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Stereoselective Synthesis of 3-Hydroxyazetidines via Regioselective Halogenation of 2,3-Epoxyamines by Using Magnesium Bromide

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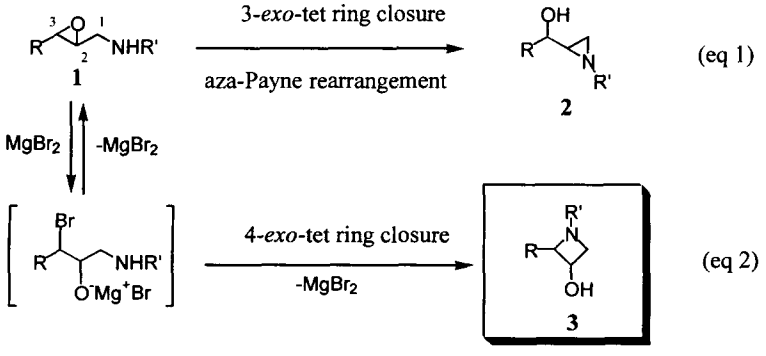
Abstract: *A novel stereoselective synthesis of 3-hydroxyazetidines starting from 2,3-epoxyamines is described. Regioselectivity of the intramolecular cyclization of 2,3-epoxyamines is controlled by the use of magnesium bromide. The cyclization proceeds with retention of the stereochemistry, caused by double inversion of two sequential S_N2 reactions of the epoxyamines.* © 1997 Elsevier Science Ltd.

Azetidin-3-one derivatives are interesting as the non-hydrolyzable isosteres of β-lactams.[1] Although 3-hydroxyazetidines seem to be good precursors for the azetidin-3-ones,[2] there have been only few examples for efficient synthesis of these compounds.[3]

On the other hand, intramolecular cyclization of 2,3-epoxyamines (**1**) leading to hydroxymethylaziridines (**2**) is known as the aza-Payne rearrangement (eq 1). This reaction proceeds through the 3-*exo*-tet type cyclization.[4] If the nitrogen reacts at the terminal C-3 carbon, 3-hydroxyazetidine derivatives (**3**) will be formed. However, the 4-*endo*-tet-like type cyclization reaction have not yet been reported, even though the case of the terminal C-3 carbon is activated by conjugate effects.[4a] Clearly, a method which allows for the control of both regio- and stereochemistry would be of great utility for the synthesis of these compounds. Herein, we report that magnesium bromides can be used effectively for the conversion of *cis*- and *trans*-2,3-epoxyamins to *trans*- and *cis*-3-hydroxyazetidines, respectively (eq 2).

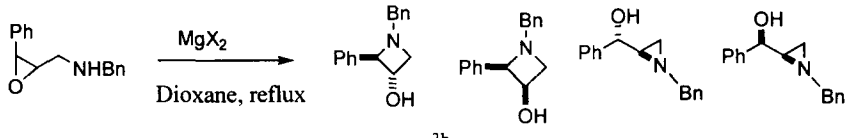


Scheme 1

2,3-Epoxyamines (**1**) were prepared from 2,3-epoxyhalides according to the previously established method[5a] and to the modified known methods.[5b,5c]

Preliminary investigations were carried out in dioxane using magnesium bromide etherate as the brominating reagent and *N*-benzyl-*N*-(*cis*-3-phenyl-2,3-epoxypropyl)amine (**1a**) as the substrate. The reaction has to be performed in the presence of 5 mol% of a magnesium bromide etherate (Table 1, Entry 2) with good regio- and stereoselectivity. The stereochemistry of the cyclization proceeded with retention,[6] because halogenation of the epoxide with magnesium bromide proceeded with inversion and the following displacement of the halogen by the amino group also proceeded with inversion. In a further experiment, we tested the efficiency of the halogenating reagent. Use of magnesium bromide etherate and magnesium bromide gave similar results (Entry 2 and 4). In the case of addition of 1 mol% of magnesium bromide etherate, it was seen that the reaction was retarded and the ratios of the hydroxymethylaziridines (**2a** and **2b**) were increased (Entry 3). Magnesium iodide is also effective, and the reaction was completed in 1h (Entry 5).

