ORGANIC LETTERS

1999
Vol. 1, No. 9
1435−1437

Applications of Aziridinium Ions. Selective Syntheses of β-Aryl-α,β-diamino Esters

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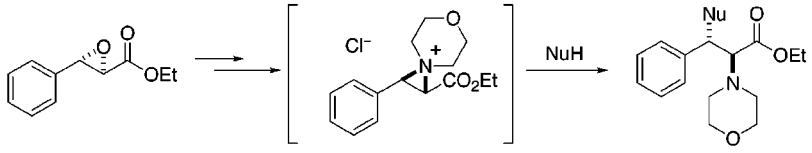
Received August 27, 1999

ABSTRACT



α,β-Diamino esters are readily prepared through stereospecific and regioselective opening of an aziridinium ion intermediate with a variety of amines. The aziridinium ion is generated from the epoxide in two steps.

α,β-Diamino esters have been recognized as key intermediates for the preparation of β-lactams.[1] A common route to α,β-diamino esters employs direct condensation of ester enolates with imines.[2,3] However, the stereochemical outcome is solvent and substituent dependent, and often proceeds directly on to the β-lactam. We report here a simple route to β-aryl-α,β-diamino esters which is regioselective and gives *erythro* products stereospecifically.

In contrast to epoxides, aziridines and even more so aziridinium ions have not yet entered mainstream organic synthesis. However, thanks to the outstanding efforts of several groups,[4] the popularity of these reactive intermediates seems to be growing rapidly. Perhaps their most important contribution is to provide the most direct means for stereospecifically generating the vicinal diamine motif on adjacent, stereogenic carbon center. Until a year or two ago, this type of diamine functionality was barely known in the literature. The beauty of the aziridinium ion is that it can be opened at moderate temperatures and under neutral, or even basic, conditions, whereas the simple parent aziridines (i.e., no electron-withdrawing substituent on nitrogen) require some degree of activation by an acidic agent. This latter requirement removes from consideration many useful nucleophiles (e.g., CN^-), since they require an alkaline environment to be effective.

The most reliable method for generating aziridinium ions is to transform the hydroxyl group of a vicinal 2°-amino alcohol into a good leaving group. With this protocol in

(1) (a) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B.; Gorman, M., Eds.; Academic Press: New York, 1982; Vols. 1−3. (b) Koppel, G. A. In *Small Ring Heterocycles-Azetidines, β-Lactams, Diazetidines and Diaziridines*; Hassner, A., Ed.; Wiley: New York, 1982. (c) Dürckheimer, W.; Blumbach, J.; Lattrel, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180.

(2) (a) Dryanska, V.; Pashkuleva, I.; Tasheva, D. *Synth. Commun.* **1997**, *27*, 1849. (b) van der Steen, F. H.; Kleijn, H.; Jastrzebski, T. B. H.; van Koten, G. *J. Org. Chem.* **1991**, *56*, 5147.

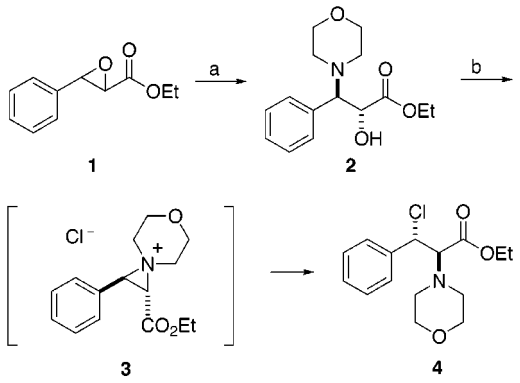
(3) For reviews of the ester enolate−imine condensation, see: (a) Brown, M. J. *Heterocycles* **1989**, *29*, 2225. (b) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447. (c) van der Steen, F. H.; van Koten, G. *Tetrahedron* **1991**, *47*, 7503.

