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Research Article

2-, 3- and 4-[^{18}F]Fluoropyridine by no-carrier-added nucleophilic aromatic substitution with K[^{18}F]F-K_{222} – a comparative study

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Summary

Compared to homoaromatic and aliphatic nucleophilic radiofluorinations, only few references can be found in the literature describing nucleophilic substitutions with [^{18}F]fluoride ion of heteroaromatic compounds such as pyridines and only reactions involving fluorination processes at the *ortho*-position (2-position) have been more intensively studied. In the present paper, the scope of the nucleophilic aromatic fluorinations at the *meta*- and *para*-position of the pyridine ring with no-carrier-added [^{18}F]fluoride ion as its activated K[^{18}F]F-K_{222} complex has been evaluated and compared to the nucleophilic aromatic fluorinations at the *ortho*-position in this pyridine series. The syntheses of 3- and 4-[^{18}F]fluoropyridines were chosen as model reactions and compared to the radiosynthesis of 2-[^{18}F]fluoropyridine. The parameters studied include the influence of the position of the leaving group at the pyridine ring, as well as the quantity of the precursor used, the type of activation (conventional heating, microwave irradiation), the solvent, the temperature and the reaction time. Using the corresponding nitro precursor, high yields were obtained at the 2-position (94% yield) using microwaves (100 W) for 2 min in DMSO. Good yields (up to 72%) were observed at the 4-position using the same conditions while practically no reaction was observed at the 3-position. About 60% yield was also obtained at both the 2- and 4-position

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using the corresponding nitro precursor at 145°C for 10 min in DMSO. Copyright © 2003 John Wiley & Sons, Ltd.

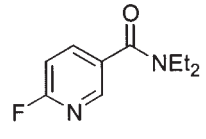
Key Words: labelling, fluorine-18, fluoropyridine, nucleophilic aromatic substitution, microwaves.

Introduction

Nucleophilic substitution by means of cyclotron-produced, no-carrier-added [^{18}F]fluoride ion is the method of choice for the synthesis of radioligands labelled with fluorine-18 (half life : 110 min) of high specific activity for Positron Emission Tomography.[1,2]

Compared to homoaromatic and aliphatic nucleophilic radiofluorinations, only few references can be found in the literature describing nucleophilic substitutions with [^{18}F]fluoride ion of heteroaromatic compounds such as pyridines and only reactions involving fluorination processes at the *ortho*-position (2-position) have been more intensively studied.

The earliest examples for the synthesis of 2-[^{18}F]fluoropyridine derivatives using nucleophilic aromatic substitution with [^{18}F]fluoride ion are : (a) the preparation of 6-[^{18}F]fluoronicotinic acid diethylamide[3] ([^{18}F]-**1**) in up to 40% decay-corrected radiochemical yield from the corresponding 2-chloropyridine derivative and [^{18}F]fluoride ion as its cesium salt, in acetamide at 200°C; (b) the preparation of 6- and 2-[^{18}F]fluoronicotine[4] ([^{18}F]-**2**,**3**) in 30 – 40% decay-corrected radiochemical yield in DMSO at 210°C for 30 min from the corresponding 2-bromopyridine derivatives and [^{18}F]fluoride ion as its cesium salt.



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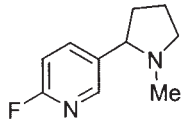

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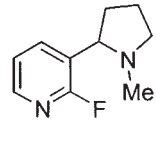

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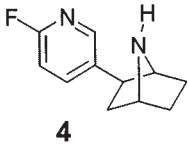

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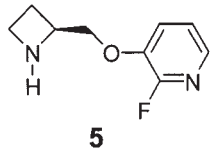

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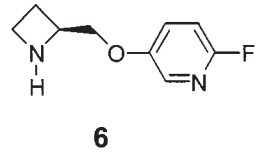

