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Nucleophilic radiofluorination at room temperature via aziridinium intermediates.

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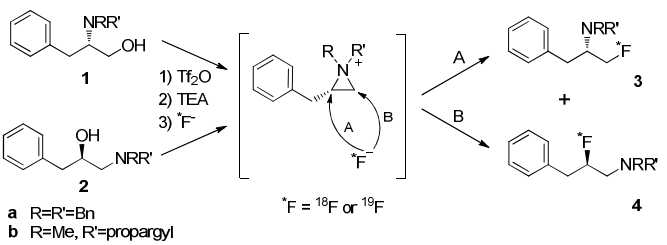
β-[^{18}F]fluoroamines were radiolabeled using anchimeric assistance of the amine. The ring opening of the aziridinium intermediate by different sources of nucleophilic fluoride at RT led to both fluorinated regioisomers with ^{18}F-incorporation yields up to 77% at RT. The radiofluorination 2-[^{18}F]fluoroethylamines afforded single compounds from the alcohol precursor at RT.

Positron emission tomography (PET) is a powerful *in vivo* imaging technique used for diagnostic and prognostic purposes, therapy monitoring and as a research tool in different clinical fields.[1] The distribution of radiopharmaceuticals labeled with fluorine-18 (half-life of 109.7 min) has allowed the considerable growth of the functional and molecular PET imaging in nuclear medicine departments. This extensive use of PET generates a demand for new radiofluorinated tracers and consequently new challenges for ^{18}F-radiochemistry leading to new methods and developments.[2]

Radiofluorinations usually occur by nucleophilic substitutions since [^{18}F]fluoride can be produced in large amounts compared to [^{18}F]F_2 and affords a high specific radioactivity.[3] For fluorine-18 incorporation, aliphatic nucleophilic substitutions are usually performed from sulfonates or halides as leaving groups.[4] In particular, [^{18}F]fluoroethylhalides or sulfonates have been extensively studied and used when the *O*- or *N*-2-[^{18}F]fluoroethyl moiety could not be directly labeled from the corresponding precursor.[5] This multistep approach requires the preparation of the ^{18}F-fluoroethylating agent including its eventual purification, followed by the alkylation reaction. Apart from 2-[^{18}F]fluoroethyl pattern, a few *β*-[^{18}F]fluoroamines have been labeled using the aziridine ring opening, albeit in low radiochemical yields.[6] More recent works obtained superior yields using aziridine activated by *N*-benzoyl, *N*-benzyloxycarbonyl[7] or *N*-phenylsulfonyl substituents.[8] The ring opening of aziridine leads to a secondary or primary amine and requires a high temperature for the radiofluorination to occur, with the exception of phenylsulfonamides, whereby a temperature of 50°C is sufficient to achieve the radiolabeling.[8a]

Recently we reported the radiofluorination of 3-fluoropiperidines starting from 3-mesylate-piperidines by a neighboring-group mechanism.[9] The retention of the *cis*-configuration when piperidine was *N*-substituted by an electron-donating group (benzyl or *n*-butyl) demonstrated the anchimeric assistance of the amine. In this case, this reaction gave higher [^{18}F]fluoride incorporation yields compared to a standard S_N2 mechanism.

Our recent findings prompted us to further study the possibility of using an aziridinium intermediate for the radiofluorination of *β*-fluoroamines. Aziridiniums have been used to generate aliphatic fluoroamines using (diethylamino)sulfur trifluoride (DAST) or Deoxo-Fluor™ (bis(2-methoxyethyl)aminosulfur trifluoride) as aziridinium generators and fluorinating reagents.[10] Tetrabutylammonium fluoride (TBAF) has been only used in a few cases as a fluorinating reagent for the ring opening of aziridiniums.[11] Based on these precedents we envisioned to develop a new labeling method of *β*-[^{18}F]fluoroamines through a S_N2 ring opening of aziridinium by [^{18}F]fluoride. Moreover, classically, this reaction occurred at RT permitting to performed radiofluorination at RT and affording milder reaction conditions towards fragile molecules when the classical S_N2 mechanism radiofluorination needs to be heated, with the exception of rare cases.[12] However, fluorine-18 radiolabeled DAST or Deoxo-Fluor were not used even if [^{18}F]DAST has been described.[13] Indeed, the preparation and use of those radiofluorinated reagents would necessitate additional steps and would lead to poor specific radioactivity due to the presence of several fluorine atoms within the reagent structure.



