Published in final edited form as:

J Labelled Comp Radiopharm. 2011 April ; 54(4): 224–228. doi:10.1002/jlcr.1853.

Syntheses of *meta*-[¹⁸F]Fluorobenzaldehyde and *meta*-[¹⁸F]Fluorobenzylbromide from Phenyl(3-Formylphenyl) Iodonium Salt Precursors

Falguni Basuli, Haitao Wu, and Gary L. Griffiths*

Imaging Probe Development Center, National Heart, Lung, and Blood Institute, National Institutes of Health, Rockville, MD 20850

Abstract

¹⁸F-labeled fluorobenzaldehydes and fluorobenzylbromides are useful synthons for the preparation of PET radiopharmaceuticals. Whereas *ortho*- and *para*-[¹⁸F]fluorobenzaldehydes can easily be prepared with high yields, the corresponding *meta*- derivatives are more problematic. In order to improve the yield of *meta*-[¹⁸F]fluorobenzaldehyde we used the corresponding diaryliodonium salt precursors, since diaryliodonium salts had already been used as precursors in preparations of ¹⁸F-labeled electron rich, as well as electron deficient, aromatic rings. Diaryliodonium salts with different counter ions [PhPhCHO]X (X = Cl, Br, OTs, OTf) were synthesized. ¹⁸F radiolabeling was performed using different bases at different temperatures in the presence of a radical scavenger, 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO). The best conversion (~80%) to *meta*-[¹⁸F] fluorobenzaldehyde was obtained using CsHCO₃ base at a reaction temperature of 110 °C. To study iodonium salt counter ion effects on radiofluorination, each precursor was separately treated with CsF[¹⁸F]/CsHCO₃ in DMF at 110 °C for 5 min in the presence of TEMPO. Our observed reactivity order was OTs < Cl < OTf < Br. *Meta*-[¹⁸F]fluorobenzaldehyde thus obtained was reduced to the corresponding alcohol with aqueous NaBH₄ at room temperature and then converted to *meta*-[¹⁸F]fluorobenzylbromide using triphenylphosphine dibromide. Formation of *meta*-[¹⁸F]fluorobenzylbromide was confirmed by HPLC and the desired product was purified on a silica Sep-Pak® plus cartridge.

Keywords

¹⁸F Radiolabeling; Iodonium salt precursors; *meta*-[¹⁸F]Fluorobenzaldehyde; *meta*-[¹⁸F]Fluorobenzylbromide

Introduction

Positron emission tomography (PET) is a very powerful non-invasive *in vivo* molecular imaging technique which provides not only information on biochemical, physiological and pharmacological processes but also offers the opportunity to study pharmacokinetics, metabolism, and mechanisms of action of novel and established drugs. Among the available PET radionuclides, ¹⁸F is favored for *in vivo* imaging because of its most suitable nuclear and chemical properties and its minimal perturbation to drug structure when substituted onto low molecular weight drugs.^{1–4}

*Correspondence to Gary L. Griffiths. griffithsgl@nih.gov.

^{18}F -labeled aryl fluorides are widely used to prepare ^{18}F radiolabeling synthons for the development of ^{18}F -labeled radiotracers. There are several approaches available (Balz-Schiemann reaction,^{5–8} Wallach reaction,^{9–11} electrophilic fluorination,^{12–14} nucleophilic displacement^{15–17}) for the synthesis of ^{18}F -radio labeled aryl fluorides. For the Balz-Schiemann reaction diazonium tetrafluoroborate is pyrolyzed in the presence of $^{18}\text{F}^-$. The major drawback of this method is the presence of ^{19}F in tetrafluoroborate, thus 25% labeling represents a theoretical maximum and tetrafluoroborate ion results in isotopic carrier reducing specific activity. The Wallach method uses decomposition of a triazene to prepare ^{18}F -labeled compounds, but also gives a low radiochemical yield. Electron rich aromatic rings can also be radiolabeled by electrophilic fluorination with $^{18}\text{F}_2$ although $^{18}\text{F}_2$ is produced along with non-radioactive fluorine gas as a carrier,¹⁸ so radiopharmaceuticals prepared using $^{18}\text{F}_2$ have low specific activity, while only half of the activity of $^{18}\text{F}_2$ can be electrophilically substituted. Up until now, the most useful route to obtain ^{18}F -labeled compounds of high specific activity is through nucleophilic fluorination by no-carrier-added $^{18}\text{F}^-$ fluoride. However, direct nucleophilic fluorination of an aromatic ring can only be done successfully and in reproducibly acceptable high yields in the presence of an appropriate leaving group $\{\text{NO}_2, \text{NMe}_3^+\text{X}^-, (\text{X} = \text{OTf}^-, \text{TsO}^-, \text{ClO}_4^-, \text{I}^-)\}$ along with an electron withdrawing group in an *ortho*- or *para*- position ($\text{NO}_2, \text{CN}, \text{CHO}, \text{RCO}, \text{COOR}$). There are only a few examples of microwave-induced ^{18}F radiolabeling of an arene ring containing an electron withdrawing group in the *meta*- position.^{19, 20}

