Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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View Article Online
DOI: 10.1039/C8OB00184G

Journal Name

ARTICLE

Stereospecific radiosynthesis of 3-fluoro amino acids: Access to enantiomerically pure radioligands for positron emission tomography

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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A variety of substituted non-racemic aziridine-2-carboxylates equivalent to amino acids were prepared and sbjected to ring opening reaction by [^{18}F/^{19}F]fluoride. The regio and stereospecific ring openig depends on the substituents on the nitrogen as well as both the carbons of aziridines. The applicability of the methods to afford access to 3-[^{18}F/^{19}F]fluoro amino acids are illustrated.

Introduction

Aziridines or 1-aza-cyclopropanes are the smallest N-containing heterocycles, analogue to oxiranes (1-oxa-cyclopropanes) and thiiranes (1-thia-cyclopropanes). The inherent strain of these narrow rings renders these functional groups vulnerable to opening in presence of nucleophiles. Hence, the aziridine is useful to make a variety of substituted amines[1,2,3]. We are particularly interested in the fluoroethyl amine motif, an important building block in synthetic chemistry to synthesize peptidomimetics and amino acids. Aliphatic amino acids labelled with fluorine-18 ($t_{1/2}$ = 110 min) are a promising class of positron emission tomography (PET) radiotracers for the use in neuroimaging. Besides abnormal tissue proliferation, derivatives of *N*-methyl-*D*-aspartate as well as *L*-Glutamate and its homologues have shown promise in assessing cellular stress in tissues due to reactive oxygen species, hypoxia and hypoglycaemia. Since 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG-PET) suffers from high retention in normal brain tissue in neuro-oncology, aminoacid-PET is becoming a powerful and versatile alternative owed to low uptake of amino acids in healthy brain tissue[4-7].

Compared to oxiranes and in particular thiiranes, aziridines lag behind in reactivity. In order to improve reactivity, the imine-nitrogen is ideally activated as a leaving group by acids or by conversion into an amide or carbamate. Consequently, anhydrous HF or Olah's HF was used to ring open aziridines in the past with recent reports using other acidic sources of fluoride (e.g. KHF_2 or NEt_3-HF complex)[8,9,10,11]. The *in situ* generation of HF-amines by combining hexafluoroisopropanol, benzoyl fluoride, Lewis base and DMPU-HF were also used to ring open activated aziridines[12,13].

The synthesis of fluorinated, aliphatic amino acids is complicated by stereochemical implications. Besides the chiral amino-acid functionality, introduction of an additional substituent creates a new stereocenter leading to four possible diastereomers as products. Due to the short half-life of fluorine-18, which is most available in the form of no-carrier added [^{18}F]fluoride ion, we sought a nucleophilic method that reliably produces one desired 2-amino-3-fluorocarboxylic acid stereoisomer in one synthetic step using activated complexes of fluoride ion. These considerations led us to investigate trans-aziridines as starting materials for producing the desired products. Due to the necessity for a carboxylic acid function on the amine-carbon configured to yield the L-amino acid motif, its influence on regioselectivity in the nucleophilic substitution must be mitigated. Electron attracting properties of carbonyl groups affect the electrophilicity of the adjacent carbon and thereby direct the nucleophile to that carbon. Steric bulk is not effective to direct the attack of small nucleophile such as fluoride. Therefore, to favour the 3-fluoro product at all, the rate constants for 3-fluorination must be increased. We surmised, that introducing allylic or benzylic functionalities at the C-3 position of aziridine-2-carboxylates leads to favorable distribution of electrophilicity centered on position-3. E.g. the relative reaction rate of substitution at allylic carbons is 8.1 times higher compared to that of an aliphatic 2° carbon (isopropyl)[14,15].

With respect to stereochemistry, the aziridine allows for two distinguished ring opening mechanisms based on nucleophilic substitution - S_N1, S_N2 – with opposite outcomes. Aziridines reacted with catalytic amounts of Lewis acid for amine coordination prior to ring opening (mostly S_N1 mechanism). Whereas the aziridines containing an activating group generally undergo ring opening in presence of nucleophiles (mostly S_N2 mechanism).

