Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **42**, 975-985 (1999)

2-[^{18}F]Fluoropyridines by No-Carrier-Added Nucleophilic Aromatic Substitution with [^{18}F]FK-K_{222} - A Comparative Study

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Summary

The scope of the nucleophilic aromatic substitution reaction of 2-substituted pyridines with no-carrier-added [^{18}F]fluoride ion (half life : 110 minutes) as its [^{18}F]FK-K_{222} activated complex, has been evaluated *via* the radiosynthesis of 2-[^{18}F]fluoropyridine, chosen as a model reaction. The parameters studied include the influence of the leaving group in the 2 position of the pyridine ring, the quantity of the precursor used, the type of activation (conventional heating, micro- & ultrasonic wave irradiations), the solvent, the temperature and the duration of the reaction. 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 were obtained when the temperature of the reaction was 180°C and the solvent DMSO. The yields for the 2-nitro- and the 2-trimethylammonium pyridine precursors were 77% and 88% respectively, after only 5 minutes 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 pyridine from 1 minute of reaction at 100 Watt in DMSO. Concerning the 2-chloro-, 2-bromo- and 2-nitropyridine, the use of 100 Watt microwave irradiations for 2 minutes gave yields comparable to those obtained for 10 minutes of conventional heating at 180°C, 22%, 71% and 88% respectively. No incorporation at all of the radioactivity could be detected when ultrasonic waves were applied, even with long reaction time and high power.

Key Words : labelling, fluorine-18, fluoropyridine, 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 high specific activity fluorine-18 (half life : 110 minutes) labelled radioligands for Positron Emission Tomography.

Compared to homoaromatic and aliphatic nucleophilic fluorinations, only few references could be found in the literature describing nucleophilic substitutions with stable [^{19}F]fluoride ion of heteroaromatic derivatives such as 2-substituted pyridines. Usually chloride or bromide ions were involved as leaving group in these reactions. 2-Fluoropyridine was obtained in 49% yield by heating 2-chloropyridine and fluoride ion in dimethylsulfone at 210°C

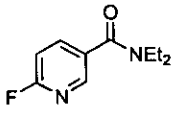
CCC 0362–4803/99/100975–11$17.50

Received 8 February 1999
Revised 11 March 1999
Accepted 30 March 1999

for 21 days[1]. It had also been obtained in 42% yield by heating 2-bromopyridine and fluoride ion in dimethylsulfone at 200°C for 7 days[1]. 2-Fluoroquinoline was prepared from 2-chloroquinoline and fluoride ion in 60% yield in boiling dimethylsulfone after 5 days[2]. 2-Fluoropyridine was also prepared from 2-nitropyridine in 60% yield by fluorodenitration using fluoride ion in HMPT at 160°C for 24 hours[3]. No example of 2-fluorodeiodination of pyridine derivatives could be found in the literature. Also, nucleophilic aromatic substitution with [^{19}F]fluoride ion of 2-substituted pyridines, bearing the well-known leaving group trimethylammonium trifluoro methanesulfonate[4,5], has not been reported.

The first examples for the synthesis of 2-[^{18}F]fluoropyridine derivatives using nucleophilic aromatic substitution with [^{18}F]fluoride ion involved : (1) the preparation of 6-[^{18}F]fluoronicotinic acid diethylamide[6] ([^{18}F]-**1**) in up to 40% radiochemical yield from the corresponding 2-chloropyridine derivative and [^{18}F]fluoride ion as its cesium salt, in acetamide at 200°C ; (2) the preparation of 2- and 6-[^{18}F]fluoronicotine[7] ([^{18}F]-**2a** and [^{18}F]-**2b**) in 30 to 40% radiochemical yield in DMSO at 210°C for 30 minutes from the corresponding 2- and 6-bromopyridine derivative, respectively and [^{18}F]fluoride ion as its cesium salt.

More recently, two potent nicotinic acetylcholine receptor ligands, norchlorofluoroepibatidine[8-13] (**3**, (±)-exo-2-(6-fluoro-3-pyridyl)-7-azabicyclo [2.2.1]heptane) and F-A-85380[14,15] (**4**, 2-fluoro-3-[2(S)-2-azetidinylmethoxy]pyridine) were labelled with fluorine-18 on the pyridine ring.