^{18}F -labeled fluorobenzaldehydes and fluorobenzylbromides represent useful synthons for the preparation of PET radiopharmaceuticals.^{21–24} Whereas *ortho*- and *para*- ^{18}F fluorobenzaldehydes can easily be prepared with high yields by nucleophilic substitution reactions where corresponding nitro groups or quaternary amines are replaced by $^{18}\text{F}^-$, the corresponding *meta*- derivatives are more problematic. Sometimes, *meta*- ^{18}F fluorobenzaldehyde is needed in order to prepare radiopharmaceuticals with an exact molecular structure of interest and current yields obtained for *meta*- ^{18}F fluorobenzaldehyde from *meta*-nitrobenzaldehyde are very low^{25–27} because the *meta*- position of benzaldehyde is comparatively electron rich. Nucleophilic $^{18}\text{F}^-$ radiolabeling of such non-activated aromatic rings can be done by introducing an activating group with its removal or modification after labeling.^{28, 29} Diaryliodonium salts represent a particularly interesting approach, since they have been shown to be useful precursors for direct nucleophilic $^{18}\text{F}^-$ introduction into both electron-rich and electron-deficient aromatic rings.^{30–37} For this reason we chose fluorination of iodonium salt precursors as a preferred route for the radiosynthesis of *meta*-fluorobenzaldehyde using n.c.a. $^{18}\text{F}^-$.

Herein, we report the syntheses and characterization of phenyl(3-formylphenyl)iodonium salts containing four different counter anions (OTf , Cl , Br , OTs) and the ^{18}F -radiolabeling of these iodonium salts in the preparations of *meta*- ^{18}F fluorobenzaldehyde and *meta*- ^{18}F fluorobenzylbromide.

Result and Discussion

There are several literature methods available for preparation of diaryliodonium salts^{38–43} and we followed the one-pot synthesis⁴² of Olofos et al., proceeding through a non-isolated tetrafluoroborate salt, to prepare phenyl(3-formylphenyl)iodonium trifluoromethanesulfonate $[\text{PhIPhCHO}]\text{OTf}$ (**1**) (Figure 1). Similarly, phenyl(3-formylphenyl)iodonium chloride $[\text{PhIPhCHO}]\text{Cl}$ (**2**) was prepared by the anion-exchange of phenyl(3-formylphenyl)iodonium tetrafluoroborate with NaCl and phenyl(3-formylphenyl)iodonium bromide $[\text{PhIPhCHO}]\text{Br}$ (**3**) was prepared by the reaction with 48% hydrobromic acid. Salt metathesis of phenyl(3-formylphenyl)iodonium chloride

[PhI(Ph)CHO]Cl (**2**) with AgOTs afforded phenyl(3-formyl phenyl)iodonium tosylate [PhI(Ph)CHO]OTs (**4**) (Figure 1).

In test reactions using ^{19}F , fluorination of triflate salt (**1**) was done with CsF in dimethylformamide, initially at different temperatures and formation of the product was monitored by high performance liquid chromatography (HPLC) analysis of the reaction mixtures (Figure 2). The ratio of two fluorinated compound shows the general trend of more fluorination on the electron deficient ring. It is known from the literature reported by Widdowson et al.⁴⁴ that radical scavenger 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) increases the yield of the desired product and gives better reaction reproducibility. We also tried the ^{19}F fluorination reaction of triflate salt (**1**) in the presence of different amounts of TEMPO (Table 1) at 110 °C and obtained better yields of the product. It is obvious from the table that the ratio of the 3-fluorobenzaldehyde to fluorobenzene increases from 33:6 to 59:3 upon the addition of 20 mol% of TEMPO with respect to iodonium salt and the increased amount of TEMPO does not have any deleterious effect on the radiofluorination yield.

