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Oxidation of Substituted 4-Fluorobenzaldehydes: Application to the No-Carrier-Added Syntheses of 4-[^{18}F]Fluoroguaiacol and 4-[^{18}F]Fluorocatechol

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The synthesis of 4-[^{18}F]fluoroguaiacol (4-[^{18}F]fluoro-2-methoxyphenol) has been achieved in no-carrier-added form starting from 2-methoxy-4-nitrobenzaldehyde, using nucleophilic aromatic substitution by [^{18}F]fluoride followed by Baeyer–Villiger oxidation of the benzaldehyde to the phenol. Demethylation with boron tribromide gave 4-[^{18}F]fluorocatechol (1,2-dihydroxy-4-[^{18}F]fluorobenzene) with an overall yield of 18–28% (EOB) in less than 2 h synthesis time. The fluorine-18 labeled intermediates and products were identical to standards of 4-fluoroguaiacol and 4-fluorocatechol prepared by the same methods. This represents a new approach to the synthesis of fluorinated phenols in fluorine-19 and fluorine-18 forms.

Introduction

The preparation of fluorinated catechols and phenols, and particularly fluorinated derivatives of the catecholamines and amino acids, is of interest in medicinal chemistry (Kirk and Creveling, 1984). In radiolabeled form, using the positron emitting radionuclide fluorine-18 ($t_{1/2} = 110$ min) such compounds have applications in the *in vivo* imaging of biological processes using positron emission tomography (Firnau *et al.*, 1986).

A variety of methods have been reported for synthesis of fluorinated phenols and catechols, and these can be divided into methods which utilize electrophilic fluorination reactions, and those which involve nucleophilic reactions based on fluoride ion. Direct electrophilic fluorinations and regiospecific fluorodemetallation reactions have been used for the chemical and radiochemical synthesis of fluorocatechols and fluorophenols, including 4-fluorocatechol (Anand *et al.*, 1975), 6-[^{18}F]fluoro-L-DOPA and 4- and 6-[^{18}F]fluoro-*m*-tyrosines [review: Kilbourn (1990)]. These methods provide aryl[^{18}F]fluorides of low specific activity which will not be acceptable with such proposed radiopharmaceuticals as 6-[^{18}F]fluorodopamine or 6-[^{18}F]fluoronorepinephrine. Chemical syntheses using fluoride ion have generally utilized the decomposition of aryl diazonium salts [Balz–Schiemann or related reactions: Corse *et al.* (1951); Furlano and Kirk (1986); Kirk *et al.* (1986); Bélanger *et al.* (1988)]. Recently, multistep syntheses of no-carrier-added high specific activity (>1000 Ci/mmol) [^{18}F]fluorinated catechols, including 6-[^{18}F]fluoro-L-DOPA, [^{18}F]fluoronorepinephrine and [^{18}F]fluorodopamine, have been published. These approaches use no-carrier-added [^{18}F]fluoride ion and nucleophilic aromatic substitution in the initial synthetic step (Ding *et al.*, 1990b; Lemaire *et al.*, 1990c).

The asymmetric centers found in 6-[^{18}F]fluoro-L-DOPA and [^{18}F]fluoronorepinephrine require either a stereospecific synthesis (Lemaire *et al.*, 1990a, b) or a chromatographic separation of enantiomers (Ding *et al.*, 1990a). We have been interested in developing a method for the rapid syntheses of [^{18}F]fluorophenols and [^{18}F]fluorocatechols using nucleophilic aromatic substitution reactions and no-carrier-added [^{18}F]fluoride ion, with a particular emphasis on synthetic methods which will not induce racemization of chiral precursors. We have begun evaluation of two synthetic approaches where, overall, benzaldehydes (or ketones) are considered as latent phenols and 2-alkoxybenzaldehydes as "synthons" for catechols, as shown in Fig. 1. The carbonyl substituent on the aromatic ring allows for facile nucleophilic substitution of an appropriate

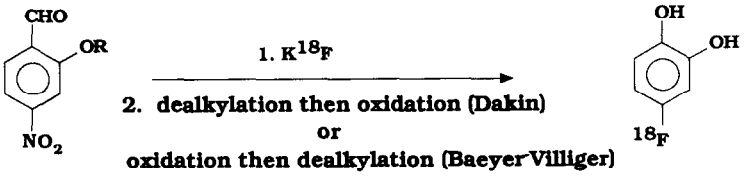

Fig. 1. General approach to [^{18}F]fluorocatechol via aldehyde oxidation reactions.

leaving group such as halogen, nitro, trimethylammonium by [^{18}F]fluoride ion [review: Kilbourn (1990)]. Conversion of benzaldehydes and aryl ketones to phenols can be achieved by Baeyer–Villager oxidations using peracids under acidic conditions (Hassall, 1967). Benzaldehydes with 2-alkoxy groups are oxidized to the corresponding 2-alkoxyphenols (Ballio *et al.*, 1952; Godfrey *et al.*, 1974; Hassall, 1967; Matsumoto *et al.*, 1984) and this method has been previously applied to preparation of a protected form of L-DOPA (Konda *et al.*, 1975). Alternatively, salicylaldehydes can be converted directly to catechols using hydrogen peroxide in basic medium [Dakin reaction: Dakin (1909); Barger (1918); Kvalnes (1934); Baker *et al.* (1953)] but as this reaction is limited to *ortho*- and *para*-hydroxy aromatic aldehyde or ketone, it can not be used for synthesis of phenols. Notably, this reaction also has been successfully utilized in the synthesis of L-DOPA (Bretschneider *et al.*, 1973).

