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Research Article

Ortho-[^{18}F]Fluoronitrobenzenes by no-carrier-added nucleophilic aromatic substitution with K[^{18}F]F–K_{222}— A comparative study

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Summary

The scope of the nucleophilic aromatic *ortho*-fluorinations from the corresponding *ortho*-halonitrobenzene precursors (halo-to-fluoro substitutions) with no-carrier-added [^{18}F]fluoride ion as its activated K[^{18}F]F–K_{222} complex has been evaluated via the radiosynthesis of *ortho*-[^{18}F]fluoronitrobenzene, chosen as a model reaction. The parameters studied include the influence of the leaving group in the *ortho* position of the phenyl ring (–Cl, –Br, –I), the quantity of precursor used, the type of activation (conventional heating or microwave irradiations), the solvent, the temperature and the reaction time. The iodo-precursor was completely unreactive and the bromo-precursor gave only low incorporation ($<10\%$) in the optimal conditions used (conventional heating at 145°C or microwave activation, 100 W for 120 s). Only the chloro-precursor was found reactive in the conditions described above and up to 70% yield was observed for the formation of *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**). In all the experiments, the unwanted *ortho*-[^{18}F]fluoro-halobenzenes, potentially resulting from the nitro-to-fluoro substitution, could not be detected. These results will be applied for the radiosynthesis of 5-[^{18}F]fluoro-6-

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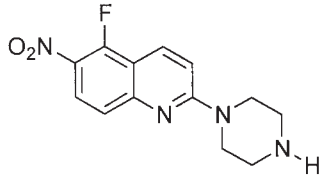
nitroquipazine, a potent radioligand for the imaging of the serotonin transporter with PET.

Key Words: fluorine-18; fluorobenzene; 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 high-specific-activity fluorine-18-(half-life: 110 min) labelled radioligands for positron emission tomography.[1] In the course of our PET programs, we were confronted with the challenging radiosynthesis of a suggested potent radioligand based on halogenated derivatives of 6-nitroquipazine[2–13] for the imaging of the serotonin transporter, namely 5-[^{18}F]fluoro-6-nitroquipazine.



This quipazine derivative possess in its chemical structure a fluorine atom *ortho* to a nitro group on a quinolinyl system. Fluoro-for-nitro aromatic substitutions are often used for the preparation of high-specific-activity fluorine-18-labelled radioligands and the nitro group has been characterized as an excellent leaving group in the nucleophilic aromatic fluorinations implicating no-carrier-added [^{18}F]fluoride ion. Due to the chemical structure of the target radiotracer, 5-fluoro-6-nitroquipazine, as well as to the limited choice of potential precursors for labelling with fluorine-18 which could be resumed as the 5-halo-6-nitro-derivatives (5-chloro, 5-bromo or 5-iodo), we were concerned about the feasability of this approach and especially, we feared the possible fluoro-for-nitro substitution leading to the unwanted 5-halo-6-fluoro-derivatives.

Since we were unable to find comparable examples of aromatic radio-fluorination in the literature, we decided to evaluate the scope of these nucleophilic aromatic fluorinations *ortho* to a nitro group with no-carrier-added [^{18}F]fluoride ion as its activated K[^{18}F]F–K_{222} complex[14] using a simple model for this reaction, the synthesis of *ortho*-

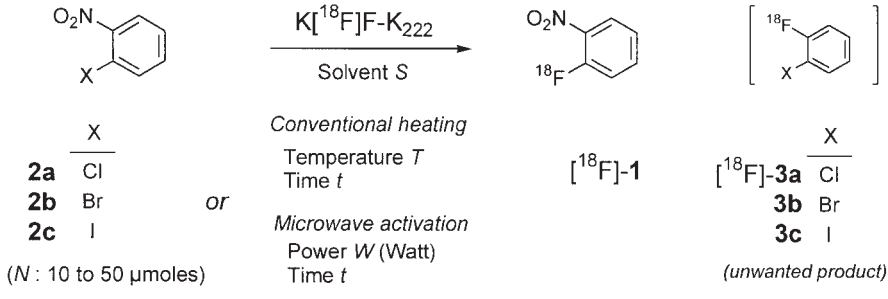
[^{18}F]fluoronitrobenzene ([^{18}F]-**1**) from the corresponding *ortho*-halonitrobenzenes (**2a–c**).

