labeled 6-fluoro-L-DOPA ([^{18}F]6-fluoro-L-DOPA) has been used to study presynaptic dopaminergic function in the human brain and to monitor gastrointestinal carcinoid tumors.

This work demonstrates that the reactivity and selectivity of F_2 toward L-DOPA in CF_3SO_3H is comparable with that in aHF. This new synthetic procedure has led to the production of [^{18}F]fluoro-L-DOPA and [^{18}F]fluoro-D-DOPA isomers in 17 $\pm$ 2% radiochemical yields (decay corrected with respect to [^{18}F]F_2). The 2- and 6-FDOPA isomers were separated by HPLC and subsequently characterized by ^{19}F NMR spectroscopy. The corresponding [^{18}F]-FDOPA enantiomers have been obtained in clinically useful quantities by a synthetic approach that avoids the use of aHF. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: electrophilic fluorination; fluorine-18; PET; radiolabeling; DOPA; cyclotron

Introduction

Positron emission tomography (PET) is a non-invasive imaging technique, which has been commonly used for the *in vivo* visualization of brain functions such as blood flow, metabolism, enzyme activity, neuroreceptors and neurotransporters.[1] Fluorine-18-labeled 6-fluoro-L-DOPA was initially developed as a routine PET tracer to assess presynaptic dopaminergic function in the human brain.[2] Dopamine is synthesized *in vivo* by the hydroxylation and the subsequent decarboxylation of the amino acid L-tyrosine, stored intraneuronally in vesicles from which it is ejected into the synapse during neurotransmission. The monitoring of intracerebral dopamine by PET requires the presence of dopamine in the brain that is labeled with a positron emitter. Dopamine, however, will not cross the blood–brain barrier upon injection into the blood stream, and is unable to reach the dopaminergic cells of the brain. The immediate dopamine precursor, L-DOPA, can, however, cross the blood–brain barrier and can therefore be employed to monitor *in vivo* intracerebral dopamine metabolism when labeled with ^{18}F.[3] Garnett *et al.* pioneered the use of 6-fluoro-L-DOPA, in conjunction with PET, to visualize regional distributions of intracerebral dopamine in the human brain.[2] Fluorine-18-labeled 6-fluoro-L-DOPA can be produced by the direct electrophilic fluorination of L-DOPA in anhydrous HF (aHF), but is formed in admixture with the 2- and 5-fluoro-L-DOPA isomers, which cannot be utilized to study the dopaminergic pathways of the brain.[4]

Although ^{18}F-FDG has been the benchmark for brain tumor detection, recent studies have shown its use for the detection of low-grade tumors and, in some cases, recurrent tumors, is problematic owing to its low specific to non-specific uptake ratio.[5] Amino acids, on the other hand, usually exhibit higher specific to non-specific uptake ratios and are consequently making major contributions to tumor detection by PET.[6] As a result, there has been a growing interest in the use of ^{18}F-labeled aromatic amino acids and PET for tumor detection. In particular, [^{18}F]6-fluoro-L-DOPA

*Correspondence to: Raman Chirakal, Nuclear Medicine, McMaster University Medical Centre, Hamilton Health Sciences, Hamilton, ON L8N 3Z5, Canada and Gary J. Schrobilgen, Department of Chemistry, McMaster University, Hamilton, ON L8S 4M1, Canada. E-mail: chiraklr@mcmaster.ca (R.C.), schrobil@mcmaster.ca (G.J.S.)

appears to have the potential to improve the detection of neuroendocrine tumors and their metastases.[6] Fluorine-18-labeled 6-fluoro-L-DOPA has also been shown to be an excellent candidate for the visualization of high-grade and low-grade tumors, and for the analyses of recurrent low-grade gliomas, which are difficult to examine by magnetic resonance imaging and are usually not detected by ^{18}F DG PET.[5]

