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Applications of Aziridinium Ions. Selective Syntheses of α,β-Diamino Esters, α-Sulfanyl-β-amino Esters, β-Lactams, and 1,5-Benzodiazepin-2-one

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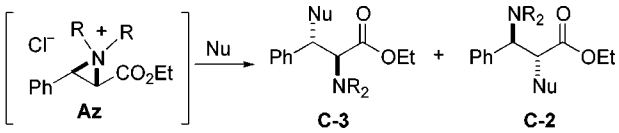
ABSTRACT



A variety of nucleophiles, including amines, thiolates, and alkoxides, were employed to open the aziridinium ions Az. The latter are opened stereospecifically and regioselectively at the C-3 position by a wide range of amines, and thiolate nucleophiles attack predominately at the C-2 position. Poor regioselectivities (ca. 1:1) were observed using nucleophiles derived from phenols, carboxylic acids, and imides. Base-mediated ring closure of the aziridinium opening products, from primary amines, gave β-lactams and a 1,5-benzodiazepin-2-one in high yields.

Aziridinium ions have received considerable attention in biological studies,[1] but in contrast to epoxides, aziridines and particularly aziridinium ions have been underutilized in organic synthesis. However, thanks to outstanding efforts by several groups, the popularity of these reactive intermediates in synthetic schemes is growing rapidly.[2] The beauty of *N*-dialkylated aziridinium ions is that they can be generated in situ under mild conditions and then captured, irreversibly by a wide range of nucleophiles, whereas simple *N*-H or *N*-alkyl aziridines require activation by an acidic agent. For simple aziridines then, the latter requirement precludes many of the most useful reagents, since nucleophiles by nature tend to be "basic".

We previously reported that α,β-diamino esters are readily prepared through stereospecific and regioselective opening of an aziridinium ion intermediate by a variety of amines.[3] The aziridinium ion is generated from the α,β-epoxy ester **1** in two steps. Furthermore, when hydrazine hydrate is used instead of the amines, the initial aziridinium opening step is followed by immediate intramolecular cyclization to afford pyrazolidin-3-one derivatives.[4] In further applications of aziridinium ions, we report here their ring opening reactions with a range of different nucleophiles along with examples where an additional step yields β-lactams and a 1,5-benzodiazepin-2-one.

The most straightforward method for generating aziridinium ions is to transform the hydroxyl group of a vicinal

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(3) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 1435.
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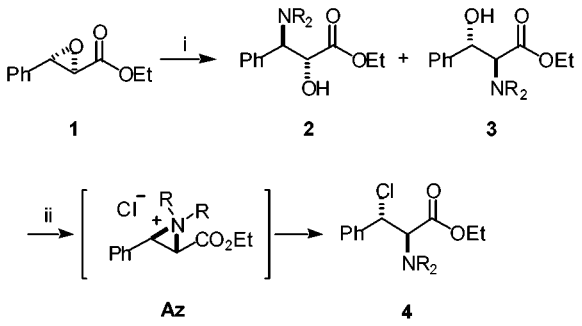
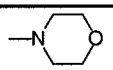
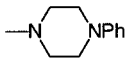
Scheme 1[a]



[a] (i) NHR_2, EtOH, reflux, 12 h; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h.

3°-amino alcohol into a good leaving group. Following this approach, epoxy ester **1** was transformed into the chloroamines **4** via the intermediate amino alcohols **2** and **3** as outlined in Scheme 1.[5] The detailed results for the four series (**a**−**d**) are given in Table 1. Treatment of epoxy ester **1** with

Table 1. Synthesis of Chloroamines **4**

entry	$-NR_2$	amino alcohol yield [%][a]; **2**:**3**[b]	chloroamine **4**; yield [%][a]
1		96; **2a**:**3a** (87:13)	**4a**; 96
2		99; **2b**:**3b** (87:13)	**4b**; 99
3	$-N(allyl)_2$	94; **2c**:**3c** (88:12)	**4c**; 99
4	$-NBn_2$	97; **2d**:**3d** (87:13)	**4d**; 94

[a] Isolated yield. [b] Analysis by HPLC (Zorbax SB-C18 reverse analytical column, 150 × 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.

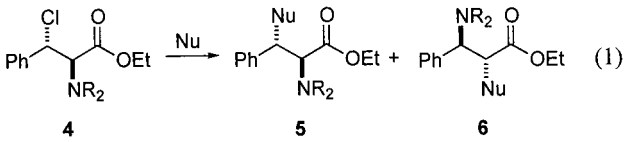
secondary amines (morpholine, 1-phenylpiperazine, diallylamine, and dibenzylamine) in refluxing EtOH gave a mixture of amino alcohols **2** and **3** (ca. 87:13). If desired, the major isomers **2a**−**2d** can be isolated by recrystallization from ether in 62−72% yield. Mesylation of the crude mixtures of regioisomers **2** and **3** gave the rearranged chloroamines **4** in near quantitative yields. In the preceding report,[3] the structure of chloroamine **4a** was secured by single-crystal X-ray diffraction and some of its stereospecific and regioselective substitution reactions, via its aziridium ion **Az**,[6] were described (e.g., entries 1 and 2, Table 2).