Table 1. Synthesis of *trans*-3-Hydroxy-2-phenylazetidine



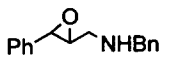
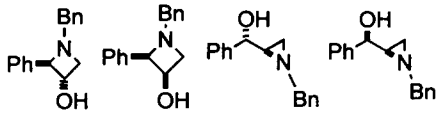
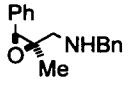
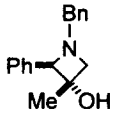
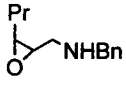
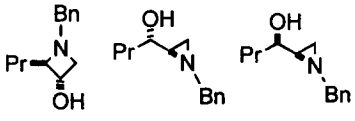
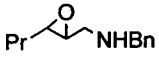
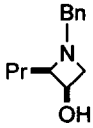
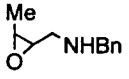
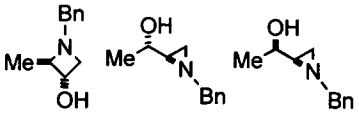
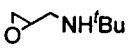
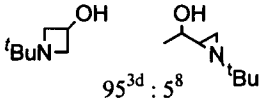
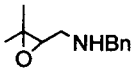
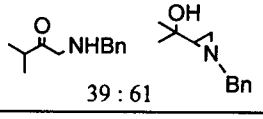
cis-**1a** *trans*-**3a**[3b] *cis*-**3b** *anti*-**2a** *syn*-**2b**

Entry	MgX_2 (mol%)	Time/h	Yield/%[a]	Product /Ratio (**3a** : **3b** : **2a** : **2b**)[b]
1	$MgBr_2$-Et_2O (50)	5	48	88 : 4.1 : 7.1 : 0.5
2	$MgBr_2$-Et_2O (5)	5	69	89 : 1.9 : 8.9 : trace
3	$MgBr_2$-Et_2O (1)	48	60	61 : trace : 32 : 7.5
4	$MgBr_2$ (5)	5	66	86 : 9.7 : 4.0 : none
5	MgI_2 (5)	1	59	85 : 9.0 : 6.5 : none

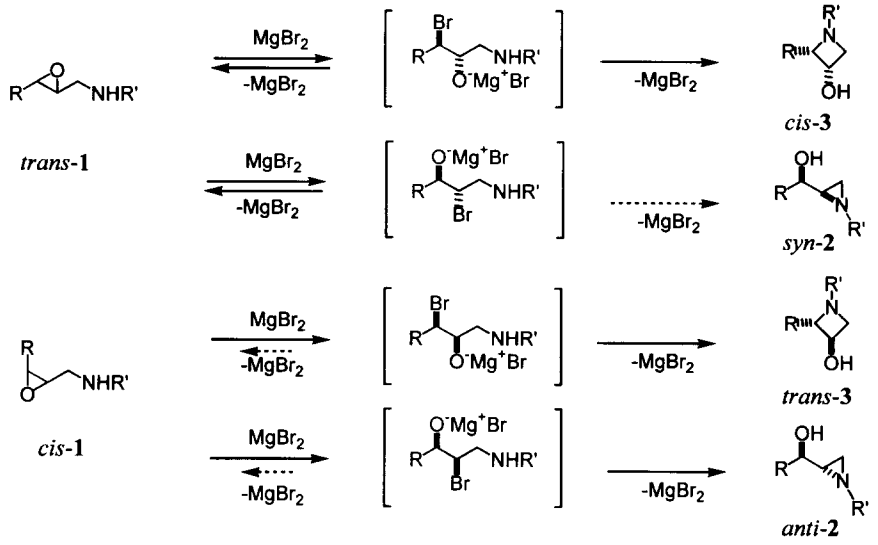
[a] Isolated yield. [b] Ratio was determined by ^1H NMR.

