Tetrahedron Letters 50 (2009) 544–547

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

[^{18}F]Fluoroamines via ring-opening of *N*-Cbz-2-methylaziridine with [^{18}F]-fluoride

Neil Vasdev [a,b,*], Erik M. van Oosten [a,c], Karin A. Stephenson [a,b], Nonik Zadikian [a,c], Andrei K. Yudin [c], Alan J. Lough [c], Sylvain Houle [a,b], Alan A. Wilson [a,b]

[a] Centre for Addiction and Mental Health, 250 College St., Toronto, Ontario, Canada M5T 1R8
[b] Department of Psychiatry, University of Toronto, 250 College St., Toronto, Ontario, Canada M5T 1R8
[c] Department of Chemistry, University of Toronto, 80 St. George St., Toronto, Ontario, Canada M5S 3H6

ARTICLE INFO

Article history:
Received 16 October 2008
Revised 14 November 2008
Accepted 18 November 2008
Available online 24 November 2008

Dedicated to Professor Raman Chirakal on the occasion of his retirement

Keywords:
Aziridine
Fluorine-18
Ring-opening
Fluoroisopropylamine
PET
1-Fluoro-2-propanamine
2-Fluoro-1-propanamine

ABSTRACT

A highly regioselective method was developed for ring-opening benzyloxycarbonyl (Cbz)-protected 2-methylaziridine with [^{18}F]-labelled fluoride. Following catalytic hydrogenation, 1-[^{18}F]fluoro-2-propanamine ([^{18}F]**1**) and 2-[^{18}F]fluoro-1-\propanamine ([^{18}F]**2**) were prepared as the major and minor products, respectively (85:15), and were characterized following acylation with benzyl chloride. This methodology is applicable towards the generation of new [^{18}F]-labelled amines for incorporation into radiopharmaceuticals.

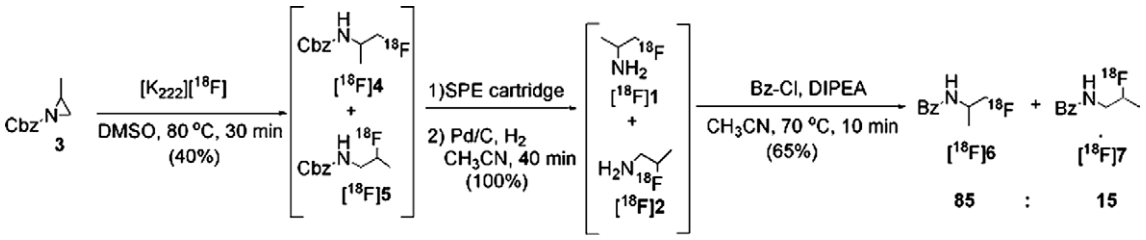
1. Introduction

Positron emission tomography (PET) has proven to be a powerful medical imaging technique for probing biological targets and processes in living subjects. The discovery of positron-emitting radiopharmaceuticals is critically dependent on new synthetic methodologies to introduce radionuclides into organic compounds.[1] No-carrier-added fluorine-18 ([^{18}F], $t_{½}$ = 109.7 min)-labelled fluoride ion is the most commonly used reagent for the preparation of high specific activity [^{18}F]-labelled radiopharmaceuticals.[2] The goal of this work was to devise a method for the facile radiosynthesis of [^{18}F]-1-fluoro-2-propanamine ([^{18}F]-fluoroisopropylamine, [^{18}F]**1**). This was an attractive target for us because we and others have been pursuing the radiosynthesis of [^{18}F]-labelled β-blockers for PET imaging of β-adrenergic receptors in the heart and central nervous system, most of which contain the isopropylamine moeity.[3,4] Reported methods to incorporate ^{18}F into the *N*-isopropyl sidechain of β-blockers are time consuming, relatively low yielding, difficult to automate and involve multiple steps, as the intermediate fluorinating agents, [^{18}F]-fluoroisopropyl tosylate[5] or [^{18}F]fluoroacetone[6], are reacted with des-fluoroisopropyl precursors. We recently reported an efficient synthesis of β-blockers, by incorporating a tosyloxy leaving group at the *N*-isopropyl moiety for rapid displacement with [^{18}F]-fluoride ion.[7,8] Nonetheless, [^{18}F]**1** represents a key intermediate which could be useful in the general radiosyntheses of β-blockers. The small versatile nucleophilic synthon [^{18}F]**1** would also complement the electrophilic [^{18}F]-labelled synthons commonly employed in PET radiochemistry such as [^{18}F]-fluoroalkyl halides,[9] and could be used to prepare focused libraries of [^{18}F]-labelled compounds and radiopharmaceuticals.