Although the applications of 6-fluoro-L-DOPA have been well studied and are extensive, drawbacks still remain because 3-*O*-methyl-[^{18}F]6-FDOPA is formed in the blood and brain by the action of catechol-*O*-methyl transferase (COMT). It has been shown that the presence of 3-*O*-methyl-[^{18}F]6-FDOPA causes non-specific accumulation of radioactivity in the brain and blood, resulting in lower signal-to-noise ratios in PET images.[7] Because aromatic amino acid decarboxylase and COMT are specific to L-DOPA, it is speculated that [^{18}F]6-fluoro-D-DOPA may not be as extensively metabolized in the brain, leading to higher signal-to-noise ratios in tumor images when compared with 6-[^{18}F]fluoro-L-DOPA. In recent *in vivo* and *in vitro* studies, Bauwens *et al.*[8] showed that the tumor-uptake to background ratio of $^{123/125}$I-labeled 2-iodo-D-tyrosine is similar to that of its L-analogue in tumor cells (*in vitro* in LAT1-expressing R1M rat rhabdomyosarcoma cells and *in vivo* in R1M tumor-bearing Wag/Rij rats). These authors also reported similar results for 2-[^{123}I]phenyl-D-alanine and its L-analogue.[9] Furthermore, van Langevelde *et al.*[10] have demonstrated that ^{14}C- and ^{11}C-labeled DL- and D-DOPA exhibit high uptakes in the tumor tissue 1 h after intravenous injection into Syrian golden hamsters with Greene melanoma. Results from the above studies suggest that both the D- and L-enantiomers of 6-[^{18}F]FDOPA may also display comparable uptakes in tumors.

Among the various methods that have been used for the synthesis of 6-[^{18}F]fluoro-DOPA,[11,12] the most common synthetic route is regioselective fluorodestannylation,[13] although, in the past, fluorodemercuration[14,15] reactions have also been extensively used. Although both methods provide high radiochemical yields, they require costly functionalized precursors, prepared and purified through tedious multi-step procedures, and considerable expertise. Moreover, metal contamination of the product may occur, requiring further purification prior to clinical use.[16] Fluorodestannylation is preferred over fluorodemercuration because of the toxicities associated with the mercury derivatives employed in this procedure. Syntheses using fluorodestannylation have the added drawback of producing insoluble $(CH_3)_3SnF$ which can obstruct tubing and valves used in automated synthetic procedures.[16] Consequently, a simplified and more routine method for the syntheses of D- and L-enantiomers of 6-FDOPA is highly desirable to facilitate further investigation of their biochemical properties in small animal studies.

The use of elemental fluorine has been perceived as a non-selective electrophilic fluorination method for aromatic compounds because the strong oxidant nature of F_2 results in exothermic radical chain reactions that lead to the formation of side products that include tars. Prior work from this laboratory has shown that direct electrophilic fluorination of L-DOPA using F_2 in aHF produced 2-, 5- and 6-fluoro-L-DOPA having a total radiochemical yield of 30% (decay corrected with respect to [^{18}F]F_2),[17] which is excellent for electrophilic radiofluorinations because the theoretical maximum radiochemical yield is 50% with respect to [^{18}F]F_2. The highly efficient fluorination of L-DOPA and other aromatic compounds in aHF is partly the result of the low reaction temperatures employed and the high solvent polarity, which favor electrophilic substitution reactions. In addition, aromatic substrates in aHF are less susceptible to oxidation by F_2 because the catechol oxygens are protonated.[18] Chambers[19] has shown that protic solvents promote electrophilic fluorination of aromatic compounds and that the reactivity of F_2, as an electrophile, varies significantly with solvent acidity. In a prior work from this laboratory, the regioselectivities of aromatic electrophilic fluorinations were shown to be dependent upon the acidity of the reaction medium. For example, although useful quantities of ^{18}F-labeled 2- and 5-fluoro-L-DOPA have been prepared by the direct fluorination of L-DOPA in various weak protic acid solvents such as HCOOH, CH_3COOH and CF_3COOH, 6-fluoro-L-DOPA could only be produced when the superacid, aHF, was used as the solvent.[20] The direct electrophilic fluorination of L-DOPA in BF_3/aHF, in particular, was shown to produce 2-, 5- and 6-fluoro-L-DOPA in a total radiochemical yield of 40%.[21]

Anhydrous HF does not readily lend itself to use in most hospital environments because of its hazardous nature and the specialized fluoroplastic equipment and expertise required for its handling. An alternative route to the production of 6-[^{18}F]fluoro-L-DOPA and 6-[^{18}F]fluoro-D-DOPA by the direct radiofluorination of their respective precursors in the superacidic medium, trifluoromethanesulfonic acid (triflic acid, CF_3SO_3H), that largely circumvents these difficulties is reported in this article.

