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# Selective syntheses of no-carrier-added 2- and 3-[$^{18}$F]fluorohalopyridines through the radiofluorination of halopyridinyl(4′-methoxyphenyl)iodonium tosylates†

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**No-carrier-added 2- and 3-[$^{18}$F]fluorohalopyridines were readily synthesized as potentially useful labeling synthons for prospective PET radiotracers through the selective radiofluorination of halopyridinyl(4′-methoxyphenyl)iodonium tosylates, themselves conveniently prepared in a single pot from iodohalopyridines.**



Positron emission tomography (PET) coupled to the use of radiotracers labeled with short-lived positron-emitters, is unique in its ability to measure biochemical processes in living human subjects, and is therefore of growing importance for clinical research and drug development.[1] In order to achieve high biochemical specificity in PET measurements, it is necessary to have rapid and simple labeling methods for introducing positron-emitting radionuclides at preferred positions in complex organic molecules.

Fluorine-18 is an especially attractive radionuclide for incorporation into PET radiotracers, because of its ready cyclotron production in high activities and high no-carrier-added (NCA) specific activities as [$^{18}$F]fluoride ion from the cyclotron-promoted $^{18}$O(p,n)$^{18}$F reaction.[2] The half-life of fluorine-18 (109.7 min) allows $^{18}$F-labeled radiotracers to be distributed to users over appreciable distances, and therefore some clinically useful PET radiotracers have reached commercialization.

Fluoropyridinyl moieties appear widely in developmental drugs, as they may often mimic phenyl groups in drug pharmacophores and may confer many of the advantages expected from judicious placement of a fluorine atom in the structure of a drug candidate, such as resistance to metabolic oxidation. Some PET radiotracers also contain $^{18}$F-labeled fluoropyridinyl groups, notably radiotracers for imaging brain nicotinic acetylcholine receptors,[3] and brain β-amyloid aggregates.[4] Until now creation of an [$^{18}$F]fluoropyridinyl moiety in a PET radiotracer has been limited mostly to direct nucleophilic substitution of a good leaving group (*e.g.*, chloro, bromo, nitro or trimethylammonium) with [$^{18}$F]fluoride ion.[5] This method has limitations. Thus, introduction of fluorine-18 into *meta* position to pyridinyl nitrogen has not been readily achievable.[6] Moreover, structural features in some prospective PET radiotracers may preclude direct labeling with [$^{18}$F]fluoride ion.

Fluorohalopyridines (halo = Cl or Br) are frequently used to introduce fluoropyridinyl moieties into drug candidates. Halo groups in *ortho* or *para* position to the pyridinyl nitrogen are effective nucleofuges and are readily and selectively replaceable to make new carbon–heteroatom bonds.[7] Furthermore, fluorohalopyridines readily participate in palladium-mediated cross-coupling reactions to make new carbon–carbon bonds[8] (Fig. 1). These cross-coupling reactions are attractive because they can often be conducted rapidly and efficiently under mild conditions, often without the need to protect other non-targeted reactive groups. Moreover, the compatibility of such reactions with the short half-life of fluorine-18 is well precedented with the homoarene 4-[$^{18}$F]fluoroiodobenzene.[9] We therefore considered that NCA [$^{18}$F]fluorohalopyridines could be useful labeling synthons for the syntheses of PET radiotracers and would expand the chemical space that might be labeled with fluorine-18. Herein we report highly selective and rapid radiosyntheses of various NCA [$^{18}$F]fluorohalopyridines, based on the radiofluorination of new diaryliodonium salts.