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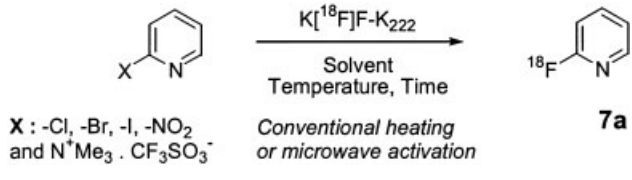
More recently, potent nicotinic acetylcholine receptor ligands, norchlorofluoroepibatidine (**4**, (±)-exo-2-(6-fluoro-3-pyridyl)-7-azabicyclo [2.2.1]heptane) as well as 2- and 6-fluoro-A-85380 (**5**, 2-

fluoro-3-[2(S)-2-azetidinylmethoxy]pyridine; **6**, 6-fluoro-3-[2(S)-2-azetidinylmethoxy]pyridine) were labelled with fluorine-18 on the pyridine ring. [^{18}F]Norchlorofluoroepibatidine ([^{18}F]-**4**) was first synthesized implying a nucleophilic aromatic bromo-to-fluoro substitution[5–8] (in DMSO, at 180–190°C for 10–15 min, 15–26% decay-corrected radiochemical yield) using the activated K[^{18}F]F-K_{222} complex.[9] It was also obtained from the corresponding 2-trimethylammonium pyridine derivative with a similar nucleophilic fluorination step (in DMSO containing the K[^{18}F]F-K_{222} complex, at 120°C for 10 min, 70% decay-corrected radiochemical yield).[10–12] 2-[^{18}F]F-A-85380 ([^{18}F]-**5**) was first synthesized by nucleophilic aromatic nitro-to-fluoro substitution in DMSO using the activated K[^{18}F]F-K_{222} complex by conventional heating at 150°C for 20 minutes or by microwave activation at 100 W for 1 min (50–60% decay-corrected radiochemical yield).[13] It was also obtained in 20% decay-corrected radiochemical yield by nucleophilic aromatic bromo-to-fluoro substitution in DMSO by conventional heating at 150°C for 20 min[14] and by nucleophilic aromatic trimethylammonium-to-fluoro substitution in DMSO by conventional heating at 145°C for 2 min or by microwave activation at 100 W for 1 min (70% decay-corrected radiochemical yield).[15] 6-[^{18}F]F-A-85380 ([^{18}F]-**6**) was synthesized by nucleophilic aromatic nitro-to-fluoro substitution in DMSO using the activated K[^{18}F]F-K_{222} complex by conventional heating at 150°C for 20 min (16–24% decay-corrected radiochemical yield).[16,17] It was also obtained in 38–48% decay-corrected radiochemical yield by nucleophilic aromatic trimethylammonium-to-fluoro substitution in DMSO by conventional heating at 150°C for 5 min.[18]

Finally, the scope of these nucleophilic heteroaromatic fluorinations of the pyridine ring at the 2-position with no-carrier-added [^{18}F]fluoride ion as its activated K[^{18}F]F-K_{222} complex was evaluated using the synthesis of 2-[^{18}F]fluoropyridine ([^{18}F]-**7a**) as a model reaction.[19]

The parameters studied included the influence of the leaving group in the 2-position of the pyridine ring (-Cl, -Br, -I, -NO_2 and -N^+Me_3), the quantity of the precursor used, the type of activation (conventional heating, microwave irradiation and ultrasonication), the solvent, the temperature and the reaction time.



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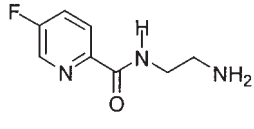
Concerning the influence of the leaving group, 2-chloro- and 2-bromopyridine gave moderate to good fluorine-18 incorporation yields while 2-nitro- and especially 2-trimethylammonium pyridine gave excellent incorporation yields. Noteworthy, 2-iodopyridine was almost unreactive. As expected, the incorporation yield increased with the quantity of precursor used : high yields were observed from about 7 μmol of precursor. Using conventional heating and regardless of the substituent in the 2-position of the pyridine ring, the best yields for the radiosynthesis of 2-[^{18}F]fluoropyridine ([^{18}F]-**7a**) were obtained when the temperature of the reaction was 180°C and the solvent DMSO. The decay-corrected yields for the 2-nitro- and the 2-trimethylammonium pyridine precursors were 77 and 88%, respectively, after only 5 min of reaction and were similar to those observed at 150°C for longer reaction times. At 120°C, neither the 2-chloro- nor the 2-bromopyridine gave any incorporation. Using microwave irradiations, excellent incorporation yields (96%) were observed for the 2-trimethylammonium leaving group from 1 min of reaction at 100 W in DMSO. Concerning the 2-chloro-, 2-bromo- and 2-nitropyridine, the use of 100 W microwave irradiation for 2 min gave yields comparable to those obtained for 10 min of conventional heating at 180°C, 22, 71 and 88%, respectively. No radioactivity incorporation at all could be detected when ultrasound was applied, even with long reaction time and high power.