Scheme 1. Fluorination of **1** and **2** via aziridinium intermediate.

Table 1. Fluorination of **1** at RT.[a]

Entry	Precursor substrate	Reagent	Base	Fluoride source (eq.)[b]	Yield (%) **3**+**4**[c]	Ratio **3**/**4**[c]
1	**1a**	Ms_2O[d]	TEA	TBAF (1.1)	20	60:40
2	**1a**	Ms_2O	TEA	TBAF (1.1)	24	60:40
3	**1a**	Ms_2O[e]	TEA[f]	TBAF (1.1)	19	59:41
4	**1a**	Ms_2O[e]	TEA[f]	TBAF (2)	40	57:43
5	**1a**	Ms_2O[e]	TEA[f]	TBAF (4)	58	52:48
6	**1a**	Ms_2O	TEA	TBAF (2)	40	48:52
7	**1a**	Ms_2O	none	TBAF (2)	0.3	48:52
9	**1a**	Ms_2O	DIPEA	TBAF (2)	56	53:47
10	**1a**	XtalFluor-E	DIPEA	TBAF (2)	58	57:43
11	**1a**	Tf_2O	DIPEA	TBAF (2)	77	55:45
12	**1a**	Tf_2O	DIPEA	CsF[g]	79	56:44
13	**1a**	Tf_2O	DIPEA	KF/18C6[g]	81	57:43
14	**1a**	Tf_2O	DIPEA	$KF/K_{2.2.2}$[g]	53	60:40
15	**1a**	Tf_2O	DIPEA	TBAF (2)	71[h]	55:45
16	**2a**	Tf_2O	DIPEA	TBAF (2)	76[h]	52:48
17	**1b**	Tf_2O	DIPEA	TBAF (2)	69[h]	52:48

[a] Precursor (0.20 mmol), reagent (1.1 eq.) in CH_2Cl_2 (1.7 mL) for 1 h at RT, then base (1.2 eq.) for 1 min followed by reaction with fluoride for 2h at RT. [b] 1 M TBAF in THF. [c] Established by HPLC. [d] At -10°C. [e] 2 eq. [f] 3 eq. [g] In acetonitrile. [h] Isolated yield.

In this study we selected (*S*)-*N,N*-dibenzylphenylalaninol (**1a**) as a model compound to validate and optimize the reaction (Scheme 1). Halogenated precursors for aziridinium formation were not chosen to avoid separation difficulties between the halogenated reactant or byproducts and the ^{18}F-fluorinated product. We started from a stable alcohol precursor reacting with mesyl anhydride (Ms_2O) to generate the aziridinium *in situ* at RT.[14] As usual [^{18}F]fluoride source, TBAF was used as the nucleophilic reagent (Table 1). The reactions led to the formation of both fluorinated isomers **3a** and **4a** (Scheme 1) demonstrating that the reaction occurred via an aziridinium intermediate contrary to a direct S_N2 mechanism which would afford formation of only one product, the isomer **4a**.[10c-d] Our results showed that the yield is dependent on the amount of TBAF and not the quantity of Ms_2O used to generate the aziridinium (Table 1, entries 2-6). The evolution of the isomer ratio **3a**/**4a** (entries 2 and 6) demonstrated the influence of the fluorination kinetics confirming the kinetic control of the reaction.[10d] The addition of base was essential for the fluorination reaction which could be due to protonation of the *β*-sulfonate-amine intermediate, which prevents the compound from ring closing as previously suggested.[15] Diisopropylethylamine (DIPEA) gave the highest yield among the tested bases. For the generation of the leaving group, triflic anhydride (Tf_2O)[16] gave a higher yield (77%) than mesyl anhydride (56%). The use of XtalFluor-E® (diethylamino(difluoro)sulfanium tetrafluoroborate) allowed aziridinium formation as efficiently as when using mesyl anhydride (entries 9 and 10).[17]

In order to anticipate the radiolabeling with [^{18}F]fluoride, classical sources of [^{19}F]fluoride were studied.[3] TBAF, cesium fluoride, and potassium fluoride in presence of 18-crown-6 ether gave similar yields (entries 11-13) while KF/ $Kryptofix_{2.2.2}$ in acetonitrile afforded a lower yield (54%). In reactions resulting in the highest yields, the isomer ratios **3a**/**4a** were approximately 56:44, independent of the fluoride source used and quite different from ratios described using DAST (70:30)[10d] or Deoxo-Fluor (80:20).[10c,18] Using the same conditions, isomers **1a** and **2a** led to similar isolated yields with the same **3a**/**4a** ratios (entries 11 and 15) demonstrating the neighboring-group mechanism and the anchimeric assistance of the amine through aziridinium formation.