Radiosyntheses were first done with compound **1** with $\text{Cs}^{18}\text{F}/\text{Cs}_2\text{CO}_3$ in dimethylformamide at 100 °C for 5 min in a microwave in the presence of 1 equiv. of TEMPO (Figure 2). Formation of *meta*-[^{18}F] fluorobenzaldehyde was confirmed by comparison of its retention time with cold standard *meta*-fluorobenzaldehyde. Radiochemical yields were determined by radio-HPLC using an in-line radio detector. Radiolabeling was also performed at different temperatures using cesium carbonate as base with maximum conversion to *meta*-[^{18}F]fluorobenzaldehyde obtained at 110 °C (Table 2) with a trace amount of [^{18}F]fluorobenzene.

The effects of different bases on radiolabeling results was tested at 110 °C with the best conversion to [^{18}F]fluorobenzaldehyde obtained when radioactivity was eluted from an anion-exchange resin (Sep-Pak light Waters Accell Plus QMA Cartridge) with CsHCO_3 (Figure 3, Table 3).

To study the effects of the counter anion of the iodonium salt on fluorination each precursor was separately treated with $\text{Cs}^{18}\text{F}/\text{CsHCO}_3$ in DMF at 110 °C in a microwave for 5 min in the presence of TEMPO. The observed order of reactivity was OTs<Cl<OTf<Br (Table 4), with use of the bromide counter ion salt resulting in an 80% conversion to the desired product.

Meta-[^{18}F]fluorobenzaldehyde thus obtained from the reaction of bromide salt (**3**) with $\text{Cs}^{18}\text{F}/\text{CsHCO}_3$ was reduced to the corresponding alcohol with aqueous NaBH_4 at room temperature which was then converted to *meta*-[^{18}F] Fluorobenzylbromide using triphenylphosphine dibromide at room temperature in 10 min. Formation of *meta*-[^{18}F]fluorobenzylbromide was confirmed by HPLC (Figure 4) and was purified by silica Sep-Pak®-plus. The total radiochemical yield starting from the elution of activity from an anion-exchange resin (Sep-Pak light Waters Accell Plus QMA Cartridge) was 20–40% (uncorrected, n = 6) in a 50 minute synthesis.

Materials and Methods

General

Trifluoromethane sulfonic acid and K222 were obtained from Fluka. Tetrabutylammonium bicarbonate TBA-HCO₃ was obtained from ABX (Radeberg, Germany). 3-Chloroperoxybenzoic acid (77% max.) from Sigma-Aldrich was dried under reduced pressure for 1 h prior to use. All other chemicals and solvents were obtained from Sigma-Aldrich and used as received. ESI mass spectrometry (MS) were performed on a 6130

Quadrupole LC/MS Agilent Technologies instrument equipped with a diode array detector using a Zorbax Stable Bond C-18 column (4.6 × 50 mm, 3.5 μm) with a flow rate of 0.5 mL/min, 5–95% B over 10 min (B = acetonitrile, A = 0.5% TFA in water). Radiosynthesis was performed manually. Formation of the product was confirmed by HPLC on Beckman Coulter System Gold instrument equipped with multi-wavelength detector using an Agilent Eclipse C18 5 μm, 9.4 × 250 mm column. All the microwave reactions were done in Biotage Initiator 2.5 using Biotage 10 mL V-shaped vials. ¹H, ¹³C, ¹⁹F NMR spectra was recorded with a Varian spectrometer at 400 MHz. Chemical shifts are reported in parts per million (δ) and are referenced to tetramethylsilane (TMS). Sep-Pak^R plus C-18, Sep-Pak^R plus silica, Sep-Pak dry cartridges were obtained from Waters.

Phenyl(3-formylphenyl)iodonium trifluoromethanesulfonate (1)—To the solution of 3-Chloroperoxybenzoic acid (815 mg, 3.64 mmol) in dry dichloromethane (20 mL) under argon was added iodobenzene (0.4 mL, 3.52 mmol) followed by BF₃·Et₂O (1.07 mL, 8.56 mmol) and the solution was stirred for 30 min at room temperature. After cooling the reaction mixture to 0 °C solid 3-formylphenylboronic acid (555 mg, 3.7 mmol) was added and stirred at 0 °C for 15 min then at room temperature for 45 min. To the reaction mixture trifluoromethanesulfonic acid (0.30 mL, 3.39 mmol) was added and stirred for 10 min. Product was precipitated out with 50 mL of Et₂O, collected by filtration and washed with Et₂O (1.2 g, 2.62 mmol, 77%).