As a model for the synthesis of no-carrier-added [^{18}F]fluorophenols we report here the syntheses of no-carrier-added 4-[^{18}F]fluoroguaiacol and 4-[^{18}F]fluorocatechol using the approach shown in Fig. 1.

Experimental

Materials and methods

Boron iodide was obtained from Alfa. All other reagents and anhydrous solvents were purchased from Aldrich Chemical Co. Analytical thin layer chromatography (TLC) was performed using Analtech precoated silica gel (GHLF) glass plate. Merck silica gel (silicagel 60, 70-230 mesh) was used for column chromatography and preparative TLC was done on precoated Merck silica gel (silicagel 60 F_{254}) glass plates. NMR spectra were obtained on a Bruker 270 MHz spectrometer using $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. Infrared spectra were taken on a Perkin–Elmer 1420 spectrometer. Low resolution mass spectra were run on a Finnigan 4021 quadrupole mass spectrometer either in electron impact (70 eV) or in chemical ionization (CI) mode. High resolution (exact mass) mass measurements were done on VG 70-250-S instrument with perfluorokerosene as reference compound. Melting points are reported uncorrected. Radiochemical yields reported here are decay corrected and are the average of at least two runs.

2-Methyl-5-nitrophenol (1)

This compound was prepared following the procedure of Ungnade and Orwoll (1955) in 70% yield, m.p. 116–117°C [lit. m.p. 115–116.5°C, Benkeser and Buting (1952)].

2-Methyl-5-nitroanisole (2)

2-Methyl-5-nitrophenol (2.33 g, 15.2 mmol) was methylated with dimethyl sulfate (2.5 g, 19.8 mmol) in presence of anhydrous potassium carbonate (8 g, 57 mmol) in 175 mL acetone under reflux (6 h) in 63% yield, m.p. 71–72°C. [lit. m.p. 73°C, Benkeser *et al.* (1952)].

2-Methoxy-4-nitrobenzyl bromide (3)

Following the procedure of Neumeyer *et al.* (1976), to a solution of 2-methyl-5-nitroanisole (2 g, 11.98 mmol) in 75 mL of CCl_4 were added *N*-bromosuccinimide (2.35 g, 13.2 mmol) and benzoyl peroxide (50 mg). The solution was stirred at 90°C for 5 h under illumination. It was then cooled, filtered and the solvent evaporated under reduced pressure. The crude solid was recrystallized from CCl_4-pentane to give 2 g (67%) of bromide.

m.p. 90–91°C; R_f (1:1 ether:hexane) = 0.5; mass spec *m/e* (rel.int.) 246 (M^+, 3), 245 (5), 244 (3), 166 (100), 108 (18), 107 (3), 106 (7), 105 (3), 91 (9), 90 (23), 89 (10).

2-Methoxy-4-nitrobenzyl acetate (4)

Preparation of this compound was done according to the procedure of Kilbourn (1980). 2-Methoxy-4-nitrobenzyl bromide (1.8 g, 7 mmol) was dissolved in glacial acetic acid (65 mL) and sodium acetate (4 g) was added. The solution was heated at 115–120°C for 7 h, then cooled, diluted with water and extracted with ethyl acetate. Combined organic layer was washed successively with saturated aq. $NaHCO_3$, $NaHSO_3$ and brine. Drying and evaporation of solvent gave crude product which was recrystallized from ethanol–hexane as a light yellow solid (1.1 g, 70%).

m.p. 53–54°C; R_f (3:7 ether:pentane) = 0.31; mass spec *m/e* (rel.int.) 225 (M^+, 23), 182 (100), 166 (35), 136 (21), 119 (21), 108 (18), 91 (21).

2-Methoxy-4-nitrobenzyl alcohol (5)

Hydrolysis (Kilbourn, 1980) was performed by adding sodium hydroxide (450 mg, 11.25 mmol) to a solution of 2-methoxy-4-nitrobenzyl acetate

(1 g, 4.45 mmol) in methanol (75 mL) and refluxing for 3 h. Methanol was distilled off under reduced pressure and the residue was dissolved in ethyl-acetate, washed with brine and dried. Evaporation of solvent afforded the alcohol as a yellow solid (770 mg, 93%).

m.p. 95–96°C, R_f (3:7 ether:pentane) = 0.12; mass spec *m/e* (rel.int.) 183 (M^+, 76), 181 (71), 168 (25), 167 (11), 166 (71), 165 (31), 150 (15), 149 (21), 138 (11), 137 (20), 136 (27), 135 (18), 120 (17), 119 (27), 108 (26), 107 (40), 106 (22), 105 (18).

