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[^{18}F]Fluorination/Decarbonylation: New Route to Aryl [^{18}F]Fluorides

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A new route to aryl [^{18}F]fluorides without electron withdrawing ring substituents has been developed. [^{18}F]Fluorobenzaldehydes, prepared from no-carrier-added (NCA) [^{18}F]fluoride using nucleophilic aromatic substitution of fluoro or nitro groups, were decarbonylated using palladium on charcoal (Pd-C). By this approach 2-methoxy-4-nitrobenzaldehyde was converted to NCA 3-[^{18}F]fluorophenol (25–30%, EOB) and 4-fluoro-2-methoxy-5-methylbenzaldehyde to carrier-added (CA) 3-[^{18}F]fluoro-4-methylphenol (30–40%, EOB). Overall synthesis time was about 2 h. Since the 4-fluoro-2-methoxy-5-methylbenzaldehyde was in turn prepared by methylation and regiospecific formylation of 3-fluoro-4-methylphenol, the overall process represents use of a removable activating group for nucleophilic aromatic substitution with [^{18}F]fluoride for preparation of CA and NCA aryl [^{18}F]fluorides.

Introduction

The Balz–Schiemann reaction, the triazene decomposition reaction and electrophilic fluorination are commonly used methods for the syntheses of aryl [^{18}F]fluorides which are not activated by an electron withdrawing group. The radiochemical yields of these reactions are often very low and more importantly, as in the case of Balz–Schiemann and electrophilic fluorination, the reactions provide products of low specific activity. Modifications of these reactions have been investigated (Ng *et al.*, 1981; Guddat *et al.*, 1989; Satyamurthy *et al.*, 1990) to overcome the difficulties associated with low yields and low specific activities. In addition, two other new approaches (Ng *et al.*, 1981; Ehrenkaufer *et al.*, 1982) have also been investigated as methods potentially suitable for incorporating NCA [^{18}F]fluoride into an unactivated aromatic nucleus. *p*-Fluoro-*n*-anisidine was prepared (Ng *et al.*, 1981) by decomposition of *m*-methoxy aryl azides in anhydrous hydrogen fluoride, and then deaminated to yield *o*-fluoroanisole in good yield. However, this reaction fails with oxygen substituents *ortho* to the azide, and with larger *O*-alkyl groups. Attempted syntheses (Ehrenkaufer *et al.*, 1982) of aryl [^{18}F]fluorides by catalytic decarbonylation of aroyl [^{18}F]fluorides with Wilkinson's catalyst [$(Ph_3P)_3RhCl$] were unsuccessful, leading instead to decarbonylation products (benzene).

An electron withdrawing group on an aromatic ring provides activation for nucleophilic aromatic displacement reactions using [^{18}F]fluoride ion, and is the method of choice for preparing aryl [^{18}F]fluorides in high yield and high specific activity. However, for the application of nucleophilic aromatic substitution to the synthesis of an aryl [^{18}F]fluoride without an electron withdrawing group, it would be essential to remove or manipulate such an activating group in some later stage of the synthesis. Shiue *et al.* (1984) reported the synthesis of NCA [^{18}F]fluorobenzene from *p*-chloro-nitrobenzene in good yield through displacement of chloride by [^{18}F]fluoride and subsequent removal of the nitro group by reduction/diazotization. This method has not been attempted on more complex molecules. Recently Hwang *et al.* (1991) reported a new procedure for syntheses of 4-[^{18}F]fluoro-1-alkyl-benzenes which involved ^{18}F-for-NO_2 substitution of 4-nitroacetophenone or 4-nitrophenylcyclopropyl ketone and the subsequent reductions (triethyl silane/trifluoroacetic acid) of the intermediate ^{18}F-labeled ketones.

Aldehydes are often used as activating groups in nucleophilic aromatic displacement reactions by [^{18}F]fluoride (Kilbourn, 1990). We have recently reported that the methoxy substituted [^{18}F]fluorobenzaldehydes can be converted to [^{18}F]fluorophenols and [^{18}F]fluorocatechols by Baeyer–Villiger oxidation reactions (Chakraborty and Kilbourn, 1991). In an extension of that work, we became interested in the feasibility of decarbonylation of such [^{18}F]fluorobenzaldehydes to the corresponding aryl [^{18}F]-

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fluorides which would then lack the electron withdrawing substitutent. Decarbonylation of a number of substituted aryl aldehydes in the presence of palladium on charcoal at elevated temperature has been previously reported (Hawthorne and Wilt, 1960). Since this method has not been applied to the syntheses of aryl [^{18}F]fluorides, we report here the decarbonylation reaction applied to two representative [^{18}F]fluorobenzaldehydes, 4-[^{18}F]fluoro-2-methoxy-5-methylbenzaldehyde ([^{18}F]**3**) and 4-[^{18}F]-fluoro-2-methoxybenzaldehyde ([^{18}F]**5**).

