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A facile synthesis of difluoromethylaziridines

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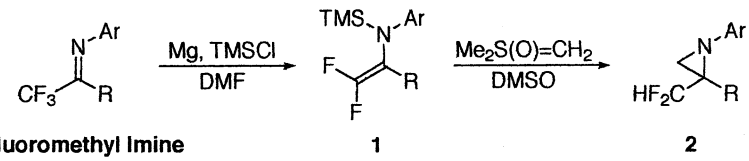
Abstract—Difluoromethylaziridines were synthesized by the reaction of dimethylsulfonium methylide with difluoroenamines which were easily prepared from trifluoromethylimines by magnesium-promoted defluorosilylation.

Introduction of fluorine into pharmacologically active substances has become an important approach in the design of more potent agonists or antagonists from the point of isogeometric modification of enzyme substrates with maximal shift of electron distribution.[1] Special attention has been paid to difluoromethyl containing compounds because they have interesting biological activities.[2] Among the pharmacologically active compounds, difluoromethylaziridines are one of the attractive key compounds because their parent nonfluorinated aziridines are useful precursors for various kinds of medicines, for example, prenylamine β-blocker, catrone MAO inhibitor, and so on.[3] However, very few synthetic methods for fluorinated aziridines[4] have been presented. One of the typical methods is a ring closure of β-amino alcohols or their equivalents, Meanwhile the ylide aziridination reaction remains rather undeveloped. In this paper, we would like to report one-pot synthesis of difluoromethylaziridines **2** by the reaction of dimethyloxosulfonium methylide with difluoroenamines **1**, which were prepared by magnesium-promoted selective C–F bond cleavage of corresponding trifluoromethylimines (Scheme 1).[5]

Reaction of difluoroenamine **1a** with dimethyloxosulfonium methylide[6] gave difluoromethylaziridine **2a**[7] in 92% yield instead of an expected cyclopropane derivative (Scheme 2, Eq. (1)).

It was suggested that desilylation of **1a** followed by aziridination of difluoromethylimine would give the corresponding aziridine **2a**. In fact, (i) desilylation of **1a** proceeded smoothly to give **3a** in 5 min under the experimental conditions;[8] (ii) aziridination of difluoromethylimine **3a**, which was prepared by desilylation with hydrated TBAF in THF, proceeded smoothly in DMSO to give corresponding difluoromethyl aziridine **2a** in 92% yield (Scheme 2, Eq. (2)).

In general, it is well known that the reactivity of common *N*-alkyl- and *N*-arylimines, especially with electron-donating *N*-substituted groups, toward nucleophiles is very low and can be improved in the presence of either Lewis acids or phase-transfer catalyst, by the modification of imine structure with electron-withdrawing groups such as tosyl group on nitrogen atom or an aromatic group on the imine carbon.[9,10] Recently, the first successful methylene transfer to the aliphatic unactivated aldimines was reported by Reetz et al.[10] However, the participating imines were not derived from corresponding ketones but mostly from aromatic and



Scheme 1.

Keywords: aziridines; enamines; imines; amino acid and derivatives; ylides.

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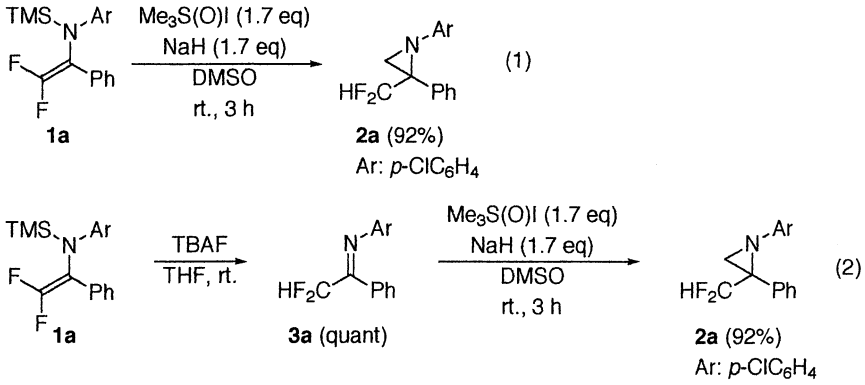


Scheme 2.

aliphatic aldehydes. So, the present reaction is the first successful aziridination of difluoromethyl aryl ketimines by sulfur-ylide.

