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Regioselective Synthesis of *N*-β-Hydroxyethylaziridines by the Ring Opening Reaction of Epoxides with Aziridine Generated In Situ

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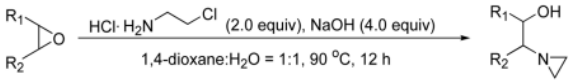
Abstract



Biologically important *N*-β-hydroxyethylaziridine intermediates were conveniently prepared by regioselective ring opening reactions of diversely substituted epoxides. Ethyleneimine generated in situ under basic conditions from β-chloroethylamine was used as a nucleophile to open the epoxides in an aqueous environment.

Aziridines are recognized as some of the most versatile synthetic intermediates in organic synthesis and for their importance in nitrogen-containing biologically active compounds.[1] Furthermore, *N*-β-hydroxyethylaziridines are one of the key types of precursors in the synthesis of natural and unnatural amino acids, β-blockers, and β-amino alcohols. Due to their significant position in synthetic organic chemistry, diverse synthetic methodologies have been reported for the preparation of aziridines.[2,3] Generally, aziridines are prepared from diazoacetates via ylide intermediates, olefins, direct conversion of epoxides, methylene transfer to carbonyl compounds and imines, and β-amino alcohol derivatives via intramolecular cyclization reactions.[2,3] Although ethyleneimine is a direct source of substituted aziridines, its use is limited by its severe acute toxicity, explosion hazard, decomposition during storage, and instability toward violent polymerization.[4]

The purpose of the present investigation was to synthesize *N*-β-hydroxyethylaziridines by ring opening of epoxides with ethyleneimine generated in situ from β-chloroethylamine. If successful, this would avoid the toxicity and polymerization problems associated with the direct use of ethyleneimine.[4] Additional advantages of this approach include employment of a limited number of steps, safety, and exploitation of the desirable properties of water as a solvent.[5]

Benzyl (*S*)-(+)-glycidyl ether (Scheme 1) was tested to determine optimal reaction conditions for subsequent use in the ring opening reactions of diverse epoxide substrates (Table 1). The epoxide was heated at 90 °C with 3.0 equiv or 2.0 equiv (entries 1 and 2) of 2-chloroethylamine hydrochloride and excess aqueous sodium hydroxide to afford the substituted *N*-β-hydroxyethylaziridine (Scheme 1) as the major product in 67% and 60% yields, respectively.

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The use of 2-bromoethylamine hydrochloride instead of 2-chloroethylamine hydrochloride (entry 5) did not improve the yield. The best result was obtained from a mixed solvent system prepared from equal volumes of dioxane and aqueous sodium hydroxide. Reactions in organic solvents with bases such as triethylamine or potassium *t*-butoxide or sodium hydride provided poor yields or no detectable product. In general, it was necessary to include dioxane in the solvent because of the limited solubility of the epoxide in water.

The ^{1}H NMR spectrum[6] of the substituted *N*-β-hydroxyethylaziridine obtained as described in Scheme 1 exhibited separate signals for each of the four aziridine protons as well as the two protons of the methylene group located between the nitrogen and the carbinol carbon. Two upfield aziridine protons occurred as doublets of doublets at δ1.16 (dd, *J* = 3.9 and 7.5 Hz, 1 H) and 1.23 (dd, *J* = 3.9 and 7.5 Hz, 1 H), while two lower field aziridine protons appeared as apparent triplets at 1.74 (dd, *J* = 3.9, 5.7 Hz, 1 H) and 1.78 (dd, *J* = 3.9, 5.8 Hz, 1 H). There was no apparent geminal coupling of the aziridine protons. On the other hand, the two protons on the methylene groups located between the nitrogen and the carbinol carbon appeared at lower field as doublets of doublets at δ 2.25 (dd, *J* = 4.8 and 12.0 Hz, 1 H) and at δ 2.40 (dd, *J* = 6.9 and 12.0 Hz, 1 H). The basic pattern of four separate signals observed for the aziridine protons did not change on conversion of the product to its TMS ether. This indicates that intramolecular hydrogen bonding between the hydroxyl group and the aziridine nitrogen is not responsible for the observation of four separate signals for the aziridine protons.

The reaction mechanism likely involves in situ formation of ethyleneimine, which then participates in the regioselective ring opening reaction of the epoxide to produce the β-*N*-hydroxyethylaziridine product. As can be seen in Table 1, the use of excess sodium hydroxide relative to 2-chloroethylamine hydrochloride afforded the desired product, whereas the use of equimolar amounts of sodium hydroxide and 2-chloroethylamine hydrochloride resulted in only a trace amount of the aziridine product detected by TLC (entry 3). Two equivalents of base are required, one to deprotonate the starting material and one to neutralize the hydrochloric acid generated in the aziridine ring closure reaction (Scheme 2). As expected, the product was optically active, producing an optical rotation $[\alpha]_D^{23} = -11.9$ (c 1, $CHCl_3$), which compares favorably with the $[\alpha]_D^{23} = +11.9$ (c 1, $CHCl_3$) value of the substituted (*R*)-*N*- β-hydroxyethylaziridine obtained from the reaction of its enantiomer, (−)-benzyl (*R*)-glycidyl ether, following the same reaction procedure outlined in Scheme 1.