The scope of these aziridinium ion-based substitutions was examined with the 16 nucleophiles (**7**−**22**) shown in Figure

(5) According to the general procedure for preparation of the chloroamino ester **4a** in refs 3 and 4, **4b**, **4c**, and **4d** were obtained with melting points of 82−84, 50−51, and 79−80 °C, respectively (see Supporting Information for spectral data).

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

Table 2. Nucleophilic Opening of the Aziridinium Ion **4**



4 **5** **6**

entry	substrate	Nu	regioselectivity[a] **5**:**6**	yield[b] [%]
1	**4a**	**7**−**12**[c]	**5**:**6** >92:8	79−93
2	**4a**	**13**	**5a**:**6a** = 95:5	84
3	**4a**	**14**	**5b**:**6b** = 97:3	83
4	**4a**	**15**[d]	**5c**:**6c** = 97:3	74
5	**4a**	**16**	**5d**:**6d** = 100:0	88
6	**4a**	**17**	**5e**:**6e** = 94:6	82
7	**4a**	**18**	**5f**:**6f** = 92:8	72
8	**4a**	**19**[d]	**5g**:**6g** = 100:0	83
9	**4a**	**20**	**5h**:**6h** = 100:0[e]	68
10	**4a**	**21**	**5i**:**6i** = 3:97[f]	99
11	**4a**	**22**	**5j**:**6j** = 18:82[f]	99
12	**4b**	**8**	**5k**:**6k** = 93:7	87
13	**4b**	**13**	**5l**:**6l** = 93:7	90
14	**4b**	**16**	**5m**:**6m** = 93:7	96
15	**4c**	**8**	**5n**:**6n** = 100:0	99
16	**4c**	**13**	**5o**:**6o** = 99:1	99
17	**4c**	**16**	**5p**:**6p** = 97:3	98
18	**4d**	**11**	**5q**:**6q** = 97:3	96
19	**4d**	**13**	**5r**:**6r** = 95:5	96

[a] Analysis by HPLC (Zorbax SB-C18 reverse analytical column, 150 × 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 of **5** and **6**. [c] Reference 3. [d] 4 equiv of nucleophile was used. [e] The sole product is that resulting from attack of the NH_2 group of 2-aminophenol at the benzylic position of the aziridinium ion **Az**. [f] Note that regioselectivitiy is reversed for thiolates (**21** and **22**).

1, and the results are summarized in Table 2.[7] Treatment of chloroamines **4a**−**4d** (1.0 equiv) with amine nucleophiles **7**−**20** (1.2 equiv) and potassium carbonate (1.0 equiv) in acetonitrile at 60 °C for 12 h gave excellent results. The

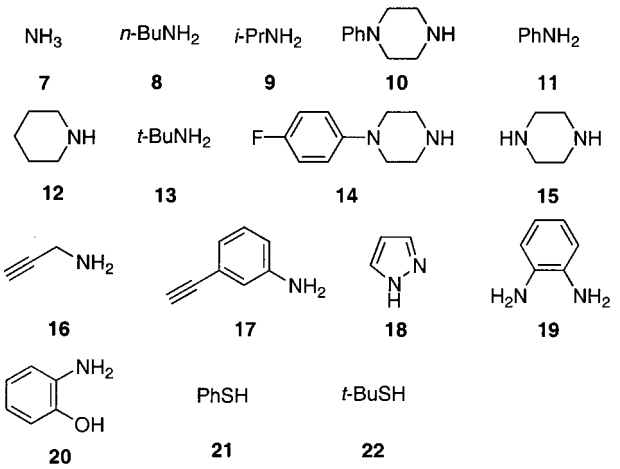


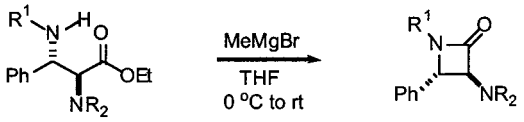
Figure 1. Nucleophiles used for the ring opening of aziridinium ions.

reactions were stereopecific in all cases, giving only the *anti* (*erythro*) relationship, and regioselectivities were greater than or equal to 92:8 (entries 3−9, 12−19). When the diamine nucleophiles **15** and **19**, with two equivalent reactive sites, were used under the standard conditions, substantial amounts of the expected dimers formed. Dimerization was circumvented by using 4 equiv of amines **15** and **19** (entries 4 and 8, Table 2) to give diamino esters **5c** and **5g**, respectively. The latter products are particularly attractive since they bear another reactive site ready for further transformation.