These results shown in Scheme 1 prompted us to investigate a scope of the one-pot synthesis of difluoromethylaziridines.

As shown in Table 1, various kinds of difluoromethylaziridines **2** were prepared directly from corresponding difluoroenamines **1** in good yields under mild conditions. In the case of *N*-*p*-chlorophenyl and *N*-phenyl enamines, the reaction proceeded smoothly to give corresponding difluoromethylaziridines **2a**, **2b** and **2c** in high yields, respectively (entries 1–3). Moreover, difluoroenamine **1d**, which was prepared from trifluoromethyl aldimine with *N*-*p*-methoxyphenyl group, gave corresponding difluoromethylaziridine **2d** in a good yield (entry 4). In the case of silylated difluoroenamine **1e**, desilylated product **2d** was obtained (entry 5). Meanwhile, enamines with *p*-methoxyphenyl and *o*, *p*-dimethoxyphenyl groups on imine carbon gave **2f** and **2g** in moderate yields along with **3f** and **3g**, respectively (entries 6 and 7).

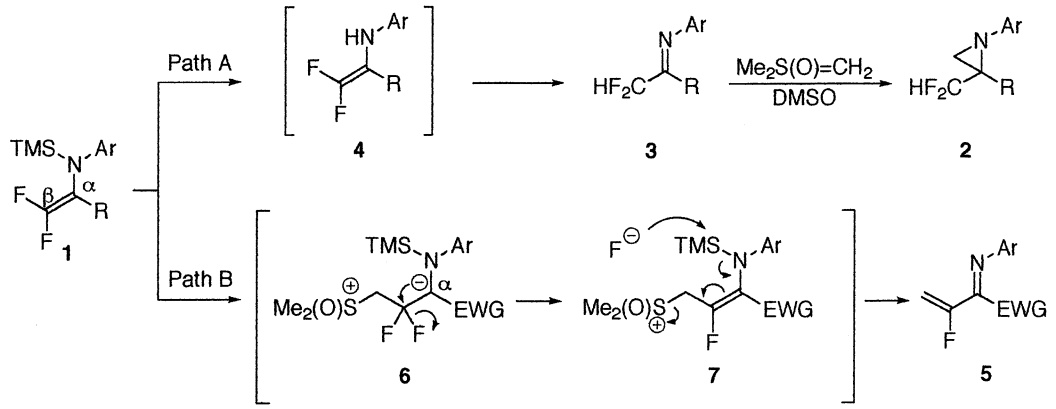
Interestingly, the reaction of difluoroenamines bearing electron-withdrawing group on imine carbon with sulfur-ylide was drastically different from aziridination, but it gave α-fluoro- α,β-unsaturated imines **5** in good yields instead of difluoromethyl aziridines (Table 1, entries 8–11). On the other hand, difluoromethylaziridine **2f** was obtained from the corresponding difluoromethyl imine **3f** in a good yield (entry 12). Moreover, difluoromethylaziridine **2h** was obtained without accompanying α-fluoro-α,β-unsaturated imines **5** from the corresponding difluoromethyl imine **3h** (entry 13).[12]

Although, the reaction mechanism is not clear at present, it is likely that the reaction course was intensively affected by the electronic nature of substituent both on nitrogen and imino carbon as shown in Scheme 3. When either the anion on the nitrogen was stabilized by electron-withdrawing group or the anion on the α-carbon was unstabilized by electron-donating group, the reaction proceeded through path A to give azirizines **2** via corresponding difluoromethyl imines **3**. The path A is highly dependent on the stabilization of the anion on nitrogen (Table 1, entry 1 versus entry 8). On

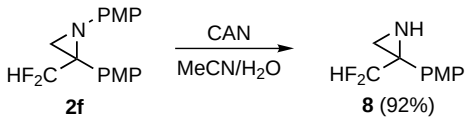
Table 1. A facile synthesis of difluoromethylaziridines[a]