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†Electronic Supplementary Information (ESI) available: Organic, radiosynthesis experimental details, tables, Spectra. See DOI: 10.1039/x0xx00000x

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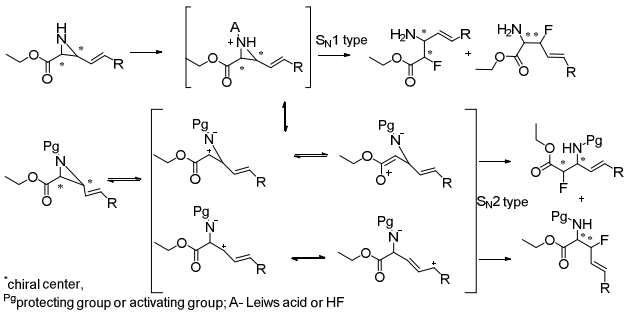


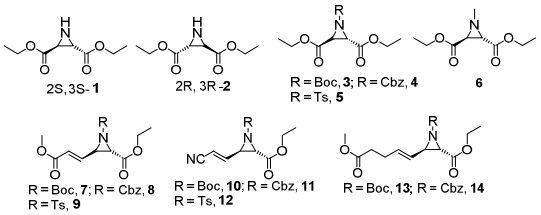
Scheme 1 Schematic of S_N1, S_N2 and regioselectivity of aziridine-2-carboxylates ring opening by fluoride ion

With respect to stereochemistry, the S_N1 mechanism tends to fail retention of the configuration giving the racemic products. The S_N2 mechanism inverts the configuration at the reaction center and gives the non-racemic product. Scheme 1 shows the possible substitution and the regioselectivity in ring opening of aziridine-2-carboxyaltes by fluoride.

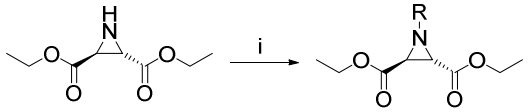
Based on these criteria, symmetric and non-symmetric *trans* aziridine-2-carboxylates with *N*-protecting groups, and *N*-methyl aziridines were synthesized to establish feasibility of obtaining only one stereoisomer as reaction product from activated fluoride ion as follows.

Results and Discussion*:*

Organic chemistry: The non-racemic starting materials **1** and **2** were prepared from the chiral pool using reported methods starting from (R,R) and (S,S) diethyl tartrate[16]. All other molecules were built-up by modifying these starting aziridines. Scheme 2 shows the one set of enantiomers of different synthesized aziridines. At first, protecting groups were introduced to **1** as shown in scheme 3 to synthesize **3, 4** and **5.** Contrary to formation of sulfonamides and carbamates, methylation of the nitrogen was not straightforward. As a result we screened the approaches surveyed in table 1 for appropriate conditions. Even the most reactive methylating reagents (MeOTs, MeOMs MeONs) did not give products in presence of weak to moderate bases. We surmised that the failed reactions might be due to the weakly basic and non-nucleophilic nature of the aziridine nitrogen. For this reason, we investigated strong bases including *n*-BuLi and KHMDS to achieve complete deprotonation of amine in presence of a



Scheme 2 Various synthesized aziridine substrates

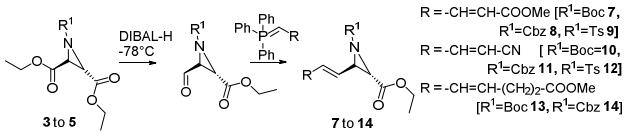


Scheme 3: Synthesis of **3, 4** and **5**. *Reagents and conditions*- i. R = Boc **3**, $(Boc)_2O$, DMAP, THF, rt, 2 d, 56%; R = Cbz **4**, Cbz-Cl, DIPEA, THF, 0°C-rt, 24 h, 97%; R = Ts **5**, $(Ts)_2O$, Pyridine, DMAP, DCM, rt, 2 days, 42%

methylating reagent (Table 1). Pleasingly, the base KHMDS for the respective methylation gave the desired compounds in good yields (Table 1, entry 15).

