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A practical route for synthesizing a PET ligand containing [^{18}F]fluorobenzene using reaction of diphenyliodonium salt with [^{18}F]F$^-$

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Abstract—The aim of this study was to develop a practical route for preparing a fluorine-18 ([^{18}F]) labelled ligand ([^{18}F]**1**) containing [^{18}F]fluorobenzene ring by employing the reaction of diphenyliodonium salt with [^{18}F]F$^-$. Diphenyliodonium tosylate (**2**) was synthesized from tributylphenylstannyl compound (**6**) with [hydroxy(tosyloxy)iodo]benzene (**7**). Using this method, [^{18}F]DAA1106 ([^{18}F]**3a**), a positron emission tomography ligand for imaging peripheral-type benzodiazepine receptor, was prepared.

There are two methods for introducing radioactive fluorine-18 (^{18}F) into a benzene ring to prepare a positron emission tomography (PET) ligand containing [^{18}F]fluorobenzene ring. One method is electrophilic substitution by which a trialkylphenystannyl precursor reacts with [^{18}F]F_2 gas to afford the desired [^{18}F]fluorinated product. [^{18}F]FDOPA, a useful PET ligand for clinical investigation of dopamine receptor, has been prepared by the reaction of a tributylphenylstannyl precursor with [^{18}F]F_2.[1] However, a significant shortcoming of this method is the extremely low producing efficiency of [^{18}F]F_2 recovered from the target, which thus gives the desired product only in a low radiochemical yield (<10%). Moreover, the specific activity of the ^{18}F product by this method is also extremely low (<1 mCi/μmol) since non-radioactive F_2 has to be employed to increase the recovering efficiency of [^{18}F]F_2 from the cyclotron target. Obviously, this level of specific activity, which is 1000-fold lower than that of a common PET [^{18}F]ligand for brain imaging, is not enough to elucidate a receptor with low density in the brain.

Another method is the nucleophilic reaction of [^{18}F]F$^-$ with a substituted phenyl precursor with S_NAr reaction mechanism. Compared with the electrophilic reaction of [^{18}F]F_2, this method using [^{18}F]F$^-$ affords a [^{18}F]fluorinated product with higher radiochemical yield and specific activity. For example, [^{18}F]flumazenil[2] and [^{18}F]altanserin,[3] two useful PET ligands for imaging the central benzodiazepine receptor and 5-HT_{2A} receptor in the brain, respectively, have been prepared by reacting the corresponding nitrobenzene precursors with [^{18}F]F$^-$. However, the achieving efficiency of this reaction is significantly dependent upon the type and position of the substitution group in the benzene ring. The presence of electron-abstracting groups in the *ortho* or *para* position of the benzene ring is an indispensable condition. Without electron-abstracting groups such as NO_2, CN, CHO, COOMe and COOH in the *ortho* or *para* position of the benzene ring accompanied by leaving groups such as NO_2, Cl, Br, I and $^+NMe_3$, the substitution reaction generally does not work well.

In this study, we determined a route for preparing a PET ligand ([^{18}F]**1**) containing [^{18}F]fluorobenzene by applying the nucleophilic reaction of [^{18}F]F$^-$ with diphenyliodonium salt (**2**) (Scheme 1). Using this method, we synthesized *N*-(2,5-dimethoxybenzyl)-*N*-(5-[^{18}F]-fluoro-2-phenoxyphenyl)acetamide ([^{18}F]DAA1106, [^{18}F]**3a**), a useful PET ligand for imaging peripheral-type benzodiazepine receptor in the brain.[4]

Diphenyliodonium salt (**2**) had been previously reported as a suitable precursor for the introduction of ^{18}F into a

