http://dx.doi.org/10.5012/bkcs.2014.35.3.699

Asymmetric Synthesis of Fluoroamines from Chiral Aziridines†

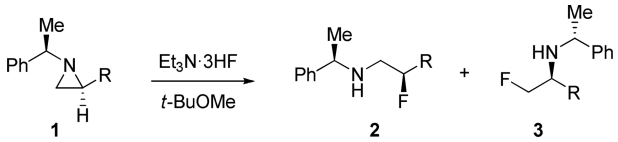
Hyeonjeong Park, Doo-Ha Yoon, Hyun-Joon Ha,* Se In Son,‡ and Won Koo Lee‡,*

*Department of Chemistry and Protein Research Centre for Bio-Industry, Hankuk University of Foreign Studies, Yongin 449-719, Korea. *E-mail: hjha@hufs.ac.kr*
*‡Department of Chemistry, Sogang University, Seoul 121-742, Korea. *E-mail: wonkoo@sogang.ac.kr*
Received September 18, 2013, Accepted November 26, 2013

Key Words : Fluoroamine, Chiral aziridine, Ring-opening reaction, Triethylamine trihydrofluoride

The fluorinated organic molecules have attracted great attentions from synthetic and medicinal chemists with wide use of various agrochemicals and pharmaceuticals.[1] Their uniqueness is originated from its electronic characteristics and the small size without altering the molecular conformations of non-fluorinated compounds.[1] The fluorine is the second most widely used atom in the commercial drugs following the amine.[1,2] Thereby, the elaboration of fluoroamines bearing two most widely used atoms in drugs is one of the most challenging problems in drug synthesis and its development.[2]

Meanwhile, chiral aziridine has been proved to be a good source of chiral amines for last decade in our laboratory[3] with the synthesis of various cyclic and acyclic amines in optically pure forms, most of which derived from ring-opening or ring-expansion reactions of highly strained aziridine ring.[4] Especially, ring-opening reactions of "non-activated" aziridines bearing electron-donating group at the ring nitrogen were successfully carried out by various nucleophiles including Grignard reagents after proper activation of the ring nitrogen with the formation of aziridinium ion or its equivalents.[5,6] However, aziridine ring opening with nucleophilic fluorine was not succeeded except the case of *N*-methylaziridinium ion.[6a] Recent success reported by Doyle's group prompted us to carry the fluorination of chiral aziridines under their reaction condition with DBN, PhCOF, 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at 50 °C in the sealed polypropylene vial.[7] At first, we tested with (*R*)-2-(benzyloxymethyl)-1-((*R*)-1-phenylethyl)aziridine (**1d**)[3] under their condition to yield the fluorinated product in less than 20% with the formation of ring-opened product and other unidentified compounds. This observation implied that the aziridine was not properly activated to accommodate the nucleophile for the ring opening under this reaction condition. Our previous study showed that the chiral aziridines we used bearing α-methylbenzyl group at the ring nitrogen are very stable under base and inert toward most nucleophiles. What we have to do is activation of "non-activated" aziridines prior to the nucleophilic ring opening reactions.[5] Application of hydrogen fluoride is proper agent for the activation of inactivated chiral aziridine ring and for the fluorination. However, direct application of hydrogen fluoride gas is inconvenient to carry in the laboratory. Thereby we decided to use hydrogen fluoride captured in triethylamine. We tried using triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) with the starting substrate, 1-[(1*R*)-1-phenylethyl]-(2*R*)-aziridine-2-carboxylate (**1a**). Finally, we succeeded to obtain the mixture of the regioisomeric fluorinated amines **2a** and **3a** in 51% yield with the ratio of 34:66 from the reaction of **1a** with 6 equivalents of triethylamine trihydrofluoride at 75 ºC in polypropylene vial (Scheme 1, and entry 1 in Table 1). The reaction in polypropylene vial showed a little better yield than that of the reaction in the glass flask.



1 2 3

Scheme 1

Under the similar reaction condition with 3 equivalents of the $Et_3N{\cdot}3HF$, we obtained the fluorinated products **2b** and **3b** in 77% yield with the ratio of 63:37 from 1-[(1*R*)-1-phenylethyl]-(2*R*)-aziridine-2-carboxamide (**1b**) (entry 2). Once we succeeded ring opening reactions with $Et_3N{\cdot}3HF$, other starting materials bearing various substituents at C2 of aziridine were utilized including 2-methoxymethyl (**1c**) and 2-benzyloxymethyl (**1d**) aziridines to yield the fluoroamines (**2c**, **3c** and **2d**, **3d**) in 62 and 54% yield with the ratios as 32:68 and 35:65 (entries 3 and 4). 2-*n*-Butylaziridine (**1e**) also yielded the reaction products (**2e** and **3e**) whose two regioisomers were not separable (entry 5). The starting (*Z*)-2-alkenylaziridines such as 2-propenyl (**1f**) and 2-butenyl (**1g**) were also reacted with fluorine nucleophile to give the regioisomeric products (**2f**, **3f** and **2g**, **3g**) in 71 and 61% yields with the ratios of 91:9 and 95:5, respectively (entries 6 and 7). Starting material (*E*)-azirdin-2-yl acrylate (**1h**) bearing olefin and carboxylate afforded the expected reaction products **2h** and **3h** with the ratio of 66:34 (entry 8).