Heteroaromatic nucleophilic substitutions of the pyridine ring at the *para*-position (4-position) has, to our knowledge never been reported whereas substitution at the *meta*-position (3-position) was only reported once. The only example of a radiosynthesis of a *meta*-[^{18}F]fluoropyridine derivative is the preparation of *N*-(2-aminoethyl)-5-[^{18}F]fluoropyridine-2-carboxamide ([^{18}F]-**8**), as a potential MAO-B imaging radiotracer,[20] implying a nucleophilic aromatic nitro-to-fluoro sub-stitution (in DMSO, at 135°C for 20 min, 35% decay-corrected radiochemical yield) using the activated K[^{18}F]F-K_{222} complex. As illustrated within this paper, this reaction can better be classified together with those conventional nucleophilic aromatic substitutions implying a strong electron-withdrawing group *para* to the leaving group.



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In the present paper, the scope of these nucleophilic aromatic fluorinations at the *meta*- and *para*-position of the pyridine ring with

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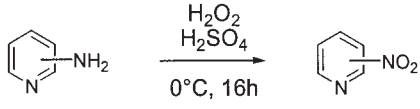
no-carrier-added [^{18}F]fluoride ion as its activated K[^{18}F]F-K_{222} complex has been evaluated and compared to the nucleophilic aromatic fluorinations at the *ortho*-position in this pyridine series. The syntheses of 3- and 4-[^{18}F]fluoropyridines ([^{18}F]-**7b**,**7c**) were chosen as model reactions and compared to the radiosynthesis of 2-[^{18}F]fluoropyridine ([^{18}F]-**7a**). The parameters studied include the influence of the position of the leaving group at the pyridine ring, as well as the quantity of the precursor used, the type of activation (conventional heating, microwave irradiation), the solvent, the temperature and the reaction time.

Results and discussion

Chemistry

Synthesis of 2-, 3- and 4-nitropyridine as precursors for labelling : 2-Nitropyridine (**9a**) was prepared from 2-aminopyridine in a mixture of concentrated sulphuric acid and 30% aqueous hydrogen peroxide at 0°C in 55% yield, using a slight modification of literature procedures.[19,21] 3-and 4-Nitropyridine (**9b** and **9c**) were prepared from the corresponding 3- and 4-aminopyridines using similar conditions to those described above in 62 and 51% yield, respectively.



9a *(ortho)* 55%
9b *(meta)* 62%
9c *(para)* 51%

Unfortunately, the corresponding pyridyltrimethylammonium trifluoromethanesulfonates could not all be prepared and therefore compared as precursors for labelling. Using protocoles adapted for the preparation of these trimethylammonium salts,[15,19,22,23] (2-pyridyl)-trimethylammonium trifluoromethanesulfonate (**10a**) could be prepared in 35% non-optimized yield from the corresponding 2-dimethylamino-pyridine in toluene at room temperature containing 1.1 equivalent of methyl trifluoromethanesulfonate.