¹H NMR (400 MHz, DMSO-d₆): δ 10.0 (s, 1H), 8.74 (t, *J* = 1.5 Hz, 1H), 8.53 (d, *J* = 8.6 Hz, 1H), 8.31 (d, *J* = 7.3 Hz, 2H), 8.18 (d, *J* = 5.5 Hz, 1H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.82 Hz, 2H). ¹³C NMR (100 MHz, DMSO-d₆): δ 192.0, 140.7, 138.8, 135.8, 135.3, 133.7, 132.9, 132.7, 132.3, 117.6, 117.1. ¹⁹F NMR (376 MHz, DMSO-d₆): δ -77.76. LC-MS (ESI positive): *rt* = 5.37 min, *m/z* 309 [M⁺]

Phenyl(3-formylphenyl)iodonium Chloride (2)—Dichloromethane solution of Phenyl(3-formylphenyl)iodonium tetrafluoroborate salt obtained by the above method was diluted with 80 mL of dichloromethane and 100 mL of saturated aqueous sodium chloride solution was added. After stirring for 30 min the dichloromethane layer was collected. Product was precipitated out with 50 mL of Et₂O, collected by filtration and washed with Et₂O (81%).

¹H NMR (400 MHz, DMSO-d₆): δ 9.98 (s, 1H), 8.64 (t, *J* = 1.6 Hz, 1H), 8.46–8.19 (m, 3H), 8.08 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.60–7.44 (m, 3H). ¹³C NMR (100 MHz, DMSO-d₆): δ 192.2, 140.5, 138.5, 135.4, 135.2, 132.7, 132.3, 131.7, 131.6, 122.1, 121.2. LC-MS (ESI positive): *rt* = 5.37 min, *m/z* 309 [M⁺]

Phenyl(3-formylphenyl)iodonium Bromide (3)—Phenyl(3-formylphenyl)iodonium tetrafluoroborate obtained by the above method was precipitated out by addition of Et₂O (80 mL), collected and washed with Et₂O. To the solution of Phenyl(3-formylphenyl)iodonium tetrafluoroborate in methanol (25 mL) was added 48% aq. HBr (2 mL) in methanol (25 mL) and the solution was stirred for 45 min. The solvent was removed and residue was washed with acetonitrile (3 × 15 mL) to afford Phenyl(3-formylphenyl)iodonium Bromide (3) (69%).

¹H NMR (400 MHz, DMSO-d₆): δ 9.99 (s, 1H), 8.68 (t, *J* = 1.6 Hz, 1H), 8.50–8.22 (m, 3H), 8.11 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.63–7.46 (m, 3H). ¹³C NMR (100 MHz, DMSO-d₆): δ 192.1, 140.6, 138.6, 135.5, 135.2, 132.9, 132.5, 131.9, 131.8, 121.2, 120.3. LC-MS (ESI positive): *rt* = 5.37 min, *m/z* 309 [M⁺]

Phenyl(3-formylphenyl) iodonium tosylate (4)—To the suspension of Phenyl(3-formylphenyl)iodonium chloride (676 mg, 1.96 mmol) in 9:1 tetrahydrofuran, water (10 mL) was added silver triflate (540 mg, 1.93 mmol) in THF. After stirring the reaction mixture for 30 min AgCl was filtered off and the filtrate was evaporated to afford Phenyl(3-formylphenyl) iodonium tosylate (4) (800 mg, 1.66 mmol, 85%).

^1H NMR (400 MHz, DMSO- d_6): δ 9.97 (s, 1H), 8.73 (t, J = 1.6 Hz, 1H), 8.53–8.11 (m, 4H), 7.70 (t, J = 7.8 Hz, 1H), 7.65–7.44 (m, 5H), 7.08 (d, J = 8.8 Hz, 2H), 2.25 (s, 1H). ^{13}C NMR (100 MHz, DMSO- d_6): δ 192.0, 146.0, 140.8, 138.8, 138.2, 135.8, 135.6, 133.4, 132.8, 132.6, 132.2, 128.5, 125.9, 117.8, 117.2, 21.23. LC-MS (ESI positive): rt = 5.37 min, m/z 309 [M^+]

