Tetrahedron Letters 51 (2010) 4246–4249

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Diastereoselective synthesis of 2-fluoroaziridine-2-carboxylates by Reformatsky-type aza-Darzens reaction

Atsushi Tarui, Naoto Kawashima, Kazuyuki Sato, Masaaki Omote, Akira Ando *

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan

ARTICLE INFO

Article history:
Received 10 April 2010
Revised 3 June 2010
Accepted 7 June 2010
Available online 11 June 2010

ABSTRACT

The reaction of ethyl dibromofluoroacetate with imines using zinc metal gave 2-fluoroaziridine-2-carboxylates via aza-Darzens reaction of the primary product of the Reformatsky reaction with high diastereoselectivity in excellent yields (quantitative yield and Dr = 85:15). This chemoselective formation of 2-fluoroaziridines was achieved by using CH_3CN as a solvent. Interestingly, the reaction proceeded without activation of zinc metal, which was necessary for the Reformatsky reaction of bromodifluoroacetate. None of α-bromo-α-fluoro-β-lactams, four-membered cyclization products, and noncyclized 3-amino-2-bromo-2-fluorocarboxylic esters, usual Reformatsky adducts, were formed.

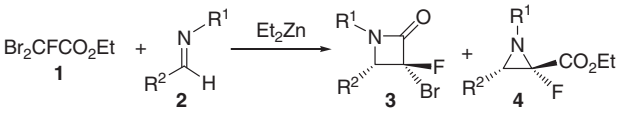
Many methods were developed to introduce fluorine functional groups to various bioactive molecules, since the interesting effects of fluorine functional groups were brought about by putting them on a suitable position of bioactive compounds.[1] Among them, fluorinated amino acids and the peptides derived from them have been attracting much attention in medicinal field.[1c,2] On the other hand, aziridine compounds have been used in many fields. For example, these compounds are used as building blocks to form α- and β-amino acids by ring-opening reaction.[3] Further, aziridine-2-carboxylates themselves have been applied to antibacterial agents[4] and SARS-CoV protease inhibitor.[5]

Recently, we reported that the Reformatsky-type reaction of ethyl dibromofluoroacetate (**1**) with imines (**2**) using Et_2Zn gave *syn*-α-bromo-α-fluoro-β-lactams (**3**) in good yields (Scheme 1).[6] The products were obtained with perfect diastereoselectivity and high chemoselectivity. In this reaction, a small amount of 2-fluoroaziridine-2-carboxylate (**4**) was isolated as a side product, which must be formed by the aza-Darzens reaction of the primary product. We call this side of reaction as the Reformatsky-type aza-Darzens reaction.

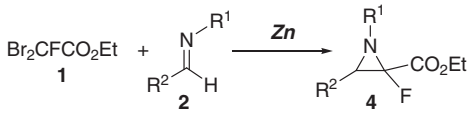
Surprisingly, only two methods for the synthesis of 2-fluoroaziridine-2-caboxylates (**4**) have been reported, in one of which the construction of fluorinated aziridine-2-carboxylate was achieved by addition of an α-fluoro-α-ethoxycarbonylcarbene to a C=N double bond[7] and in the other by addition of a nitrene to an α-fluoro-α,β-unsaturated ester.[8] However, these reactions gave the products only in low yields. Further, it was troublesome to generate the nitrene or carbene species. Recently, Jubault and co-workers reported Et_2Zn-promoted reactions of **1** with ketone in the presence of *N*,*N*-dimethylaminoethanol as an additive to give fluorinated glycidic esters via common Darzens reaction.[9]

Our previous results[6] stimulated us to examine the Reformatsky-type aza-Darzens reaction of **1** with imines (**2**) in order to obtain 2-fluoroaziridine-2-carboxylate (**4**) selectively (Scheme 2). In this report, we wish to describe our recent results on the Zn-mediated chemo- and stereoselective formation of **4** by adjusting the reaction condition.

Using our previous condition,[6] the reaction of **1** with benzylidenebenzylamine (**2a**) and Et_2Zn in Et_2O at −10 °C gave **3a** as a main product with a small amount of **4a** (Table 1, entry 1). Depending on the reaction conditions, the ratio of products changed dramatically. The desired product **4a** was obtained selectively in CH_3CN (entry 2). Conventional Reformatsky condition using activated Zn metal also led to selective formation of **4a** (entry 3). Interestingly, unac-



Scheme 1. Diastereoselective Reformatsky-type synthesis of α-bromo-α-fluoro-β-lactams.