The radiofluorination of aryl(4′-methoxyphenyl)iodonium tosylates has emerged as a valuable route to simple [$^{18}$F]-fluoroarenes[10,11] including 3-[$^{18}$F]fluoropyridine.[12] In one study,

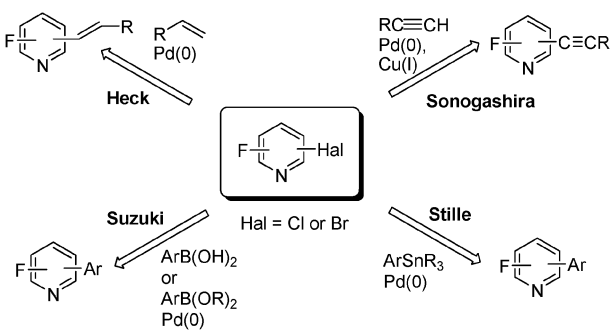


**Fig. 1** Versatility of fluorohalopyridines in cross-coupling reactions.

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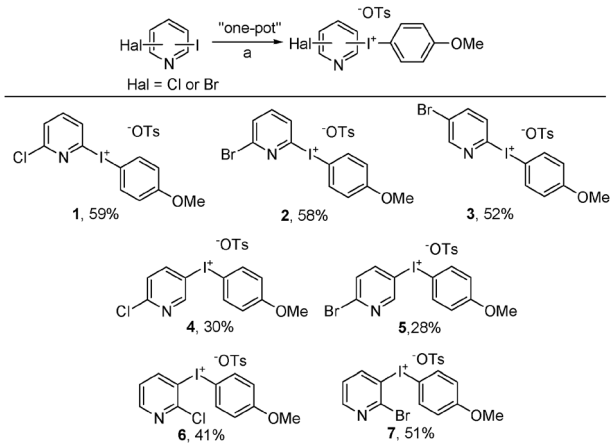
† Electronic supplementary information (ESI) available: Experimental details, $^{1}$H and $^{13}$C NMR spectra of halopyridinyl(4′-methoxyphenyl)iodonium tosylates, and selected radio-chromatograms. See DOI: 10.1039/c2cc35005j



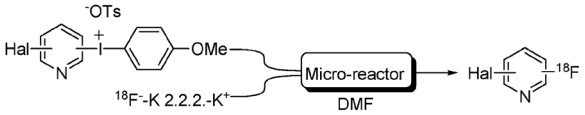

**Scheme 1** Syntheses of halopyridinyl(4′-methoxyphenyl)iodonium tosylates. *Reagent and conditions*: (a) (i) *m*-CPBA (1.1 equiv.) $CHCl_3$, r.t.; (ii) *p*-TsOH·$H_2O$ (1.1 equiv.); (iii) anisole (5 equiv.), 40 °C, 2 h.

this type of aryl radiofluorination reaction occurred selectively even when another halo nucleofuge was also present in the iodonium salt.[13] Accordingly, we considered that NCA [$^{18}$F]fluorohalopyridines might be accessible *via* the radiofluorination of appropriate halopyridinyl(4′-methoxyphenyl)iodonium tosylates, if these might be synthesized.

Recently, we reported one-pot syntheses of azide-functionalized aryl(4′-methoxyphenyl)iodonium tosylates as precursors to '[$^{18}$F]click synthons' from iodophenyl azides or iodobenzyl azides by treatment with *m*-CPBA (*m*-chloroperbenzoic acid) and *p*-TsOH·$H_2O$, followed by treatment with anisole.[14] With this convenient procedure, we were also successful in converting several iodohalopyridines into halopyridinyl-(4′-methoxyphenyl)iodonium tosylates in moderate to good yields (28–59%).‡ No pyridine-*N*-oxide byproducts were observed (Scheme 1).

A commercial microfluidic apparatus (NanoTek; Advion, Louisville, TN) was used to explore the radiofluorination of the prepared halopyridinyl(4′-methoxyphenyl)iodonium tosylates with NCA [$^{18}$F]fluoride ion. This is a practical platform for quickly optimizing radiofluorination reaction parameters, and results are useful for setting conditions for batch reactions in radiotracer syntheses.[15] We have previously described details of the configuration and operation of the microfluidic apparatus.[10] Dry [$^{18}$F]fluoride ion-kryptofix 2.2.2-K$^+$ complex ($^{18}$F$^-$-K 2.2.2-K$^+$) and the iodonium salt were separately dissolved in DMF and each loaded into a storage loop of the apparatus. Each solution was then infused into the fused silica micro-reactor (internal volume 31.7 μL) at equal set rates (4–10 μL min$^{-1}$) and at a set temperature. Radioactive effluents were quenched with aqueous MeCN and analyzed with reverse phase HPLC equipped with a radioactivity detector. Reaction temperature and time were varied over 6 to 10 runs to obtain optimal decay-corrected radiochemical yields (RCYs). Radioactivity adsorption is commonly observed during radiofluorination with dry NCA [$^{18}$F]fluoride ion. In this study, recovery of radioactivity from the microfluidic apparatus was 79 ± 6% (mean ± SD, $n$ = 7). We report RCYs from starting [$^{18}$F]fluoride ion, including that being lost by adsorption.