10a *(ortho)* 35%
10b *(meta)* -
10c *(para)* -

11a *(ortho)* -
11b *(meta)* 40%
11c *(para)* 37%

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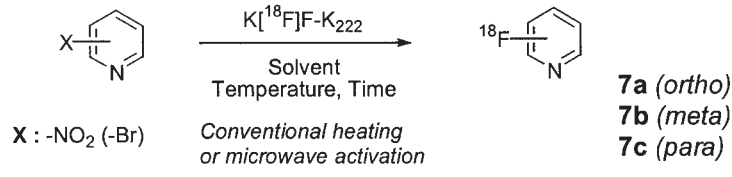
Noteworthy, starting from 3- or 4-dimethylaminopyridine using similar conditions (toluene containing 1.1 equivalent of methyl trifluoromethanesulfonate), at room temperature or lower (0°C, −20°C or −78°C), only the corresponding 3- and 4-dimethylamino-l-methylpyridinium trifluoromethanesulfonates (**11b** and **11c**) were obtained (37–40% yield). The desired (3-pyridyl)-trimethylammonium- and (4-pyridyl)-trimethylammonium trifluoromethanesulfonates (**10b** and **10c**) were not observed. With 2-dimethylaminopyridine using the same conditions that are described above (toluene containing 1.1 equivalent of methyl trifluoromethanesulfonate), heating at 80°C is needed in order to obtain the 2-dimethylamino-l-methylpyridinium trifluoromethanesulfonate (**11a**). Under these conditions, the (2-pyridyl)-trimethylammonium trifluoromethanesulfonate is still present (ratio **11a** and **10a** : 4/1, determined using ^{1}H NMR).

Radiochemistry

K[^{18}F]F-K_{222} complex was prepared from cyclotron-produced, no-carrier-added [^{18}F]fluoride ion batches (specific radioactivity : 5 Ci/μmol at end of bombardment (EOB); typical batch : 550–650 mCi (20.3–24.0 GBq) of [^{18}F]fluoride ion at EOB).



In a first set of experiments, the influence of the reaction time and position of the nitro function as leaving group in the pyridine ring were studied. A DMSO solution (600 μl) containing 17 μmol of 2-, 3- or 4-nitropyridine as precursor for labelling (**9a-c**) was transferred to 30–60 mCi (EOB, 1.11 – 2.22 GBq) of the dried K[^{18}F]F-K_{222} complex in a reaction vial (Vacutainer® tube). The tube (not sealed) was then placed in a heating block for 1 – 15 min at 145°C without stirring the contents.

As shown in Table 1, the 2-nitro-derivative (**9a**) was reactive under the conditions described above (conventional heating, 145°C). The yield of 2-[^{18}F]fluoropyridine ([^{18}F]-**7a**) increased with the reaction time up to 10 min, and then decreased. High incorporation yields were observed from 2 to 10 min of reaction (60–66% yield). These data are in accordance with already published results.[19] The 4-nitro-derivative (**9c**)

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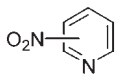
Table 1. Yields of 2-[^{18}F]fluoro-, 3-[^{18}F]fluoro- and 4-[^{18}F]fluoropyridine ([^{18}F]-7a-c) using conventional heating at 145°C or microwave activation at 100 W: Influence of the reaction time[a]

Reaction time (min)		Heating 145°C 0.5′	2′	5′	10′	15′	Microwaves 100 W 0.5′	1′	2′
	ortho	16	60	64	66	38	40	81	94
	meta	0	0	0	1	1	0	1	2
	para	15	47	52	60	43	30	65	72

[a] Conditions : precursor : 17 μmol ; K[^{18}F]F-K_{222} complex : 30–60 mCi (EOB, 1.11 – 2.22 GBq) Solvent: DMSO (600 μL); heating block for 1 – 15 min at 145°C or microwave oven (100 W) for 0.5 – 2 min ; no stirring. Indicated yields are the average of three independent runs.

was also reactive under the conditions described above. As shown for 2-[^{18}F]fluoropyridine ([^{18}F]-**7a**), the yield of 4-[^{18}F]fluoropyridine ([^{18}F]-**7c**) increased with the reaction time up to 10 min (47–60%), and then decreased. In each run, the remaining radioactivity at the end of the experiment was measured and 85% – 95% of the initial radioactivity placed in the vessel was still present. The decrease in the radiochemical yield with time was therefore not attributed to volatiles but to decomposition of the formed 2- and 4-[^{18}F]fluoropyridine ([^{18}F]-**7a**/**7c**). The 3-nitro-derivative (**9b**) was unreactive and only 1% of 3-[^{18}F]fluoropyridine ([^{18}F]-**7b**) could be observed.