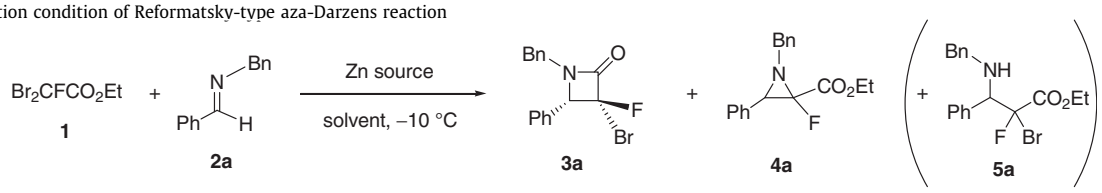


Scheme 2. The Reformatsky-type aza-Darzens reaction of **1** with imines.

* Corresponding author. Tel.: +81 72 866 3140; fax: +81 72 866 3142.
E-mail address: aando@pharm.setsunan.ac.jp (A. Ando).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.06.030

Table 1
Screening of reaction condition of Reformatsky-type aza-Darzens reaction



Entry	Solv.	Zn source	Time (h)	Yield of **3a**[a] (%)	Dr of **3a**[b] (*syn*:*anti*)	^{19}F NMR yield of **4a** (%)	Dr of **4a**[b] (*syn*:*anti*)	Yield of **5a** (%)
1	Et_2O	Et_2Zn	1	76	100:0	8	0:100	ND
2	CH_3CN	Et_2Zn	6	ND	—	91	82:18	ND
3	CH_3CN	Activated Zn powder	6	ND	—	95	85:15	ND
4	CH_3CN	Unactivated Zn powder	6	ND	—	Quant.	85:15	ND

[a] Isolated yields.
[b] Determined by ^{19}F NMR.

tivated Zn metal also gave **4a** with high diastereoselectivity and in quantitative yield (entry 4). The configuration of the major diastereomer of **4a** was determined to be *syn* by vicinal H–F coupling constant on ^{19}F NMR spectroscopy.[10] In all cases, noncyclized ethyl 3-benzylamino-2-bromo-2-fluoro-3-phenylpropionate (**5a**), the usual Reformatsky adduct, was not obtained.

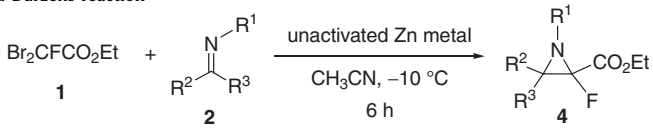
As shown above, we achieved chemoselective formation of **4a** by using CH_3CN as a reaction media and found that the yield of **4a** was not affected by activation of zinc.[11,12]

Next, the scope and limitations of this Reformatsky-type aza-Darzens reaction were explored under the optimized reaction condition shown above (Table 2). The imines from aromatic aldehydes gave the corresponding 2-fluoroaziridine-2-carboxylates in excellent yields regardless of the substituents on the phenyl ring (entries 1–6). In the cases of aliphatic aldimine (**2g**) and ketimine (**2h**), the corresponding fluoroaziridine products were not observed by ^{19}F NMR spectroscopy (entries 7 and 8). The substituents on the nitrogen (R^1) did not affect this reaction essentially (entries 9–12). In the case of imine (**2j**), the product was obtained in low yield probably due to the bulkiness of the N-substituent. The yield of **4j** was improved by prolongation of the reaction time (entry 11). In all cases, the products (**4**) were obtained with high and similar diastereoselectivities.

However, these fluorinated aziridine compounds (**4**) were not so stable as that reported for fluorinated epoxides.[9] So **4** must be stored at −30 °C to avoid their decomposition. Especially, *syn*-isomers **4** were less stable than *anti*-isomers. Therefore their yields and diastereoratios were determined by ^{19}F NMR spectroscopy of crude mixtures.