**Table 1** NCA radiofluorination of halopyridinyl(4′-methoxyphenyl)-iodonium tosylates in DMF




[$^{18}$F]**8**, Hal = 6-Cl, 2-$^{18}$F
[$^{18}$F]**9**, Hal = 6-Br, 2-$^{18}$F
[$^{18}$F]**10**, Hal = 5-Br, 2-$^{18}$F
[$^{18}$F]**11**, Hal = 6-Cl, 3-$^{18}$F
[$^{18}$F]**12**, Hal = 6-Br, 3-$^{18}$F
[$^{18}$F]**13**, Hal = 2-Cl, 3-$^{18}$F
[$^{18}$F]**14**, Hal = 2-Br, 3-$^{18}$F

| | | Conditions | | RCY[b] (%) | |
|---|---|---|---|---|---|
| Entry | Substrate[a] | Temp (°C) | Time[c] (s) | [$^{18}$F]Fluoro-halopyridine | 4-[$^{18}$F]Fluoro-anisole |
| 1 | **1** | 100 | 236 | [$^{18}$F]**8**, 60 | 3 |
| 2 | **2** | 180 | 236 | [$^{18}$F]**9**, 53 | 0 |
| 3 | **3** | 120 | 236 | [$^{18}$F]**10**, 64 | 0 |
| 4 | **4** | 180 | 236 | [$^{18}$F]**11**, 28 | <1 |
| 5 | **5** | 160 | 236 | [$^{18}$F]**12**, 30 | 0 |
| 6 | **6** | 180 | 188 | [$^{18}$F]**13**, 36 | 0 |
| 7 | **7** | 160 | 236 | [$^{18}$F]**14**, 28 | 2 |

[a] 5 mM in DMF. [b] Best RCY from starting [$^{18}$F]fluoride ion from among 6–10 different runs under different conditions. [c] Residence time in micro-reactor.

For the prepared set of halopyridinyl(4′-methoxyphenyl)-iodonium salts (**1–7**), radiofluorination under observed best conditions gave the corresponding [$^{18}$F]fluorohalopyridines ([$^{18}$F]**8**–[$^{18}$F]**14**) in moderate to good RCYs (28–64%), and with high selectivity with regard to the alternative unwanted product 4-[$^{18}$F]fluoroanisole (Table 1). Importantly, although halo substituents in *ortho* position to pyridinyl nitrogens are highly susceptible to substitution by nucleophiles, including [$^{18}$F]fluoride ion,[5] no radioactive products from such halogen substitution were observed, even at elevated temperatures (see ESI†, Fig. S1, for radio-chromatograms from the radiofluorination of **1** between 30 and 200 °C). Generally, the type of halo substituent, chloro or bromo had small effect on the RCY of the [$^{18}$F]fluorohalopyridine (*cf.*, entry 1 with 2, 4 with 5, and 6 with 7). The 3-[$^{18}$F]fluorohalopyridines ([$^{18}$F]**11**–[$^{18}$F]**14**; entries 4–7) were obtained in about half the RCY of the 2-[$^{18}$F]fluorohalopyridines ([$^{18}$F]**8**–[$^{18}$F]**10**; entries 1–3). Nevertheless, incorporation of [$^{18}$F]fluoride ion into the 3-position was still usefully high, especially considering the high activities in which [$^{18}$F]fluoride ion can be produced.[2] Preceding the use of iodonium salt precursors, incorporation of [$^{18}$F]fluoride ion into 3-position had only been possible in 3-halopyridines having an electron-withdrawing group in *para* position to the halogen.[16] Even when halogen was in 2-position and adjacent to the hypervalent iodine, radiofluorination occurred selectively at the 3-position (entries 6 and 7), with no chromatographic evidence of other radioactive product formation (Fig. 2).