Compound **1** has been successfully prepared via fluorination of cyclic sulfamidates,[10] deoxyfluorination of amino alcohols,[11] chiral sulfoxide chemistry[12] or as a minor product after ring-opening an unprotected aziridine with Olah's reagent.[13] These methodologies, however, are not readily amenable for radiolabelling with fluorine-18. Exploitation of aziridine chemistry seemed a plausible route to [^{18}F]**1** as nucleophilic ring-opening of aziridines is well documented.[14] However, in contrast to other halide nucleophilic additions to aziridines, there have been relatively few reports describing the ring-opening of aziridines with nucleophilic sources

* Corresponding author. Tel.: +1 416 535 8501x4680; fax: +1 416 979 4656.
E-mail address: neil.vasdev@camhpet.ca (N. Vasdev).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.11.074



Scheme 1. Preparation of [^{18}F]**1** and [^{18}F]**2** identified after in situ acylation (% conversion shown in parentheses).

of fluoride.[15] Examples of [^{18}F]-fluoride ion to ring-open azirdines[16–18] or azetidinium salts[19] are even more sparse. We report the ring-opening of benzyloxycarbonyl (Cbz)-protected 2-methylaziridine (**3**) with [^{18}F]-fluoride to prepare the synthetically versatile amine, [^{18}F]**1,** as the major regioisomer.

2. Results and discussion

A balance of electronic and steric properties controls the regioselectivity of aziridine ring-opening reactions. It was the goal of the present work to regioselectively ring-open an N-activated 2-methylaziridine with [^{18}F]-fluoride ion to preferentially prepare labelled fluoroamine [^{18}F]**1**. Since attack at this unsymmetrical aziridine can occur at either the secondary or tertiary carbon of 2-methyl-azridine,[20] we planned to control the regioselectivity and efficiency of the nucleophilic ring-opening by the choice of solvent and by modifying the substituent on nitrogen.[21,22] Previous work has demonstrated that 2-methylaziridine and its derivatives can be fluorinated under acidic conditions.[13] However, attack at the 3° carbon resulted in 2-fluoro-propanamine (**2**) and its derivatives as the dominant regioisomers. The Cbz-protecting group was chosen to protect 2-methylaziridine for this ^{18}F-labelling, as it can be rapidly removed under non-acidic conditions, is stable under the basic conditions condusive to nucleophilic attack by [^{18}F]-fluoride and has a chromophore which allows convenient monitoring of reaction progress by HPLC/UV.

As ring-opening of **3**, followed by deprotection, should generate the volatile fluoroamines [^{18}F]**1** and [^{18}F]**2**, unlabelled acylated compounds **6** and **7** were prepared and used as HPLC standards to identify the products and intermediates. 2-Methylaziridine was reacted with Cbz-chloride (to prepare compound **3**) or benzoyl (Bz) chloride, under Schotten-Baumann conditions using triethylamine as the base, to yield protected aziridines in good yields (⩾80%). Compound **6** was also prepared by Schotten–Baumann benzoylation of **1**·HCOOH, using *N,N*-diisopropylethylamine as the base. The latter compound was prepared by reductive alkylation of benzylamine with fluoroacetone and sodium cyanoborohydride as the selective reducing agent[23] (79%), followed by a sluggish catalytic hydrogenation (70%, 3 days).[10] Compound **7** was prepared by reaction of benzoyl-protected 2-methylaziridine with anhydrous HF as previously described,[13] with modified apparatus[24] at 4 °C for 10 min (53%).

Ring-opening of **3** with potassium cryptand, [^{18}F]-fluoride ([K_{222}][^{18}F]), followed by deprotection was successfully achieved to yield [^{18}F]**1** as the dominant regioisomer (Scheme 1)[25] by nucleophilic attack at the 2° aziridine carbon. Protected aziridine **3** was fluorinated under basic conditions (40–80% conversion by HPLC, n >25), generating N-protected fluoroamine intermediates [^{18}F]**4** and