Following these observations, the procedure was extended to various 2,3-epoxyamines (**1**). As shown by the examples compiled in Table 2, reasonable yields of the expected 3-hydroxyazetidines (**3**) were obtained (Table 2, Entry 1-8), except in the case of a dimethy substituted derivative, which gave hydroymethylaziridine (**2**) as the main product and a ketone derivative as a minor product (Entry 9). Also, when we applied magnesium iodide as the halogenation reagent for *N*-benzyl-*N*-(*trans*-3-phenyl-2,3-epoxypropyl)amine, *trans*-3-hydroxyazetidine (**3a**) was obtained as an unexpected steroisomer (Entry 3). Thus, magnesium iodide is not effective for the stereospecific synthesis of **3**. In the case of *cis*-2,3-epoxyamines, the formation of small amounts of the corresponding hydroymethylaziridines (**2**) as side-products was observed (Entry 5 and 7). Magnesium bromide is well known as an effective halogenating reagent for epoxides.[7] Accordingly, the rapid formation of β-halohydrine intermediates should be expected by the attack of magnesium halide, and the next cyclization step would be the rate-determining step. In the case of *trans*-2,3-epoxyamines (**1**), the rapid equilibration between the starting materials and the β-halohydrine intermediates will take place. On the other hand, equilibration of β-halohydrines and *cis*-2,3-epoxyamine (**1**) will not occur or is very slow, because the *cis*-substituted groups are not preferred for the reproduction of the epoxide ring. Thus, a small amount of hydroxymethylaziridines is formed (Scheme 2).

Table 2. Synthesis of 3-Hydroxyazetidines[a)]

Entry	Substrate	MgX_2 (5 mol %)	Time h	Yield[b)] %	Product Ratio[c)]
					
1		$MgBr_2$-Et_2O	8	79	6.1[3b] : 94 : trace : trace
2		$MgBr_2$	3	73	6.5[3b] : 92 : trace : 1.3
3		MgI_2	2	52	93[3b] : 7.0 : none : none
4		MgI_2	24	77[3b]	
5		$MgBr_2$-Et_2O	12	78	 89 : 11 : trace
6		$MgBr_2$-Et_2O	9	58	
7		$MgBr_2$-Et_2O	8	31	 67[3c] : 17 : 16
8		$MgBr_2$-Et_2O	3	69	 95[3d] : 5[8]
9		$MgBr_2$-Et_2O	10	58	 39 : 61

[a)] All reactions were conducted in refluxed anhydrous 1,4-dioxane. [b)] Isolated Yield.
[c)] Ratios were determined by ^1H NMR spectroscopy.



Scheme 2

A typical procedure for the synthesis of *trans*-**3a** is as follows. *N*-Benzyl-*N*-(*cis*-3-phenyl-2,3-epoxypropyl)amine **1a** (239 mg, 1.0 mmol) and magnesium bromide etherate (12.8 mg, 0.05 mmol) are refluxed in dry dioxane (10 ml) for the consumption of **1a**, monitored by TLC. The reaction mixture was passed through silica-gel short column chromatography with ethylacetate as an eluent. The eluted mixture was distilled using Kugelrohar apparatus. The products were almost pure and were found to consist of *trans*-**3a**, *cis*-**3b**, *anti*-**2a**, and *syn*-**2b** in a 89 : 1.9 : 8.9 : trace ratio by ^{1}H NMR analyses.

In summary, a broadly applicable and simple procedure for the efficient cyclization of 2,3-epoxyamines (**1**) to 3-hydroxyazetidines (**3**) has been developed. Research is ongoing to investigate the application of this methodology to other heterocyclic systems.

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