Our findings attest to the power of aryl hypervalent iodine substituents to promote *ipso* radiofluorination even in the absence of strong electron-withdrawing groups and even in the presence of strong nucleofugic substituents. These results and preceding reports[10,11,17] further suggest that these reactions occur by non-classical $S_NAr$ mechanisms, for example

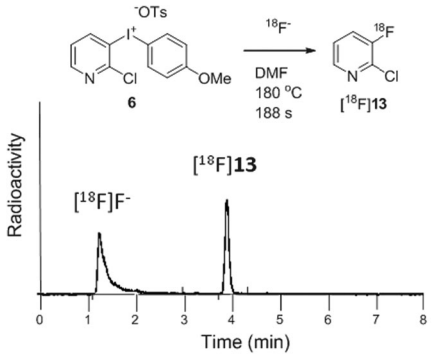



**Fig. 2** Radio-chromatogram from the analysis of products from the reaction of **6** with NCA [$^{18}$F]fluoride ion.

the proposed turnstile mechanism in which [$^{18}$F]fluoride ion first interacts with the hypervalent iodine.[10]

In summary, we developed a one-pot synthesis of halopyridinyl-(4′-methoxyphenyl)iodonium tosylates for use as precursors to NCA [$^{18}$F]fluorohalopyridines. These iodonium salts were used to produce [$^{18}$F]fluorohalopyridines rapidly and in useful RCYs, including the otherwise difficult to access 3-[$^{18}$F]fluoro-haloisomers. This methodology should be applicable to the radiosynthesis of the full range of NCA mono-[$^{18}$F]fluoro-mono-halopyridine isomers as useful labeling synthons in fluorine-18 chemistry and will therefore expand the possibilities for new PET radiotracer development.

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## Notes and references

‡ *Representative synthesis of iodonium salts*: (6-Chloropyridin-2-yl)-(4′-methoxyphenyl)iodonium tosylate (**1**) was prepared as follows. *m*-CPBA (0.49 g, 2.2 mmol, 77% max. content) was added to a solution of 2-chloro-6-iodopyridine (0.48 g, 2.0 mmol) in $CHCl_3$ (20 mL) at r.t. The mixture was stirred at r.t. until it became a pale yellow solution (*ca.* 15 min). *p*-TsOH·$H_2O$ (0.42 g, 2.2 mmol) and then anisole (1.08 g, 10 mmol) were added. The mixture was gradually heated to 40 °C and held at this temperature for about 2 h while the mixture became a yellow solution. Consumption of generated [hydroxy(tosyloxy)iodo]halopyridine was verified with KI starch paper. Reaction solvent was then removed *in vacuo*. The residual yellow oil was triturated with $Et_2O$. The generated solid was washed with $Et_2O$ and recrystallized from MeCN/$Et_2O$ to give **1** as a white solid (0.62 g, 59%). mp = 122–124 °C; $^1$H-NMR (MeCN-$d_3$) $\delta$ 8.05 (dd, $J$ = 0.4, 8 Hz, 1H), 7.98 (dd, $J$ = 2, 6.8 Hz, 2H), 7.78 (t, $J$ = 8 Hz, 1H), 7.59 (dd, $J$ = 0.4, 8 Hz, 1H), 7.48 (d, $J$ = 8 Hz, 2H), 7.12 (d, $J$ = 7.6 Hz, 2H), 7.03 (dd, $J$ = 2.4, 7.2 Hz, 2H), 3.84 (s, 3H), 2.33 (s, 3H); $^{13}$C-NMR (MeCN-$d_3$) $\delta$ 164.2, 152.2, 145.6, 144.1, 140.2, 139.5, 135.6, 131.3, 129.5, 129.0, 126.7, 118.7, 103.9, 56.7, 21.4; HRMS $[M - OTs]^+$ Calc'd for $C_{12}H_{10}NOClI$: 345.9496, Found: 345.9502.

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