Entry	Substrate	R	Ar	Yield (%)[b]	
				2/**5**	**3**
1	**1a**	C_6H_5	*p*-ClC_6H_4	92 (**2a**)	0
2	**1b**	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	90 (**2b**)	0
3	**1c**	C_6H_5	C_6H_5	62 (**2c**)	0
4	**1d**	H	*p*-$MeOC_6H_4$	78 (**2d**)	0
5	**1e**	TMS	*p*-$MeOC_6H_4$	52 (**2d**)	0
6	**1f**	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	32 (**2f**)	25 (**3f**)
7	**1g**	*o*,*p*-$(MeO)_2C_6H_3$	*p*-$MeOC_6H_4$	41 (**2g**)	42 (**3g**)
8	**1h**	C_6H_5	*p*-$MeOC_6H_4$	48 (**5h**)[d]	26 (**3h**)
9	**1i**	*p*-ClC_6H_4	*p*-$MeOC_6H_4$	41 (**5i**)[d]	25 (**3i**)
10	**1j**	2-Thienyl	*p*-$MeOC_6H_4$	36 (**5j**)[d]	38 (**3j**)
11	**1k**	CO_2Et	*p*-$MeOC_6H_4$	79 (**5k**)	0
12	**3f**	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	57 (**2f**)	0
13[c]	**3h**	C_6H_5	*p*-$MeOC_6H_4$	70 (**2h**)	8 (**3h**)

[a] The reactions were carried out by the procedure shown in Ref. 11.
[b] Isolated yield.
[c] The reaction was carried out for 9 h.
[d] A mixture of *syn* and *anti* isomer.



Scheme 3.



Scheme 4.

the other hand, when both the anion on nitrogen was unstabilized by electron-donating group and the anion on the α-carbon was stabilized by electron-withdrawing group, α,β-unsaturated imines **5** were obtained. In path B, initial addition of sulfur-ylide to β-carbon of difluoroenamine followed by elimination of fluoride anion and subsequent the fluoride anion attack on silyl group resulted in the formation of **5** as a final product. It is noteworthy that ethyl 3-fluoro-2-imino-3-butenoate (**5k**)[13] was obtained predominantly from ethyl 2-amino-3,3-difluoroacrylate (**1k**), in which anion on α-carbon in strongly stabilized by ethoxycarbonyl group.

N-*p*-Methoxyphenyl group of **2f** was easily and selectively removed by the oxidation with CAN to give *N*-nonsubstituted aziridine **8** in 92% yield, which would be transformed to a variety of functionalized difluoromethyl aziridines and amines (Scheme 4).

In summary, one-pot synthesis of difluoromethylaziridines by the reaction of difluoroenamines **1** with dimethyloxosulfonium methylide was achieved where the favorable reaction course was controlled by electronic nature of substituents both on nitrogen and imine carbon.

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References

1. (a) *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R.; Kobayashi, Y., Eds.; Elsevier: Amsterdam, 1982; (b) Walsh, C. *Tetrahedron* **1982**, *38*, 871; (c) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1990; (d) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R.; Kobayashi, Y.; Yagupolski, L. M., Eds.; Elsevier Science: Amsterdam, 1993.
2. For example: (a) Kuo, D.; Rando, R. R. *Biochemistry* **1981**, *20*, 506; (b) Dibari, C.; Pastore, G.; Roscigno, G.; Schechter, P. J.; Sjoerdsma, A. *Ann. Intern. Med.* **1986**, *105*, 83; (c) Seiler, N.; Jung, M. J.; Koch-Wester, J., Eds. *Enzyme-activated Irreversible Inhibitors*, North-Holland: Amsterdam, 1978; (d) Schirlin, D.; Gerhart, F.; Hornsperger, J. M.; Hamon, M.; Wagner, J.; Jung, M. J. *J. Med. Chem.* **1988**, *31*, 30.
3. *Medicinal Chemistry*, *An Introduction*; Tsuda, Y.; Ninomiya, I.; Kaneto, H., Eds., Nankodo: Japan, 1996.
4. (a) Katagiri, T.; Ihara, H.; Kashino, S.; Furuhashi, K.; Uneyama, K. *Tetrahedron: Asymmetry* **1997**, *8*, 2933; (b) Bravo, P.; Crucianelli, M.; Ono, T.; Zanda, M. *J. Fluorine Chem.* **1999**, *97*, 27; (c) Katagiri, T.; Takahashi, M.; Fujiwara, Y.; Ihara, H.; Uneyama, K. *J. Org. Chem.* **1999**, *64*, 7323.
5. (a) Amii, H.; Kobayashi, T.; Hatamoto, Y.; Uneyama, K. *Chem. Commun.* **1999**, 1323; (b) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2000**, *41*, 7893; (c) Amii, H.; Kobayashi, T.; Uneyama, K. *Synthesis* **2000**, 2001; (d) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 3103; (e) Amii, H.; Hatamoto, Y.; Seo, M.; Uneyama, K. *J. Org. Chem.* **2001**, *66*, 7216.
6. For reviews of sulfur ylides: (a) Trost, B. M.; Melvin, L. S., Jr. *Sulfur Ylides*; Academic Press: New York, 1975; (b) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353; (c) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5298.
7. Selected spectra data for compound **2a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.72 (s, 1H), 2.74 (dd, $J_{H-F}=1.8$, 3.6 Hz, 1H), 5.56 (t, $J_{H-F}=54.6$ Hz, 1H), 6.94 (d, $J=9.0$, Hz, 2H), 7.18 (d, $J=9.0$ Hz, 2H), 7.32–7.37 (m, 3H), 7.46–7.52 (m, 2H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6 as an internal standard) δ 42.8 (dd, $J_{H-F}=54.6$ Hz, $J_{F-F}=289.0$