Results similar to those shown in Table 1 were obtained for all three precursors (**9a-c**) when the above protocol was modified. The K[^{18}F]F-K_{222} complex was first dissolved in 600 μl of DMSO and then added to a reaction vial containing 17 μmol of the precursor **9a-c**. Finally, the reaction vial was tightly sealed and placed in a heating block for 1 to 15 min at 145°C without stirring the contents.

In another set of experiments, the influence of the reaction time and the position of the nitro function as leaving group in the pyridine ring was studied using microwave activation. A DMSO solution (600 μl) containing 17 μmol of 2-, 3- or 4-nitropyridine as precursor for labelling (**9a-c**) was transferred to 30–60 mCi (EOB, 1.11 – 2.22 GBq) of the dried K[^{18}F]F-K_{222} complex in a reaction vial (Vacutainer® tube). The tube (not sealed) was then placed in a dedicated microwave oven and irradiated (100 W).

As shown in Table 1, the 2-nitro-derivative (**9a**) was highly reactive under the conditions described above (microwave activation, 100 W). High incorporation yields were observed at 100 W from 1 minute of reaction (81% yield) to 2 minutes of reaction (94% yield). These data

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are in accordance with already published results.[19] The 4-nitro-derivative (**9c**) was also reactive under the conditions described above and up to 72% yield was obtained, hi both cases, the yield of 2- and 4-[^{18}F]fluoropyridine ([^{18}F]-**7a**/**7c**) increased with the reaction time up to 2 minutes. The 3-nitro-derivative (**9b**) was unreactive and only 1–2% of 3-[^{18}F]fluoropyridine ([^{18}F]-**7b**) could be observed.

In a last set of experiments, the influence of the nature of the leaving group at the 3-position and in particular the absence of reactivity towards nucleophilic hetero-aromatic substitution was shortly investigated using another precursor for labelling, 3-bromopyridine. A DMSO solution (600 µl) containing 17 µmol or more (up to 100 µmol) of 3-bromopyridine as precursor for labelling was transferred to 30–60 mCi (EOB, 1.11 – 2.22 GBq) of the dried K[^{18}F]F-K_{222} complex in a reaction vial (Vacutainer® tube). The tube (not sealed) was then placed in a dedicated microwave oven and irradiated (100 W) or placed in a heating block for 1–15 min at 145°C without stirring the contents. Alternatively, the K[^{18}F]F-K_{222} complex was first dissolved in 600 µl of DMSO and then added to a reaction vial containing the 3-bromo derivative. The reaction vial was tightly sealed and placed in a heating block for up to 60 min at 170–200°C without stirring. With 3-bromopyridine as precursor for labelling, the influence of the solvent was also studied using DMF, acetonitrile and a mixture of DMSO/H_2O (95:5 v:v). Whatever the conditions used, the 3-bromo-derivative was completely unreactive and the desired 3-[^{18}F]fiuoropyridine ([^{18}F]-**7b**) could not be detected.

Conclusion

The scope of the nucleophilic aromatic radiofluorination at the *meta*- and *para*-position of the pyridine ring with no-carrier-added [^{18}F]fluoride ion as its activated K[^{18}F]F-K_{222} complex has been evaluated and compared to the nucleophilic aromatic radiofluorination at the *ortho*-position in the pyridine series. Using the corresponding nitro precursor, high yields were obtained at the 2-position (94% yield) using microwaves (100 W) for 2 min in DMSO. Good yields (up to 72%) were observed at the 4-position using the same conditions while practically no reaction was observed at the 3-position. About 60% yield was also obtained at both the 2- and 4-position using the corresponding nitro precursor at 145°C for 10 min in DMSO.