Results and discussion

In choosing an alternative solvent medium for electrophilic fluorination of L-DOPA, a high solvent acidity is required to facilitate and enhance the regioselectivity of

DOI: 10.1002.jlcr

the reaction. Triflic acid was selected because of its high Hammett acidity ($H_0 = -13.8$), which places it in the superacidic category along with aHF ($H_0 = -15.1$),[22] and its resistance to oxidation by F_2. Moreover, CF_3SO_3H has a favorable liquid range (f.p. −40 to −45°C; b.p. 162°C),[23] both it and its conjugate base are not sources of fluoride ions, even in the presence of very strong Lewis acid fluoride ion acceptors, and the solubilities of amino acids are high in both CF_3SO_3H and aHF, which is expected to promote greater product yields. There have been numerous applications of CF_3SO_3H in organic syntheses such as salt formation, polymerization, ester formation and Friedel–Crafts reactions.[24] Moreover, Coe *et al.*[25] used 10% CF_3SO_3H in $CFCl_3$ solvent to promote electrophilic fluorinations of aromatic compounds containing the $(CH_3)_3Si$ group. The use of CF_3SO_3H minimizes side reactions encountered in direct electrophilic fluorinations that utilize F_2 and reduces the difficulties and hazards associated with the use of aHF.[23] Prior studies from this laboratory have shown increased regioselective fluorination of the C6 position in electrophilic fluorinations of L-DOPA, with increasing solvent acidity.[20] Consequently, in the present study, the direct fluorination of L-DOPA was carried out in 99% CF_3SO_3H to maximize the yield of 6-fluoro-L-DOPA.

CF_3SO_3H as a direct fluorination medium

The direct regioselective fluorination of DOPA in 99% CF_3SO_3H (Table 1) produced clinically useful quantities of ^{18}F-labeled 2- and 6-FDOPA. Fewer side products and higher relative isomeric ratios of 6-FDOPA (Table 1) were observed by preparative HPLC (Figure 1) at lower reaction temperatures, suggesting that 6-FDOPA is a kinetically favored product. It is noteworthy that the highest radiochemical yield was obtained when a 3:1 molar ratio of DOPA:F_2 was used. A typical fluorination of DOPA in CF_3SO_3H at 4°C resulted in a radiochemical yield of 19.7% compared with 15.6% when a 1.6:1 molar ratio of DOPA:F_2 was used. The preparative HPLC findings are in agreement with the analytical HPLC UV and radiochromatograms obtained for the products of the direct fluorination of L-DOPA in CF_3SO_3H at −40°C (Figure 2).

Reduction of the number of side products is a major advantage of direct radiofluorination of L-DOPA in CF_3SO_3H (Figure 1(a)) over radiofluorinations carried out in BF_3/aHF (Figure 4) or aHF[15] and serves to facilitate the isolation of 6-FDOPA from the final reaction mixture. The use of CF_3SO_3H as the solvent medium resulted in a decay-corrected total radiochemical yield of 19.7% for the FDOPA isomers, which is sufficient for clinical use.

Table 1 Radiochemical yields (RCY) of FDOPA resulting from direct fluorination of DOPA in CF_3SO_3H[a]

Temperature (°C)	RCY (%)[b]	Number of trials	Relative ratio[c] (2-, 5- and 6-FDOPA)
RT	19.3 ± 2	6	38:15:47
4	15.6 ± 3	6	36:7:57
−30	11.4 ± 2	2	36:5:59
−40	14.5 ± 2	2	33:0:67

[a] Reactions were carried out in 99% CF_3SO_3H.