Experimental

Materials and methods

All reagents, 10% Pd-C and anhydrous solvents were purchased for Aldrich Chemical Company The preparations of 2-methoxy-4-nitrobenzaldehyde (**4**) and 4-fluoro-2-methoxybenzaldehyde (**5**) have been reported earlier (Chakraborty and Kilbourn, 1991). Nylon membrane filters (Nylon Acrodisc 13, 0 2 μm) were obtained from Gelman Sciences, Ann Arbor, Mich. Analytical thin layer chromotography (TLC) was performed using an Analtech precoated silica gel (GHLF) glass plate Merck silica gel (silicagel 60, 70 -230 mesh) was used for column chromatography. NMR spectra were obtained on Bruker 360 MHz spectrometer using $CDCl_3$ as the solvent and tetramethysilane 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.

*3-Fluoro-4-methylphenol (**1**)* This was prepared from 3-fluoro-4-methylaniline following the known procedure (Ungnade and Orwoll, 1955) in 90% yield, mass spec. *m/e* (rel. int.) 126 (M^+, 80), 125 (100), 108 (5), 97 (7), 95 (6), 77 (8). Benzoyl derrivative, m.p 75–76 C (lit. m.p 77 C; Brown *et al*., 1949)

*3-Fluoro-4-methylanisole (**2**)* Methylation [$(CH_3)_2SO_4/K_2CO_3$] of **1** gave the desired compound in 63% yield after purification by column chromatography

*4-Fluoro-2-methoxy-5-methylbenzaldehyde (**3**).* 3-Fluoro-4-methylanisole was formylated using α,α-dichloromethyl methyl ether in presence of titanium(IV) chloride following the procedure of Gross *et al.* (1963) to give **3** in 73% yield after purification by column chromatography, m p 64–65 C; R_f (15: 85 EtOAc: Hex) = 0.48; mass spec. (rel int.) 168 (M^+, 100), 167 (59), 151 (32), 137 (14), 123 (18), 122 (17), 109 (30); ^{1}H-NMR: δ 2.21 (3*H*, s, OCH_3), 3.89 (3H, s, Ar-CH_3), 6.64 (1H, d, J^{ortho}_{HF} = 11.3 Hz, ArH-3), 7 67 (1H, d, J^{meta}_{HF} = 9Hz, ArH-6), 10.33 (1H, s, —CHO); IR (KBr) 1660 (CHO), 1610, 1570 cm^{-1}. Anal. (exact mass): calcd for $C_9H_9FO_2$ 168.0587, found, 168.0595

*Synthesis of 3-fluorophenol from 4-fluoro-2-methoxybenzaldehyde (**5**) by decarbonylation and demethylation.* A mixture of 10% Pd-C (75 mg) and 4-fluoro-2-methoxybenzaldehyde (77 mg) in 3 mL of 1,2,3,4-tetramethylbenzene was heated at 235 240 C for 4 h The reaction mixture was then cooled, filtered over celite and washed with pentane The filtrate was concentrated under reduced pressure and dissolved in 15 mL of dry CH_2Cl_2 The solution was cooled to −70 C and a solution of boron tribromide (1 M in CH_2Cl_2, 4 mL) was added dropwise After stirring for another 30 min cold bath was removed and stirring continued for another 2.5 h. Then excess BBr_3 was decomposed by addition of ice and product was extracted into 2 N NaOH. The aqueous layer was acidified with cold 6 N HCl solution and extracted with ethylacetate Ethylacetate was washed with water, dried and evaporated under reduced pressure to give a product in 75% yield TLC and mass fragmentation pattern were identical with those of authentic 3-fluorophenol. Anal (exact mass) calcd for C_6H_5OF 112.0324, found, 112 0313