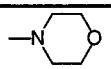
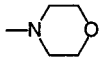
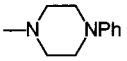
We also examined a few nucleophiles other than amines including thiolates, aroxides, carboxylates, and imides. In sharp contrast to the selective openings of the aziridinium ions at the C-3 (benzylic) position by amine nucleophiles, selective ring opening at the C-2 (α-carbonyl) position was observed for thiolate nucleophiles such as **21** and **22** (entries 10 and 11, Table 2). This C-2 selectivity with aziridinium ions (**Az**), which finds precedent in related openings of analogous *N*-sulfonylaziridines[8] and epoxides,[9] is usually attributed to the "phenacyl effect".[10] Unfortunately, the reaction of chloroamine **4a** with aroxides (*o*-phenyl phenol sodium salt, 7-hydroxy-4-methylcoumarin sodium salt) and the potassium salts of benzoic acid and phthalimide under the same conditions did not show any selectivity (ca. 1:1).

An attractive use for primary amine-based opening products **5a**, **5d**, and **5m** is closure to the *β*-lactams **24a**, **24b**, and **24c**, respectively (eq 2 and Table 3).[11] The ring closure occurs readily and in high yield when diamino esters **5a**, **5d**, and **5m** are deprotonated using methylmagnesium bromide.[12] A common route to *β*-lactams employs direct condensation of ester−enolates with imines, but the stereochemical outcome is solvent and substituent dependent.[13] The present reaction sequence from **1** to **24** provides an efficient and stereospecific route to *anti*-3-amino-*β*-lactams. Another example of a base-mediated ring closure is provided by the reaction of diamino ester **5g** with methylmagnesium bromide in THF or sodium hydride in DMSO, which furnished 1,5-benzodiazepin-2-one **25** in good yield (eq 3).[14]

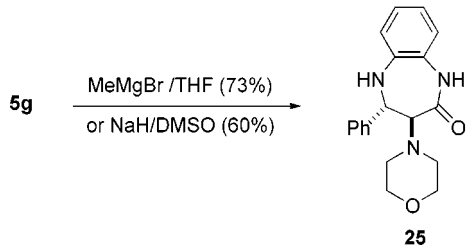
Table 3. Synthesis of *β*-Lactams **24**



5 **24** (2)

entry	R^1	$-NR_2$	substrate	product yield [%][a]
1	*t*-Bu		**5a**	**24a** (88)
2			**5d**	**24b** (90)
3	*n*-Bu		**5m**	**24c** (99)

[a] Isolated yield.



25 (3)

In summary, we have examined a variety of nucleophiles for opening aziridinium ions **Az** generated from chloroamines **4**. All openings proceeded stereospecifically, but only amines (C-3 attack) and thiolates (C-2 attack) gave high regioselectivity. A few examples of useful further transformations of products **5**, cyclizations to *β*-lactams and to a 1,5-benzodiazepin-2-one, are described.

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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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(7) **General procedure for the reaction of chloro esters 4 with nucleophiles** (eq 1, Table 2): To a stirred suspension of chloro ester **4** (1.0 mmol) and K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (2 mL) was added the nucleophile (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 pipet), which was washed with 10 mL of EtOAc. The combined filtrates were concentrated to give the products as the indicated (Table 2) mixture of regioisomers **5** and **6**. Product mixtures **d**, **e**, **g**, **m**, **n**, **o**, and **p** remained as oils, whereas **a**, **b**, **c**, **f**, **h**, **i**, **j**, **k**, **l**, **q**, and **r** crystallized. Recrystallization of these latter product mixtures from CH_2Cl_2/hexane or ether gave regioisomerically pure samples of **5a**, **5b**, **5c**, **5f**, **5h**, **5i**, **5j**, **5k**, **5l**, **5q**, and **5r** with melting points of 69−70, 241−242, 97−99, 122−123, 114−115, 63−65, 118−119, 71−73, 42−44, 112−114, and 87−89 °C, respectively (see Supporting Information for spectral data on all products). Although only performed here on a 1.0 mmol scale, these nucleophilic/aziridinium substitutions have proven equally reliable on a 13 g scale.

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(9) (a) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696. (b) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta* **1983**, *16*, 67.

(10) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed; Harper & Row: New York, 1987; p 38.

(11) To a cold (0 °C) solution of **5a** (0.1 g, 0.3 mmol) in THF (2 mL) was added MeMgBr (0.2 mL of 3.0 M solution in ether, 0.6 mmol) dropwise. The resulting solution was stirred at room temperature for 24 h and then quenched by the addition of saturated aqueous NH_4Cl (1 mL). The mixture was extracted with CH_2Cl_2 (10 mL × 2), and the combined organic layers were washed with water (5 mL × 2) and brine (5 mL × 2), dried over Na_2SO_4, and concentrated. The residue was filtered through a short plug of silica gel (2 cm in a pipet), which was washed with 10 mL of EtOAc. The combined filtrates were concentrated to give azetidin-2-one **24a** (80.0 mg, 88%) with a melting point of 86−88 °C. As described for **24a**, **24b** (an oil) and **24c** (mp 78−80 °C) were obtained in 90% and 99% yields, respectively (see Supporting Information for spectral data on all products).

(12) Kametani, T.; Huang, S.-P.; Yokohama, S.; Suzuki, Y.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 2060.

(13) 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.

(14) The reaction was performed successfully on a 2 g scale.