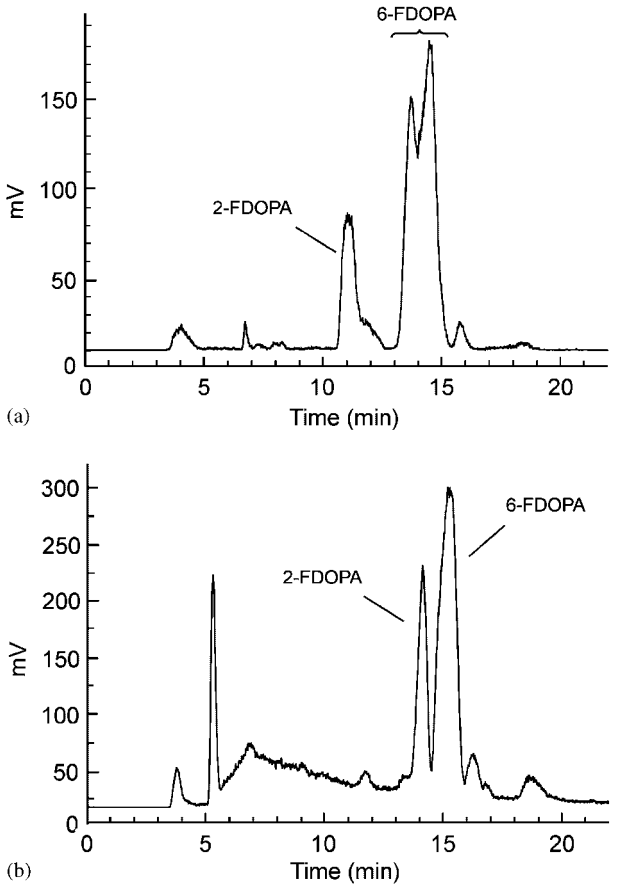

Figure 1 Typical preparative HPLC radiochromatograms for reaction mixtures resulting from the direct fluorination of L-DOPA in 99% CF_3SO_3H at (a) −40°C and (b) 4°C. Small differences in retention times result from minor variations in mobile phase concentrations or flow rates. Peak splitting resulted from detector saturation.

The ^{19}F NMR spectra of 2-FDOPA (−139.6 ppm, broad singlet, $\Delta\nu_{1/2} = 16$ Hz), 5-FDOPA (−135.6 ppm, doublet, $^3J(F–H_6) = 11.3$ Hz) and 6-FDOPA (−126.4 ppm, doublet of doublets, $^3J(F–H_5) \approx {}^4J(F–H_2) = 9.0$ Hz) are in agreement with those reported in the literature.[26] The peak integrations corresponding to the FDOPA isomers in the ^{19}F NMR spectra matched with those of the ^{18}F-labeled FDOPA isomers in the HPLC radiochromatograms.