The substrates **7** to **14** were made via selective reduction of one ethyl ester of diacids **3, 4, 5** to their aldehyde derivatives followed by the subsequent olefination with the corresponding Wittig reagents (Scheme 4). For the synthesis of **13** and **14**, the corresponding Wittig reagent was made using KHMDS base and [3-(Methoxycarbonyl)propyl]triphenyl-phosphoniumbromide *in situ* prior to the addition of corresponding aldehyde. The major products in all the Wittig reactions are *E* isomers except with the –tosyl aziridine **12** where approximately equal amounts of *E* and *Z* isomers were obtained. Two sets of enantiomers were made for the aziridine precursors in order to obtain *D* and *L* forms of fluorinated compounds. Aziridines **1** to **5** to give 3-fluoro aspartic acid equivalents, **6** is the fluorinated N-methyl aspartic acid equivalent, **7** to **9** lead to 2-amino-3-fluoro adipic acids, **10** to **12** 3-fluoro lysine equivalents and **13, 14** to give 2-amino-3-fluoro-suberic acid equivalents. It was noticed that the ring opening mechanism occurred via S_N2 pathway as the NMR analysis shown a single isomer, therefore *anti* configuration was assigned to fluorinated products.

Aziridines **1** to **4** were chosen as model substrates to ring open by fluoride ion. Several fluorinating agents were screened to ring open **1** or **3** or **4**. Table 2 shows the various reaction conditions and fluorinating sources used. None of the fluorinating agents, except entries 13-14, gave the desired fluorinated products. Metal fluorides and tetrabutyl ammonium fluorides (TBAF) gave trace amounts of products (^{19}F NMR). While rather low yields were obtained we attributed the limitation to concurrent side reactions. Observed side products originating from elimination are the main culprit. The HF reagents such as DMPU-HF (65% HF), and Olah's Pyridine-HF (70% HF) gave the fluorinated intermediates in isolable yield. Another HF reagent $Et_3N.3HF$ did not give any fluorinated product.



Scheme 4: Synthesis of alkenyl aziridines **7** to **14**

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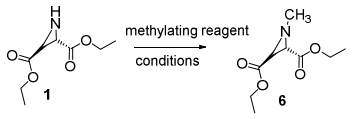
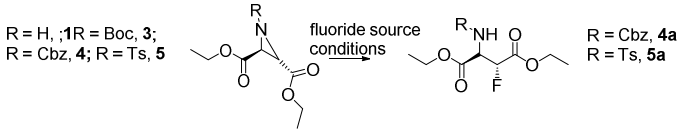
Table 1 *N*-methylation reaction optimization of **1**[a]



Entry	Base	Methyl source	Solvent	Temp (°C)	Time	Isolated Yield (%)
1	NaH	CH_3I	THF or DMF	0-rt	16 h	0
2	K_2CO_3	Methyl nosylate	CH_3CN or DMF	rt	24 h	0
3	DBU	Methyl nosylate	THF or DMF	rt	24 h	0
4	-	37% HCHO, Pd/C, H_2	EtOH	rt	12 h	0
5	DIPEA	Methyl nosylate	THF	rt-50	50 h	0
6	K_2CO_3	Methyl tosylate	DMF	rt	26 h	0
7	DIPEA	Methyl tosylate	THF	rt	24 h	0
8	Proton sponge	Methyl mesylate	THF or CH_3CN	rt	30 h	0
9	$NaHCO_3$	Methyl mesylate	DMF or CH_3CN	rt	90 h	0
10	$NaHCO_3$	Methyl mesylate	EtOH	rt	120 h	5
11	-	37% HCHO, $(CH_3COO)_3BHNa$	DCE	rt	25 h	0
12	$NaHCO_3$	Methyl tosylate	EtOH	rt	95 h	7
13	NaH	Methyl tosylate	DMF	0-rt	14 h	4
14	n-BuLi	CH_3I	THF	-78-rt	4 h	15
15	KHMDS	Methyl tosylate	THF	0 – rt	7 h	40
	KHMDS	Methyl mesylate	THF	0 – rt	14 h	5
	KHMDS	CH_3I	THF	0 – rt	14 h	11