Table 2. Radiofluorination via aziridinium.[a‡]

Entry	Precursor substrate	[^{18}F]Fluoride source[b]	Reaction temperature	Yield (%) [^{18}F](**3**+**4**)[c]	Ratio [^{18}F](**3**/**4**)[d]
1	**1a**	**A** (15/18)	RT	58 ± 2	67:33
2	**1a**	**A** (15/18)	40°C	70 ± 9	64:34
3	**1a**	**A** (15/18)	90°C	83 ± 1	67:33
4	**1a**	**B** (6)	RT	31 ± 8	59:41
5	**1a**	**B** (23)	RT	56 ± 6	66:34
6	**1a**	**B** (23)	90°C	66 ± 5	65:35
7	**1a**	**B** (41)	RT	58 ± 6	65:35
8	**1a**	**C** (50/60)	40°C	44 ± 6	57:43
9	**1a**	**C** (50/60)	RT	45 ± 10	60:40
10	**1a**	**D** (14)	RT	4 ± 2	56:44
11	**2a**	**B** (23)	RT	40 ± 1	66:34
12	**1b**	**B** (23)	RT	26 ± 3	45:55
13	**2b**	**B** (23)	RT	40 ± 4	45:55

[a] n = 3. [b] Quantities in µmol (carbonate / cryptand): **A** = [^{18}F]$KF/K_{2.2.2}$, **B** = [^{18}F]TBAF, **C** = [^{18}F]KF/18-Crown-6, **D** = [^{18}F]CsF. [c] Incorporation yield established by radio-TLC. [d] Established by radio-HPLC.

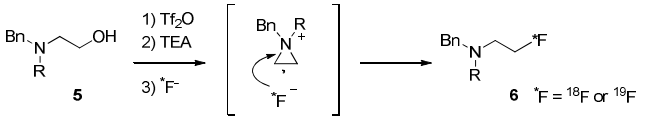
The optimal conditions for the preparation of the aziridinium intermediate were used for the ^{18}F-radiochemistry (Table 2). Comparing the different [^{18}F]fluoride sources used, [^{18}F]$KF/K_{2.2.2}$ and [^{18}F]TBAF gave similar ^{18}F-incorporation yields of around 57%, higher than those obtained from [^{18}F]KF/18-crown-6. [^{18}F]CsF afforded a weak yield differing from the result obtained for the [^{19}F]-fluorination. Heating the reaction led to an increase of the incorporation yield up to 83% at 90°C with [^{18}F]$KF/K_{2.2.2}$. However, heating did not change the incorporation yield when [^{18}F]KF/18-crown-6 was used. The radiofluorination reaction was performed starting from the isomeric precursor **2a** leading to the formation of the two radiofluorinated products [^{18}F]**3a** and [^{18}F]**4a** in same ratio as for isomer **1a** (entries 5 and 11).

N,N-Methylpropargylphenylalaninol (**1b**) and (*R*)-1-(*N,N*-methylpropargylamino)-3-phenylpropan-2-ol (**2b**) correspond to the precursors of [^{18}F]fluorodeprenyl [^{18}F]**3b**, a radiopharmaceutical used to image monoamine oxidase B

(MAO-B).[19] The [^{18}F]fluoride incorporation yields were 23% and 40% respectively, for the labeling of this radiotracer and the isomer ratio was inverted in favor of 1-[^{18}F]fluoropropyl isomer [^{18}F]**3b**. The preparation of [^{18}F]fluorodeprenyl was previously described by heating a mixture of the two chloride isomers in the presence of [^{18}F]fluoride and resulted in 50% incorporation yield.[20] However, the ^{18}F-isomer ratio was not specified. In this case, no evidence was provided of an aziridinium ring opening by [^{18}F]fluoride since the competitive S_N2 mechanism would occur at the temperature used for the reaction (120°C).