DOI: 10.1002.jlcr

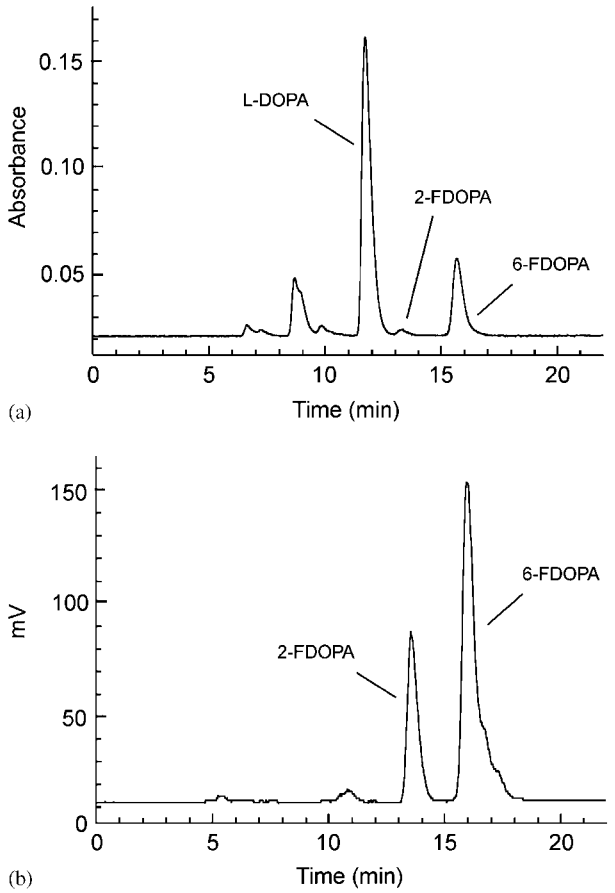

Figure 2 Typical analytical HPLC UV (a) and radiochromatogram (b) for a reaction mixture resulting from the direct fluorination of L-DOPA in 99% CF_3SO_3H at −40°C.

Figure 3 shows a typical ^{19}F NMR spectrum after isolation of 6-FDOPA from the final product mixture and Table 2 lists the relative intensities of fluorinated species in the aforementioned sample. Higher purity 6-FDOPA samples can be obtained when the corresponding peak in the radiochromatogram is collected at longer HPLC retention times; this, however, results in lower activities.

Removal of CF_3SO_3H by evaporation proved to be difficult and time consuming owing to its high boiling point (162°C) and low vapor pressure (1 Torr at 42°C).[22] Anion exchange proved to be an efficient method for the removal of CF_3SO_3H over a short time period (<5 min). Approximately 42 ± 2% (decay corrected with respect to $[^{18}F]F_2$) of the theoretical maximum activity was eluted from the column using 30 mL of 0.1 M HCl. The ^{19}F NMR spectrum of the eluate (pH, 4–5) indicated removal of most of the triflic acid in the reaction mixture. The retention of a small amount of FDOPA remaining on the column (typically <0.5%) was confirmed by elution of the anion exchange resin with an additional 5 mL of 0.1 M HCl, followed by HPLC analysis of the eluate. Attempts to recover the remaining FDOPA from the column by using higher HCl concentrations (0.5, 1 and 2 M) resulted in the co-elution of CF_3SO_3H with FDOPA.

Other direct fluorination media

CF_3SO_3H/HCOOH. Because the direct removal of CF_3SO_3H from the product under dynamic vacuum is problematic owing to its low vapor pressure, solutions of CF_3SO_3H in formic acid were also investigated in an attempt to reduce the amount of CF_3SO_3H. Formic acid has been used as a solvent in the selective fluorination of substrates containing carbon centers of high electron density.[27] In the present study, it was shown that increasing the solvent acidity results in fewer side products and higher yields of 6-FDOPA (Table 3). In addition, smaller amounts of 5-FDOPA were produced at higher concentrations of CF_3SO_3H which is significant because 5-FDOPA cannot be fully separated from 6-FDOPA using HPLC, because of their very similar retention times. As a result, CF_3SO_3H is preferred over CF_3SO_3H/HCOOH as the solvent medium for the production of 6-FDOPA.

BF_3/CF_3SO_3H. The presence of a Lewis acid, such as BF_3 or AsF_5, in aHF has been shown to increase radiochemical yields of the monofluorinated amino acids in direct fluorinations.[21] In particular, BF_3/HF media have been utilized to significantly improve radiochemical yields of 6-FDOPA.[21] The radiofluorination of L-DOPA in BF_3/CF_3SO_3H at 4°C did not, however, result in a significantly higher radiochemical yield (Table 3). This is in agreement with a previous study by Coenen *et al.*[28] in which the use of BF_3/CF_3COOH as a solvent medium for the fluorination of phenylalanine did not result in a significant increase in the radiochemical yield when compared with yields obtained in CF_3COOH.

Materials and methods

Reagents and chemicals

Enriched $[^{18}O]O_2$ (^{18}O, 99 atom%, Isotec), neon (Air Products, 99.999%), 1% F_2 in neon (Canadian Liquid Air), boron trifluoride (Matheson, 99.5%), helium (Matheson, 99.9999%), CF_3SO_3H (Fluka, 99.8%) and HPLC-grade CH_3CN (Caledon) were used without further purification and/or drying. Sterile, deionized water was used in all aqueous procedures.