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Experimental

General

2- and 3-fluoropyridine, 2-, 3- and 4-aminopyridine, 2- and 4-dimethylaminopyridine are commercially available and were purchased from Aldrich, Fluka or Sigma France. 3-Dimethylaminopyridine was available from Maybridge UK. 4-fluoropyridine can be synthesized according to literature procedures.[24–27] All other chemicals were purchased from Aldrich, Fluka or Sigma France. All purchased chemicals were used without further purification. TLC were run on pre-coated plates of silicagel $60F_{254}$ (Merck). The compounds were localized using a UV-lamp at 254 nm. Radioactive spots were detected using a Berthold TraceMaster 20 automatic TLC linear analyser. Flash chromatography was conducted on silicagel 63–200 μm (Merck) at 0.3 bars (Ar). NMR spectra were recorded on a Bruker AMX (300 MHz) apparatus using the hydrogenated residue of the deuteriated solvents (CD_2Cl_2, $\delta = 5.32$ ppm; DMSO-d_6, $\delta = 2.50$ ppm) and/or TMS as internal standards for ^{1}H NMR as well as the deuteriated solvents (CD_2Cl_2, $\delta = 53.8$ ppm; DMSO-d_6, $\delta = 39.5$ ppm; CD3OD, $\delta = 49.3$ ppm) and/or TMS as internal standards for ^{13}C NMR. The chemical shifts are reported in ppm, downfield from TMS (s, d, t, dd, b for singlet, doublet, triplet, doublet of doublet and broad respectively). The mass spectra (MS), DCI/NH_4^+, were measured on a Nermag R10-10 apparatus. Radiosyntheses using fluorine-18 were performed in a 7.5 cm-lead shielded cell using a computer assisted Zymate robot system (Zymark corporation, USA). Microwave activation was performed with a MicroWell 10 oven (2.45 GHz), Labwell AB, Sweden.

Chemistry

Nitropyridines:general procedure for the nitration of aminopyridines. 1.0 g (10.6 mmol, MW : 94.12) of the adequate aminopyridine were dissolved in 10 ml of concentrated sulphuric acid and the resulting solution was cooled to 0°C using an ice-bath. To this solution was added dropwise a cooled (5°C) mixture of 30% aq hydrogen peroxide (15 ml) in 30 ml of concentrated sulphuric acid while the temperature was maintained below 15°C. The solution was stirred at room temperature overnight and then carefully basified with 3M aq KOH. The resulting mixture was then filtered and extracted with EtOAc. The

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organic layers were combined, washed with water and brine, dried over Na_2SO_4 and concentrated to dryness. The residue was chromatographed on silica gel (heptane/EtOAc : 70/30 to 50/50) to give the desired nitropyridine in moderate yields.

2-Nitropyridine. The procedure described above was used with 2-aminopyridine and afforded, after chromatography, 2-nitropyridine as a yellow solid (55%). ^{1}H NMR (CD_2Cl_2, 298.0 K) : δ : 8.66 (bdd, $J_{app} \sim$ 1.1 & 4.6 Hz, 1 H, H-6); 8.26 (d, J : 8.2 Hz, 1 H, H-3); 8.13 (td, J : 1.8 & 7.7 Hz, 1 H, H-4); 7.76 (ddd, J : 0.9 & 4.6 & 7.5 Hz, 1 H, H-5); ^{13}C NMR (CD_2Cl_2, 298.0 K): δ : 157.1 [C]; 149.2 [CH]; 140.3 [CH]; 129.6 [CH]; 118.2 [CH]; MS ($C_5H_4N_2O_2$): 142 [M + NH_4^+]; 125 [M + H^+].

3-Nitropyridine. The procedure described above was used with 3-aminopyridine and afforded, after chromatography, 3-nitropyridine as a yellow solid (62%). ^{1}H NMR (CD_2Cl_2, 298.0 K) : δ : 9.41 (s, 1 H, H-2); 8.91 (bd, J : 4.5 Hz, 1 H, H-6); 8.47 (bd, J : 8.4 Hz, 1 H, H-4); 7.54 (dd, J : 4.8 & 8.4 Hz, 1 H, H-5); ^{13}C NMR (CD_2Cl_2, 298.0 K) : δ : 155.3 [CH]; 145.3 [CH]; 144.7 [C]; 131.3 [CH]; 124.2 [CH]; MS ($C_5H_4N_2O_2$) : 125 [M + H^+].

4-Nitropyridine. The procedure described above was used with 4-aminopyridine and afforded, after chromatography, 4-nitropyridine as a yellow solid (51%). ^{1}H NMR (CD_2Cl_2, 298.0 K): δ : 8.94 (d, J : 4.8 Hz, 2 H, H-2,6); 8.01 (d, J : 4.8 Hz, 2 H, H-3,5); ^{13}C NMR (CD_2Cl_2, 298.0 K) : δ : 153.9 [2 × CH]; 152.5 [C]; 116.4 [2 × CH]; MS ($C_5H_4N_2O_2$): 125 [M + H^+].