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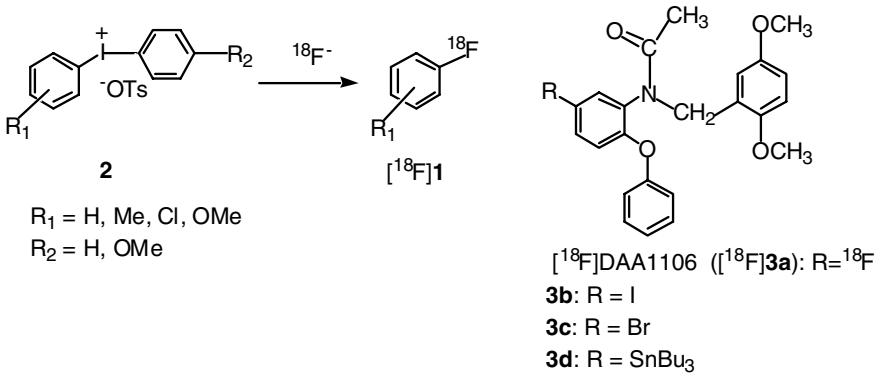
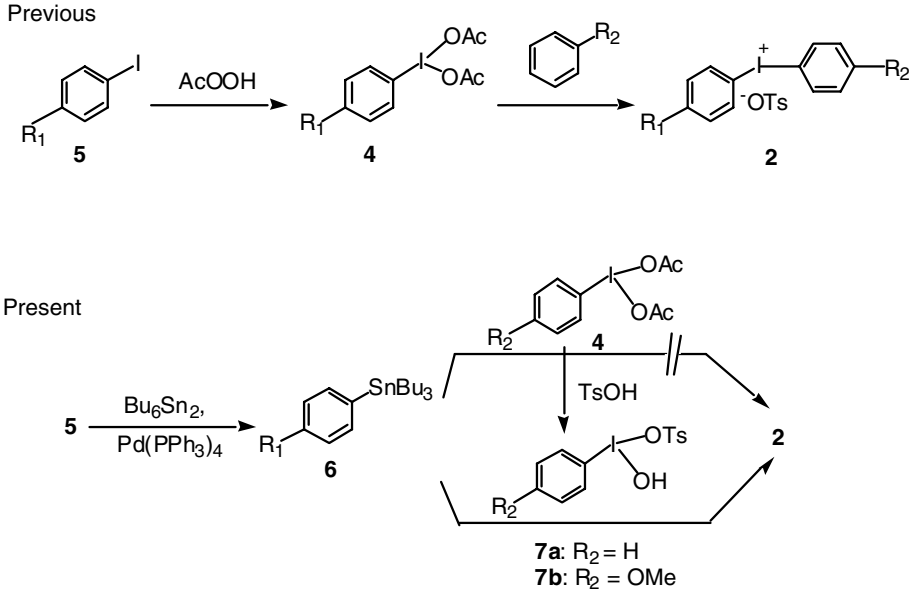


Scheme 1. Synthesis of [^{18}F]ligand ([^{18}F]**1**) containing a [^{18}F]fluorobenzene ring.

benzene ring by the nucleophilic reaction of [^{18}F]F^- (Scheme 1).[5–8] Due to the excellent property of phenyliodonium as a leaving group, the reaction of diphenyliodonium salt (**2**) with [^{18}F]F^- could proceed well to yield [^{18}F]fluorobenzene product ([^{18}F]**1**).[9–12] In particular, its ability to introduce ^{18}F into an electron-rich benzene ring without further activating groups thus induced a growing interest in PET chemistry. To date, some reports regarding the nucleophilic reaction of [^{18}F]F^- with **2** have been published; however, this reaction has not been successfully used to synthesize a practical PET ligand. The main reason is that the diphenyliodonium compound **2** is difficult to prepare starting from a precursor of the PET ligand commonly with some functional substitution groups or with more complicated chemical structures.

There are several methods for synthesizing diphenyliodonium salt with counter ions such as tosylate (**2**) as well as acetate and triflate.[13,5–7,9,12] These methods commonly apply a key intermediate, iodosobenzene diacetate (**4**), synthesized by the oxidation of iodobenzene (**5**) with peracetic acid (AcOOH) and then coupled with a benzene ring in CF_3COOH or CF_3SO_3H to yield **2** as a triflate or trifluoroacetate (Scheme 2).[13,5] However, an iodine analogue of a PET ligand with functional substitution groups is not stable for AcOOH. For example, while trying to oxidize the iodine analogue **3b** (Scheme 1) with AcOOH, the corresponding iodosobenzene diacetate product could not be obtained. Moreover, the coupling of iodosobenzene diacetate with benzene in strong acid was too severe for some functional groups.

Therefore, to apply the reaction of **2** with [^{18}F]F^- for the synthesis of a PET ligand containing [^{18}F]fluorobenzene, it is necessary to determine a reliable and practical route for synthesizing **2**. Our present route is shown in Scheme 2. In place of the oxidation of **5** to **4**, we firstly converted **5** to tributylphenylstannyl compound (**6**), an excellent precursor also for preparing radioactive phenyl products labelled by ^{11}C, ^{76}Br and ^{123}I. The usefulness of **6** guaranteed the regioselective introduction of ^{18}F into the benzene ring. In the present study, tributylphenylstannyl compound **6** with various substitution



Scheme 2. Synthesis of diphenyliodonium tosylates (**2**).

groups (R = H, Me, Cl and OMe) was synthesized by reacting the corresponding iodo-(**5**) or bromobenzene analogues with di(tributyltin) in toluene under the presence of Pd catalyst, as shown in Scheme 2.