The ring opening reaction of epoxides using substrates with different substituents was examined next, employing the optimal reaction conditions determined from the study reported in Table 1. The reaction of *p*-chlorostyrene epoxide (entry 2, Table 2) provided the *N*-β-hydroxyethylaziridine product in higher yield (83%) than was obtained with the styrene substrate (65%, entry 3).

In the case of epoxides fused to carbocyclic rings (entries 4 and 5), the results were similar to each other regardless of the difference in ring size. The C_2-symmetric substrate *trans*-stilbene oxide (entry 6) provided the aziridine product in 65% yield, close to that of the two epoxides fused to carbocycles. Similarly, the ring opening reactions of two epoxides substituted with straight hydrocarbon chains (entries 7 and 8) afforded yields that were similar to the others. The formation of byproducts was generally low (<5%). In some cases, epoxide hydrolysis products were detected.

A comparison experiment[7] was conducted with pure ethyleneimine and benzyl (*S*)-(+)-glycidyl ether using the optimal reaction condition (Scheme 3). The expected ring-opened product displayed the same NMR spectrum as the substance obtained as described in the Scheme 2. In this reaction, the yield after purification was 69%, similar those listed in Table 2. This result is consistent with the mechanistic pathway involving formation of aziridine from

2-chloroethylamine prior to nucleophilic ring opening of the epoxide. The formation of aziridine from 2-chloroethylamine in the reaction mixtures studied here is also consistent with the conditions previously reported for the synthesis of aziridine from 2-choroethylamine in aqueous sodium hydroxide.[4] Furthermore, the 65% yield reported for entry 3 (Table 1) is comparable to the 48% yield reported for the reaction of aziridine with styrene epoxide in aqueous solution at 100 °C.[8]

In cases for which regioisomeric reaction products are possible, only one regioisomer was isolated as evidenced by the ^{1}H NMR spectral data. The observed regioisomers were consistently derived from nucleophilic attack of the aziridine nitrogen atom on the less-substituted carbon atom of the epoxide. It is possible that small amounts of the regioisomers might have formed but were removed during purification of the product.

In conclusion, we have established a regioselective ring opening reaction of epoxides to yield β-hydroxy aziridines by in situ generation of ethyleneimine using a mixed solvent system of aqueous sodium hydroxide and 1,4-dioxane. The formation of ethyleneimine likely occurs prior to ring opening of epoxide. This protocol offers the advantage of avoiding the use of ethyleneimine as a starting material in the synthesis of *N*-β-hydroxyethylaziridines.[8,9]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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6. The ^{1}H NMR spectrum was obtained using $CDCl_3$. ^{1}H and ^{13}CNMR spectrum, mass and elemental analysis data are available in the supporting information
7. The reaction was carried out in a 1:2:4 molar ratio of epoxide:ethylenimine:NaOH with heating at 90 °C for 12 h in a mixed solvent system of water and 1,4-dioxane (1:1). Total water volume, including water volume used in aqueous NaOH solution, was adjusted to the same solvent volume of 1,4-dioxane

used in the reaction. A stock solution of sodium hydroxide was prepared by dissolving 40 g of NaOH in 60 mL of water..