2-Methoxy-4-nitrobenzaldehyde (6)

A mixture of 2-methoxy-4-nitrobenzyl alcohol (700 mg, 3.8 mmol) in CH_2Cl_2 (150 mL) and activated MnO_2 (2.1 g, 24 mmol) was stirred at room temperature for 5 h (Kilbourn, 1980). It was filtered over celite and solvent evaporated under reduced pressure. The residue after column chromatography and elution with chloroform–hexane (1:1) gave a solid (480 mg, 70%). Recrystallization from CH_2Cl_2–pentane provided pure aldehyde as light yellow needles.

m.p. 120–121°C; R_f ($CHCl_3$) = 0.6; mass spec *m/e* (rel.int.) 181 (M^+, 100), 180 (22), 166 (37), 165 (18), 164 (21), 163 (37), 149 (22), 139 (10), 136 (11), 135 (28), 134 (34), 122 (13), 120 (36), 119 (23), 118 (13).

^{1}H-NMR: δ 4.06 (3H, s, OCH_3), 7.8–8.01 (3H, m, ArH), 10.12 (1H, s, CHO); i.r. (KBr) 1680, 1600, 1570 cm^{-1}; Anal. (exact mass): Calcd for $C_8H_7NO_4$ 181.0375, found 181.0382.

2-Hydroxy-4-nitrobenzaldehyde (7)

A solution of BBr_3 in CH_2Cl_2 (4 mL, 4 mmol) was added dropwise to a stirred solution of 2-methoxy-4-nitrobenzaldehyde (190 mg, 1.05 mmol) in CH_2Cl_2 (50 mL) at −70°C. After the addition, the cold bath was removed and the solution stirred overnight. Excess BBr_3 was destroyed by addition of ice-cold water and the layers separated. The organic layer was washed with brine, dried and the solvent evaporated under reduced pressure. A sample of the crude 2-hydroxy-4-nitrobenzaldehyde after purification by column chromatography and elution with chloroform–hexane (1:1) gave a solid.

m.p. 134–135°C [lit. m.p. 134–135°C, Segesser *et al.* (1942)]. However for preparation of the MEM ether (below), the bulk of the sample was not purified.

2-Hydroxy-4-nitrobenzaldehyde methoxyethoxymethyl ether (8)

The crude salicylaldehyde **7** was dissolved in CH_2Cl_2 (5 mL) and the solution was cooled in ice-water bath. Then diisopropylethylamine (350 μL, 2 mmol) and methoxyethoxymethyl (MEM) chloride (230 μL, 2 mmol) were added via syringe (Corey *et al.*, 1976). After 30 min the cold bath was removed and the solution stirred overnight. Water was added, the layers separated, and the organic layer washed with water, dried and evaporated. The crude product was purified by column chromatography (1:1 $CHCl_3$:hexane) to give pure compound as yellow solid (205 mg, 76%).

m.p. 75°C; mass spec (Cl,NH_3) *m/e* (rel.int.) 273 ($M + NH_4^+$, 100), 258 (4), 257 (3), 243 (10), 226 (48), 136 (51).

^{1}H-NMR: δ 3.37 (3H, s, OCH_3), 3.58 (2H, t, OCH_2), 3.9 (2H, t, OCH_2), 5.5 (1H, brs, OCH_2O), 7.9–8.0 (2H, dd, ArH), 8.16 (1H, s, ArH), 10.11 (1H, s, CHO).

i.r. (KBr) 1680, 1600, 1580 cm^{-1}. Anal. (exact mass, $M + NH_4^+$): Calcd for $C_{11}H_{17}N_2O_6$, 273.1087, found 273.1064.

5-Fluoro-2-methylphenol (9)

This was prepared from 5-fluoro-2-methylaniline by diazotization in a similar manner for preparation of **1**. The phenol was obtained as red liquid in 90% yield. It was used without further purification for the synthesis of 5-fluoro-2-methylanisole (below). A portion of crude phenol was derivatized with 4-nitrobenzoyl chloride in pyridine. The crude nitrobenzoyl ester after purification by column chromatography (1:1 chloroform:hexane) and recrystallization from ether–pentane provided pure compound as needles.

m.p. 110–111°C [lit. m.p. 113°C, Allen *et al.* (1959)].

5-Fluoro-2-methylanisole (10)

Methylation of 5-fluoro-2-methylphenol gave the desired compound as an oil in 95% yield which was used without further purification for the next step.

4-Fluoro2-methoxybenzaldehyde (11)

Benzylic oxidation (Bhatt and Perumal, 1981) was done by adding a solution of 5-fluoro-2-methylanisole (2.5 g, 18 mmol) in 135 mL of acetonitrile to a solution of potassium peroxysulfate (9.72 g, 36 mmol) and copper(II) sulfate (0.9 g, 3.6 mmol) in 90 mL of water. Pyridine (2.88 g, 36 mmol) was added and the mixture stirred at 65–70°C for 3 h. The reaction mixture was then cooled and solvent was evaporated under reduced pressure. The residue taken into CH_2Cl_2, washed with 2 N HCl and water, dried and evaporated. The crude product was chromatographed (1:19 ethyl acetate:hexane) to yield pure aldehyde (1.3 g, 48%).

m.p. 57°C; R_f = 0.53 (1:1 ether:hexane), 0.59 ($CHCl_3$); mass spec *m/e* (rel.int.) 154 (M^+, 100), 153 (82), 139 (16), 139 (16), 138 (19), 137 (48), 136 (33), 123 (31), 122 (33), 110 (44), 109 (27), 108 (20), 97 (20), 96 (28), 95 (61), 94 (54).