(4) (a) de Sousa, S. E.; O'Brien, P.; Poumellec, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1483. (b) Liu, Q.; Marchington, A. P.; Rayner, C. M. *Tetrahedron* **1997**, *53*, 15729. (c) Liu, Q.; Marchington, A. P.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 511. (d) Rayner, C. M. *Synlett* **1997**, 11. (e) Richardson, P. F.; Nelson, L. T. J.; Sharpless, K. B. *Tetrahedron Lett.* **1995**, *36*, 9241. (f) Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585. (g) Gmeiner, P.; Junge, D.; Kaertner, A. *J. Org. Chem.* **1994**, *59*, 6766. (h) Liu, Q.; Simms, M. J.; Boden, N.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1363. (i) Freedman, J.; Vaal, M. J.; Huber, E. W. *J. Org. Chem.* **1991**, *56*, 670. (j) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. (k) Rosen, T.; Fesik, S. W.; Chu, D. T. W.; Parnet, A. G. *Synthesis* **1988**, 40. (l) Tanner, D.; Somfai, P. *Tetrahedron* **1986**, *42*, 5657.

10.1021/ol990256d CCC: $18.00
Published on Web 10/06/1999

mind, ethyl 2-hydroxy-3-morpholino-3-phenylpropionate **2**[5] was obtained from the *trans*-glycidic ester **1** and morpholine (Scheme 1). Mesylation of compound **2** according to the

Scheme 1



a. morpholine, EtOH, reflux, 12 h; **2**, 72%. b. MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; **4**, 96%.

literature procedure[6] gave directly the rearranged chloro ester **4** as a single isomer.[7] The structure was confirmed by an X-ray analysis (Figure 1).[8]

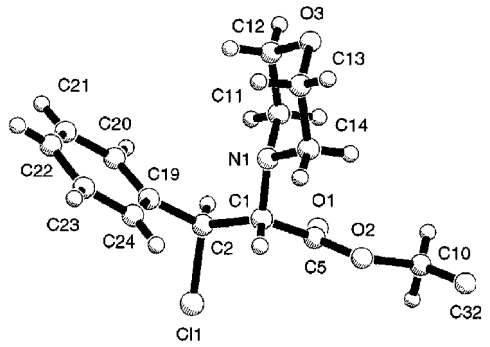
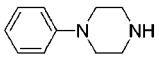
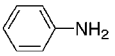


Figure 1. ORTEP plot of the crystal structure of **4**.

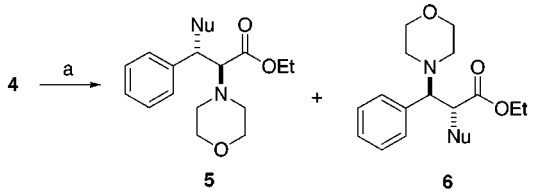
The stable, crystalline β-chloroamine **4** then serves as the source for regeneration, on demand, of aziridinium ion intermediate **3**.[9] The latter ion reacts efficiently and regioselectively with a wide range of amines (Table 1).[10]

Table 1. α,β-Diamino Esters via Aziridinium Ion **3**

entry	NuH	regioselectivity[a] **5:6**	yield[b] [%]
1		**5a** : **6a** = 92:8	85
2		**5b** : **6b** = 93:7	88
3		**5c** : **6c** = 95:5	80
4		**5d** : **6d** = 95:5	84
5		**5e** : **6e** = 97:3	93
6		**5f** : **6f** = 100:0	79
7	NH_3	**5g** : **6g** = 96:4	81

[a] Analysis by HPLC (Zorbax SB-C18 reverse phase analytical column, 150 x 4.6 mm; Gradient eluent 80/20 to 0/100 H_2O/MeCN containing 0.1% TFA, 0.5 mL/min for 15 min) by intergration of absorption at 254 nm. [b] Isolated yield for regioisomers (**5** and **6**) after filtration and drying to constant weight.