The synthesis of *para*-[^{18}F]fluoronitrobenzene has often been reported using aromatic nucleophilic substitution of various leaving groups, such as chlorine,[15–17] bromine,[15–17] nitro,[17] dimethylsulfonium[18] and trimethylammonium[19,20] whereas the synthesis of *meta*-[^{18}F]fluoronitrobenzene has only been reported using substitution of nitro[17] and trimethylammonium[19,20] groups. The synthesis of *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**) has been reported thrice. It was prepared from *ortho*-dinitrobenzene with Rb[^{18}F]F in DMSO at 150°C for 20 min in 58% radiochemical yield[15–16] and from *ortho*-nitrophenyldimethylsulfonium methylsulfate with *n*-Bu_4N[^{18}F]F in DMSO or acetonitrile at 100°C for 10 min in 34% and 57% radiochemical yield, respectively.[18] The synthesis of *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**) has never been evaluated from the corresponding *ortho*-halonitrobenzenes (**2a–c**) even though a few examples in the fluorine-19 chemistry have been reported (for a review, see ref. 21) for these substitutions.

In this paper, the parameters studied for these nucleophilic aromatic *ortho*-fluorinations include the influence of the halogen as the leaving group (–Cl, –Br, –I), the quantity of the precursor used, the type of activation (conventional heating, microwave irradiation), the solvent, the temperature and the reaction time.

Radiochemistry

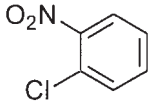
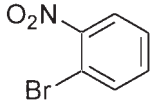
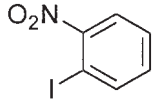
As illustrated in the following scheme, the nucleophilic aromatic fluorination of *ortho*-halonitrobenzene (**2a–c**) should give access to the desired *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**), but could as well lead to the unwanted *ortho*-[^{18}F]fluorohalobenzenes [^{18}F]-**3a–c**.



In a first set of experiments, the influence of the leaving group in the *ortho*-position of the phenyl ring was studied together with mass and reaction time using conventional heating. 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). A DMSO solution (600 μl) containing 10–50 μmol (2.0, 5.0 or 8.0 mg) of the precursor **2a–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. The reaction vial (not sealed) was then placed in a heating block for 1–30 min at 140°C without stirring.

As shown in Table 1, only the chloro-derivative (**2a**) was reactive under the conditions described above (conventional heating, 145°C). The yield of *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**) increased with the reaction time up to 3 min and then decreased. The incorporation yields also increased with the quantity of precursors engaged in the reaction and up to 48% of [^{18}F]-**1** could be observed with 8 mg of starting material. 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 *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**). Surprisingly, the

Table 1. Yields of *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-1) using conventional heating at 145°C: influence of the leaving group, reaction time and mass[†]

Substituent			Time of reaction (min)[‡]					
X		Mass (mg)	1′	3′	5′	10′	20′	30′
	**2a**	2.0	11	17	11	4	0	0
		5.0	29	46	39	33	19	13
		8.0	36	48	42	40	29	27
	**2b**	2.0	0	0	0	0	0	0
		5.0	3	0	0	0	0	0
		8.0	4	3	4	2	0	0
	**2c**	2.0	0	0	0	0	0	0
		5.0	0	0	0	0	0	0
		8.0	0	0	0	0	0	0

[†] Indicated yields are the average of three independent runs.
[‡] Conditions: K[^{18}F]F–K_{222} complex: 30–60 mCi (EOB, 1.11–2.22 GBq); solvent: DMSO (600 μl); heating block without stirring for 1–30 min at 145°C.

bromo-derivative was almost unreactive and only 4% of *ortho*-[^{18}F]fluoro-nitrobenzene ([^{18}F]-**1**) could be observed for 8 mg of starting material. The iodo-derivative was completely unreactive. In all experiments, the unwanted *ortho*-[^{18}F]fluoro-halobenzenes ([^{18}F]-**3a–c**) could not be detected.

When higher temperatures were used, comparable results were obtained: only the chloro-derivative was reactive. Under the conditions described above (180°C for example, data not shown in Table 1), up to 35% of *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**) could be observed for 8 mg of starting material after 5 min.

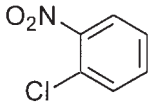
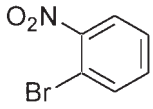
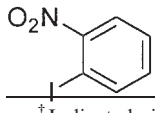
Results similar to those shown in Table 1 were obtained for all three precursors (**2a–c**) when the above protocol was modified. The K[^{18}F]F–K_{222} complex was first dissolved in 600 µl of DMSO and then added to a reaction vial containing 10–50 µmol (2.0, 5.0 or 8.0 mg) of the precursor **2a–c**. Finally, the reaction vial was tightly sealed and placed in a heating block for 1–30 min at 145°C without stirring.