^{1}H-NMR: δ 3.98 (3H, s, OCH_3), 6.6 (2H, m, ArH), 7.85 (1H, m, ArH), 10.3 (1H, s, CHO).

i.r. (KBr) 1670 (CHO), 1600, 1580 cm^{-1}. Anal. (exact mass): Calcd for $C_8H_7FO_2$, 154.0430, found 154.0420.

4-Fluoro-2-methoxyphenol (12)

Oxidation was performed according to the procedure of Matsumoto *et al.* (1984). To a solution of 4-fluoro-2-methoxybenzaldehyde (166 mg, 1.07 mmol) in 3 mL of methanol, H_2SO_4 (3 drops) and 30% aq. H_2O_2 (211 mg, 1.86 mmol) were added and the solution stirred at room temperature for 24 h under N_2. The methanol was evaporated and the residue was dissolved in ether. The phenol was extracted into 10% NaOH solution. The alkaline solution was cooled and acidified with HCl(c) and extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The crude product (160 mg) thus obtained was purified by preparative layer chromatography (1:1 ether:hexane) and product (100 mg, 70%) was obtained as colorless oil: $R_f = 0.45$ (1:1 ether:hexane), 0.78 (1:9 MeOH:CH_2Cl_2); mass spec *m/e* (rel.int.) 142 (M^+, 100), 127 (96), 99 (54), 70 (10).

^{1}H-NMR: δ 3.87 (3H, s, OCH_3), 5.38 (1H, br s, OH), 6.52–6.64 (2H, m, ArH), 6.8–6.86 (1H, m, ArH).

i.r. (neat) 3400–3500 (OH), 1615 (Ar), 1370 cm^{-1}, Anal. (exact mass): Calcd for $C_7H_7FO_2$, 142.0430, found 142.0432.

4-Fluorosalicylaldehyde (14)

To a stirred solution of 4-fluoro-2-methoxybenzaldehyde (160 mg, 1.04 mmol) in CH_2Cl_2 (10 mL) at -70°C, a solution of BBr_3 (5 mL, 5 mmol) in CH_2Cl_2 was added dropwise. After stirring for another 2 h at that temperature, the cold bath was removed and the solution stirred overnight. Excess of reagent was then decomposed with ice and water and the layers separated. The organic layer was then dried and evaporated to give the crude product. Purification by preparative layer chromatography ($CHCl_3$) yielded 80 mg (55%) of white solid.

m.p. 68°C; $R_f = 0.64$ ($CHCl_3$), 0.5 (1:1 ether:hexane), 0.75 (1:9 MeOH:CH_2Cl_2); mass spec *m/e* (rel.int.) 140 (M^+, 84), 139 (100), 111 (12), 94 (13), 83 (30), 81 (10), 57 (20).

^{1}H-NMR: δ 6.65–6.77 (2H, dd, ArH), 7.54–7.6 (1H, dd, ArH), 9.26 (1H, s, OH), 9.48 (1H, s, CHO).

i.r. (KBr) 3400, 1650, 1615, 1585 cm^{-1}. Anal. (exact mass): Calcd for $C_7H_5FO_2$, 140.0274, found 140.0278.

4-Fluorocatechol (13)

To a stirred solution of 4-fluoroveratrole (500 mg, 3.2 mmol) in 15 mL of CH_2Cl_2 at -70°C, a solution of BBr_3 (15 mL, 15 mmol) in CH_2Cl_2 was added dropwise. After 30 min the cold bath was removed, and after 2 h excess BBr_3 was decomposed with water. The mixture was saturated with NaCl and organic layer was decanted. Drying and evaporation of solvent gave 4-fluorocatechol as light brown solid in 80% yield. Sublimed product had m.p. 88–89°C. [lit. m.p. 90–91°C, Coarse and Ingraham (1951)]; $R_f = 0.08$ ($CHCl_3$), 0.31 (1:1 ether:hexane), 0.57 (1:9 MeOH:CH_2Cl_2); mass spec *m/e* (rel.int.) 128 (M^+, 100), 110 (6), 99 (10), 82 (47), 81 (11), 80 (4).

^{1}H-NMR: δ 5.0 (1H, br s, OH), 5.5 (1H, br s, OH) 6.47–6.53 (1H, m, ArH), 6.54–6.67 (1H, m, ArH), 6.75–6.8 (1H, m, ArH).

i.r. (KBr) 3300–3500 (OH), 1620, 1600, 1510 cm^{-1}.

Preparation of potassium [^{18}F]fluoride/Kryptofix 222

[^{18}F]Fluoride ion was produced by proton irradiation of oxygen-18 enriched water (86% isotropic enrichment; Mound Laboratories) held in all-silver target [1 mL target volume; Mulholland *et al.* (1989)]. An aliquot of the [^{18}O]water/[^{18}F]fluoride solution was added to a mixture of the aminopolyether 4,7,13,16,21,24-hexaoxa-1,10-diazabiclo[8.8.8]hexacosane (Kryptofix 222) (10 mg, 0.027 mmol) and potassium carbonate (1 mg, 0.007 mmol) and dried under a stream of dry nitrogen at 100°C in a glass sample vial (Hamacher *et al.*, 1986). Residual water was removed by azeotropic distillation with acetonitrile, and the residue dissolved in dimethyl sulfoxide (DMSO) for use in fluorination reactions.