3- ^{18}F Fluorobenzylbromide— ^{18}F -Fluoride (17–30 mCi) was eluted from an anion-exchange resin (Sep-Pak light Waters Accell Plus QMA Cartridge) into a 10 mL Biotage V-shaped vials with 0.4 mL aqueous (2.5 mg/mL) solution of CsHCO_3 followed by 1 mL of acetonitrile and dried under nitrogen at 110 °C. The residue was further azeotropically dried with (3×1 mL) acetonitrile. Dimethyl formamide (1 mL) solution of Phenyl(3-formylphenyl)iodonium Bromide (3) (1–2 mg) and TEMPO (0.5–1 mg) were added, the vial was sealed and heated at 110 °C in a microwave for 5 min. The vial was cooled, 6 mL water was added and the solution was passed through a preconditioned (5 mL ethanol, 10 mL water, 20 mL air) C-18 plus Sep-Pak[®] cartridge to catch 3- ^{18}F fluorobenzaldehyde. The Sep-Pak cartridge was washed with 4 mL of 0.2 M HCl, 4 mL water and the aldehyde was converted to 3- ^{18}F fluorobenzyl alcohol on the Sep-Pak by passing 1 mL of an aqueous (30 mg) solution of NaBH_4 . The cartridge was dried for 5 min by passing nitrogen and 3- ^{18}F fluorobenzyl alcohol was eluted from the Sep-Pak cartridge with 3 mL dichloromethane, passed through a small column filled with K_2CO_3 and then a Sep-Pak dry cartridge (Na_2SO_4 , 2.85 g) into a sealed vial with a vent needle, containing triphenylphosphine dibromide (90 mg). This solution was stirred for 10 min at room temperature. 3- ^{18}F fluorobenzylbromide thus obtained was purified by silica plus Sep-Pak[®] cartridge. Formation of the product was confirmed by comparing the HPLC retention (UV detector at 254 nm) time (9.4 min) with standard 3-fluorobenzylbromide using a semi-preparative HPLC column (Agilent Zorbax C-18, 5 μ , 9.4 $\times$ 250 mm), mobile phase: acetonitrile, water with 0.1 % TFA 40:60. Over 98% radiochemically pure product (20–40%, uncorrected, n = 6) was obtained in a total synthesis time of 50 min.

Conclusion

In conclusion, the method we described can be regarded as an efficient general procedure suitable for the preparation of ^{18}F -labeled *meta*-fluorobenzaldehyde and *meta*-fluorobenzylbromide. A diaryliodonium salt having a bromide counter-ion appears to be the preferred precursor for the radiosynthesis of ^{18}F *meta*-fluorobenzaldehyde. As an example of the application of the agent, the use of ^{18}F *meta*-fluorobenzaldehyde in the total synthesis of an ^{18}F -radiolabeled version of the important tyrosine kinase inhibitor and approved anti-cancer drug, Lapatinib[®], is in progress.

Acknowledgments

The authors like to thank Christine Enders for excellent technical assistance. This study was funded by National Institutes of Health through its 2004 Roadmap for Medical Research Initiative.