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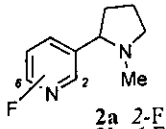
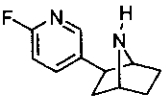


2a *2*-F
2b *6*-F



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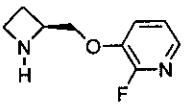

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[^{18}F]Norchlorofluoroepibatidine ([^{18}F]-**3**) was first synthesized implying a nucleophilic aromatic bromo-to-fluoro substitution[8-10] (in DMSO, at 190°C for 15 minutes, 15 to 26% radiochemical yield) using the activated [^{18}F]FK-K_{222} complex[16]. It has also been obtained from the corresponding 2-substituted trimethylammonium pyridine derivative precursor with a similar nucleophilic fluorination step (in DMSO containing the [^{18}F]KF-K_{222} complex, at 120°C for 10 minutes, 70% radiochemical yield)[11-13]. [^{18}F]F-A-85380 ([^{18}F]-**4**) was synthesized by nucleophilic aromatic nitro-to-fluoro substitution in DMSO by conventional heating at 150°C for 20 minutes or by microwave activation at 100 Watt for 1 minute (50-60% decay-corrected radiochemical yield)[14]. It has also been obtained in 20% decay-corrected radiochemical yield by nucleophilic aromatic bromo-to-fluoro substitution in DMSO by conventional heating at 150°C for 20 minutes[15].

In the present paper, the scope of these nucleophilic aromatic fluorinations of the pyridine ring with no-carrier-added [^{18}F]fluoride ion as its activated [^{18}F]FK-K_{222} complex has been evaluated. The synthesis of 2-[^{18}F]fluoropyridine ([^{18}F]-**6**) was chosen as a model reaction. The parameters studied include 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, micro- & ultrasonic wave irradiations), the solvent, the temperature and the reaction time.

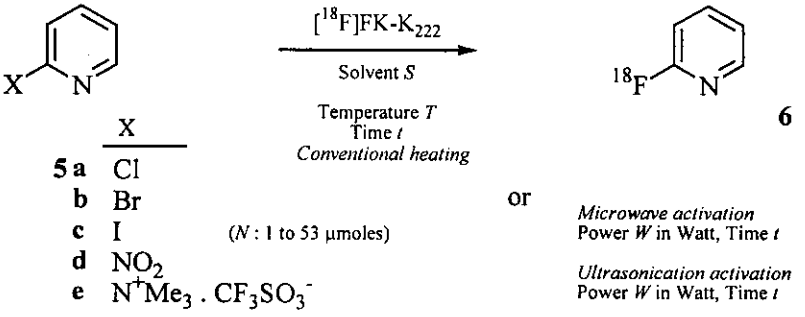
Results and Discussion

Chemistry : Preparation of the precursors for labelling and references

2-Nitropyridine (**5d**) was prepared from 2-aminopyridine in a mixture of concentrated sulphuric acid and 30% aqueous hydrogen peroxide at 0°C in 52% yield. (2-Pyridyl)-trimethylammonium trifluoromethanesulfonate (**5e**) was prepared in 24% non-optimized yield from the corresponding dimethylaminopyridine in toluene at room temperature containing 1.4 equivalent of methyl trifluoromethanesulfonate. 2-Chloro-, 2-bromo- and 2-iodopyridine (**5a-c**), as well as reference compound 2-fluoropyridine (**6**) were commercially available.

Radiochemistry

[^{18}F]FK-K_{222} complex was prepared from cyclotron-produced, no-carrier-added [^{18}F]fluoride ion (specific radioactivity : 5 Ci/μmol at End Of Bombardment (EOB)).



Conventional heating

In the first set of experiments, the influence of the leaving group in the 2 position of the pyridine ring was studied. A DMSO solution (600 μL) of 30-60 mCi (EOB, 1.11 to 2.22 Gbq) of [^{18}F]FK-K_{222} (representing 6-12 nmoles) was transferred to a reaction vial containing 40 to 55 μmoles of the precursor **5a-e**. The reaction vial was then tightly sealed and conventionally heated (heating block) for 5, 10 and 20 minutes at 150°C.