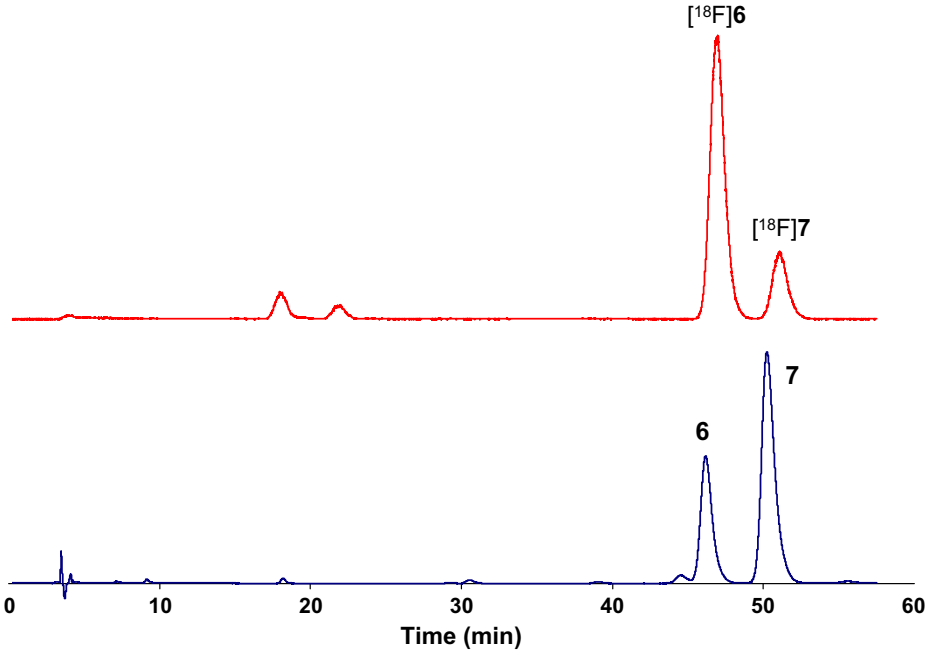


Figure 1. HPLC chromatograms showing regioisomers [^{18}F]**6** and [^{18}F]**7** formed after ring-opening of **3** with [K_{222}][^{18}F] followed by deprotection and acylation. The γ-trace (top) shows that [^{18}F]**6** and [^{18}F]**7** are formed in a 85:15 ratio, respectively. The UV trace (λ = 254 nm; bottom) shows the reaction mixture spiked with a 1:2 ratio of compound **6** to **7**, thereby confirming the identity of the regioisomers. HPLC conditions: mobile phase: 10:90 CH_3CN/H_2O + 0.1 N ammonium formate + 1% formic acid (pH 4); column: GraceSmart RP 18 (250 × 4.6 mm, 5μ); flow rate: 0.9 mL/min.

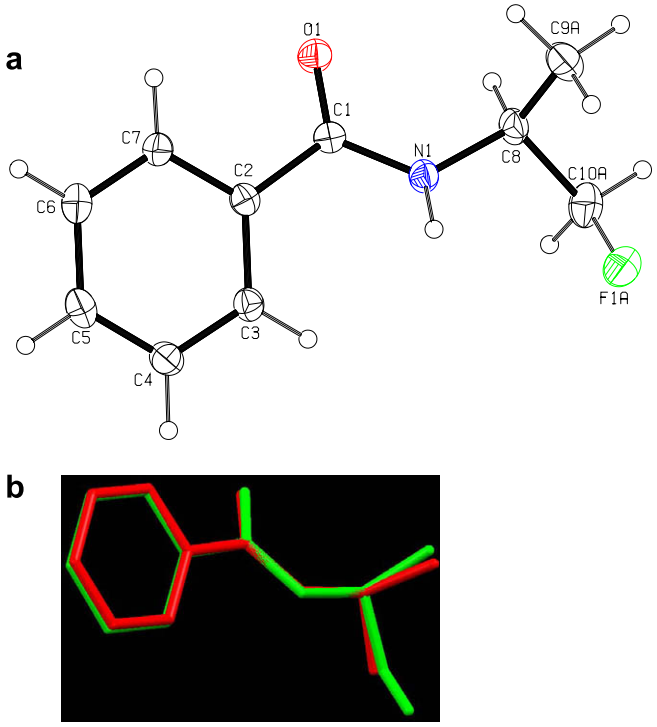


Figure 2. (a) X-ray crystal structure of **6** and (b) overlay of the X-ray crystal structures of **6** and *N*-isopropylbenzamide.