[a]Reactions were performed with 1 (0.4 mmol), methyl source (0.4 to 0.8 mmol), solvent (2.5 mL) *n*≥2; DBU 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA *N*-ethyl-*N,N*-diisopropylamine, KHMDS potassium bis(trimethylsilyl)amide, THF tetrahydrofuran, DCE 1,2-dichloroethane, DMF *N,N*-dimethylformamide

Table 2 Screening of fluoride sources to ring open **1, 3, 4**[a]



Entry	Aziridine	Fluoride source	Solvent	Temperature(°C)	Time	Yield (%)
1	1	$Et_3N.3HF$	CH_3CN or DCE	rt-50	48 h	-
2		TBAF $(tBuOH)_4$[b]	DMSO or CH_3CN	rt-80	6 h	-
3		Olah's HF	DCE	rt	24 h	-
4		DMPU-HF	DCE	rt	24 h	-
5	3	TBAF $(tBuOH)_4$	CH_3CN	rt - 80	6 h	-
6		[KF][K_{222}]	CH_3CN or DMSO	rt - 80	16 h	Trace
7		[KF][18-C-6]	CH_3CN	rt - 50	84 h	-
8		TBAF[c]	CH_3CN or THF	rt - 50	26 h	Trace
9		[CsF]	DMSO	rt - 80	16 h	-
10	4	[KF][K_{222}]	DMSO or CH_3CN	rt - 80	24 h	-
11		TBAF $(tBuOH)_4$	CH_3CN	rt - 80	6 h	-
12		$Et_3N.3HF$	DCE	rt	60 h	-
13[d]		Olah's HF	DCE	0 - rt	48 h	16
14[d]		DMPU-HF	DCE	0 - rt	48 h	24
		DMPU-HF	TBME	0 – rt	48 h	6
		DMPU-HF	DCM	0 – rt	48 h	13
		DMPU-HF	THF	0 – rt	48 h	5
15[e]	5	TBAF (*t*BuOH)$_4$	CH_3CN	50	30 min	31

[a]Aziridine (0.3 mmol), Fluoride (0.3 to 3.0 mmol), solvent (2 mL); HF reactions in 6 mL PE vial; *n*≥2; [b]for preparation see reference[17]; [c]1 M in THF; [d]isolated yield, [e]see radio chemsitry section; DCM 1,1-dichloromethane, DCE 1,2-dichloroethane, DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone, 18-crown-6- 1,4,7,10,13,16-hexacyclopctadecane, K_{222}crypt-222

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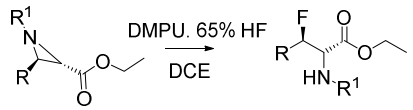
Table 3 Ring opening of various aziridines by DMPU-HF[a]



Entry	Substrate	R^1	R	Temperature	Time	Product	Isolated yield %[b]
1[c]	**4**	-Cbz	-COOEt	0°C-rt	48 h	**4a**	24
2[d]	**6**	$-CH_3$	-COOEt	rt-50°C	7 d	**6a**	6
3	**7**	-Boc	-CH=CH-COOMe	0°C	30 min	**7a**	32
4	**8**	-Cbz	-CH=CH-COOMe	0°C	1 h	**8a**	43
5	**9**	-Ts	-CH=CH-COOMe	0°C - rt	1 h	**9a**	48
6	**10**	-Boc	-CH=CH-CN	0°C	30 min	**10a**	21
7	**11**	-Cbz	-CH=CH-CN	0°C	1 h	**11a**	45
8	**12**	-Ts	-CH=CH-CN	0°C - rt	1 h	**12a**	37
9[e]	**13** or **14**	-Boc or -Cbz	$-CH=CH-CH_2-CH_2-COOMe$	-78°C (DCM) 0°C-rt	1 h 2-10 h	- -	0