*Synthesis of 3-fluoro-4-methylphenol (**1**) by decarbonylation and demethylation of 4-fluoro-2-methoxy-5-methylbenzaldehyde (**3**)* 4-Fluoro-2-methoxy-5-methylbenzaldehyde (84 mg) was decarbonylated with 10% Pd-C (75 mg) in 3 mL of 1,2,3,4-tetramethylbenzene at 240 250 C for 5 h The mixture was filtered over celite, washed with pentane and filtrate was concentrated. Demethylation with BBr_3 and work up as above provided a product (85%) identical (TLC and mass spec) with a sample of **1** prepared from 3-fluoro-4-methylaniline (*vide infra*) Anal (exact mass) calcd for C_7H_7OF 126.0481, found, 126 0478

Preparation of potassium [^{18}F]fluoride Kryptofix 222 [^{18}F]Fluoride ion was produced by proton irradiation of ^{18}O enriched water (97%, Isotec) 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-diazabicyclo[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 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 DMSO for use in fluorination reactions

General procedure for [^{18}F]fluoride ion displacement reactions. Resolubilized K^{18}F/Kryptofix (15 25 mCi) in 200 μL of anhydrous DMSO was added to 3 4 mg of substrate **3**, **4** or **5**, and heated at 120 C for 10 min The solution was then cooled, diluted with waer and passed through C-18 Sep-Pak After washing C-18 Sep-Pak with another 5 mL of water, product was eluted with ether, dried (Na_2SO_4) and after filtration, solvent was evaporated in a stream of N_2 The

radiochemical yields were 60–70%. These ^{18}F-labeled products were used for the next step without further purification.

Procedures for decarbonylation of [^{18}F]fluorobenzaldehydes. (A) The decarbonylation of [^{18}F]fluorobenzaldehydes [^{18}F]**3** and [^{18}F]**5** (5–10 mCi) was done by heating the compounds at 250–255°C in 150–200 μL 12,3,4-tetramethylbenzene in presence of 10% Pd-C (30–40 mg) for 50–60 min. The solution was then cooled and filtered (celite or nylon membrane). The radiochemical yields of the products after filtration of catalyst were 70–80% with radiochemical purities > 90% and were used for the demethylation step without isolation of the products. (B) The decarbonylation of compound [^{18}F]**3** was also done in 2,4,6-trimethylpyridine under the same conditions as above. The crude mixture was filtered through a membrane filter, acidified with cold 6 N HCl solution and [^{18}F]**2** was isolated by extraction into pentane. The radiochemical yields of the products were 60–70% with radiochemical purities > 90%.

Procedure for methyl ether cleavage of [^{18}F]fluoroanisoles. Cleavage of methyl ethers was done by adding a solution of BBr_3 (excess) in methylene chloride to a cold (0–5°C) solution of [^{18}F]fluoroanisole [^{18}F]**2** or **6** (1–4 mCi) in 1,2,3,4-tetramethylbenzene. After keeping the reaction mixture at room temperature for 15–20 min, excess BBr_3 was decomposed by addition of ice and [^{18}F]fluorophenols were extracted into sodium hydroxide solution. Aqueous portion was then acidified with cold dilute sulfuric acid, and product isolated using a C-18 Sep-Pak. The radiochemical yields of [^{18}F]fluorophenols were 60–70% and radiochemical purities >95%.

Results and Discussion

The [^{18}F]fluorination/decarbonylation approach to [^{18}F]fluoroanisoles is shown in Fig. 1, and represents a new concept for the preparation of aryl [^{18}F]fluorides bearing no electron withdrawing group. The application of this procedure involves three steps: (1) syntheses of appropriately substituted benzaldehyde precursors, (2) nucleophilic aromatic displacements by [^{18}F]fluoride and (3) decarbonylations of the intermediate [^{18}F]fluorobenzaldehydes.

Sytheses of substituted benzaldehyde precursors

Syntheses of 2-methoxy-4-nitrobenzaldehyde (**4**) and 4-fluoro-2-methoxybenzaldehyde (**5**) have been reported earlier (Chakraborty and Kilbourn, 1991).

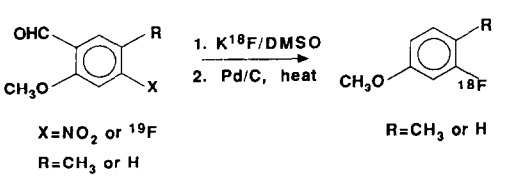
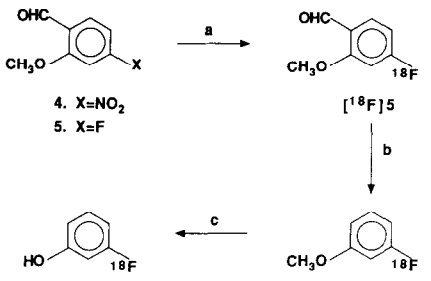