In another set of experiments, the influence of the solvent was studied. The K[^{18}F]F–K_{222} complex was solubilized in 600 µl of various solvents and transferred to a reaction vial containing 8 mg of the chloro-derivative **2a**. The reaction vial was then tightly sealed and conventionally heated (heating block) for 10 min at 145°C. Incorporation yields were highest when DMSO or sulfolane were the solvents (35–40% 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 used as solvent were lower ($<15\%$). Almost no incorporation was observed in xylene.

In a last set of experiments, the influence of the leaving group, the mass and reaction time was also studied using microwave activation. A DMSO solution (600 µl) containing 10–50 µmol (2.0, 5.0 or 8.0 mg) of the precursor **2a–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. The reaction vial (not sealed) was then placed in a dedicated microwave oven and irradiated (100 W).

As shown in Table 2, the chloro-derivative (**2a**) was reactive under the conditions described above (microwave activation, 100 W). The yield of *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**) increased with the reaction time up to 120 s and then plataued for 60 s. When longer reaction times were applied, the yields decreased as observed for the conventional heating at 145°C (Table 1). As for the previous sets of experiments, the remaining

Table 2. Yields of *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-1) using microwave activation at 100 W: influence of the leaving group, reaction time and mass[†]

Substituent			Time of reaction (s)[‡]					
X		Mass (mg)	30	60	90	120	150	180
	**2a**	2.0	26	33	37	32	35	35
		5.0	19	37	48	47	54	51
		8.0	25	42	55	57	71	63
	**2b**	2.0	2	2	2	2	0	0
		5.0	2	2	2	2	1	1
		8.0	4	5	7	6	4	2
	**2c**	2.0	0	0	0	0	0	0
		5.0	0	0	0	0	0	0
		8.0	0	0	0	0	0	0

[†] Indicated yields are the average of three independent runs.
[‡] Conditions: K[^{18}F]F–K_{222} complex: 30–60 mCi (EOB, 1.11–2.22 GBq); solvent: DMSO (600 µl); microwave oven (100 W).

radioactivity at the end of the experiment was measured for each run and 85–95% of the initial radioactivity placed in the vessel was still present. The decrease in the radiochemical yield was therefore not attributed to volatiles but to decomposition of the formed *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**). The incorporation yields also increased with the quantity of precursors used in the reaction and up to 71% of [^{18}F]-**1** could be observed with 8 mg of starting material. The bromo-derivative was slightly more reactive than with conventional heating but no more than 10% yield could be observed for the *ortho*-[^{18}F]fluoronitrobenzene ([^{18}F]-**1**). The iodo-derivative was still completely unreactive. In all experiments, the unwanted *ortho*-[^{18}F]fluorohalobenzenes ([^{18}F]-**3a–c**) could not be detected.

Experimental section

General

Chemicals, TLCs and HPLCs. Chemicals (including 1-fluoro-2-nitrobenzene (**1**), 1-chloro-2-nitrobenzene (**2a**), 1-bromo-2-nitrobenzene (**2b**), 1-iodo-2-nitrobenzene (**2c**), 1-chloro-2-fluorobenzene (**3a**), 1-bromo-2-fluorobenzene (**3b**), 1-iodo-2-fluorobenzene (**3c**)) were purchased from

Aldrich, Fluka or Sigma France unless otherwise stated, and were used without further purification. TLCs were run on pre-coated plates of silica gel $60F_{254}$ (Merck). The compounds were localized (1) when possible at 254 nm using a UV-lamp and/or (2) by iodine staining and/or (3) by dipping the TLC-plates in a 1% ethanolic ninhydrin solution (or in a 1% aqueous $KMnO_4$ solution) and heating on a hot plate. Radioactive spots were detected using a Berthold TraceMaster 20 automatic TLC linear analyzer. HPLCs were run on Waters or Shimadzu systems. For example, Waters systems equipped with a 510 pump, 440 UV detector or 481 and 486 UV-multi-wavelength detectors; the effluent was also monitored for radioactivity with a Geiger–Müller counter; column: semipreparative C-18 Zorbax® SB, Hewlett-Packard (250×9.4 mm); porosity: 5 μm; temperature: RT; UV detection at λ: 254 nm; tem-perature: RT; UV detection at λ: 254 nm.

Isotope availability. No-carrier-added aqueous [^{18}F]fluoride ion was produced in a CGR-MeV 520 cyclotron by irradiation of a 2 ml water target using a 20 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 refs. 22 and 23.

Miscellaneous. Radiosyntheses using fluorine-18, including the semi-preparative HPLC purifications 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. 1-*Fluoro*-2-*nitrobenzene* (**1**): TLC: Rf (EtOAc/heptane: 30/70): 0.5. Rf (CH_2Cl_2/heptane: 50/50): 0.4. HPLC: Rt: 6.1 min (H_2O/CH_3CN: 50/50 (v:v); flow rate: 6.0 ml/min).

