Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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

A R T I C L E   I N F O
Article history:
Received 10 April 2010
Revised 3 June 2010
Accepted 7 June 2010
Available online 11 June 2010

A B S T R A C T

The reaction of ethyl dibromofluoroacetate with imines using zinc metal gave 2-fluoroaziridine-2-carboxylates via azido-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 CH3CN 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.

© 2010 Elsevier Ltd. All rights reserved.

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. Among them, fluorinated amino acids and the peptides derived from them have been attracting much attention in medicinal field. 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. Further, aziridine-2-carboxylates themselves have been applied to antibacterial agents and SARS-CoV protease inhibitor.

Recently, we reported that the Reformatsky-type reaction of ethyl dibromofluoroacetate (1) with imines (2) using Et2Zn gave syn-α-bromo-α-fluoro-β-lactams (3) in good yields (Scheme 1). 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-fluorooaziridine-2-carboxylates (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 and in the other by addition of a nitrene to an α-fluoro-α,β-unsaturated ester. 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 Et2Zn-promoted reactions of 1 with ketone in the presence of N,N-dimethylenanoethanol as an additive to give fluorinated glycidic esters via common Darzens reaction.

Our previous results 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, the reaction of 1 with benzylidenebenzylamine (2a) and Et2Zn in Et2O 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 CH3CN (entry 2). Conventional Reformatsky condition using activated Zn metal also led to selective formation of 4a (entry 3). Interestingly, unac-
tivated Zn metal also gave 4a with high diastereoselectivity and in
quantitative yield (entry 4). The configuration of the major diaste-
reomer of 4a was determined to be syn by vicinal H–F coupling
constant on 19F NMR spectroscopy.11 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 CH3CN 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 con-
dition shown above (Table 2). The imines from aromatic aldehydes
gave the corresponding 2-fluoroaziridine-2-carboxylates in excel-
 lent yields regardless of the substituents on the phenyl ring (entries
1–6). In the cases of aliphatic aldehyde (2g) and ketimine
(2h), the corresponding fluoroaziridine products were not ob-
served by 19F NMR spectroscopy (entries 7 and 8). The substituents
on the nitrogen (R1) 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.3 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 19F NMR spectroscopy of
crude mixtures.

We propose the mechanism of this Reformatsky-type aza-Dar-
zens reaction of 1 with imine (2a) as shown in Figure 1. Recently,
we reported the tentative mechanism for the formation of α-bromo-
ω-fluoro-ω-lactams by Et2Zn-promoted Reformatsky-type reaction of
1 with imine in Et2O.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 Et2O 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, CH3CN, 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-Dar-
zens-type intramolecular cyclization, where coordination of sol-

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

| Entry | Solv. | Zn source | Time (h) | Yield of 3a (%) | Dr of 3a (syn:anti) | 19F NMR yield of 4a (%) | Dr of 4a (syn:anti) | Yield of 5a (%) |
|-------|-------|-----------|----------|----------------|------------------|------------------------|------------------|--------------|
| 1     | Et2O  | Et2Zn     | 1        | 76             | 100:0            | 8                     | 0:100            | ND           |
| 2     | CH3CN | Et2Zn     | 6        | 93             | 85:15            | 89:12                  | 10:91            | ND           |
| 3     | CH3CN | Activated Zn powder | 6 | ND             | 95              | 85:15                  | ND               | ND           |
| 4     | CH3CN | Unactivated Zn powder | 6 | ND             | Quant.          | 85:15                  | ND               | ND           |

a) Isolated yields.
b) Determined by 19F NMR.
c) The reaction was carried out for 48 h.

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

| Entry | R1  | R2  | R3  | 19F NMR yield of 4a (%) | Dr of 4a (syn:anti) |
|-------|-----|-----|-----|-------------------------|------------------|
| 1     | H–  | Ph– | H–  | 85:15                   | Quant.           |
| 2     | Ph– | H–  | H–  | 85:15                   | 81:19            |
| 3     | H–  | 4-Cl-Ph– | H–  | 83:17                   |                 |
| 4     | H–  | 4-MeOCO–Ph– | H–  | 83:17                   |                 |
| 5     | H–  | 4-MeOCO–Ph– | H–  | 83:17                   |                 |
| 6     | H–  | 4-Me–Ph– | H–  | 83:17                   |                 |
| 7     | H–  | PhCH2CH2– | H–  | 83:17                   |                 |
| 8     | Ph– | H–  | Me– | 83:17                   |                 |
| 9b    | Me– | Ph– | H–  | 72:28                   |                 |
| 10    | Benzhydryl– | Ph–   | H–  | 84:16                   |                 |
| 11c   | Benzhydryl– | Ph–   | H–  | 83:17                   |                 |
| 12    | Ph– | Ph– | H–  | 100:0                   |                 |

a) Determined by 19F NMR.
b) The reaction was carried out for 28 h.
c) The reaction was carried out for 48 h.
vent to Zn of 9 seemed to disturb the activation of ester carboxyl moiety. This assumption was supported that the mixture of 3a and 4a was obtained by the reaction of 1 with imine (2a) using Et2Zn and Et2O as a solvent in the presence of PPh3, which must be a better monoanion ligand than CH3CN.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-fluorooaziridine-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 CH3CN. No, 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) Béguel, J.-P.; Delpon, B. D. Bioorganic and Medicinal Chemistry of Fluorine: John Wiley & Sons: New Jersey, 2008; (c) Fluorine in Medicinal Chemistry and Biological Activity; 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.; Steff, N.; Degel, B.; Schulz, F.; Breuning, A.; Schiller, M.; Vick, R.; Ziebuhr, F.; Schirmer, T. Bioorg. Med. Chem. Lett. 2005, 15, 5365–5369.

6. Tarui, A.; Kawashima, N.; Sato, K.; Omote, M.; Aono, 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.; Ito, H. IIT 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 (106 mg, 3 mmol) in CH3CN (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 NaHCO3, 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 MgSO4. The solvent was removed in vacuo without heating and the residue was purified by column chromatography (SiO2, AcOEt/hexane = 5:95) to give the corresponding 2-fluoroaziridine-2-carboxylate (4a). The chemical yield was obtained from 19F 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 (CDCl3, 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); 13C NMR (CDCl3, 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); 19F NMR (CDCl3, 90 MHz) δ: –114.8 (1F, d, J = 7.7 Hz); MS m/z = 299 (M+); HRMS (EI) Calcd for C9H12F4NO2: 299.132 [M+] (M)+: 299.131 (M+) (M+); IR (neat) cm–1: 1747.

anti-4a: A colorless oil; 1H NMR (CDCl3, 400 MHz) δ: 1.24 (3H, t, J = 7.1 Hz), 3.61 (1H, d, J = 4.5 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); 13C NMR (CDCl3, 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); 19F NMR (CDCl3, 90 MHz) δ: –106.6 (1F, m); MS m/z = 299 (M+); HRMS (EI) Calcd for C12H13FNO2: 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 CH3CN.