[^{18}F]**5**. A C-18 solid-phase extraction cartridge purification was conducted prior to quantitative catalytic hydrogenation, to prepare the new amines, [^{18}F]**1** and [^{18}F]**2**. Characterization of both regioisomers was performed by in situ benzoylation of the mixture (65% conversion) to prepare *N*-acyl fluoroamines [^{18}F]**6** and [^{18}F]**7** in an 85:15 ratio, as identified by HPLC (Fig. 1) and corresponded to an 8% decay-corrected radiochemical yield from [^{18}F]-fluoride ($n = 3$).

As part of our ongoing studies of the *N*-isopropyl and *N*-fluoroisopropyl moieties in PET radiopharmaceutical discovery, we recently reported the single-crystal structure of *N*-isopropylbenzamide.[26] Figure 2a shows the X-ray crystal structure of compound **6**[27], and Figure 2b shows its overlay with *N*-isopropylbenzamide and shows that both compounds have similar geometries. In the molecular structure of **6**, the $-CH_3$ group and the $-CH_2F$ group bonded to C8 are disordered, with equal occupancies, over the two sites which correspond to an interchange of these groups. One of the disordered half occupancy F atoms is, in turn, rotationally disordered about the C–C bond with relative occupancies 0.40:0.10. In the crystal structure, molecules are linked in one-dimensional chains via intermolecular N–H···O hydrogen bonds. This represents the first X-ray crystal structure of the *N*-fluoroisopropyl moiety.

3. Conclusion

This work demonstrates the feasibility of preparing [^{18}F]fluoroamines by ring-opening of Cbz-protected aziridines and a rare example of regioselective fluoride attack at the 2° carbon of an unsymmetrical aziridine. Further studies are underway to study the influence of the nitrogen substituent on the regioselectivity of ring-opening of substituted aziridines with [^{18}F]- or ^{19}F-fluoride. Extension of this chemistry to symmetrical aziridines and other unsymmetrical aziridines to create new [^{18}F]fluoroamines and radiopharmaceuticals is also ongoing in our laboratory.

Caution: Precautionary measures should be established prior to repeating aspects of this work, particularly when ^{18}F and the highly toxic 2-methylaziridine and/or anhydrous HF are employed. All work with 2-methylaziridine should be carried out in a well ventilated fume-hood, and appropriate safety precautions should be taken. Before commencing work with anhydrous HF, first-aid treatment procedures should be available and known to all laboratory personnel.

Acknowledgements

The authors gratefully acknowledge the assistance of Armando Garcia, Winston T. Stableford, Min Wong, and for production of [^{18}F]-fluoride. We also thank Dr. Iain D. G. Watson for helpful discussions, and Dr. Raman Chirakal and Rezwan Ashique for their expertise with the anhydrous HF reaction. Financial support for this work was provided by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Canadian Institutes for Health Research in the form of a Collaborative Health Research Projects Grant (CHRPJ 322787-06), and an NSERC Postdoctoral Fellowship to K.A.S.