Primary and secondary amines as well as ammonia and aniline gave excellent results. Notably, the reactions were stereospecific in all cases, giving only the *anti* (*erythro*) relationship, and regioselectivities greater than or equal to 92:8 in all cases (eq 1 and Table 1). The relative stereo-



(1)

a. NuH (1.2 equiv.), K_2CO_3, CH_3CN, 60 °C, 12 h

chemistry and other features of structure **5e** (Nu = 4-phenylpiperazino, entry 5, Table 1) follows from the X-ray crystal structure (Figure 2). Regioselectivities were also confirmed by LC-MS analysis in which regioisomers **5** and **6** can be differentiated by their different fragmentation patterns. For

(5) **Preparation of Aminohydroxy Ester 2**. The epoxy ester (**1**, 15.3 g, 80 mmol) and morpholine (7.3 mL, 7.3 g, 80 mmol) were dissolved in ethanol (80 mL), and the mixture was heated at reflux (open to the atomosphere) for 12 h. The resulting mixture was cooled to ambient temperature and concentrated in vacuo to afford the crude product (an 87:13 mixture of **2** and its regioisomer). Recrystallization from ether furnished the pure regioisomer **2** (16 g, 72%) as a colorless crystalline solid: mp 89−91 °C; TLC (EtOAc/hexane (1:2)) R_f = 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J = 7.2 Hz, 3 H), 2.40−2.45 (m, 2 H), 2.52−2.55 (m, 2 H), 3.09 (br s, 1 H), 3.54 (d, J = 4.4 Hz, 1 H), 3.67−3.69 (m, 4 H), 3.98−4.08 (m, 2 H), 4.72 (d, J = 4.4 Hz, 1 H), 7.24−7.29 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 51.4 (2 C), 61.4, 66.8 (2 C), 69.9, 72.1, 128.1 (2 C), 128.2, 129.1 (2 C), 135.4, 172.6; FAB-MS *m*/*z* (rel intensity) 280 (M^+ + 1, 35), 176 (100).

(6) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.

(7) **Preparation of Chloroamino Ester 4.** To a cold (0 °C) stirred solution of **2** (15.6 g, 55.9 mmol) and Et_3N (8.5 mL, 6.2 g, 61.5 mmol) in CH_2Cl_2 (60 mL) was added the MsCl (4.7 mL, 7.1 g, 61.5 mmol) dropwise. After the addition was completed, the reaction was allowed to warm to room temperature (ice bath removal) and stirred for 3 h. The resulting crude reaction mixture was filtered through a short pad of silica gel. The filtrate was concentrated and recrystallized from CH_2Cl_2/hexane to give chloro ester **4** (16.0 g, 96%) as a colorless solid: mp 66−67 °C; TLC (EtOAc/hexane (1:2)) R_f = 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.2 Hz, 3 H), 2.36−2.41 (m, 2 H), 2.58−2.63 (m, 2 H), 3.28−3.40 (m, 4 H), 3.69 (d, J = 10.8 Hz, 1 H), 4.00−4.33 (m, 2 H), 5.14 (d, J = 10.8 Hz, 1 H), 7.30−7.39 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.0 (2 C), 59.1, 60.8, 67.0 (2 C), 73.5, 127.7 (2 C), 128.3 (2 C), 128.5, 138.4, 168.5; FAB-MS *m*/*z* (rel intensity) 298 (M^+ + 1, 40), 262 (M^+ − Cl, 40), 172 (81).

(8) Details of the crystal structure information can be obtained from the Director of the Cambridge Crystallographic Data Center, University of Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

(9) For the synthesis and reactions of isolable aziridinium ions, see: Crist, D. R.; Leonard, N. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 962.

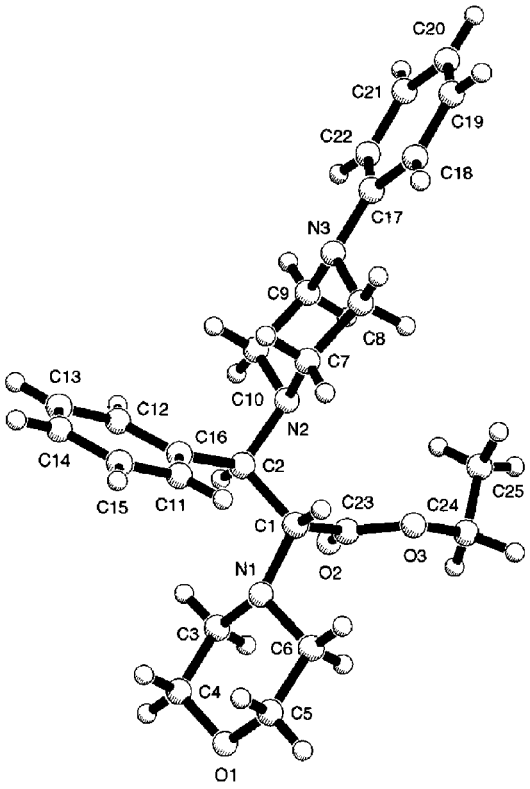


Figure 2. ORTEP plot of the crystal structure of **5e**.