DOI: 10.1002.jlcr

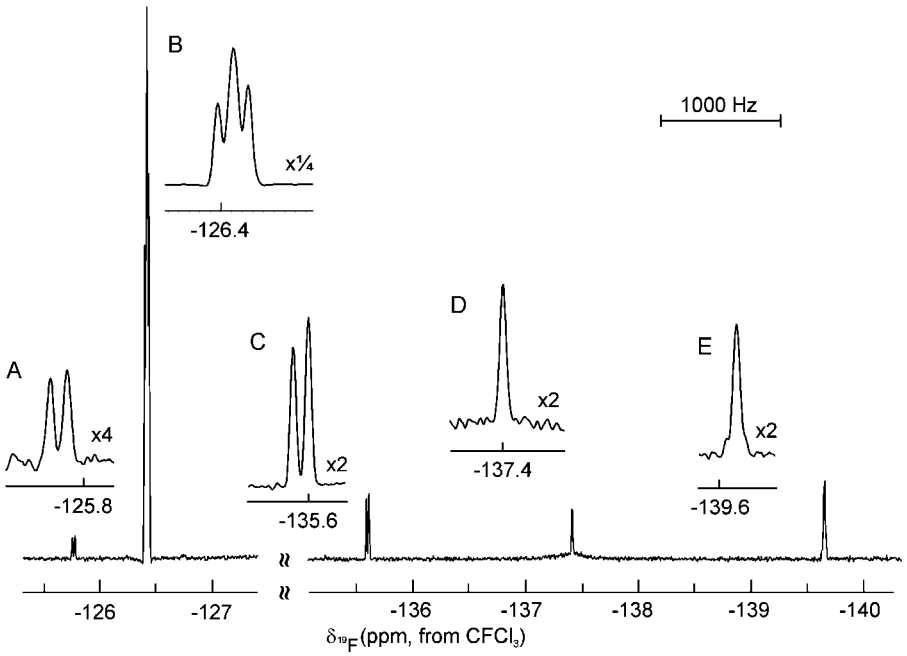

Figure 3 Fluorine-19 NMR spectrum of 6-FDOPA isolated from the product mixture using preparative HPLC. Peaks B, C and E correspond to 6-, 5- and 2-FDOPA, respectively. Small amounts of unidentified fluorinated side products were also observed (A and D). The ^{19}F NMR spectrum also showed two singlets at −75.7 (unidentified) and −79.9 ppm (residual CF_3SO_3H) which are not shown.

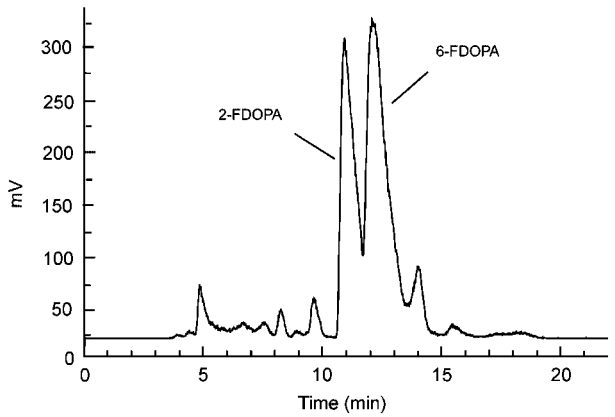

Figure 4 Typical preparative HPLC radiochromatograms for reaction mixtures resulting from the direct fluorination of L-DOPA in BF_3/HF at −65°C. Small differences in retention times result from minor variations in mobile phase concentrations or flow rates. Peak splitting resulted from detector saturation.