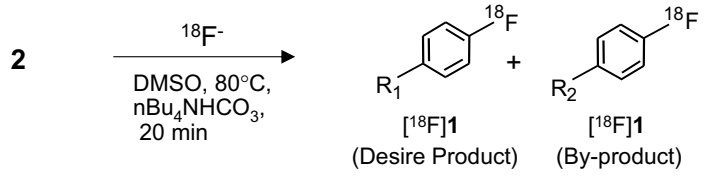
Since **6** could not react with **4**, we thus converted **4** to more reactive [hydroxy(tosyloxy)iodo]benzene analogue (**7**). Commercial [hydroxy(tosyloxy)iodo]benzene **7a** (R = H, Koser's reagent[14]) reacted with **6** to yield **2** (R_1 = H, Me, Cl and OMe; R_2 = H) in a high chemical yield (51–72%).[9] On the other hand, based on the consideration that the nucleophilic reagent $[^{18}F]F^-$ attacking the diphenyliodonium salt occurs preferably at the electron-deficient benzene ring, we designed anisyliodonium as a leaving group to increase the regioselectivity of ^{18}F into a desired benzene ring as much as possible. The reaction of **4** with toluenesulfonic acid in anhydrous CH_3CN gave **7b** (R = OMe), which has never been reported as a novel compound. However, we found that **7b** was so unstable that it was immediately decomposed while being purified from the reaction mixture. Thus, we reacted **4** with toluenesulfonic acid to give **7b** in situ, which was directly treated with **6** in anhydrous CH_3CN to give crude **2** under the atmosphere of N_2. The resulting precipitate was filtered and washed with diethyl ether several times to yield pure **2** to apply for radiosynthesis. By this procedure, starting from **5**, we prepared **2** with various substitution groups (R_1 = OMe, Me, H, and Cl; R_2 = OMe) in chemical yields of >80%.

Next, we carried out the reaction of **2** with $[^{18}F]F^-$ to optimize conditions to achieve high $[^{18}F]$fluorinating efficiency. The nucleophilic substitution of the non-carried added $[^{18}F]F^-$ proceeds via S_NAr-mechanism to yield $[^{18}F]$**1** and the corresponding iodobenzenes.[11] The reaction of **2** ($R_1 = R_2$ = H, 2–5 mg) with $[^{18}F]F^-$ (0.5–1 mCi) in several anhydrous solvents (500 μL) at 50–150 °C for 5–30 min gave $[^{18}F]$**1** with radiochemical yields of 25–82%. Among the reaction solvents, DMSO was favourable for $[^{18}F]$fluorination over other solvents such as CH_3CN, THF and DMF. Moreover, while using microwaves to radiate the reaction mixture, $[^{18}F]$fluorination progressed rapidly at 5 min to give 50–78% reaction efficiency. On the other hand, compared to Kryptofix$_{222}$ (10 mg) as the phase-transfer reagent, the application of tetrabutylammonium bicarbonate (nBu$_4$NHCO$_3$, 10 mg) gave higher efficiency of $[^{18}F]$fluorination. As control, while not using $[^{18}F]F^-$, the reaction mixture of **2** ($R_1 = R_2$ = H) with same equivalent of nBu$_4$NF was heated in THF under reflux for 8 h to give **1** in 84% chemical yield.

Table 1 shows the reaction results of **2** with $[^{18}F]F^-$ according to the reaction conditions listed. These reactions (entries 1–8) gave moderate or high efficiency (32–90%) of $[^{18}F]$fluorination. In addition to $[^{18}F]$fluorinating efficiency, we further determined the regioselectivity of $[^{18}F]F^-$ into the desired benzene ring. As expected, the reaction of $[^{18}F]F^-$ attacking **2** occurred preferably at the relatively electron-deficient benzene ring. As shown in entries 5–8, the reaction of **2** substituted by the 4-methoxy group in the benzene ring with $[^{18}F]F^-$ gave the desired product $[^{18}F]$**1** (R_1 = Me, Cl and H) in a higher ratio than the byproduct $[^{18}F]$**1** (R_2 = OMe). These results revealed that the regioselectivity of ^{18}F was dependent upon electron effects of the two benzene rings. Obviously, the electron density in the anisole ring is higher than that in benzene, toluene and chlorobenzene rings, which gave $[^{18}F]$**1** (R_1 = Me, Cl and H) with a higher ratio than $[^{18}F]$**1** (R_2 = OMe). Thus, by distinguishing the electron density of the two benzene rings in **2**, the desired $[^{18}F]$fluorinating product could be preferably obtained.