example, the fragment ion $[C_6H_5CHNu]^+$ was clearly observed for all of the **5** regioisomers in Table 1.

One can also prepare these α,β-diamino esters without isolation of intermediate **4**, for example, using *tert*-butylamine as nucleophile in the "one-pot" procedure.[11] Diamino esters **5** and **6** (Nu = *t*-BuNH_2) were obtained in high yield (>99%) and with the same regioselectivity as in the sequential, two-step approach.

Finally, it is noteworthy that for all of the aziridinium ion opening reactions examined here (Table 1), pure products arise after filtration of the crude reaction mixture through a plug of silica gel. The ability to obtain pure products from this reaction without resorting to column chromatography makes it an ideal candidate for scale-up. In fact, the reaction in Table 1, entry 5, has been performed successfully on a 13 g scale.[12]

Acknowledgment. We thank the National Institute of General Medical Sciences, National Institutes of Health (GM-28384), the National Science Foundation (CHE-9531152), and the W. M. Keck Foundation for financial support and are grateful to Dr. M. G. Finn, Dr. W. Pringle, and Dr. M. Matsui for helpful discussions and Dr. M. Sabat (University of Virginia) for X-ray structure analysis.

Supporting Information Available: Complete characterization data (^{1}H and ^{13}C NMR and mass spectral data) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) **General Procedure for the Preparation of α,β-Diamino Esters** (**5**, Table 1). To a stirred suspension of chloro ester **4** (297 mg, 1.0 mmol) and K_2CO_3 (138 mg, 1 mmol) in CH_3CN (2 mL) was added the amine (1.2 mmol) at room temperature, and the mixture was heated at 60 °C (open to air) for 12 h. The resulting mixture was then cooled to ambient temperature and filtered through a short plug of silica gel (3 cm in a pipette), which was washed with 10 mL of EtOAc. The combined filtrates were concentrated to give α,β-diamino ester products as the indicated (Table 1) mixture of regioisomers **5** and **6**. Product mixtures **a**, **f**, and **g** remained as oils, whereas **b**, **c**, **d**, and **e** crystallized. Recrystallization of these latter product mixtures from CH_2Cl_2/hexane gave regioisomerically pure samples of **5b**, **5c**, **5d**, and **5e** with melting points of 64−66 °C, 69−70 °C, 106−108 °C, and 137−138 °C, respectively (see Supporting Information for spectral data on all products).

(11) **One-Pot Procedure.** To a cold (0 °C) stirred solution of ester **2** (279 mg, 1.0 mmol) and Et_3N (150 μL, 111 mg, 1.1 mmol) in CH_3CN (2 mL) was added the MsCl (90 μL, 137 mg, 1.2 mmol) dropwise. The reaction was allowed to warm to room temperature (ice bath removal). After stirring at room temperature for 3 h, K_2CO_3 (280 mg, 2.0 mmol) was added followed by *tert*-butylamine (530 μL, 365 mg, 5.0 mmol). The mixture was heated at 60 °C (open to air) for 12 h. The same purification procedure as in ref 9 gave 340 mg (>99%) of regioisomers **5a** and **6a** (92:8).

(12) Compounds **5e** and **6e** (13.1 g, 91%, **5e**:**6e** = 97:3) were obtained according to the general procedure described in ref 9 from chloro ester **4** (10.1 g, 34.0 mmol), K_2CO_3 (4.7 g, 34.0 mmol) in CH_3CN (70 mL), and 1-phenylpiperazine (6.6 g, 6.2 mL, 40.8 mmol).