As shown in Table 1, yields of 2-[^{18}F]fluoropyridine ([^{18}F]-**6**) were higher when nitro- or trimethylammonium were the substituents as leaving group and this, independently of the reaction time used (5, 10 or 20 minutes). Very high incorporation yields were observed for the trimethylammonium substituent from 5 minutes of reaction (89% yield). Similar yields were observed after 10 or 20 minutes of reaction. Comparable yields were only obtained for the nitro substituent when long reaction times (20 minutes) were applied. Noteworthy, **5c** was almost unreactive in the conditions used (0% after 5 and 10 minutes, to 1% yield after 20 minutes), although the iodo substituent is usually considered an excellent leaving group. For the chloro- and bromo substituent, the incorporation yields increase with the reaction time. For the three reaction times studied, the yields starting from **5b** (bromo) were higher than from **5a** (chloro). After 5 minutes of reaction, almost no conversion was observed for the chloro- or the bromo substituent at 150°C (1% yield). The maximum yields obtained for the chloro- and the bromo substituent (after 20 minutes) were 23% and 25%, respectively.

In two complementary sets of experiments the influence of the leaving group in the 2 position of the pyridine ring was studied at 120°C and 180°C using conditions similar to those described above for 150°C (DMSO solution of the [^{18}F]FK-K_{222} complex, 40 to 55 μmoles of the precursor, conventional heating).

Temperature	Substituent	Time of reaction (min)		
	X [a]	5	10	20
120°C	Cl, Br or I	0 [c]	0 [c]	0 [c]
	NO_2	11 *	76 (2)	82 (2)*
	N^+Me_3 [b]	81 (2)	87 (2)*	91 (2)
150°C	Cl	1 (4)	3 (4)	23 (4)
	Br	1 (4)	16 (4)	25 (4)
	I	0 [c]	0 [c]	1
	NO_2	52 *	85 (5)	92
	N^+Me_3 [b]	89 (2)	89 (2)*	90 (2)
180°C	Cl	11	28 (2)	57 *
	Br	56 (2)*	60 *	87 (2)*
	I	2 (2)	5 *	19 (2)*
	NO_2	77 *	88 *	89 (4)*
	N^+Me_3 [b]	88 (2)*	91 (2)*	92 (2)

Indicated yields are the average of three independent runs unless otherwise stated in parentheses. Deviation : +/- 2% (* 5%).

Conventional heating (heating block) - Solvent : DMSO (600 μL).
[a] *N* (μmoles) of precursors : Cl : 52.8, Br : 52.4, I : 50.7, NO_2 : 40.3, N^+Me_3 : 42.6 - [b] $CF_3SO_3^-$ salt - [c] traces could be detected on the radiochromatogram.

Table 1 : Influence of the leaving group in the 2 position of the pyridine ring.

Concerning the trimethylammonium substituent, after 10 minutes of reaction, the incorporation yields at 120°C were similar to those observed at 150°C (87% to 91% yield). Concerning the nitro substituent, for the three reaction times studied, incorporation yields were lower at 120°C than at 150°C, the major difference being observed after 5 minutes of reaction : 11% yield and 52% yield for 120°C and 150°C, respectively. At 150°C, the yield after 20 minutes of reaction was 82%. At 120°C, the chloro-, the bromo- and the iodo substituent gave hardly any incorporation, even after 20 minutes of reaction. Regardless of the substituent, the best incorporation yields in all our experiments were obtained when the temperature of the reaction was 180°C. The yields for the nitro- and the trimethylammonium substituent were 77% and 88% respectively after only 5 minutes of reaction, and were similar to those observed at 150°C for longer reaction times (85% to 92% yield). For the chloro-, bromo- and iodo substituent, the yield increased with the reaction time, the iodo still being the less reactive and the bromo still being the more reactive. After 20 minutes of reaction at 180°C, yields were 57%, 87% and 19% for the chloro-, bromo- and iodo substituent, respectively.

A further set of experiments was designed in order to determine the influence of the quantity of precursor used. A DMSO solution (600 µL) of the [^{18}F]FK-K_{222} complex was transferred to a reaction vial containing 1.0 to 40.3 µmoles of the nitro precursor. The reaction vial was then tightly sealed and conventionally heated (heating block) for 10 minutes at 180°C.