Hz, 1F), 44.9 (dd, $J_{H-F}=54.6$ Hz, $J_{F-F}=289.0$ Hz, 1F); IR (neat) 1494 cm^{-1}. GC/MS m/z 279 (M^+, 44), 278 (100), 227 (27). Anal. calcd for $C_{15}H_{12}ClF_2N$: C, 64.41; H, 4.32; N, 5.01. Found: C, 64.13; H, 4.32; N, 5.12.

8. Desilylative imine formation from **1a** occurred in DMSO, NaH/DMSO or $Me_3S(O)I$/DMSO.
9. (a) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2341; (b) Tewari, R. S.; Awasthi, A. K.; Awasthi, A. *Synthesis* **1983**, 330; (c) Aggarwal, V. K.; Stenson, R. A.; Jones, R. V. H.; Fieldhouse, R.; Blacker, J. *Tetrahedron Lett.* **2001**, *42*, 1587; (d) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1443.
10. Reetz, M. T.; Lee, W. K. *Org. Lett.* **2001**, *3*, 3119.
11. Typical procedure was as follows: To a mixture of sodium hydride (1.7 mmol, prewashed with *n*-hexane) and trimethyloxosulfonium iodide (1.7 mmol) was added DMSO (5.0 mL) at room temperature. Vigorous gas evolution was observed. The mixture was stirred at room temperature for 30 min. A solution of difluoroenamine **1a** (1.0 mmol) in DMSO (5.0 mL) was added at room temperature. After being stirred for 3 h, the mixture was poured onto cold ice–water. The biphasic mixture was extracted with ether. The extracts were washed with brine, dried over $MgSO_4$ and evaporated. The crude product was purified by silica gel column chromatography (ether/hexane = 1/9) to give difluoromethylaziridine **2a** in 92% yield as yellow oil.
12. Difluoromethylaziridine **2k** ($R=CO_2Et$) was not obtained because desilylation of ethyl 2-amino-3,3-difluoroacrylate (**1k**) gave the corresponding enamine **4k** ($R=CO_2Et$) rather than the imine **3k** ($R=CO_2Et$). Likewise, ethyl 3,3-difluoro-2-hydroxy acrylate is known to be isolated. Osipov, S. N.; Golubev, A. S.; Sewald, N.; Michel, T.; Kolomiets, A. F.; Fokin, A. V.; Burger, K. *J. Org. Chem.* **1996**, *61*, 7521.
13. Selected spectra data for compound **5k**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.07 (t, $J=7.2$ Hz, 3H), 3.80 (s, 3H), 4.15 (q, $J=7.2$ Hz, 2H), 5.26 (dd, $J_{H-H}=3.9$, $J_{H-F}=45.7$ Hz, 1H), 5.41 (dd, $J_{H-H}=3.9$, $J_{H-F}=15.0$, Hz, 1H), 6.85 (d, $J=9.2$ Hz, 2H), 6.94 (d, $J=9.2$ Hz, 2H); ^{19}F NMR (188 MHz, $CDCl_3$, C_6F_6 as an internal standard) δ 46.8 (dd, $J_{H-F}=15.0$, 45.7 Hz, 1F) IR (neat) 1738 cm^{-1}; GC/MS m/z 251 (M^+, 1), 92 (74), 77 (100). Anal calcd for $C_{13}H_{14}FNO_3$: C, 62.14; H, 5.62; N, 5.57. Found: C, 61.92; H, 5.71; N, 5.53.