Fluorine-18-labeled F_2 was produced by the nuclear reaction, $^{18}O(p,n)^{18}F$, using a Siemens RDS 112 proton cyclotron, operating at 11 MeV, and the 'double shoot' method[29,30] in the Nuclear Medicine Department of Hamilton Health Sciences. An aluminum target (11 mL) was pressurized to 14–16 atm with 99% enriched $[^{18}O]O_2$ and irradiated for 20 min using a 30 μA proton beam (production shoot). After irradiation, $[^{18}O]O_2$ was recovered from the target by condensation at −196°C into a cryo-trap consisting of molecular sieves (Varian VacSorb, 5 Å) contained in a 316 stainless steel Whitey® cylinder (75 mL). The target was pumped to remove trace amounts of $[^{18}O]O_2$ and subsequently filled with 1% F_2 (40–50 μmol) in neon, pressurized to 20 atm with neon, and irradiated for 10 min in a 15 μA proton beam (recovery shoot). Portions of the $[^{18}F]F_2$/Ne mixture were periodically released from the target into a continuous stream of helium until the target pressure dropped to 2 atm. Helium was used as the sweep gas to transfer $[^{18}F]F_2$ from the target into the hot cell.

Table 2 Relative intensities of fluorinated species in an HPLC-purified 6-FDOPA sample resulting from direct fluorination of DOPA in CF_3SO_3H at 4°C

Fluorinated product	Relative ratio[a]
2-FDOPA	7.3
5-FDOPA	6.8
6-FDOPA	79.7
Combined unassigned byproducts	6.2

[a] Relative intensities were determined from integrated ^{19}F NMR spectra.

Electrophilic fluorinations in CF_3SO_3H, CF_3SO_3H/HCOOH and BF_3/ CF_3SO_3H using $[^{18}F]F_2$ and F_2

DOPA (13 mg, 66 μmol), dissolved in 0.5 mL of the appropriate solvent, was loaded into a 5/16 in

DOI: 10.1002.jlcr

Table 3 Radiochemical yield (RCY) of FDOPA resulting from direct fluorination of DOPA in CF_3SO_3H/HCOOH and BF_3/CF_3SO_3H

Solvent	Temperature (°C)	RCY[a] (%)	Relative ratio (2-, 5- and 6-FDOPA)
99% CF_3SO_3H	4	19.7	36:7:57
30% CF_3SO_3H in HCOOH	4	25.8	38:26:36
20% CF_3SO_3H in HCOOH	−15	8.8	4:60:36
BF_3/CF_3SO_3H	4	20.5	39:4:57

[a] Radiochemical yields have been decay corrected with respect to $[^{18}F]F_2$. A 3:1 molar ratio of DOPA:F_2 was used in each reaction.

o.d. × 5/32 in i.d. FEP (tetrafluoroethylene/hexafluoropropylene copolymer) reaction vessel connected to an FEP Y-piece. A 1/16 in o.d. × 1/32 in i.d. FEP tube, connected to the $[^{18}F]F_2$ target at one end, was fed through the sidearm of the Y-piece into the reaction vessel. The other arm of the Y-piece was connected to a separate 1/16 in o.d. FEP tube, which was immersed in 1 M NaOH. The reaction vessel and contents were allowed to equilibrate at selected temperatures in a liquid nitrogen cooled CH_3OH bath. The BF_3/CF_3SO_3H solvent mixture was prepared by bubbling BF_3 into the CF_3SO_3H/DOPA solution at 4°C until saturation was achieved, and was followed by equilibration at 4°C for 15 min prior to fluorination.

Fluorine-18-labeled F_2 gas (typically 40 μmol) was passed through a solution of DOPA in CF_3SO_3H and the effluent gas was passed through 1 M NaOH before it was vented into the hot cell. The amount of $[^{18}F]F_2$ that had reacted was determined by counting the amount of radioactivity present in the reaction mixture.

Removal of residual CF_3SO_3H from the reaction mixture was achieved using a 250 × 10 mm anion exchange column (Bio-Rad AG 1–X8 in acetate form). The reaction mixture was loaded onto the column and 20 mL of 0.1 M HCl was used as the eluent. The eluate was then evaporated on a rotary evaporator and was subsequently isolated and analyzed by preparative and analytical HPLC, respectively.