References

1. Le Bars D. J Fluorine Chem. 2006; 127:1488–1493.

2. Cai L, Lu S, Pike VW. *Eur J OrgChem*. 2008;2853–2873.
3. Ametamey SM, Honer M, Schubiger PA. *Chem Rev*. 2008; 108:1501–1516. [PubMed: 18426240]
4. Papash AI, Alenitsky YG. *Phys Part Nucl*. 2008; 39:597–631.
5. Atkins HL, Christman DR, Fowler JS, Hauser W, Hoyte RM, Kloppe JF, Lin SS, Wolf AP. *J Nucl Med*. 1972; 13:713–719. [PubMed: 5056684]
6. Palmer AJ, Clark JC, Goulding RW. *Int J Appl Radiat Isot*. 1977; 28:53–65. [PubMed: 323160]
7. Eakins MN, Palmer AJ, Waters SL. *Int J Appl Radiat Isot*. 1979; 30:695–700. [PubMed: 544526]
8. Argentini M, Wiese C, Weinreich R. *J Fluorine Chem*. 1994; 68:141–144.
9. Tewson TJ, Welch MJ. *J Chem Soc Chem Commun*. 1979:1149–1150.
10. Ng JS, Katzenellenbogen JA, Kilbourn MR. *J Org Chem*. 1981; 46:2520–2528.
11. Pages T, Langlois BR, Bars DL, Landais P. *J Fluorine Chem*. 2001; 107:329–335.
12. Adam MJ, Ruth TJ, Jivan S, Pate BD. *J Fluorine Chem*. 1984; 25:329–337.
13. Miller PW, Long NJ, Vilar R, Gee AD. *Angew Chem Int Ed*. 2008; 47:8998–9033.
14. Forsback S, Eskola O, Bergman J, Haaparanta M, Solin O. *J Label Compd Radiopharm*. 2009; 52:286–288.
15. Ryzhikov NN, Seneca N, Krasikova RN, Gomzina NA, Shchukin E, Fedorova OS, Vassiliev DA, Gulyas B, Hall H, Savic I, Halldin C. *Nucl Med Biol*. 2005; 32:109–116. [PubMed: 15721755]
16. Shen B, Ehrlichmann W, Uebele M, Machulla HJ, Reischl G. *Appl Radiat Isot*. 2009; 67:1650–1653. [PubMed: 19433364]
17. Becaud J, Mu L, Karamkam M, Schubiger PA, Ametamey SM, Graham K, Stellfeld T, Lehmann L, Borkowski S, Berndorff D, Dinkelborg L, Srinivasan A, Smits R, Koks B. *Bioconjugate Chem*. 2009; 20:2254–2261.
18. Bida GT, Ehrenkauf RL, Wolf AP, Fowler JS, MacGregor RR, Ruth TJ. *J Nucl Med*. 1980; 21:758–762. [PubMed: 6772745]
19. Lazarova N, Simeon FG, Musachio JL, Lu S, Pike VW. *J Label Compd Radiopharm*. 2007; 50:463–465.
20. Guo N, Alagille D, Tamagnan G, Price RR, Baldwin RM. *Appl Radiat Isot*. 2008; 66:1396–1402. [PubMed: 18417350]
21. Iwata R, Horvath G, Pascali C, Bogani A, Yanai K, Kovacs Z, Ido T. *J Label Compd Radiopharm*. 2000; 43:873–882.
22. Akgun E, Sajjad M, Portoghese PS. *J Label Compd Radiopharm*. 2006; 49:857–866.
23. Donohue SR, Halldin C, Schou M, Hong J, Phebus L, Chernel E, Hitchcock SA, Gardinier KM, Ruley KM, Krushinski JH, Schaus J, Pike VW. *J Label Compd Radiopharm*. 2008; 49:146–152.
24. Thonon D, Kech C, Paris J, Lemaire C, Luxen A. *Bioconjugate Chem*. 2009; 20:817–823.
25. Suzuki H, Yazawa N, Yoshida Y, Furusawa O, Kimura Y. *Bull Chem Soc Jpn*. 1990; 63:2010–2017.
26. Hwang DR, Dence CS, Mckinnon ZA, Mathias CJ, Welch MJ. *Nucl Med Biol*. 1991; 18:247–252.
27. Lemaire C, Damhaut P, Plenevaux A, Cantineau R, Christiaens L, Guillaume M. *Appl Radiat Isot*. 1992; 43:485–494.
28. Shen B, Loffler D, Zeller KP, Uebele M, Reischl G, Machulla HJ. *Appl Radiat Isot*. 2007; 65:1227–1231. [PubMed: 17681802]
29. Shen B, Loffler D, Reischl G, Machulla HJ, Zeller KP. *J Label Compd Radiopharm*. 2010; 53:113–119.
30. Pike VW, Aigbirhio FI. *J Chem Soc Chem Commun*. 1995:2215–2216.
31. Shah A, Pike VW, Widdowson DA. *J Chem Soc Perkin Trans*. 1998; 1 :2043–2046.
32. Wust FR, Knies T. *J Label Compd Radiopharm*. 2003; 46:699–714.
33. Ermert J, Hocke C, Ludwig T, Gail R, Coenen HH. *J Label Compd Radiopharm*. 2004; 47:429–442.
34. Wust FR, Knies T. *J Label Compd Radiopharm*. 2004; 47:457–468.
35. Ross TL, Ermert J, Hocke C, Coenen HH. *J Am Chem Soc*. 2007; 129:8018–8025. [PubMed: 17536798]