General procedure for the [^{18}F]fluoride ion displacement of 4-nitrobenzaldehyde derivatives

Typically, resolubilized [^{18}F]fluoride ion ($K^{18}F$/Kryptofix) in 100 μL of anhydrous DMSO was added to 1–2 mg of the substrate **6** or **8** and heated at 120°C for 25 min. The solution was cooled, added to 10 mL of water and the mixture passed through an activated C18-Sep Pak. Ether (1–2 mL) was then used to elute the organic product, followed by drying (Na_2SO_4), filtration and evaporation of solvent. The yields of 4-[^{18}F]fluoro-2-methoxy benzaldehyde were 50–60%. MEM ether **8** gave somewhat lower yields (30–40%) of [^{18}F]**15**. These were used for the next step without any further purifications.

General procedures for cleavage of ethers

For cleavage of methyl ethers [^{18}F]**11** or [^{18}F]**12** a solutions of either BCl_3, BBr_3 or BI_3 (Dean *et al.*, 1966; Lansinger *et al.*, 1979; McOmie *et al.*, 1968) in methylene chloride was added at 0–5°C to a solution of [^{18}F]**11** or [^{18}F]**12** in CH_2Cl_2. Then it was kept at 0°C or at room temperature for 25 min for BCl_3 or BBr_3 and 2–25 min for BI_3 reactions. Products were isolated by evaporation of CH_2Cl_2, addition of ice and isolation by C18-Sep Pak. Average yields of 4-[^{18}F]fluorocatechol from 4-[^{18}F]fluoro-2-methoxy phenol were 50–60% (>98% pure). Cleavage (Corey *et al.*, 1976) of MEM ether [^{18}F]**15** was done by adding 1–2 drops of trifluoroacetic acid (TFA) to a solutions of [^{18}F]**15** in methylene chloride and heating the mixture at 110–120°C for 20 min. TLC analysis indicated complete conversion to [^{18}F]**14** ($CHCl_3$, R_f **15** = 0.21, R_f **14** = 0.64). Product was isolated by cooling the reaction mixture, blowing off excess TFA and solvent in a stream of N_2 followed by C18-Sep

Pak purifications. Average yield of 4-[^{18}F]fluorosalicylaldehyde after deprotection was 60–70% with radiochemical purity >85%.

General procedures for Dakin oxidations

Peroxide oxidations under basic conditions were performed by adding 30% aq. hydrogen peroxide to a solution of crude 4-[^{18}F]fluorosalicylaldehyde in 0.5 mL methanol or pyridine (Baker *et al.*, 1953; Barger, 1918) and in presence of different bases [aq. 12.5 N KOH, aq. 25% $(CH_3)_4NOH$]. Reactions were then allowed to stand at room temperature or heated at 100°C for 10–30 min. After acidification of reaction mixture, products were isolated by C18-Sep Pak work up and were analyzed by TLC and comparison to authentic standards.

General procedures for Baeyer–Villiger oxidations

Peroxide oxidations under acidic condition (Matsumoto *et al.*, 1984) were done by heating a methanolic solution of 4-[^{18}F]fluoro-2-methoxy benzaldehyde ([^{18}F]**11**) in presence of 30% aq. H_2O_2 and $KHSO_4$ at 110–120°C for 25 min. The reactions mixture was then cooled, diluted with water, passed through a C18-Sep Pak and eluted with pentane. Identification of products was made by TLC analysis and comparison to authentic standards. Average yield of 4-[^{18}F]fluoro-2-methoxy phenol was 70–80% with radiochemical purity >85%. Attempted oxidation of MEM ether [^{18}F]**15** under similar conditions gave 4-[^{18}F]fluorocatechol in 30% radiochemical yield, accompanied by polar product(s).

Results and Discussion

The synthetic approach to 4-[^{18}F]fluorophenols shown in Fig. 1 is a new concept for the preparation of this important class of radiolabeled compounds. The application of this approach to 4-[^{18}F]fluorocatechol synthesis, using salicylaldehydes as "synthons" for catechols, required three distinct steps:

(1) synthesis of appropriately substituted benzaldehyde precursors;
(2) evaluation of the oxidation reaction on a macroscopic scale with preparation and characterization of intermediates and final products; and
(3) evaluation of the synthetic approach for preparation of no-carrier-added 4-[^{18}F]fluorocatechol.

Synthesis of 2-(alkoxy)-4-nitrobenzaldehydes

The appropriately substituted benzaldehydes were prepared in a multistep procedure outlined in Fig. 2. This is a straightforward sequence of reactions which has been previously applied to the synthesis of the isomeric 2-nitro-4-methoxybenzaldehyde (Kilbourn, 1980). Overall, the yield of 2-methoxy-4-nitrobenzaldehyde was 13% (not optimized). This was then converted to the known 4-nitrosalicyladehyde by methyl ether cleavage with BBr_3, and the MEM ether prepared by alkylation with MEM–Cl in 76% yield.

Chemical syntheses of 4-fluoro-2-methoxybenzaldehyde, 4-fluoroguaiacol and 4-fluorocatechol

5-Fluoro-2-methylphenol, 5-fluoro-2-methylanisole, and 4-fluoro-2-methoxybenzaldehyde were prepared as shown in Fig. 3, with an overall yield of benzaldehyde of 34–38%. The 4-fluoro-2-methoxybenzaldehyde was then converted to 4-fluoro-2-methoxyphenol by Baeyer–Villager oxidation (acidic H_2O_2); the desired phenol was obtained in 70% isolated yield and completely characterized by spectroscopic methods.