Fig. 1. General approach to aryl [^{18}F]fluorides via decarbonylation reactions.



a, K^{18}F/Kryptofix/DMSO; b, 10% Pd-C, solvent, heat; c, BBr_3

Fig. 2. Synthesis of CA 3-[^{18}F]fluoro-4-methylphenol from 3-fluoro-4-methylphenol

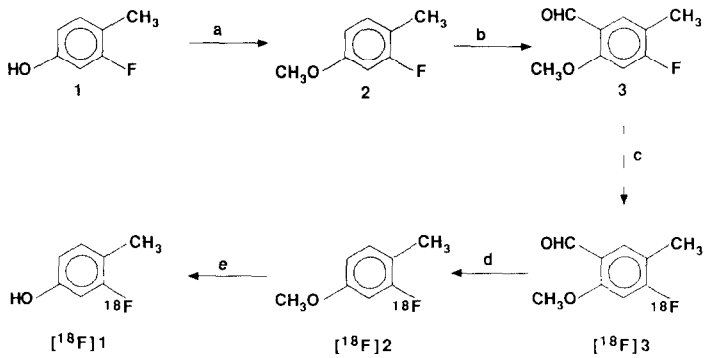
4-Fluoro-2-methoxy-5-methylbenzaldehyde (**3**) was prepared (Fig. 2) in 73% yield by formylation of 3-fluoro-4-methylanisole using α,α-dichloromethyl methyl ether in presence of titanium(IV) chloride following the literature procedure (Gross *et al.*, 1963). In the ^{1}H-NMR spectrum of the compound, two doublets observed at δ 6.64 (J = 11.3 Hz) and 7.67 (J = 9.0 Hz), each integrating for one proton, could be assigned to protons *ortho* (H-3) and *meta* (H-6) with respect to the fluorine, based on the chemical shifts and ^{19}F–^{1}H coupling constants, supporting the position of aldehyde as *para* to fluorine. However, the position (*ortho* or *para*) of the aldehyde with respect to a leaving group in the aromatic ring is irrelevant since either compound would provide the same product [^{18}F]**2** after [^{18}F]fluorination and decarbonylation reactions.

Nucleophilic aromatic displacement reaction by [^{18}F]fluoride ion

Nucleophilic aromatic displacement reactions using K^{18}F/Kryptofix in DMSO at 120°C with all the substituted benzaldehydes gave corresponding [^{18}F]fluorobenzaldehydes in 60–70% yields with > 90% radiochemical purities. However, we have not removed the chemical impurities which arise from use of the nitrobenzaldehyde and the [^{18}F]fluorobenzaldehyde was used without purification for the next step.

The decarbonylation of [^{18}F]fluorobenzaldehydes

The decarbonylation of substituted [^{18}F]fluorobenzaldehydes is based on the work of Hawthorne *et al.* (1960). Reactions were done by heating the [^{18}F]fluorobenzaldehydes in 1,2,3,4-tetramethylbenzene in the presence of 10% palladium on charcoal. The Pd-C could be removed by filtration on celite or a nylon membrane (pore size 0.2 μm) filter. The latter procedure was found to be very convenient and the volume of the solution could be kept to a minimum after filtration and rinsing with solvent. The radiochemical yields of decarbonylation reactions after filtration of Pd-C were 70–80% and radiochemical purities as indicated by TLC were >90%. The decarbonylation products, obtained as solutions in 1,2,3,4-



a, $(CH_3)_2SO_4/K_2CO_3$; b, $Cl_2CHOCH_3/TiCl_4$; c, $K^{18}F$/Kryptofix/DMSO; d, 10% Pd-C, solvent, heat; e, BBr_3

Fig 3 Syntheses of CA and NCA 3-[^{18}F]fluorophenols

tetramethylbenzene, were used directly in the demethylation reactions using BBr_3. The final products, [^{18}F]fluorophenols, were extracted into NaOH solution, acidified with dilute sulfuric acid and isolated by C-18 Sep-Pak. The radiochemical purities of [^{18}F]fluorophenols as determined by TLC were >95%. This acid/base extraction also provided separation of products [^{18}F]**1** and **7** from the solvent (1,2,3,4-tetramethylbenzene). However, the intermediate decarbonylation products such as [^{18}F]-fluoroanisole [^{18}F]**2** could be more easily isolated by substituting 2,4,6-trimethylpyridine for 1,2,3,4-tetramethylbenzene; upon acid workup of the reaction, the product could be extracted into pentane, with the basic solvent retained in the acidic aqueous layer Use of substituted pyridine as a solvent would be of particular value for the preparation of non-phenolic aryl [^{18}F]fluorides