Analyses of reaction mixtures using HPLC

The ring-fluorinated isomers of D- and L-DOPA were analyzed using a reverse-phase analytical HPLC column (Keystone Scientific, Inc., Bellefonte, PA, USA 16823, Fluophase PFP, 5 μm, 150 × 10 mm). A solution of 0.2% CF_3CO_2H in water containing 7% CH_3CN was used as the mobile phase with a flow rate of 2.5 mL min^{-1}. The column eluate was monitored by using a Waters 490E Programmable Multi-wavelength Detector set at 280 and 230 nm in conjunction with a Beckman 170 Radioisotope Detector. A typical UV chromatogram of the reaction mixture showed peaks at 11, 12 and 14 min corresponding to DOPA, 2-FDOPA and 6-FDOPA, respectively. The DOPA peak was identified by injection of a standard solution that eluted at 11 min. The peaks appearing at 12 and 14 min corresponded to those appearing in the radiochromatogram at 13 and 15 min, respectively. Each peak was collected and assayed for radiochemical yield. After a 24-h decay period, both HPLC collected samples were combined and analyzed by ^{19}F NMR spectroscopy to obtain the relative molar amounts of products which were shown to be 2- and 6-FDOPA. The isomeric ratios of the mono-fluorinated aromatic amino acids were determined by integrations of the HPLC radiochromatogram peaks and ^{19}F NMR spectra.

Fluorine-18-labeled DOPA isomers were also analyzed by the use of a reverse-phase preparative HPLC column (Keystone Scientific, Inc., Bellefonte, PA, USA 16823, Fluophase PFP, 5 μm, 250 × 10 mm). A solution of 17 mg of ascorbic acid in 500 mL of 0.1% CH_3CO_2H was used as the mobile phase with a flow rate of 3.5 mL min^{-1}. The eluate from the column was monitored using a UV detector set at 280 nm and a Geiger-Müller counter (Bicron SWGM B980C) coupled to a rate meter (Bicron Erick-Tech™). The 2- and 6-FDOPA isomers (typically appearing at 12 and 14 min on the radiochromatogram) were collected, radio-assayed and subsequently analyzed using ^{19}F NMR spectroscopy.

Nuclear magnetic resonance spectroscopy

The ^{19}F NMR spectra were recorded on a Bruker Avance 200 (4.6976 T) or DRX-500 (11.7440 T) spectrometer using pulse widths of 1 μs corresponding to bulk magnetization tip angles of ~90°. Typical ^{19}F NMR spectra, obtained at 11.7440 T, were accumulated over spectral widths of 14 kHz (acquisition time, 1.16 s), using 300 scans and 32 K memories, yielding data point resolutions of 0.35 Hz/point. Fluorine-19 NMR spectra, obtained at 4.6976 T, were accumulated over spectral widths of 17 kHz (acquisition time, 0.94 s), using 200 scans and 32 K memories, yielding data point resolutions of 0.53 Hz/point. Spectra were referenced at room temperature to external $CFCl_3$. The chemical shift convention used is that positive and negative signs indicate chemical shifts to high and low frequencies relative to that of the reference compound.

DOI: 10.1002.jlcr

Conclusions

A fast, efficient and versatile method for the production of 6-fluoro-L-DOPA and 6-fluoro-D-DOPA, in high yields, in CF_3SO_3H has been developed as an alternative to aHF for use in a hospital environment. It has been shown that the direct fluorination of D- and L-DOPA in CF_3SO_3H is a viable method for the production of mono-fluorinated aromatic amino acid isomers in clinically useful quantities. In a typical fluorination reaction, 12 ± 2 mCi of 6-[^{18}F]fluoro-DOPA was produced starting with 200 mCi of [^{18}F]F_2. The radiochemical yield ($17 \pm 2\%$) obtained from the current method is not only sufficient for investigation of the biochemical behavior of 6-[^{18}F]fluoro-D-DOPA using small animal imaging but is also sufficient for clinical use in human subjects. The application of 6-fluoro-D-DOPA as a PET tracer for brain tumor imaging is currently under investigation.

Acknowledgements

We thank Dr Karen Gulenchyn, Chief of Nuclear Medicine, and Ms Carol Dunne, Manager of Nuclear Medicine, Hamilton Health Sciences, for granting permission to use hospital facilities for this research. We also thank Dr Hélène P. A. Mercier for her assistance in preparing the figures for this article.

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