N (µmoles)	40.3	19.4	7.3	3.2	2.0	1.0
Yields	89 (4)*	88 *	81 (2)*	55 (2)	0 a	0 a

Indicated yields are the average of three independent runs unless otherwise stated in parentheses. Deviation : +/- 2% (* 5%).

Conventional heating (heating block) - Precursor : 2-nitropyridine - Solvent : DMSO (600 µL) - Temperature : 180°C - Time : 10 min.
a traces could be detected on the radiochrematogram.

Table 2 : Influence of the quantity of precursor.

As shown in Table 2, the incorporation yields increased as expected with the quantity of precursor. High yields (81% to 89%) were observed with about 7 µmol of precursor. Below 7 µmol, a sharp drop off in the yield was observed giving only 55% at 3.2 µmol and no incorporation at 2.0 µmol and less.

In another set of experiments, the influence of the solvent was studied. The [^{18}F]FK-K_{222} complex was solubilized in 600 µL of various solvents and transferred to a reaction vial containing 40.3 µmoles of the nitro precursor. The reaction vial was then tightly sealed and conventionally heated (heating block) for 10 minutes at 150°C.

Solvent	Sulfolane	DMSO	DMF	CH_3CN	DMSO/H_2O 9:1
Yield	88 (2)	85 (5)	71 (2)*	69 (2)*&	1 (2)@

Indicated yields are the average of three independent runs unless otherwise stated in parentheses. Deviation : +/- 2% (* 5%).

Conventional heating (heating block) - Precursor : 2-nitropyridine : 40.3 µmol - Solvent : 600 µL - Temperature : 150°C (& 120°C only) - Time : 10 min. @ 89% yield with the (2-pyridyl)-trimethylammonium trifluoromethane sulfonate precursor.

Table 3 : Influence of the solvent.

Table 3 shows the yields obtained in different solvents : sulfolane, DMSO, DMF, acetonitrile and a mixture of DMSO/H_2O (9:1 v:v). Incorporation yields were the highest when DMSO or sulfolane were the solvents (85% to 88% yield). However, sulfolane being solid at room temperature, DMSO was preferred for its easy utilization in these reactions. The yields obtained when DMF or acetonitrile were the solvent were lower (71% and 69%, respectively). Almost no incorporation was observed when 10% of water was added to DMSO except when the precursor used was the (2-pyridyl)-trimethylammonium trifluoromethanesulfonate.

Microwave activation

Several experiments were performed using microwave activation instead of conventional heating. The influence of the leaving group in the 2 position of the pyridine ring was studied at different power and reaction times. A DMSO solution (600 µL) of the [^{18}F]FK-K_{222} complex was transferred to a Pyrex tube containing 40 to 55 µmoles of the precursor. The Pyrex tube was left unsealed and then placed in a microwave oven for 1, 2 and 4 minutes at a power of 50 Watt or 1 and 2 minutes at a power of 100 Watt.

Power (Watt)	Substituent	Time of reaction (min)		
	X [a]	1	2	4
50	Cl	0 [(2)c]	1 [(2)]	26 [(2)*]
	Br	0 [(2)c]	1	68 [(2)]
	I	0 [c]	1	8 [(2)]
	NO_2	3	67 [*]	76
	N^+Me_3 [b]	77 [(2)]	94 [(2)]	96 [(1)]
100	Cl	1 [(2)]	22 [(2)]	- [d]
	Br	11 [(2)]	71 [(2)*]	- [d]
	I	1	14 [(4)*]	- [d]
	NO_2	59 [(2)]	88	- [d]
	N^+Me_3 [b]	96	90 [d]	- [d]

Indicated yields are the average of three independent runs unless otherwise stated in parentheses. Deviation : +/- 2% (* 5%).

Microwave activation - Solvent : DMSO (600 µL).
[a] *N* (µmoles) of precursors : Cl : 52.8, Br : 52.4, I : 50.7, NO_2 : 40.3, N^+Me_3 : 42.6 - [b] $CF_3SO_3^-$ salt - [c] traces could be detected on the radiochromatogram - [d] part or totality of the reaction mixture sprayed out of the tube.

Table 4 : Influence of the leaving group in the 2 position of the pyridine ring.