Finally, authentic standards of 4-fluorosalicylaldehyde and 4-fluorocatechol were prepared by demethylation of 4-fluoro-2-methoxybenzaldehyde and 4-fluoroveratrole, respectively. This provided the fluorocatechol with an unequivocal assignment of aromatic substitution.

Radiochemical syntheses of 4-[^{18}F]fluoroguaiacol and 4-[^{18}F]fluorocatechol

Nucleophilic aromatic displacement reactions using K^{18}F/Kryptofix in DMSO at 120°C with 2-alkoxy-4-nitrobenzaldehydes gave the corresponding 4-[^{18}F]fluoro-2-alkoxybenzaldehydes with >90% radiochemical purities (Fig. 4). Yields of 4-[^{18}F]fluoro-2-methoxybenzaldehyde were consistently in the 50–60% range, and slightly lower (30–40%) for the corresponding MEM ether. These yields have not been optimized, but are consistent with the yields reported for isomeric methoxy-substituted nitrobenzaldehydes, including 2-nitro-4-methoxybenzaldehyde, 3-methoxy-4-nitrobenzaldehyde and 2-nitro-3-methoxybenzaldehyde (Lemaire *et al.*, 1990c; Ding *et al.*, 1990b).

Two approaches to oxidation of the benzaldehyde to the catechol were evaluated. The first, a Dakin reaction (Fig. 4) using peroxide under basic conditions, required the salicylaldehyde [^{18}F]**14**. Rapid demethylation of 4-[^{18}F]fluoro-2-methoxybenzaldehyde with BCl_3, BBr_3 or Bl_3 in methylene chloride proved to be problematic. Although the aldehyde functionality next to the ether linkage should facilitate the cleavage i.e. <30 min for BCl_3 (Dean *et al.*, 1986), <5 min for Bl_3 (Lansinger *et al.*, 1979), we have observed that these reactions were only 20–40% complete along with other product(s), as evidenced by radioactivity which remained at the origin upon TLC analysis (Chakraborty and Kilbourn, 1991). Overall inconsistency of the results and formation of numerous products in this step led us to evaluate a MEM ether as the phenol protecting group which could more easily be removed. Despite the fact that the MEM either gives a lower yield in the initial [^{18}F]fluorination step, the demethylation with trifluoroacetic acid proceeded smoothly to give 4-[^{18}F]fluorosalicylaldehyde in 60–70% yield and >85% radiochemical purity.

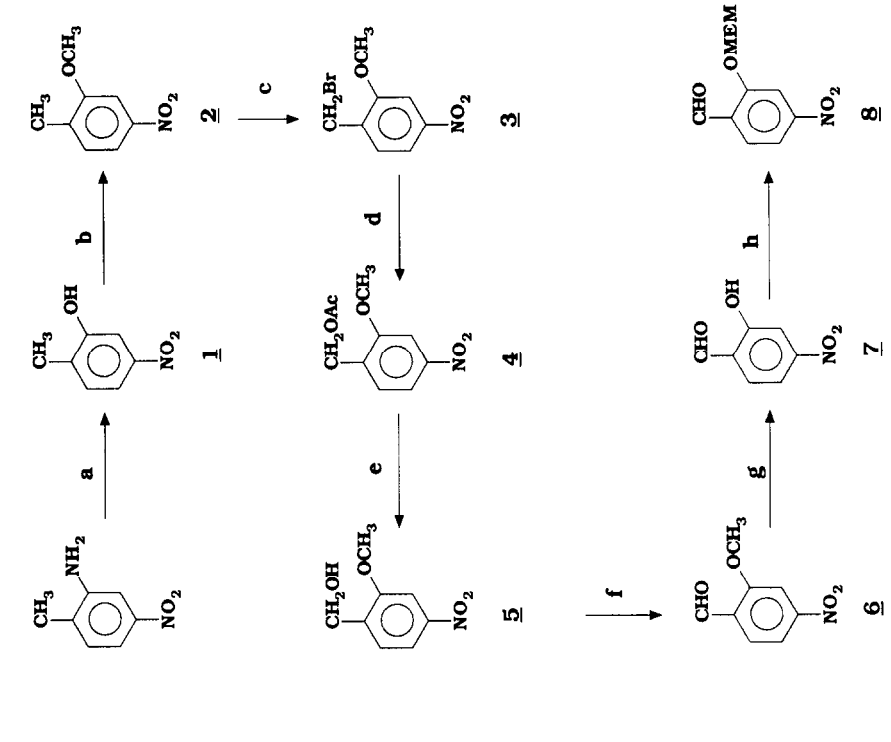

Fig. 2. Synthesis of 2-(alkoxy)-4-nitrobenzaldehydes.