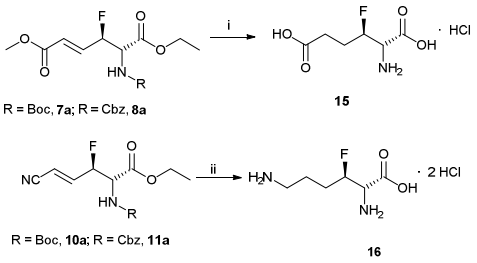
[a]Reactions were performed with Aziridine (0.3 mmol), DMPU-65%HF (1.2 mmol), DCE (1 mL), in 6 mL PE vial; $n \geq 2$; [b]similar yields were obtained with another set of starting aziridines; [c]3 mmol 65%HF; [d]4.5 mmol Olah's-70%HF; [e]only side products also with Olah's-HF, Et_3N-HF

Given the ease of making the reference compounds, HF reagents was used for synthesis of reference materials. However, with fluorine-18 ($t_{1/2}$ 110 min) this is not an option because of the problems associated with [^{18}F]HF reagent(s) preparation and stoichiometry[18,19]. Table 3 shows the ring opening of the mentioned aziridine substrates with DMPU-65% HF except the entry 2, in which Olah's 70% HF was used. Since the absence of activating group on nitrogen of **6** and the weak acidic nature of HF complexes to protonate these amines, the fluorinated products were obtained in very low yield (Table 3, entry 2). Lewis acids such as yttrium triflate or copper triflate were used to coordinate the amine prior to ring opening by fluoride. Most of the starting material was consumed in presence of catalytic amounts of these acids but the products obtained are complex fluorinated side products. The high reactivity towards ring opening of aziridine substrates **7** to **12** arise from the adjacent allylic group and also the nitrogen activating groups (Table 3, entries 3-8). Partial hydrolysis of the protective groups was noticed under the acidic reaction conditions in all the cases accounting to the moderate yields.

The fluorinated intermediates **7a, 8a** and **10a, 11a** were further modified to synthesize 2-amino-3-fluoro adipic acid **15** and 3-fluoro lysine **16** respectively. Scheme 5 shows the reaction steps to prepare **15, 16**.

At this point, the remaining challenge was to find a non-acidic fluoride complex as used in radiochemistry to achieve the desired fluorination reaction. We suspected that our fluoride complexes contains too much moisture under stoichiometric conditions[20] and prepared TBAF(tBuOH)$_4$. This effort was rewarded ring opened products when sulfonamides were used, though none of the other starting materials reacted. This allowed for analysis of the stereochemical product distribution under radiochemical conditions.

With respect to the expected products, aziridines **1** to **6** are symmetric in nature and therefore the regioselectivity discussion can be ignored. Non-symmetric aziridines **7** to **12** are prone to ring open at C_3 because the adjacent allylic group



Scheme 5: Synthesis of **15** and **16.** *Reagent and conditions* i. a) Pd/C, H_2, EtOH, $CHCl_3$, 40 min, b) 4M HCl (aq), reflux, 20 h, **15** (81%) ii. a) Pt/Al_2O_3, H_2, EtOH, few drops conc.HCl, 1 h, b) 4M HCl (aq), reflux, 16 h, **16** (36%)

which we believe stabilizes the S_N2 transition state and increases the rate constant. It was noticed that an electron withdrawing group conjugated to olefin is necessary to obtain the desired fluorinated products. Indeed, aziridines **13**-**14**, which were expected to give 2-amino-3-fluoro suberic acid, did not lead to fluorination. Instead, -OH group substitution was noticed giving the diastereomeric products.[SI] With confirmation of the stereoselective outcome as a motivation we began translation of the chemistry into a radiolabeling protocol.