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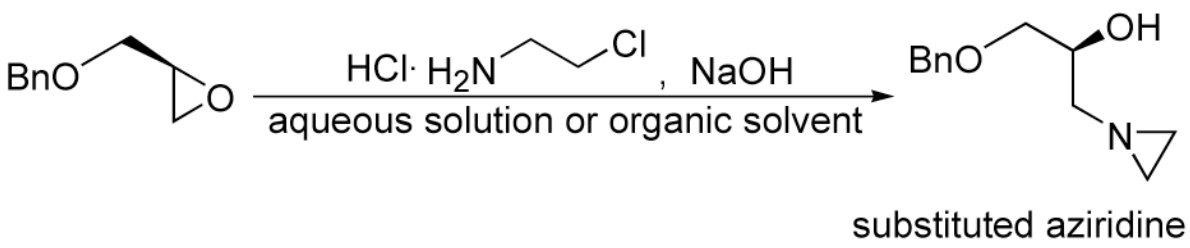
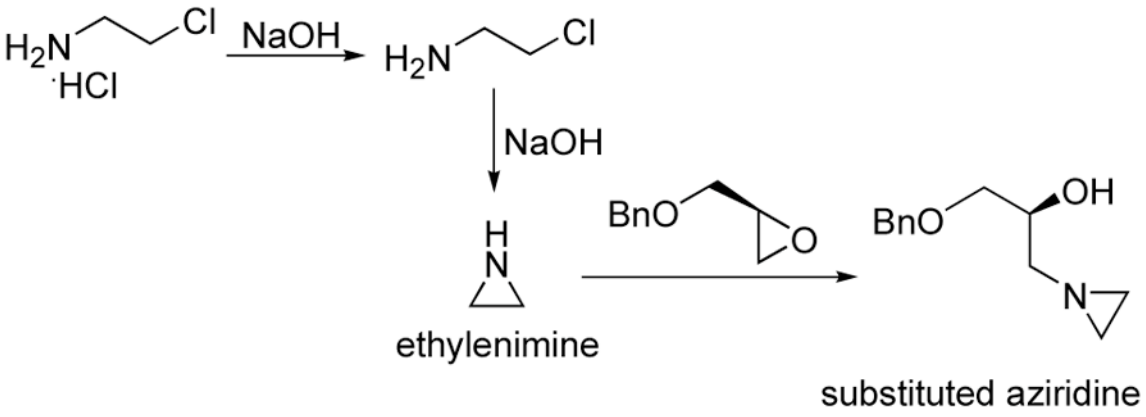
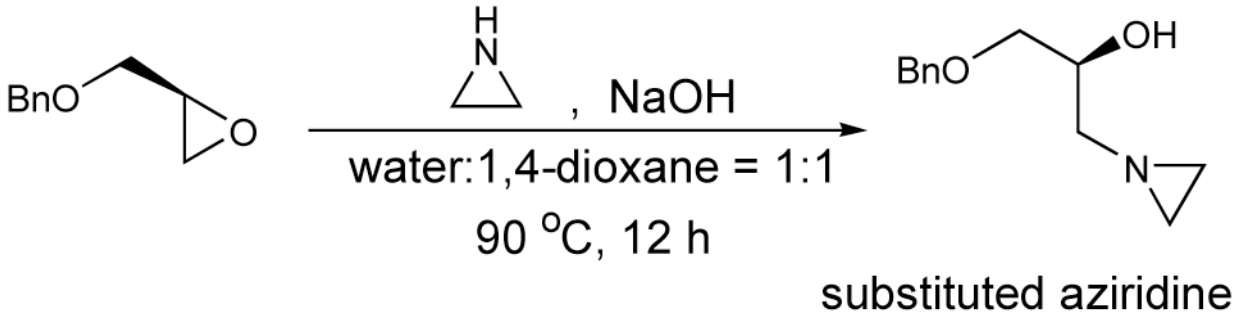


Scheme 1.



Scheme 2.



Scheme 3.

Table 1

Optimization Reactions with 2-Chloroethylamine Hydrochloride in Aqueous Dioxane Solution or in Organic Solvents[a]

entry	2-chloroethylamine hydrochloride (equiv)	NaOH or base (equiv)	solvent (°C)	yield (%)[b]
1	3.0	NaOH (6.0)	water/dioxane (90)	67
2	2.0	NaOH (4.0)[c]	water/dioxane (90)	60
3	1.5	NaOH (1.5)	water/dioxane (90)	trace
4	1.05	NaOH (2.1)	water/dioxane (90)	43
5	1.5[d]	NaOH (3.0)	water/dioxane (90)	22
6	2.0	Et_3N (4.0)	dioxane (90 to 100)	trace
7	2.0	Et_3N (4.0)	DMF (90 to 100)	20
8	2.0	*t*-BuOK (4.0)	THF (70)	not detected[e]
9	2.0	NaH (4.0)	DMSO (70)	not detected[e]

[a] Each reaction mixture was stirred for 12 h at 90 °C.

[b] Reaction yield refers to the pure products isolated after flash column chromatography.

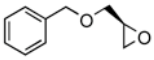
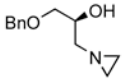
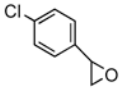
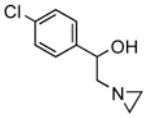
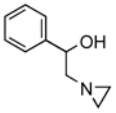
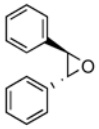
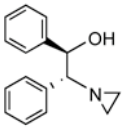
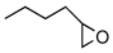
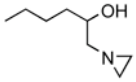
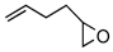
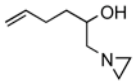
[c] Reaction was performed with 0.1 equiv of NaI additive.

[d] 2-Bromoethylamine hydrochloride was used instead of 2-chloroethylamine.

[e] No desired product was obtained.

Table 2

Regioselective Ring Opening of Epoxides with in situ Generated Ethylenimine in the Same Reaction Pot[a,b]

entry	epoxide	product	yield (%)[c]
1			67[d]
2			83
3			65
4			60
5			58
6			65
7			67
8			61

[a] Reactions proceeded in a 1:2:4 molar ratio of epoxide:2-chloroethylamine hydrochloride:NaOH. A stock solution of sodium hydroxide was prepared by dissolving 40 g of NaOH in 60 mL of water.

[b] Typically, the reaction mixture was heated at 90 °C for 12 h in a 1:1 volume ratio of water:1,4-dioxane.

[c] Reaction yield refers to the isolated pure products obtained after flash column chromatography.

[d] Reaction proceeded in a 1:3:6 molar ratio of epoxide:2-chloroethylamine:NaOH.