As shown in Table 4, yields obtained for 2-[^{18}F]fluoropyridine were higher when nitro- or trimethylammonium substituents were the leaving group and this independently of the power applied (50 or 100 Watt). High incorporation yields were observed for the trimethylammonium substituent from 1 minute of reaction at 50 Watt (77% yield). Excellent yields were also observed after 1 minute at 100 Watt (96%). Somewhat lower yields were obtained for the nitro substituent at 50 and 100 Watt. Almost no reaction was observed at 50 Watt after 1 minute. As for the nitro substituent, the incorporation yields with a chloro-, bromo- and iodo substituent increase with reaction time. Again, the iodo substituent was rather unreactive under the conditions used (maximum observed yield : 14% for 100 Watt after 2 minutes). For the three reaction times studied, the yields obtained with the bromo compound (**5b**) were higher than with the chloro compound (**5a**). After 2 minutes of reaction, almost no reaction was observed for the chloro- or the bromo substituent at 50 Watt (1% yield). The maximum yields obtained for the chloro- and the bromo substituent at 50 Watt (after 4 minutes) were 26% and 68%, respectively and at 100 Watt (after 2 minutes) 22% and 71%, respectively.

Ultrasonic activation

Finally, several experiments were performed using ultrasonic activation instead of conventional heating. This set of experiments was only performed with 2-nitropyridine (**5d**) as the precursor. A DMSO solution (600 µL) of the [^{18}F]FK-K_{222} complex was transferred into a Pyrex tube containing 40.3 µmoles of the nitro precursor. The unsealed Pyrex tube was placed in the cavity of an ultrasonic wave generator for 5 to 30 minutes at a power of 100 to 450 Watt. Under the conditions used, no incorporation of radioactivity could be detected even with long reaction times (up to 30 minutes) and maximum power (450 Watt).

Experimental

General : Chemicals (including 2-chloropyridine (**5a**), 2-bromopyridine (**5b**) and 2-fluoropyridine (**6**)) were purchased from Aldrich, Fluka or Sigma France unless otherwise stated, and 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). HPLCs were run on Waters systems equipped with a 510 pump and a UV detector (440 fixed wavelength or 481/486 multiwavelength) ; the effluent was also monitored for radioactivity with a Geiger-Müller counter. HPLC column & conditions : column : semipreparative C-18 µBondapak Waters (300 x 7.8 mm); porosity : 10 µm ; temperature : RT ; UV detection at λ : 254 nm. NMR spectra were recorded on a Bruker AMX (300 MHz) apparatus using the hydrogenated residue of the deuteriated solvents ($CDCl_3$, δ = 7.26 ppm ; CD_2Cl_2, δ = 5.32 ppm) and/or TMS as internal standards for ^{1}H NMR as well as the deuteriated solvents (CD_2Cl_2, δ = 53.8 ppm ; $CDCl_3$, δ = 77.1 ppm) and/or TMS as internal standards for ^{13}C NMR. The chemical shifts are reported in ppm, downfield either from TMS (d, t, dd, b for doublet, triplet, doublet of doublet and broad respectively ; * : interchangeable assignments). The mass spectra (MS), DCI/NH_4^+, were measured on a Nermag R10-10 apparatus. Microwave activations were performed with a MicroWell 10 oven (2.45 GHz), Labwell AB, Sweden. Ultrasonication activations were performed with a Branson Sonifier 450 (20 KHz), Branson Ultrasonics Corp., USA. Radiosyntheses were performed in a 5 cm lead-shielded confinement using a computer assisted Zymate robot system (Zymark corporation, USA).

Chemistry

2-Iodopyridine (5c) : synthesized by Syntheval, France. Rf : 0.7 (Heptane/EtOAc : 60/40) ; 0.5 (Heptane/EtOAc : 50/50) ; 0.37 (Heptane/EtOAc : 90/10) ; HPLC Rt : 12.6 min (acetonitrile/water/TFA : 10/90/0.15 ; flow rate : 5.0 mL/min) ; 10.4 min (acetonitrile/water/TFA : 5/95/0.15 ; flow rate : 9.0 mL/min) ; 18.0 min (acetonitrile/water/TFA : 5/95/0.15 ; flow rate : 5.0 mL/min) ; ^{1}H NMR ($CDCl_3$, 298.0K) : δ : 8.38 (bd, J_{app} ~ 2.7 Hz, 1H, H-6) ; 7.73 (d, J : 7.7 Hz, 1H, H-3) ; 7.34* (dd, J : 7.5 & 2.1 Hz, 1H, H-4) ; 7.28* (m, 1H, H-5) ; ^{13}C NMR ($CDCl_3$, 298.0K) : δ : 150.8 [CH] ; 137.5 [CH] ; 135.0 [CH] ; 123.0 [CH] ; 118.1