Radiochemistry: Very few publications are known for the chemistry with aziridines and [^{18}F]fluoride ion and have described the aziridine ring opening by [^{18}F]fluoride to obtain biologically important motifs[18,19,21-23]. All synthesized aziridine precursors in this work were subjected to ring opening by various [^{18}F]fluoride ion systems. Similar disappointing results, as with non-radioactive fluoride, were noticed with [^{18}F]fluoride. Initially, aziridines **3** and **4** were reacted with potassium-crypt-222 cryptate [^{18}F]fluoride ion complex in

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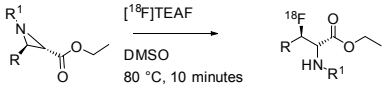
various solvents and temperatures with conventional heating (SI, T1). Some ^{18}F incorporation was noticed in most of the labeling reactions, but the labelled products were not the desired ones[26]. The same substrates were then reacted with other combinations of fluorine-18, phase transfer catalyst and bases such as tetraethyl ammonium bicarbonate ($TEAHCO_3^-$), tetrabutyl ammonium hydroxide (TBAOH), cesium carbonate (Cs_2CO_3), crypt-222-potassium oxalate ($K_2C_2O_4$), and 18-C-6/$KHCO_3$. Changing the [^{18}F]fluoride systems had no impact on the result. Other aziridines **6**, **7**, **8**, **10** and **11** were also reacted with above [^{18}F] fluoride systems (SI, T2). The failed radioactive experiments are in line with the non-radioactive experiments (Table 2). Attempts to ring open with pyridine. [^{18}F]HF[24] and DMAP.[^{18}F]HF[25] were unsuccessful as expected.

Table 4 shows several of the attempted conditions and the [^{18}F]labelled products. With respect to the results, we felt that harder complex cations performed worse than softer alternatives such as TEA and TBA**.** Only the –tosyl activated aziridines were labelled as expected giving the desired [^{18}F] intermediate products (Table 4, entries 3, 7, 10). Having noticed the formation of desired [^{18}F]intermediates with tosyl aziridines, labeling conditions were further optimized. The fluoride systems [^{18}F]KF(crypt-222), [^{18}F]TEAF, [^{18}F]TBAF in different solvents and temperatures were used to ring open the tosyl aziridines. All of them gave the desired fluorine-18 labelled intermediates and also tosyl [^{18}F]fluoride ([^{18}F]TsF) as a minor product (SI, T3 for optimization conditions).

Table 4 [a][^{18}F]incorporated yields based on radio TLC (n≥10)



Entry	Aziridine	R^1	Product	Conversion (±5%)[b]
1	**3**	-Boc	[^{18}F]**3a**	-
2	**4**	-Cbz	[^{18}F]**4a**	-
3	**5**	-Ts	[^{18}F]**5a**	70
4	**6**	-CH_3	[^{18}F]**6a**	-
5	**7**	-Boc	[^{18}F]**7a**	-
6	**8**	-Cbz	[^{18}F]**8a**	-
7	**9**	-Ts	[^{18}F]**9a**	19
8	**10**	-Boc	[^{18}F]**10a**	-
9	**11**	-Cbz	[^{18}F]**11a**	-
10	**12**	-Ts	[^{18}F]**12a**	24

[a]Labelings were performed with [^{18}F] (0.2 to 1.1 GBq), aziridine (10 µmol), $TEAHCO_3^-$ (10 µmol), DMSO (0.3 mL); [b]50% Ethyl acetate in hexanes and the yields were related to the total radioactivity

Table 5: [a]Radiochemical yields of [^{18}F]intermediates and tosyl [^{18}F]fluoride (n≥4)

Entry	Aziridine	Product	Yield (±4%)	[^{18}F]TsF (±2%)
1	**5**	[^{18}F]**5a**	57	3
2	**9**	[^{18}F]**9a**	9	3
3	**12**	[^{18}F]**12a**	16	5