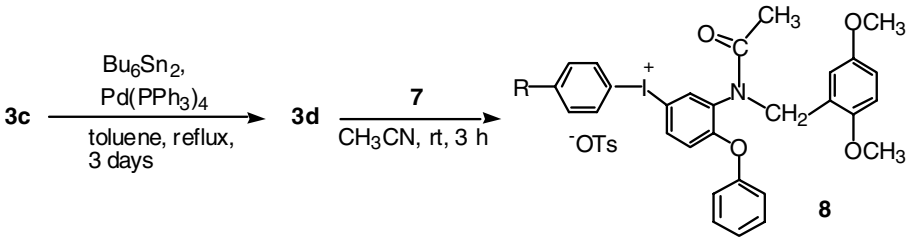
Finally, we used this method to prepare $[^{18}F]$**3a**, which is a ^{18}F vision of $[^{11}C]$DAA1106,[4] a PET ligand for imaging peripheral-type benzodiazepine receptor in the brain in our facility. The $[^{18}F]$ligand has some advantages over ^{11}C vision especially in delivery usefulness. For the bromine analogue **3 c**,[15] two diphenyliodonium compounds **8** were prepared by the reaction of **3d** with **7a** (R = H)

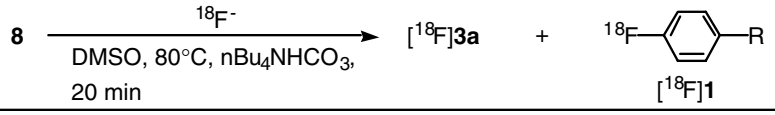
Table 1. Reaction of diphenyliodonium tosylate (**2**) with $[^{18}F]F^-$



Entry	R_1	R_2	Yield of fluorination[a] (%)	Ratio (%)	
				$[^{18}F]$**1** (R_1)	$[^{18}F]$**1** (R_2)
1	H	H	90	100	0
2	Me	H	53	19	81
3	Cl	H	32	53	47
4	OMe	H	80	2	98
5	OMe	OMe	90	100	0
6	Me	OMe	45	80	20
7	H	OMe	79	94	6
8	Cl	OMe	86	93	7

[a] Radiochemical yield was determined by analytical HPLC of the reaction mixture. All results were presented as mean values (n = 3) with a maximum range of ±5%. The radioactive products were identified using authentic non-radioactive samples.





R	Yield of [^{18}F]fluorination (%)		Ratio (%)
8a: R = H	74	3	97
8b: R = OMe	65	71	29

*: Radiochemical yield was determined by analytical HPLC of the reaction mixture. All results were presented as mean values (n =3) with a maximum range of ±5%. The radioactive products were identified using authentic non-radioactive samples.

Scheme 3. Radiosynthesis of [^{18}F]DAA1106 ([^{18}F]**3a**).

and **7b** (R = OMe), respectively (Scheme 3). Since **8a** and **8b** were unstable, they were used for radiosynthesis after the respective coupling reaction without further purification. [^{18}F]Fluorinating reactions were immediately accomplished by heating **8a** and **8b** (5 mg) with [^{18}F]F^-(3–5 mCi)/nBu$_4$NHCO$_3$ (10 mg) in DMSO (500 μL) at 80 °C for 20 min, respectively. After the reaction, the radioactive mixture was analyzed to determine the [^{18}F]fluorination efficiency and the ratio of [^{18}F]**3a** to the byproduct [^{18}F]**1** (R = H or OMe). As shown in Scheme 3, the two reactions gave high [^{18}F]fluorination efficiency (74% and 65%). For the [^{18}F]fluorination of **8a** (R = H), the byproduct [^{18}F]**1** (R = H) was formed with a high ratio (97%), whereas [^{18}F]**3a** could not be obtained. For the [^{18}F]fluorination of **8b** (R = OMe), [^{18}F]**3a** was obtained in 71% ratio and [^{18}F]**1** (R = OMe) was only yielded with a low ratio (29%). This result supported that the relatively electron-deficient ring of the diphenyliodonium salt is preferred for nucleophilic attack by [^{18}F]F^-.[7,11] To our knowledge, this is the first report of a practical PET ligand containing [^{18}F]fluorobenzene synthesized by the reaction of diphenyliodonium salt with [^{18}F]F^-.

In conclusion, we determined a suitable method for preparing a practical PET ligand [^{18}F]**1** containing [^{18}F]fluorobenzene ring with an electron-donating group using the reaction of diphenyliodonium salt (**2**) with [^{18}F]F^-. We are trying to synthesize other useful PET ligands containing [^{18}F]fluorobenzene using this reaction.

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