[C] ; NMR data in accordance with the structure and directly comparable to those described for **5a** and **5b** [17]; MS 205 (C_5H_4NI) : 223 [M + NH_4^+] ; 206 [M + H^+].

2-Nitropyridine (5d) : prepared from 2-aminopyridine using a slightly modified literature procedure[18]. 6.0 g (63.7 mmoles, MW : 94.12) of 2-aminopyridine were dissolved in 30 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 (50 mL) in 100 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 organic layers were condensed, 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 give 4.1 g of 2-nitropyridine as a yellow powder (52%). Rf : 0.30 (heptane/EtOAc : 50/50) ; HPLC Rt : 7.3 min (acetonitrile/water/TFA : 10/90/0.15 ; flow rate : 5.0 mL/min) ; 5.0 min (acetonitrile/water/TFA : 5/95/0.15 ; flow rate : 9.0 mL/min) ; 9.1 min (acetonitrile/water/TFA : 5/95/0.15 ; flow rate : 5.0 mL/min) ; ^{1}H NMR (CD_2Cl_2, 298.0K) : δ : 8.66 (bdd, J_{app} ~ 1.1 & 4.6 Hz, 1H, H-6) ; 8.26 (d, J : 8.2 Hz, 1H, H-3) ; 8.13 (td, J : 1.8 & 7.7 Hz, 1H, H-4) ; 7.76 (ddd, J : 0.9 & 4.6 & 7.5 Hz, 1H, H-5) ; ^{13}C NMR (CD_2Cl_2, 298.0K) : 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^+].

(2-Pyridyl)-trimethylammonium trifluoromethanesulfonate (5e) : To a solution of 5.0 g of 2-dimethylaminopyridine (40.9 mmoles, MW : 122.28) in 85 mL of toluene was added 6.5 mL of methyl trifluoromethanesulfonate (56.25 mmoles, MW : 167.11, 1.4 eq). The solution was stirred at room temperature for 3 h under an argon atmosphere and then diluted with 100 mL of water. This aqueous solution was washed twice with 100 mL of CH_2Cl_2 and concentrated until crystals precipitated. The white crystals were filtered off and dried under vacuum for 24 h to give 2.8 g of (2-pyridyl)-trimethylammonium trifluoromethanesulfonate (24%). Rf : 0.34 (MeOH/EtOAc : 50/50) ; HPLC Rt : 4.6 min (acetonitrile/water/TFA : 10/90/0.15 ; flow rate : 5.0 mL/min) ; 3.5 min (acetonitrile/water/TFA : 5/95/0.15 ; flow rate : 9.0 mL/min) ; 6.4 min (acetonitrile/water/TFA : 5/95/0.15 ; flow rate : 5.0 mL/min) ; ^{1}H NMR (CD_2Cl_2, 298.0K) : δ : 8.60 (d, J : 4.2 Hz, 1H, H-6) ; 8.11 (t, J : 7.5 Hz, 1H, H-4) ; 8.00 (d, J : 8.1 Hz, 1H, H-3) ; 7.60 (t, J : 5.4 Hz, 1H, H-5) ; 3.68 (s, 9H, CH_3) ; ^{13}C NMR (CD_2Cl_2, 298.0K) : 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].

Radiochemistry

Production of aqueous [^{18}F]F$^-$

[^{18}F]F$^-$ was produced on a CGR-MeV 520 cyclotron by irradiation of a 2 mL water target (water-cooled stainless-steel target holder equipped with a 12 μm He-cooled titanium window) using a 16 MeV proton beam on 95% enriched [^{18}O]water [^{18}O(p,n)^{18}F]. On average, about 550-650 mCi (20.3-24.0 GBq) of [^{18}F]F$^-$(specific radioactivity : 5 Ci/μmol) is routinely obtained in our laboratory at EOB for a 20 μA, 30 min (36000 μCoulomb) irradiation.