[a]Labelings were performed with [^{18}F] (0.3 to 1 GBq), aziridine (10 µmol), $TEAHCO_3^-$ (10 µmol), DMSO (0.3 mL); 50°C, 10 minutes; Decay corrected yields based on the starting radioactivity

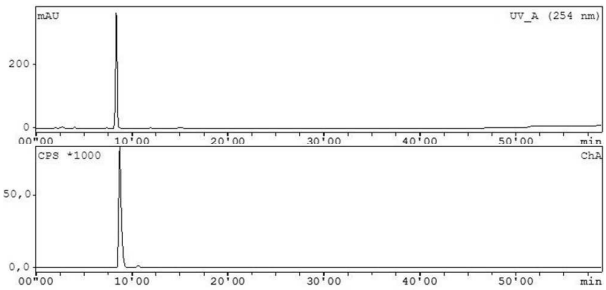


Figure 1 Radio-HPLC, UV traces of [^{18}F]**5a** (below), [^{19}F]**5a** (top); Supelco supelcosil ABZ plus C_{18}, 5 µm, 250 x 4.6 mm, CH_3CN:H_2O (50:50), 1 mL/min

The desired [^{18}F]products and tosyl [^{18}F]fluoride were separated from free fluorine-18 using C_{18} and silica cartridges. Table 5 shows the decay corrected radiochemical yields of (synthesis time of 35-40 minutes from end of bombardment (EOB)) [^{18}F]products and tosyl [^{18}F]fluoride. The radiolabelled products were identified by co-elution with the authentic samples. HPLC analyses of [^{18}F]**9a** and [^{18}F]**12a** have also shown an additional radioactive signal co-eluting with the desired radioactive products not visible by TLC. We presumed this additional radioactive peak belongs to the C_2 ring opened product. As mentioned before, a similar soluble and anhydrous [^{19}F]TBAF(*t*BuOH)$_4$ was used to ring open tosyl aziridines. The [^{19}F]fluoride ring opened products with this source are in line with the [^{18}F]fluoride ring opened products. Figure 1 shows the radio-HPLC, UV traces of [^{18}F/^{19}F]**5a**

Conclusions

In conclusion, we have prepared enantiomerically pure acid and base sensitive aziridines equivalent to various amino acid precursors and subjected to ring opening with [^{18}F/^{19}F]fluoride ions. The -tosyl aziridines were found superior compared to –Boc or –Cbz aziridines towards ring opening by non-acidic [^{18}F/^{19}F]fluoride sources. Non-activated *N*-methyl aziridines led to dissatisfactory results. We are convinced that the presented results bode well for production of novel amino acid radiotracers.

Conflicts of interest

There are no conflicts to declare.

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DOI: 10.1039/C8OB00184G

Acknowledgements

Financial support from the faculty of Mathematics and Natural Sciences (realomics SRI), University of Oslo is gratefully acknowledged.

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26 The unknown ^{18}F-labelled products were assumed as some hydrolyzed products resulting from the basic labeling reaction conditions. To confirm this, the unknown ^{18}F-labelled products were isolated from free fluorine-18 using C_{18} cartridges and subjected to acidic hydrolysis or hydrogenation followed by hydrolysis reactions. These reactions followed by work-up resulted in complete loss of activity, whereas the reaction mixture gave mainly the baseline species in radio-HPLC and radio-TLC (normal phase, reverse phase TLCs) with the amino-acid standard mobile phase systems.

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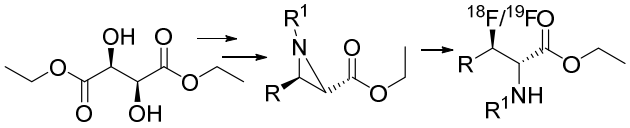
DOI: 10.1039/C8OB00184G



R = amino acid side chain

R^1 = protecting/activating groups