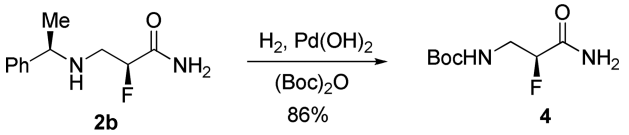
Most ring opening reactions of "non-activated" aziridine by fluoride yielded both products (**2** and **3**) which were derived from ring-opening at C2 and C3 of the aziridine ring.[5] Our early observations[5,8] of ring-opening reactions with various nucleophiles showed that the reaction proceeded favorably at C2 of aziridine-2-carboxylate and at C3 of its

†This paper is to commemorate Professor Myung Soo Kim's honourable retirement.

Table 1. Fluoroamines (**2** and **3**) from chiral aziridines (**1**) from the reaction with $Et_3N{\cdot}3HF$ in *t*-BuOMe

Entry	Compds	R	$Et_3N{\cdot}3HF$ (eq.)	Temp (°C)	Time (h)	Yield[a] (%)	Ratio[b] (**2**:**3**)
1	**1a**	CO_2Et	6	75	48	51	34:66
2	**1b**	$CONH_2$	3	75	60	77	63:37
3	**1c**	CH_2OCH_3	5	75	36	62	32:68
4	**1d**	CH_2OBn	5	75	24	54	35:65
5	**1e**	$(CH_2)_3CH_3$	5	50	24	62	nd[c]
6	**1f**	(*Z*)-$CHCHCH_3$	3	50	7	71	91:9
7	**1g**	(*Z*)-$CHCHCH_2CH_3$	4	50	15	61	95:5
8	**1h**	(*E*)-$CHCHCO_2Et$	4	60	5	73	66:34

[a]Isolated yields not optimized. [b]Ratio of isolated compounds. [c]The ratio was not able to be determined.



Scheme 2

amide. However, this observation in the entries 1 and 2 in the Table 1 shows reversal regio-preference which may be originated from the characteristic of fluoride. A fluoride as a nucleophile seems quite different from most nucleophiles.[9] All other cases including substituted alkyl and alkenyl aziridines showed the predicted regiochemical pathways.

The ring opened product β-amino-α-fluorocarboxamide (**2b**) were hydrogenated to remove the benzyl group in the presence of $Pd(OH)_2$ and $(Boc)_2O$ to give *N*-Boc-amine (**4**) in 86% yield (Scheme 2). This compound (**4**) is valuable for the preparation of various nitrogen-containing compounds including β-amino-α-fluoronitrile and orthogonally protected 1,3-diamino-2-fluoropropane.

In conclusion we described an efficient preparation of fluoroamines by the ring-opening reactions of chiral aziridines with $Et_3N{\cdot}3HF$. At most cases both regioisomers were obtained from the ring openings at C2 and C3 positions depending on the substituents at C2 of the starting substrates.

Acknowledgments. This work was supported by the HUFS Grant (2013).

References

1. (a) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing: Oxford, 2006. (b) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell Publishing-CRC Press: Boca Raton, FL, 2004. (c) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (d) Hiyama, T. *Organofluorine Compounds: Chemistry and Applications*; Springer-Verlag: Berlin, 2000.
2. (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, 2009. (b) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992. (c) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303.
3. Lee, W.-K.; Ha, H.-J. *Aldrichimica Acta* **2003**, *36*, 57.
4. (a) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599. (b) Osborn, H. M. I.; Sweeney, J. B. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (c) Zwanenburg, B.; ten Holte, P. In *Stereoselective Heterocyclic Chemistry III*; Metz, P., Ed.; Springer: Berlin, 2001; pp 93-124. (d) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (e) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (f) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
5. Stankovic, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643.
6. (a) Kim, Y.; Ha, H.-J.; Yun, S. Y.; Lee, W. K. *Chem. Commun.* **2008**, 4363. (b) Yoon, D.-H.; Kang, P.; Lee, W K.; Kim, Y.; Ha, H.-J. *Org. Lett.* **2012**, *14*, 429.
7. Kalow, J. A.; Schmitt, D. E.; Doyle, A. G. *J. Org. Chem.* **2012**, *77*, 4177.
8. Yook, C.-M.; Eum, H.; Ha, H.-J.; Kang, K. Y.; Lee, W. K. *Bull. Korean Chem. Soc.* **2011**, *32*, 2879.
9. (a) D'hooghe, M.; Catak, S.; Stankovic, S.; Waroquier, M.; Kim, Y.; Ha, H.-J.; Van Speybroeck, V.; De Kimpe, N. *Eur. J. Org. Chem.* **2010**, 4920. (b) D'hooghe, M.; De Kimpe, N. *Synlett* **2006**, 2089. (c) Catak, S.; D'hooghe, M.; De Kimpe, N.; Waroquier, M.; Van Speybroeck, V. *J. Org. Chem.* **2010**, *75*, 885.