Preparation of the [^{18}F]FK-K$_{222}$-complex

The 2 mL of aqueous [^{18}F]fluoride from the target were passed through an ion exchange resin (AG1X8, Bio-Rad, 100-200 mesh, ionic form : chloride, washed with 10 mL 1M aq NaOH and then rinsed with 100 mL of water) in order to recover the enriched [^{18}O]water. Either of the following procedures can be used for the preparation of the [^{18}F]FK-K$_{222}$-complex.

Procedure A : The [^{18}F]fluoride ion was eluted from the resin using 1.5 mL of a 3.0 mg/mL aqueous K_2CO_3 solution. In order to distribute equally this activity over n tubes (n = 2, 4, 6, 8, 10 or 12), the quantity of K_2CO_3 was firstly adjusted to n times 4.5 mg with a 25.0 mg/mL aqueous K_2CO_3 solution and secondly, the total volume of the solution was adjusted to 3.0 mL with water. This new aqueous [^{18}F]fluoride solution was then equally distributed over the n tubes each containing 15.0 to 17.0 mg of Kryptofix® K$_{222}$ (4, 7, 13, 16, 21, 24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane). Finally, the volume of each fraction was adjusted to 1.5 mL with water. The resulting solutions were then independently gently concentrated to dryness at 110-120°C under a nitrogen stream for 20 min.

Procedure B : The [^{18}F]fluoride ion was eluted from the resin using 1.0 mL of a 4.5 mg/mL aqueous K_2CO_3 solution. In order to distribute equally this activity over n tubes (n = 2, 4, 6, 8, 10 or 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 15.0 to 17.0 mg of Kryptofix® K$_{222}$ (4, 7, 13, 16, 21, 24-hexaoxa-1,10-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 110-120°C under a nitrogen stream for 10 min.

General procedure for the preparation of 2-[^{18}F]fluoropyridine

Conventional heating : The [^{18}F]FK-K$_{222}$ complex (on average 30 to 60 mCi (1.11 to 2.22 GBq, EOB, representing 6-12 nmoles)) as a white semisolid residue was dissolved in 200 µL of a freshly distilled solvent *S* and transferred to a 2 mL reaction vial containing *N* µmoles of the precursor for labelling *P*. The evaporation tube was rinsed twice with 200 µL of solvent *S* 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 sealed with a Teflon cap and heated in a heating block without stirring at a temperature *T* and during a time *t*.

S : Sulfolane, DMSO, DMSO/water 9:1, DMF or acetonitrile ; *N* : 1 to 53 µmoles ; *P* : 2-chloropyridine, 2-bromopyridine, 2-iodopyridine, 2-nitropyridine or (2-pyridyl)-trimethylammonium trifluoromethanesulfonate ; *T* : 120°C, 150°C or 180°C ; *t* : 5 to 20 minutes.

Microwave activation : The procedure described above was slightly modified and the 2 mL reaction vial was replaced by a Pyrex tube. This tube, not sealed, was placed in the microwave oven. Microwaves (power *W* and during a time *t*) were then applied to the system.

W : 50 to 200 Watt ; *t* : 1 to 4 minutes.

Ultrasonic activation : The procedure described above for the conventional heating was slightly modified and the 2 mL reaction vial was again replaced by a Pyrex tube. This tube, not sealed, was placed in the cavity of an ultrasonic wave generator. Ultrasonic waves (power *W* and during a time *t*) were then applied to the system.

W : 100 to 450 Watt ; *t* : 5 to 30 minutes.

In all cases, the reaction vial or the tube was then cooled using an ice/water bath and the remaining radioactivity was measured. 85% to 95% of the initial radioactivity placed in the vessel was still present. The resulting, often dark-coloured reaction mixture was then analyzed by radiochromatography.

The reaction yield was calculated from the TLC-radiochromatogram and defined as the radioactivity area of 2-[^{18}F]fluoropyridine over total fluorine-18 radioactivity area ratio (SiO_2-TLC, eluent : heptane/EtOAc : 60/40, Rf : 2-[^{18}F]fluoropyridine : 0.7 and Rf : [^{18}F]fluoride ion : 0.0).