1-*Chloro*-2-*nitrobenzene* (**2a**): TLC: Rf (EtOAc/heptane: 30/70): 0.5. Rf (CH_2Cl_2/heptane: 50/50): 0.4. HPLC: Rt: 7.7 min (H_2O/CH_3CN: 50/50 (v:v); flow rate: 6.0 ml/min).

1-*Bromo*-2-*nitrobenzene* (**2b**): TLC: Rf (EtOAc/heptane: 30/70): 0.5. Rf (CH_2Cl_2/heptane: 50/50): 0.4. HPLC: Rt: 8.6 min (H_2O/CH_3CN: 50/50 (v:v); flow rate: 6.0 ml/min).

1-*Iodo*-2-*nitrobenzene* (**2c**): TLC: Rf (EtOAc/heptane: 30/70): 0.5. HPLC: Rf (CH_2Cl_2/heptane: 50/50): 0.4. Rt: 9.0 min (H_2O/CH_3CN: 50/50 (v:v); flow rate: 6.0 ml/min).

1-*Chloro*-2-*fluorobenzene* (**3a**): TLC: Rf (EtOAc/heptane: 30/70): 0.75. Rf (CH_2Cl_2/heptane: 50/50): 0.8.

1-*Bromo*-2-*fluorobenzene* (**3b**): TLC: Rf (EtOAc/heptane: 30/70): 0.75. Rf (CH_2Cl_2/heptane: 50/50): 0.8.

1-*Iodo*-2-*fluorobenzene* (**3c**): TLC: Rf (EtOAc/heptane: 30/70): 0.75. Rf (CH_2Cl_2/heptane: 50/50): 0.8.

Radiochemistry

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 was passed through an anion exchange resin (Sep-Pak® Light Waters Accell™ Plus QMA Cartridge. The cartridge with the trapped [^{18}F]fluoride ion was washed with aq $NaHCO_3$ (1 M, 5 ml) and then rinsed with 15 ml of H_2O). See refs. 22 and 23 for more practical details. 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® 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 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.

1-[^{18}F]Fluoro-2-nitrobenzene ([^{18}F]-1). 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 sealed with a Teflon cap and heated in a heating block without stirring at a temperature *T* and during a time *t*.

The reaction vessel was then cooled using an ice/water bath and the remaining radioactivity was measured. About 85–95% 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 1-[^{18}F]Fluoro-2-nitrobenzene ([^{18}F]-**1**) over total fluorine-18 radioactivity area ratio. An aliquot was injected onto HPLC: Radiosynthesized 1-[^{18}F]fluoro-2-nitrobenzene ([^{18}F]-**1**) co-eluted with an authentic sample of commercially available 1-fluoro-2-nitrobenzene (**1**).

General procedure using conventional heating or microwave activation in a non-sealed reactor: Six hundred microlitres of freshly distilled solvent containing *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 30–60 mCi (1.11–2.22 GBq, EOB, representing 6–12 nmol)). The tube (not sealed) was then placed in a heating block without stirring at a temperature *T* and during a time *t* or in a dedicated microwave oven and irradiated (power *W* during a time *t*). The remainder of the preparation used the same procedure as described above.

Conclusion

The scope of the nucleophilic aromatic *ortho*-fluorinations from the corresponding *ortho*-halonitrobenzene precursors (halo-to-fluoro substitutions) with no-carrier-added [^{18}F]fluoride ion as its activated K[^{18}F]F–K_{222} complex has been evaluated via the radiosynthesis of *ortho*-[^{18}F]fluoronitrobenzene, chosen as a model reaction. The parameters studied include the influence of the leaving group in the *ortho* position of the phenyl ring (−Cl, −Br, −I), the quantity of precursor used, the type of activation (conventional heating or microwave irradiations), the solvent, the temperature and the reaction time. The iodo-precursor was completely unreactive and the bromo-precursor gave only low incorporation ($<10\%$) in the optimal conditions used (conventional heating at 145°C or microwave activation, 100 W for 120 s). Only the chloro-precursor was found reactive under the

conditions described above and up to 70% yield was observed for the formation of *ortho*-[^{18}F]fluoronitrobenzene [^{18}F]-**1**). In all the experiments, the unwanted *ortho*-[^{18}F]fluoro-halobenzenes, potentially resulting from the nitro-to-fluoro substitution, could not be detected. These results will be applied to the radiosynthesis of 5-[^{18}F]fluoro-6-nitroquipazine, a potent radioligand for the imaging of the serotonin transporter with PET.

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