We propose the mechanism of this Reformatsky-type aza-Darzens reaction of **1** with imine (**2a**) as shown in Figure 1. Recently, we reported the tentative mechanism for the formation of α-bromo-α-fluoro-β-lactams by Et_2Zn-promoted Reformatsky-type reaction of **1** with imine in Et_2O.[6] There, chemo- and diastereoselective formation of **3a** was achieved by the addition of stable (*Z*)-zinc bromofluoroenolate (**6**) to imine, where low coordination power of Et_2O makes the generation of chair-like transition state favorable. Intramolecular cyclization of intermediate (**7**) to ester carbonyl group was promoted by the intramolecular coordination of zinc to carbonyl moiety to give **3a**.[6] On the other hand, the strongly coordinating solvent, CH_3CN, could coordinate with Zn of the enolate **8** leading to reversible equilibrium of *E*/*Z* isomer of **8**. And also the coordination could destroy the chair-like transition state to give another open-chain transition state (TS-1–TS-4). The Reformatsky adduct (**9**) gave the aziridine ring **4a** via aza-Darzens-type intramolecular cyclization, where coordination of sol-

Table 2
Scope and limitations of Reformatsky-type aza-Darzens reaction



Entry	**2**				^{19}F NMR yield of **4** (%)	Dr of **4**[a] (*syn*:*anti*)
	R^1	R^2	R^3			
1	Bn–	Ph–	H–	**2a**	Quant.	85:15
2	Bn–	4-Cl–C_6H_4–	H–	**2b**	91	85:15
3	Bn–	4-CF_3–C_6H_4–	H–	**2c**	94	83:17
4	Bn–	4-MeOCO–C_6H_4–	H–	**2d**	94	81:19
5	Bn–	4-MeO–C_6H_4–	H–	**2e**	Quant.	87:13
6	Bn–	4-Me–C_6H_4–	H–	**2f**	93	83:17
7	Bn–	$PhCH_2CH_2$–	H–	**2g**	ND	—
8	Bn–	Ph–	Me–	**2h**	ND	—
9[b]	Me–	Ph–	H–	**2i**	70	72:28
10	Benzhydryl–	Ph–	H–	**2j**	28	84:16
11[c]	Benzhydryl–	Ph–	H–	**2j**	60	83:17
12	Ph–	Ph–	H–	**2k**	85	100:0

[a] Determined by ^{19}F NMR.
[b] The reaction was carried out for 28 h.
[c] The reaction was carried out for 48 h.