36. Zhang MR, Kumata K, Suzuki K. *Tetrahedron Lett.* 2007; 48:8632–8635.
37. Chun JH, Lu S, Lee YS, Pike VW. *J Org Chem.* 2010; 75:3332–3338. [PubMed: 20361793]
38. Koser GF, Wettach RH. *J Org Chem.* 1980; 45:1542–1543.
39. Kitamura T, Matsuyuki J, Taniguchi H. *Synthesis.* 1994:147–148.
40. Carroll MA, Pike VW, Widdowson DA. *Tetrahedron Lett.* 2000; 41:5393–5396.
41. Stang PJ. *J Org Chem.* 2003; 68:2997–3008. [PubMed: 12688766]
42. Bielawski M, Aili D, Olofsson B. *J Org Chem.* 2008; 73:4602–4607. [PubMed: 18505294]
43. Phipps RJ, Grimster NP, Gaunt MJ. *J Am Chem Soc.* 2008; 130:8172–8174. [PubMed: 18543910]
44. Carroll MA, Nairne J, Smith G, Widdowson DA. *J Fluorine Chem.* 2007; 128:127–132.

Figure 1.
Syntheses of iodonium salts.

Figure 2.
Fluorination reactions of Compounds **1–4**.

Figure 3.

HPLC analysis {Column: Agilent Eclipse C18 5 m, 9.4×250 mm; eluent: 40% B (A = 0.1% TFA in water, B = acetonitrile); flow rate = 4 mL/min} of an aliquot taken from the crude reaction mixture of iodonium salt **1** with Cs[^{18}F]F after 5 min at 110 °C. Red line is for the radiodetector and the blue line is for the UV detector, *meta*-[^{18}F] fluorobenzaldehyde rt at 9.45 min.

Figure 4.

HPLC analysis {Column: Agilent Eclipse C18 5 μ m, 9.4 $\times$ 250 mm; eluent: 40% B (A = 0.1% TFA in water, B = acetonitrile); flow rate = 4 mL/min} of 3-[18 F]fluorobenzylbromide after Sep-Pak purification. Red line is for radiodetector and the blue line is for the UV detector, *meta*-[18 F]fluorobenzylbromide at 11.68 min.

Table 1Effect of TEMPO on fluorination (^{19}F) of compound **1**.

TEMPO (mol%)	Yield (%) ^a (n = 2)	
	[^{19}F]I	[^{19}F]II
0	33	6
20	59	3
50	60	2
75	62	2
150	57	3

^aYield was determined by HPLC

Table 2Effect of temperature on radiolabeling of compound **1**.

Base (1 mg)	Temperature(°C)	RCY ^a (%; n ≥ 2)	
		[¹⁸ F]I	[¹⁸ F]II
Cs ₂ CO ₃	100	24	2
Cs ₂ CO ₃	110	30	3
Cs ₂ CO ₃	120	10	1
Cs ₂ CO ₃	130	6	0.3

RCY = radiochemical yield;

^a radio-labeling was carried out with 3-5 mCi of activity, 1-2 mg of precursor, 0.5-1 mg TEMPO in DMF (1 mL). Yield was determined by radio HPLC.

Table 3Effect of different bases on radiolabeling of compound **1**.

Base/amount (mg or μ L)	Temperature($^{\circ}$ C)	RCY ^a (%; n $\geq$ 2)	
		[18 F]I	[18 F]II
Cs ₂ CO ₃ /1	110	30	3
CsHCO ₃ /1	110	60	5
TBAF/30	110	40	4
KHCO ₃ /K222/1/5	110	50	5
K ₂ CO ₃ /K222/1/5	110	20	6

^a radio-labeling was carried out with 3-5 mCi of activity, 1-2 mg of precursor, 0.5-1 mg TEMPO in DMF (1 mL). Yield was determined by radio HPLC.

Table 4Effect of counter anion on radiolabeling of iodonium salts **1-4**.

Compound	Base (1 mg)	Temperature(°C)	RCY ^a (% , n ≥ 2)	
			[¹⁸ F]I	[¹⁸ F]II
[PhIPhCHO]OTf (1)	CsHCO ₃	110	60	5
[PhIPhCHO]Cl (2)	CsHCO ₃	110	28	9
[PhIPhCHO]Br(3)	CsHCO ₃	110	80	6
[PhIPhCHO]OTs (4)	CsHCO ₃	110	20	3

^a Radio-labeling was carried out with 3-5 mCi of activity, 1-2 mg of precursor, 0.5-1 mg TEMPO in DMF (1 mL). Yield was determined by radio HPLC.