The time, temperature and quantity of Pd-C necessary for these decarbonylation reactions were not fully optimized and might vary depending on the substrate (Hawthorne and Wilt, 1960). At the temperatures we have used here, the TLC analyses showed the decarbonylated products were major (>90%) components in all cases after 50 min reaction time. Shorter reaction times gave various percentages of starting material and decarbonylated product. Although the decarbonylation was done for 50–60 min, the overall procedures of [^{18}F]fluorination and decarbonylation could be conveniently performed within 2 h. Further elaboration of the product aryl [^{18}F]fluorides to more complex structures would require additional steps and synthesis time.

The identity of all the aryl [^{18}F]fluorides were determined by TLC comparisons with that of the unlabeled authentic compounds prepared by independent methods. In addition, the same procedures of decarbonylation and demethylation were performed on the corresponding "cold" unlabeled fluorobenzaldehydes **3** and **5**. The isolated fluorophenols were identified by comparisons (TLC, mass spec fragmentation pattern and high resolution mass spectra) with authentic samples. Throughout this study, we have determined the identity and purity of radiolabeled products only, and have not accounted for chemical impurities such as the 3-nitroanisole which would be formed by decarbonylation of the 2-methoxy-4-nitrobenzaldehyde used as one of the precursors (Hawthorne and Wilt, 1960) Formation of such impurities could be avoided by the application of aryltrimethylamonium triflates as precursors for [^{18}F]fluorination (Haka *et al.*, 1989)

The mechanism of the decarbonylation reaction is not well understood (Wilt and Abegg, 1968), and there have been limited studies on the scope and the limitations of this reaction (Hawthorne and Wilt, 1960; Newman and Zahm, 1943, Rylander, 1973) Carbomethoxy, lactone, methoxy, methylenedioxy, isopropylidenedioxy, nitro, carboxylic acid and substituted amino substituents on aromatic rings are reported to be unaffected by the reaction conditions (Basa, 1975; Carabateas *et al.*, 1984; Ishi *et al*, 1990, Rylander, 1973; Shirasaka *et al*, 1990; Tadano *et al*, 1987). The decarbonylation can also be successfully applied to pyridinecarboxaldehydes (Bailey *et al*, 1973; Hawthorne and Wilt, 1960; Kirby *et al*, 1979) Certain functional groups, among them aliphatic and olefinic aldehydes, ketones and carbon–oxygen single bonds adjacent to aromatic nucleus, aliphatic carboxylic acids, aryl chlorides, anhydrides, unsaturated esters, aryl formates, primary alcohols and acyl halides, may be either reduced or decarbonylated by Pd-C (House, 1972; Isabelle *et al*, 1977, Rylander, 1973, Shishido *et al.*, 1987 Verbicky *et al.*, 1982) The reaction may also lead to aromatization, isomerization (*cis* and *trans*), disproportionation, hydrogenolysis and rearrangements (Hiroya *et al*, 1987; House 1972, Isabelle *et al.*, 1977; Rylander, 1973). Finally, this approach to ^{18}F labeling will not be applicable when either the starting material or the final products are thermally labile

Summary

This procedure demonstrates the feasibility of decarbonylation of substituted [^{18}F]fluorobenzaldehydes to aryl [^{18}F]fluorides, and has been successfully applied to the NCA syntheses of electron rich compounds such as [^{18}F]fluoroanisoles and [^{18}F]fluorophenols.

From a practical point of view, this method is a simple, two step procedure and provides aryl [^{18}F]fluorides in moderate yield. The method described here utilizes a nucleophilic aromatic displacement reaction by [^{18}F]fluoride ion in the initial fluorination step and thus should be useful for preparation of a wide variety of NCA aryl [^{18}F]fluorides which do not have electron withdrawing groups; this sequence is not limited to preparation of fluorophenols (Hawthorne and Wilt, 1960). The synthesis of 3-[^{18}F]fluoro-4-methylphenol ([^{18}F]**1**) beginning from 3-fluoro-4-methylphenol (**1**) also demonstrates the feasibility of preparing aryl [^{18}F]fluorides by use of an essentially removable activating group. As there are a number of methods available for the direct introduction of an aldehyde group onto an aromatic ring (March, 1985), a wide range of radiopharmaceuticals might be labeled with [^{18}F]fluoride by this approach.

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