References and notes

1. Ametamay, S. M.; Honer, M.; Schubiger, P. A. *Chem. Rev.* **2008**, *108*, 1501–1516.
2. Cai, L.; Lu, S.; Pike, V. W. *Eur. J. Org. Chem.* **2008**, *17*, 2853–2873.
3. van Waarde, A.; Vaalburg, W.; Doze, P.; Bosker, F. J.; Elsinga, P. H. *Curr. Pharm. Des.* **2004**, *10*, 1519–1536.
4. Kopka, K.; Law, M. P.; Breyholz, H.-J.; Faust, A.; Holtke, C.; Riemann, B.; Schober, O.; Schafers, M.; Wagner, S. *Curr. Med. Chem.* **2005**, *12*, 2057–2074.
5. De Groot, T. J.; Elsinga, P. H.; Visser, G. M.; Vaalburg, W. *Appl. Radiat. Isot.* **1992**, *43*, 1335–1339.
6. Zheng, L.; Berridge, M. S.; Ernsberger, P. *J. Med. Chem.* **1994**, *37*, 3219–3230.
7. Stephenson, K. A.; Wilson, A. A.; Meyer, J. H.; Houle, S.; Vasdev, N. *J. Med. Chem.* **2008**, *51*, 5093–5100.
8. Stephenson, K. A.; van Oosten, E. M.; Wilson, A. A.; Meyer, J. H.; Houle, S.; Vasdev, N. *Neurochem. Int.* **2008**, *53*, 173–179.
9. Wilson, A. A.; DaSilva, J. N.; Houle, S. *Nucl. Med. Biol.* **1996**, *23*, 487–490.
10. Posakony, J. J.; Tewson, T. J. *Synthesis* **2002**, *6*, 766–770.
11. Nomoto, T.; Fukuhara, T.; Hara, S. *Synlett* **2006**, 1744–1746.
12. Matteo Zanda, personal communication.
13. Alvernhe, G. M.; Ennakoua, C. M.; Lacombe, S. M.; Laurent, A. J. *J. Org. Chem.* **1981**, *46*, 4938–4948.
14. Fokin, V. V.; Wu, P. In *Aziridines and Epoxides in Organic Synthesis*, Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006; pp 443–477.
15. Hu, X. E. *Tetrahedron* **2004**, *60*, 2701–2743.
16. Farrokhzad, S.; Diksic, M.; Yamamoto, L. Y.; Feindel, W. *Can. J. Chem.* **1984**, *62*, 2107–2112.
17. Gillings, N. M.; Gee, A. D. *J. Labelled Compd. Radiopharm.* **1997**, 764–765.
18. Lehel, Sz.; Horvath, G.; Boros, I.; Mikecz, P.; Marian, T.; Szentmiklosi, A. J.; Tron, L. *J. Labelled Compd. Radiopharm.* **2000**, *43*, 807–815.
19. Kiesewetter, D. O.; Eckelman, W. C. *J. Labelled Compd. Radiopharm.* **2004**, *47*, 953–969.
20. Veselkov, N. Y.; Chernitskii, K. V.; Bobylev, V. A. *Chem. Heterocycl. Compd.* **1991**, *7*, 716–721.
21. Lin, P.-Y.; Bellos, K.; Stamm, H.; Onistschenko, A. *Tetrahedron* **1992**, *48*, 2359–2372.
22. Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
23. Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
24. Vasdev, N.; Chirakal, R.; Schrobilgen, G. J.; Nahmias, C. *J. Fluorine Chem.* **2001**, *111*, 17–25.
25. Reactive [K_{222}][^{18}F] was prepared and azeotropically dried with anhydrous CH_3CN as previously described.[28] Compound **3** (4 mg, 20 μmol) in 250 μL DMSO was added, and the mixture was vortexed prior to heating at 80 °C for 30 min. The reaction mixture was removed from heat and diluted with 5 mL H_2O, and loaded onto a C18 solid-phase extraction cartridge (Sep-Pak® light; activated with 5 mL CH_3CN, followed by 5 mL H_2O). The cartridge was subsequently washed with 5 mL H_2O, and the crude mixture containing intermediates [^{18}F]**4** and [^{18}F]**5** was eluted with 2 × 500 μL anhydrous CH_3CN into a 5-mL glass V-vial (Wheaton) containing 10 mg of activated palladium on charcoal (10%). The vial was sealed with a Teflon septum and a hydrogen balloon was applied, followed by stirring at room temperature for 30 min, at which point a solution containing Bz-Cl (3 μL), DIPEA (5 μL) and 17 μL CH_3CN was added. Upon heating at 70 °C in an oil bath for 10 min, the crude reaction mixture was filtered and passed through a C-18 Sep-Pak as described above prior to analysis by analytical HPLC (Fig. 1). Compounds [^{18}F]**6** and [^{18}F]**7** were concurrently isolated by semi-preparative HPLC (mobile phase: 25/75 MeOH/

H_2O + 0.1 N ammonium formate; column: Luna C18(2) (250 × 10 mm, 10 μm); flow rate: 8 mL/min; t_R = 20 min) in an overall synthesis time of 3 h.
26. van Oosten, E. M.; Lough, A. J.; Vasdev, N. *Acta Crystallogr., Sect. E* **2008**, *64*, o1005.
27. X-ray quality crystals were obtained by slow evaporation from CD_3OD. Crystal structure of **7**: $C_{10}H_{12}FNO$, T = 150(2) K, orthorhombic, $P2_12_12_1$, Z = 4, a = 9.1895(5) Å, b = 9.7813(5) Å, c = 10.3191(6) Å, V = 927.53(9) Å^3, R_1 = 0.0428, wR_2 = 0.1019 for $I > 2\sigma(I)$, GOF on F^2 = 0.969. Crystallographic data (excluding structure factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 686703. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.
28. Vasdev, N.; Seeman, P.; Garcia, A.; Stableford, W. T.; Nobrega, J. N.; Houle, S.; Wilson, A. A. *Nucl. Med. Biol.* **2007**, *34*, 195–203.