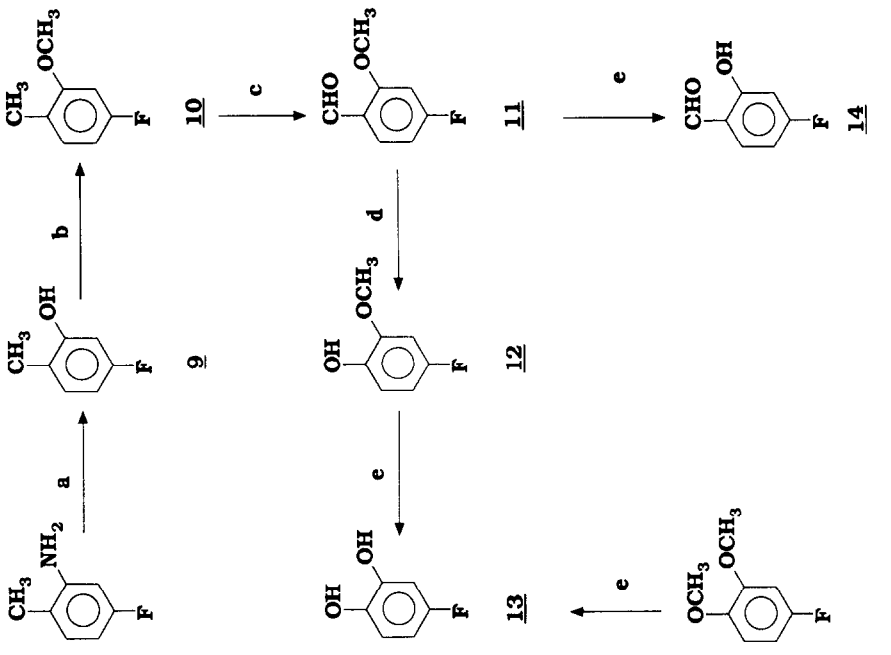

Fig. 3. Synthesis of 4-fluorosalicylaldehyde, 4-fluoroguaiacol and 4-fluorocatechol.

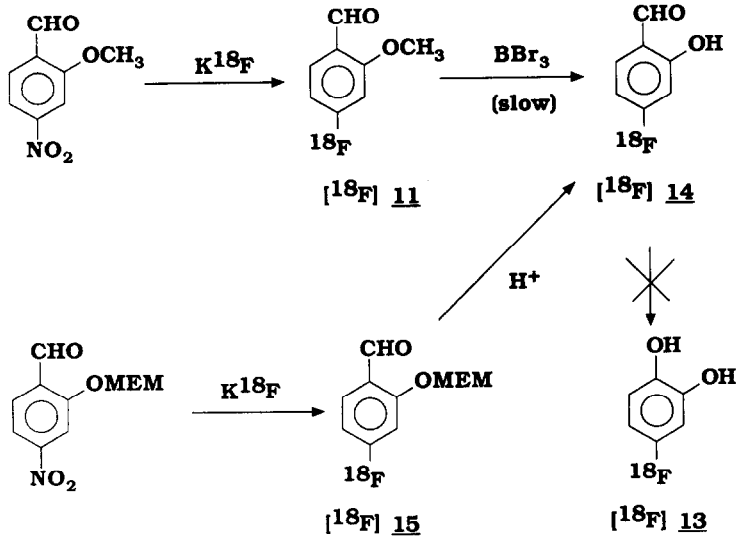

Fig. 4. Attempted synthesis of 4-[^{18}F]fluorocatechol via Dakin oxidation salicylaldehyde.

We have reported earlier (Chakraborty and Kilbourn, 1991) that Dakin oxidations of crude products from the boron halide cleavages of [^{18}F]**11** gave mixtures of fluorine-18 labeled products, one of which (~45%) was identical to authentic 4-fluorocatechol on TLC analysis. Surprisingly, we were unable to clearly identify any [^{18}F]fluorocatechol after Dakin oxidation of the relatively pure aldehyde [^{18}F]**14** obtained from the cleavage of the MEM ether [^{18}F]**15**. Instead, we obtained either unreacted salicylaldehyde or under more forcing conditions mixtures of salicylaldehyde and a highly polar product (30–80%). Use of different solvents or changing the nature of the base apparently did not yield any 4-[^{18}F]fluorocatechol. The reasons for unsuccessful isolation of the desired 4-[^{18}F]fluorocatechol are unclear at this time. It is possible that the reaction does not proceed significantly at room temperature, and under forcing conditions the product may be rapidly and quantitatively converted to another species through further oxidation or ring-opening reactions. We were similarly unsuccessful in Dakin oxidation (KOH, H_2O_2, 25°C, 24 h) of the isomeric 2-hydroxy-3-fluorobenzaldehyde to 3-fluorocatechol. However, Dakin oxidations of substituted benzaldehydes and ketones are well precedented, including the successful oxidation of 5-fluoro-2-hydroxyacetophenone to 4-fluorocatechol (Corse and Ingraham, 1951). At this point, we feel that Dakin oxidation of 4-[^{18}F]fluorosalicylaldehyde to 4-[^{18}F]fluorocatechol is not a practical approach to fluorine-18 labeled catechols. Evaluation of appropriate reaction conditions for successful Dakin oxidations of [^{18}F]**14** will require further study.