General procedure for methylation of dimethylpyridines. To a solution of 0.5 g of the adequate dimethylaminopyridine (4.09 mmol, MW : 122.28) in 10 ml of toluene was added 0.520 ml of methyl trifluoromethanesulfonate (4.50 mmol, MW : 167.11, d : 1.450, 1.1 eq). The solution was stirred at room temperature or higher, but also 0, −20 or −78°C for 60 min under an argon atmosphere. The precipitate was then filtered off, washed with small portions of cold ether and dried under vacuum for 10 h.

(2-Pyridyl)-trimethylammonium trifluoromethanesulfonate. The procedure described above was used with 2-dimethylaminopyridine (temperature : ambient) and afforded (2-pyridyl)-trimethylammonium trifluoromethanesulfonate as a white solid (35%). ^{1}H NMR (CD_2Cl_2, 298.0 K) : δ : 8.60 (d, J : 4.2 Hz, 1 H, H-6); 8.11 (t, J : 7.5 Hz, 1 H, H-4); 8.00 (d, J : 8.1 Hz, 1 H, H-3); 7.60 (t, J : 5.4 Hz, 1 H,

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H-5); 3.68 (s, 9 H, CH_3); 1 H NMR (DMSO-d_6, 298.0 K) : δ : 8.68 (bd, *J* : 4.0 Hz, 1 H, H-6); 8.23 (td, *J* : 1.0 & 6.0 Hz, 1 H, H-4); 8.10 (d, *J* : 9.0 Hz, 1 H, H-3); 7.72 (dd, *J* : 6.0 & 9.0 Hz, 1 H, H-5); 3.60 (s, 9 H, CH3); ^{13}C NMR (CD_2Cl_2, 298.0 K) : δ : 156.8 [C]; 149.5 [CH]; 141.7 [CH]; 126.9 [CH]; 121.2 [q, *J* : 319 Hz, CF_3]; 114.9 [CH]; 55.7 [CH_3].

2-Dimethylamino-l-methylpyridinium trifluoromethanesulfonate. The procedure described above was used with 2-dimethylaminopyridine (temperature used : 80°C) and afforded 2-dimethylamino-1-methylammonium trifluoromethanesulfonate (contaminated with (2-pyridyl)-trimethylammonium trifluoromethanesulfonate) as a white solid (30%). ^{1}H NMR (DMSO-d_6, 298.0 K) : δ : 8.40 (d, *J* :9.0 Hz, 1 H, H-6); 8.16 (t, J : 9.0 Hz, 1 H, H-4); 7.53 (d, *J* : 9.0 Hz, 1 H, H-3); 7.31 (t, *J* : 9.0 Hz, 1 H, H-5); 4.02 (s, 3 H, CH_3); 3.09 (s, 6 H, $2 \times CH_3$).

3-Dimethylamino-l-methylpyridinium trifluoromethanesulfonate. The procedure described above was used with 3-dimethylaminopyridine (temperature used : room temperature, 0, −20 or −78°C) and afforded 3-dimethylamino-l-methylpyridinium trifluoromethanesulfonate as a white solid (40%). ^{1}H NMR (CD_2Cl_2, 298.0 K) : δ : 8.08 (s, 1 H, H-2); 7.83 (d, *J* : 6.0 Hz, 1 H, H-6); 7.64 (td, *J* : 6.0 & 9.0 Hz, 1 H, H-5); 7.49 (dd, *J* : 2.0 & 9.0 Hz, 1 H, H-4); 4.34 (s, 3 H, CH_3); 3.11 (s, 6 H, $2 \times CH_3$).

4-Dimethylamino-l-methylpyridinium trifluoromethanesulfonate. The procedure described above was used with 4-dimethylaminopyridine (temperature used : room temperature, 0, −20 or −78°C) and afforded 4-dimethylamino-l-methylpyridinium trifluoromethanesulfonate as a white solid (37%). ^{1}H NMR (CD_2Cl_2, 298.0 K) : δ : 7.99 (d, *J* : 7.2 Hz, 2 H, H-2,6); 6.84 (d, *J* : 7.2 Hz, 2 H, H-3,4); 3.95 (s, 3 H, CH_3); 3.21 (s, 6 H, $2 \times CH_3$).