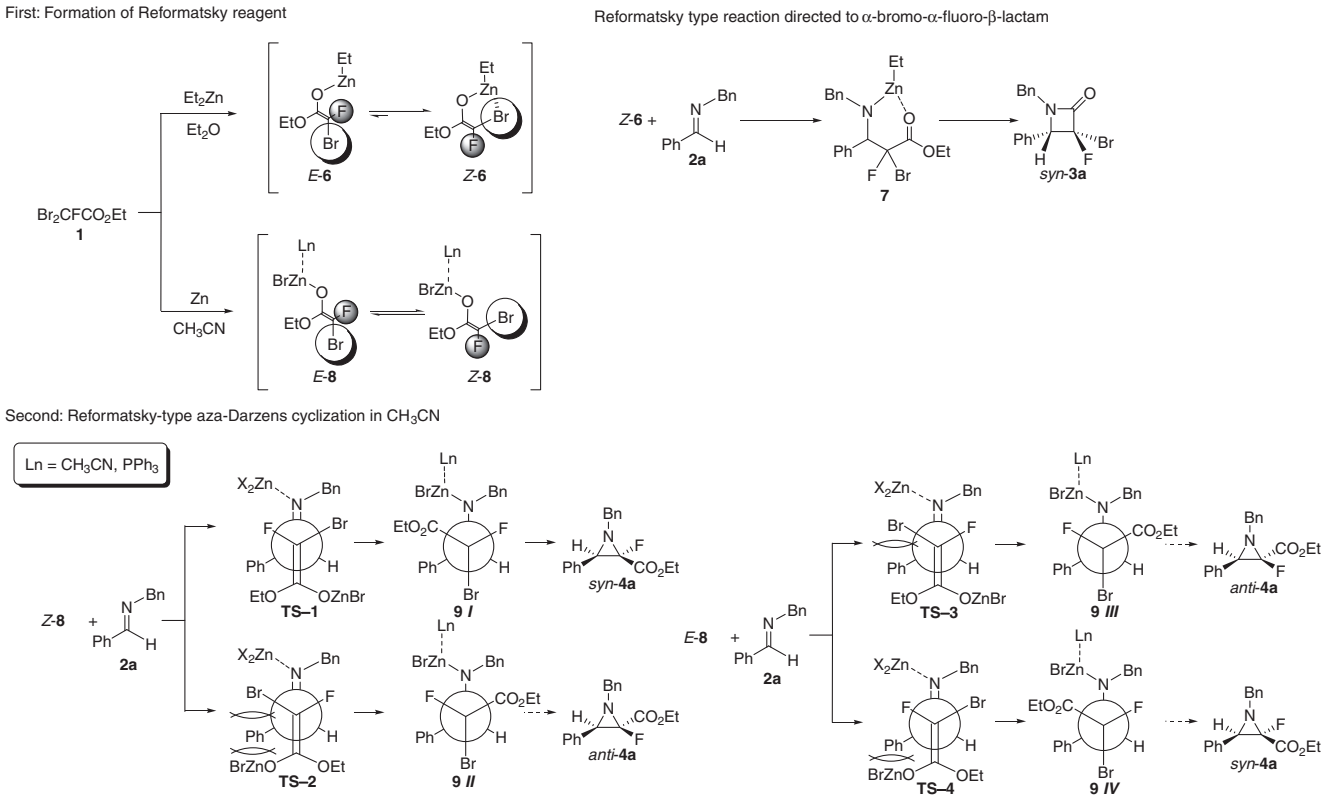


Figure 1. Tentative mechanism for the diastereoselective outcome.

vent to Zn of **9** seemed to disturb the activation of ester carbonyl moiety. This assumption was supported that the mixture of **3a** and **4a** was obtained by the reaction of **1** with imine (**2a**) using Et_2Zn and Et_2O as a solvent in the presence of PPh_3 which must be a better monovalent ligand than CH_3CN.[13] In this transition model, the *syn* isomer is obtained mainly from TS-1, in which there is little steric repulsion. On the other hand, other transition states (TS-2–TS-4) have some steric repulsion between bromine and phenyl group and between phenyl group and the other functional group. *Z*-**8** used for TS-1 might be provided from equilibrium of *E*-**8** and *Z*-**8**. As a result, the selective generation of *syn* isomer was achieved by dynamic kinetic resolution.

In conclusion, we established a new methodology for 2-fluoroaziridine-2-carboxylates by chemo- and diastereoselective Reformatsky-type aza-Darzens reaction of ethyl dibromofluoroacetate with imines using Zn metal. The Reformatsky reagent of **1** was generated without any activation of zinc. This chemoselective reaction was achieved by carrying out in CH_3CN. Now, we are planning the synthesis of bioactive compounds with fluorinated aziridine ring and the ring-opening reaction of **4** for the synthesis of α-fluoro-α- or β-amino acids.