Radiosynthesized 2-[^{18}F]fluoropyridine derivative co-migrated (SiO_2-TLC) and co-eluted (C18-HPLC) with an authentic sample of commercially available 2-fluoropyridine.

Conclusion

The scope of the nucleophilic aromatic substitution of 2-substituted pyridines with no-carrier-added [^{18}F]fluoride ion as its [^{18}F]FK-K_{222} activated complex, has been evaluated *via* the radiosynthesis of 2-[^{18}F]fluoropyridine, chosen as a model reaction. The parameters studied include the influence of the leaving group in the 2 position of the pyridine ring, the quantity of the precursor used, the type of activation (conventional heating, micro- & ultrasonic wave irradiations), the solvent, the temperature and the reaction time.

Acknowledgement

The authors wish to thank cyclotron operators Mr Daniel Gouel and Mr Christophe Peronne for performing the irradiations, as well as the Section Analyses Instrumentation Spectroscopiques (Mr Henri Virelizier) for recording the MS spectra.

References

1. Finger G.C., Starr L.D., Dickerson H.S., Gutowsky H.S. and Hamer J. - J. Org. Chem. 1666-1668 (1963).
2. Hamer J., Link W.J., Jurjevich A. and Vigo T.L. - Rec. Trav. Chim. 81: 1058-1060 (1962).
3. Bartoli G., Latrofa A., Naso F. and Todesco P.E. - J. Chem. Soc., Perkin Trans. I, 2671 (1972).

4. Haka M.S., Kilbourn M.R., Watkins L. and Toorongian S.A. - J. Label. Compds. Radiopharm. 27: 823-833 (1989).
5. Dollé F., Hinnen F., Vaufrey F., Tavitian B. and Crouzel C. - J. Label. Compds. Radiopharm. 39: 319-330 (1997).
6. Knust E.J., Machulla M.-J. and Molls M. - J. Label. Compds. Radiopharm. 19: 1643-1644 (1982).
7. Ballinger J., Bowen B.M., Firnau G., Garnett E.S. and Teare F.W. - Int. J. Appl. Radiat. Isot. 35: 1125-1128 (1984).
8. Horti A.G., Ravert H.T., London E.D. and Dannals R.F. - J. Label. Compds. Radiopharm. 28: 355-365 (1996).
9. Horti A.G., Scheffel U., Stathis M., Finley P., Ravert H.T., London E.D. and Dannals R.F. - J. Nucl. Med. 38: 1260-1265 (1997).
10. Villemagne V.L., Horti A.G., Scheffel U., Ravert H.T., Finley P., Clough D.J., London E.D., Wagner H.N. and Dannals R.F. - J. Nucl. Med. 38: 1737-1741 (1997).
11. Ding Y.S., Liang F., Fowler J.S., Kuhar M.J. and Carroll F.I. - J. Label. Compds. Radiopharm. 39: 828-832 (1997).
12. Ding Y.S., Gatley J., Fowler J.S., Volkow N.D., Aggarwal D., Logan J., Dewey S.L., Liang F., Carroll F.I. and Kuhar M.J. - Synapse 24: 403-407 (1996).
13. Liang F., Navarro H.A., Abraham P., Kotian P., Ding Y.S., Fowler J.S., Volkow N.D., Kuhar M.J. and Carroll F.I. - J. Med. Chem. 40: 2293-2295 (1997).
14. Horti A., Koren A.O., Ravert H.T., Musachio J.L., Mathews W.B., London E.D., Dannals R.F. - J. Label. Compounds Radiopharm. 41: 309-318 (1998).
15. Dollé F., Valette H., Bottlaender M., Hinnen F., Vaufrey F., Guenther I., Crouzel C. - J. Label. Compounds Radiopharm. 41: 451-463 (1998).
16. Hamacher K., Coenen H.H. and Stöcklin G. - J. Nucl. Med. 27: 235-238 (1986).
17. The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra, edition I (1993), C.J. Pouchert and J. Behnke, Aldrich Chemical Company, Inc, Milwaukee, Wisconsin USA 53201.
18. Wiley R.H. and Hartman J.L. - J. Am. Chem. Soc. 73: 494 (1951).