Radiochemistry

Radioisotope production. No-carrier-added aqueous [^{18}F]fluoride ion was produced on a CGR-MeV 520 cyclotron by irradiation of a 2 ml water target using a 17 MeV proton beam on 95% enriched [^{18}O]water by the [^{18}O(p,n)^{18}F] nuclear reaction and was transferred to the appropriate hot cell. Typical production : 550–650 mCi (20.3-24.0 GBq) of [^{18}F]F^- at the end of bombardment for a 20 μA, 30 min (36,000 μC) irradiation. A complete description of the target hardware and operation can be found in references.[8,15]

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Preparation of the K[^{18}F]F-K_{222}-complex. In order to recover and recycle the [^{18}O]water target, the 2 ml of aqueous [^{18}F]fluoride from the target were passed through an anion exchange resin (Sep-Pak® Light Waters Accell™ Plus QMA Cartridge, ionic form : chloride, washed with 5 ml IM aq. NaHCO3 and then rinsed with 50 ml of water) by He pressure (1.5–2.0 bar). Helium is blown through the column to extract the last traces of [^{18}O]water. The [^{18}F]fluoride ion was then eluted from the resin using 1.0 ml of a 4.5 mg/ml aqueous K_2CO_3 solution into a Vacutainer® tube. In order to distribute equally this activity over *n* tubes (Vacutainer® tube, $n = 2–12$), the quantity of K_2CO_3 was firstly adjusted to n times 4.5 mg with a 50.0 mg/ml aqueous K_2CO_3 solution and secondly, the total volume of the solution was adjusted to 2.0 ml with water. This new aqueous [^{18}F]fluoride solution was then equally distributed over the *n* tubes each containing 12.0–15.0 mg of Kryptofix®222 (K_{222}: 4,7,13,16,21,24-hexaoxa-l,10-diazabicyclo[8.8.8]hexacosane). Finally, the volume of each fraction was adjusted to 1.0 ml with water. The resulting solutions were then independently gently concentrated to dryness at 145–150°C under a nitrogen stream for 10 min to give no-carrier-added K[^{18}F]F-K_{222} complex as a white semi-solid residue.

Preparation of [^{18}F]fluoropyridines. General procedure using conventional heating in a sealed reactor : The K[^{18}F]F-K_{222} complex (Vacutainer® tube, on average 30 – 60 mCi (1.11 – 2.22 GBq, EOB, representing 6–12 nmol)) was dissolved in 200 µl of a freshly distilled solvent and transferred to a 5 ml pyrex® reaction vial containing N µmol of the precursor for labelling. The evaporation tube was rinsed twice with 200 µl of solvent which was then added to the reaction mixture. Resolubilization efficiencies were about 60–90% of the original [^{18}F]fluoride ion. The reaction vial was then tightly closed with a Teflon cap and heated in a heating block at a temperature *T* and during a time *t* without stirring the contents. The reaction vessel was then cooled using an ice/water bath and the remaining radioactivity was measured. Eighty five—Ninety five percent of the initial radioactivity placed in the vessel was still present. The reaction mixture was then analyzed by radiochromatography. The reaction yield was calculated from the TLC-radiochromatogram and defined as the radioactivity area of [^{18}F]fluoropyridines over total fluorine-18 radioactivity area ratio.

General procedure using conventional heating or microwave activation in a non-sealed reactor : 600 µl of freshly distilled solvent containing

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N μmol of the precursor for labelling were directly added into-the Vacutainer® tube containing the dried K[^{18}F]F-K_{222} complex (on average 30 to 60 mCi (1.11 – 2.22 GBq, EOB, representing 6–12 nmol)). The tube (not sealed) was then placed in a heating block at a temperature *T* and during a time *t* or in a dedicated microwave oven and irradiated (power *W* during a time *t*) without stirring the contents. The remainder of the preparation used the same procedure as described above.

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