To extend our method to a larger number of radiopharmaceuticals, we applied it to the radiofluorination of 2-[^{18}F]fluoroethylamines (Table 3). In this case, the opening of the aziridinium ring led to a unique radiofluorinated product since the non-substituted aziridinium is symmetric. We applied the reaction conditions we defined for **1a**. The radiofluorination at RT afforded radiolabeled products in incorporation yields of 14-31% (Table 3). These incorporation yields had to be compared to a two-step radiosynthesis consisting in the preparation of a 2-[^{18}F]fluoroethylsulfonate or halide followed by a *N*-alkylation leading to the *N*-[^{18}F]fluoroethylamine product, frequently obtained within poor radiochemical yields.[5]

Table 3. Fluorination and radiofluorination via aziridinium.‡

Entry	Precursor	Products	Isolated yield (%)	RCY (%)[a,b]
				
1	**5a R=Bn**	**6a**	35	26 ± 5
2	**5b R=allyl**	**6b**	42	14 ± 3
3	**5c R=propargyl**	**6c**	52	31 ± 10

[a] n = 3. [b] Incorporation yield established by radio-TLC.

The radiosynthesis with high levels of radioactivity was performed on a commercially available GE TRACERLab® FX module. We were able to prepare more than 1 GBq of a mixture of [^{18}F]**3a** and [^{18}F]**4a** with a 70:30 ratio at RT within 70 min. The specific radioactivities of [^{18}F]**3a** and [^{18}F]**4a** were high (130-320 GBq/µmol at the of end of bombardment) and similar to usual fluorine-18 specific radioactivities obtained in our lab.[9]

In summary, we have developed a nucleophilic radiofluorination method at RT *via* the ring opening of an aziridinium intermediate. *β*-[^{18}F]Fluoroamines have been obtained at RT in one radioactive step by nucleophilic substitution from the corresponding *β*-aminoalcohol precursor. High specific radioactivity was obtained using a commercial radiosynthesis module. The one-pot ^{19}F-fluorination was also efficient with TBAF, leading to the two isomer products in ratios differing from the classical reaction using DAST or Deoxo-Fluor. The neighboring-group mechanism involving the aziridinium formation was demonstrated by obtaining the two possible isomers from both isomeric alcohols. The method allowed the radiolabeling of *N,N*-substituted-2-[^{18}F]fluoroethylamines in one radioactive step giving access to numerous radiopharmaceuticals in one step at RT. Ongoing work will investigate the application of this method to routine radiopharmaceuticals and further explore the limitations and scope of this new nucleophilic radiofluorination.

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Notes

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† Electronic Supplementary Information (ESI) available: Experimental details, ^{1}H, ^{13}C and ^{19}F NMR spectra and selected HPLC radiochromatograms. See DOI: 10.1039/c000000x/

‡ *Radiofluorination procedure:* Triflic anhydride (1 M in CH_2Cl_2, 37 µL), precursor **1** or **5** (33 µmol) in CH_2Cl_2 (260 µL) reacted 1 h at RT. DIPEA (40 µmol) in CH_3CN (200 µL) was added. After 1 min, the reaction mixture was transferred into the vial containing dry [^{18}F]fluoride (40 MBq) and tetrabutylammonium carbonate. The solution was stirred at RT for 30 min.

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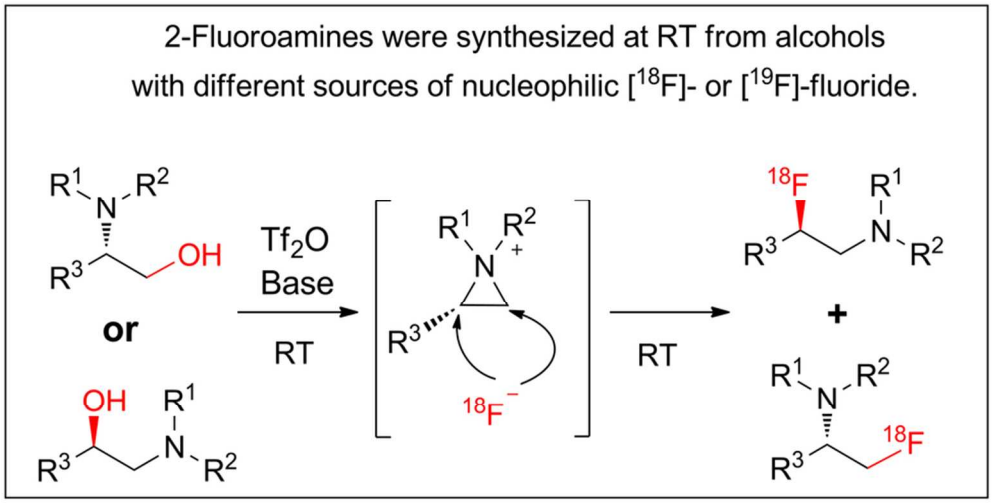

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