We then investigated the feasibility of the second approach where oxidation of the benzaldehyde to the phenol is done under acidic conditions (Fig. 5). In addition to numerous examples of such transformations (Baeyer–Villiger oxidation) using different types of organic peracids (Ballio *et al.*, 1952; Godfrey *et al.*, 1974; Hassall, 1967; Konda *et al.*, 1975), the use of 30% aq. H_2O_2 in presence of acidic catalysts such as H_2SO_4 or $KHSO_4$ has been recently described (Matsumoto *et al.*, 1984). This method uses methanol and the end products are phenols and/or methyl benzoates depending on the aryl ring substituents. We hypothesized that the 2-alkoxyphenol product might be more stable to further oxidation reactions than the catechol formed in the Dakin reaction. Application of this oxidation method to 4-fluoro-2-methoxybenzaldehyde gave the expected 4-fluoroguaiacol in 70% isolated yield, demonstrating that this approach might be successfully applied to the radiochemical synthesis of the fluorine-18 labeled derivatives.

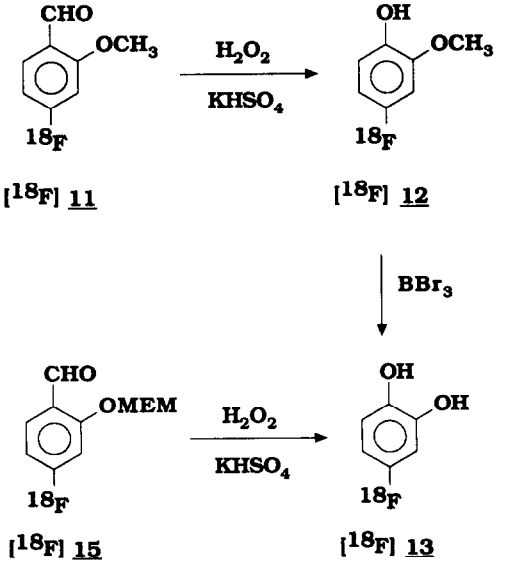

Fig. 5. Synthesis of 4-[^{18}F]fluoroguaiacol and 4-[^{18}F]fluorocatechol.

Initial attempts at the reaction of 4-[^{18}F]fluoro-2-methoxybenzaldehyde with 30% aq. H_2O_2 in presence of H_2SO_4 at 100–110°C gave a mixture of products, but a switch to $KHSO_4$ as catalyst gave crude 4-[^{18}F]fluoro-2-methoxyphenol in 70–80% yield and radiochemical purity >85%. The product could be further purified by collection on a C18-Sep Pak and elution with pentane. The isolated 4-[^{18}F]fluoroguaiacol was converted in 50–60% yields to 4-[^{18}F]fluorocatechol by dealkylation with BBr_3 in methylene chloride, with a radiochemical purity >98%.

Finally, we have investigated the possibility of directly converting a suitably protected 4-[^{18}F]fluoro-2-alkoxybenzaldehyde directly to 4-[^{18}F]fluorocatechol by $H_2O_2/KHSO_4$ oxidation in a single-pot reaction (Fig. 5). The MEM protected salicaylaldehyde was reacted with $H_2O_2/KHSO_4$/methanol system, and 4-[^{18}F]fluorocatechol was formed in 30% radiochemical yield, accompanied by another polar product. Presumably, the MEM-protected aldehyde is first oxidized to the phenol, and subsequently the MEM ether is cleaved by the acidic conditions. Further work on optimization of this simplified approach is under way, particularly the development of one-pot method of nucleophilic [^{18}F]fluorination, oxidation and protecting group cleavage.

Throughout this study, we have determined the identity and purity of the radiolabeled products only, and have not accounted for the chemical impurities which arise from the nitrobenzaldehyde used in the initial [^{18}F]fluorination reaction. Formation of the corresponding nitroguaiacol and nitrocatechol is unlikely, as Baeyer–Villiger oxidations of nitrobenzaldehydes leads to nitrobenzoic acids (or esters) rather than the nitrophenols (Hassall, 1967; Matsumoto *et al.*, 1984). Formation of such chemical impurities might be avoided by the application of aryltrimethylammonium triflates, previously described as reactive precursors for [^{18}F]fluorination which can be readily separated from the product aryl [^{18}F]fluorides (Haka *et al.*, 1989). Alternatively, the formation of distinctly different chemical species (nitrobenzoic acids vs [^{18}F]fluorophenols) should be advantageous for HPLC purification of final fluorine-18 labeled products.

Summary

This application of Baeyer–Villiger oxidations, where aldehydes are considered as latent phenols, holds considerable promise as a rapid and simple method for synthesis of [^{18}F]fluorophenols and [^{18}F]fluorocatechols. Appropriate choices in protecting groups may allow the entire sequence to be done in a single pot and should allow the synthesis to proceed without racemization of a chiral center, as has previously been shown for a preparation of L-DOPA (Konda *et al.*, 1975). We have also demonstrated the feasibility of using MEM ethers for the protection of phenolic hydroxy groups in the synthesis of compounds bearing short lived isotopes. We are currently investigating the extension of this approach to the synthesis of such potential radiotracers as 6-[^{18}F]fluoro-(β-fluoromethylene-*m*-L-tyrosine (Palfreyman *et al.*, 1985; DeJesus *et al.*, 1990), 6-[^{18}F]fluoro-*m*-L-tyrosine, 6-[^{18}F]fluorometharaminol (Mislankar *et al.*, 1988), 6-[^{18}F]fluorodopamine and [^{18}F]fluoroctopamine.

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