References and notes

1. (a) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619–8683; (b) Bégué, J.-P.; Delpon, B. D.. *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons: New Jersey, 2008; (c)*Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; John Wiley & Sons: New Jersey, 2009.
2. (a) Percy, J. M. *Contemp. Org. Synth.* **1995**, 251; (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3207; (c) Welch, J. T. Selective Fluorination in Organic and Bioorganic Chemistry, Ed.; ACS Symposium Series 456; American Chemical Society: Washington DC, 1991.; (d) Olah, G. A.; Chambers, R. D.; Prakash, G. K. S. *Synthetic Fluorine Chemistry*; John Wiley & Sons: New York, 1992; (e) Edmonds, M.; Peddie, V. *Chem. New Zealand* **2006**, *70*, 85–87.
3. (a) Lim, Y.; Lee, W. K. *Tetrahedron Lett.* **1995**, *36*, 8431–8434; (b) Davis, F. A.; Zhang, Y.; Rao, A.; Zhang, Z. *Tetrahedron* **2001**, *57*, 6345–6352; (c) Xiong, C.; Wang, W.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2002**, *67*, 1399–1402; (d) Shishido, Y.; Ito, F.; Morita, H.; Ikunaka, M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6887–6890; (e) Manaka, T.; Nagayama, S.; Desadee, W.; Yajima, N.; Kumamoto, T.; Watanabe, T.; Ishikawa, T.; Kawahata, M.; Yamaguchi, K. *Helv. Chim. Acta* **2007**, *90*, 128–142.
4. Sharma, P.; Kumar, A.; Upadhyay, S.; Sahu, V.; Singh, J. *Eur. J. Med. Chem.* **2009**, *44*, 251–259.
5. Martina, E.; Stiefl, N.; Degel, B.; Schulz, F.; Breuning, A.; Schiller, M.; Vicik, R.; Ziebuhr, F.; Schirmeister, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5365–5369.
6. Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **2010**, *51*, 2000–2003.
7. Seyferth, D.; Woodruff, R. *J. Org. Chem.* **1973**, *38*, 4031–4039.
8. Usuki, Y.; Fukuda, Y.; Iio, H. *ITE Lett. Batteries New Technol. Med.* **2001**, *2*, C29–C32.
9. Lemonnier, G.; Zoute, L.; Quirion, J. C.; Jubault, P. *Org. Lett.* **2010**, *12*, 844–846.
10. The vicinal H–F coupling constant of major isomer (7.7 Hz) was bigger than that of the minor isomer (4.6 Hz). The relative configuration means that for H–F configuration. Relationship of stereoisomer and H–F coupling constant was described following book: Dorbier, W. R., Jr.; In *Guide to Fluorine NMR for Organic Chemist*; John Wiley & Sons: New Jersey, 2009, pp 46–47.
11. *Preparation of 2-fluoroaziridine-2-carboxylate* (**4a**): ethyl dibromofluoroacetate (**4**; 0.41 mL, 3 mmol) was added to a suspension of Zn (196 mg, 3 mmol) in CH_3CN (8 mL) at −10 °C. The resulting mixture was stirred at same temperature for 1 h. To the yellow emulsion of mixture, imine (**2a**; 0.19 mL, 1 mmol) was added at −10 °C, and the resulting mixture was stirred at same temperature for 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the mixture was filtered through Celite pad. The filtrate was extracted with AcOEt, and then the extract was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo without heating and the residue was purified by column chromatography (SiO_2, AcOEt/hexane = 5:95) to give the corresponding 2-fluoroaziridine-2-carboxylate (**4a**). The chemical yield was obtained from ^{19}F NMR of the crude mixture; benzotrifluoride (BTF) was used as an internal standard.
12. *Spectroscopic data of* **4a**: *syn*- and *anti*-isomers were separated by column chromatography.
syn-**4a**: A colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.02 (3H, t, J = 7.1 Hz), 3.36 (1H, d, J = 7.7 Hz), 4.07 (3H, m), 4.23 (1H, d, J = 13.9 Hz), 7.34 (10H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.7, 51.1 (m), 54.1 (d, J = 13 Hz), 61.9, 86.3 (d, J = 263 Hz), 127.2, 127.5, 127.7, 127.8, 127.9, 128.4, 133.1, 137.5, 164.3 (d, J = 36 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ: −114.8 (1F, d, J = 7.7 Hz); MS m/z = 299 (M^+); HRMS (EI) Calcd for $C_{18}H_{18}FNO_2$: 299.132 (M^+), found: 299.131 (M^+); IR (neat) cm^{-1}: 1747.
anti-**4a**: A colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.24 (3H, t, J = 7.1 Hz), 3.61 (1H, d, J = 4.6 Hz), 4.06 (1H, dd, J = 14.1, 4.2 Hz), 4.17 (1H, dd, J = 14.1, 3.8 Hz), 4.27 (2H, q, J = 7.1 Hz), 7.33 (10H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ:

14.0, 51.6 (m), 55.1 (d, J = 2 Hz), 62.5, 84.7 (d, J = 255 Hz), 127.2, 127.8, 127.8, 128.0, 128.1, 128.4, 133.3, 133.4, 137.4, 165.2 (d, J = 35 Hz); ^{19}F NMR ($CDCl_3$, 90 MHz) δ: −106.6 (1F, m); MS m/z = 299 (M^+); HRMS (EI) Calcd for $C_{18}H_{18}FNO_2$: 299.132 (M^+), found: 299.132 (M^+); IR (neat) cm^{-1}: 1736.

13. The reaction gave *syn*-**3a** in 33% yield and the diastereomixture of **4a** in 44% yield (*syn*/*anti* = 32%/12%). Total *syn*/*anti* ratio of product was 84/16, which was consistent with the diastereoratio in CH_3CN.