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$NaHSO_3$-PROMOTED RING OPENINGS OF *N*-TOSYLAZIRIDINES AND EPOXIDES WITH H_2O

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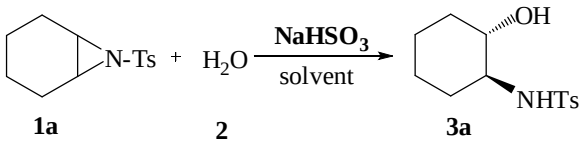
Abstract – $NaHSO_3$-oriented ring openings of a wide variety of *N*-tosylaziridines and epoxides with H_2O under mild conditions in acetone was found to be a convenient and effective method, which provided the desired β-aminoalcohols and β-diols in good to excellent yields and with uniformly high regioselectivity.

β-Aminoalcohols are very useful building blocks for the preparation of drugs, natural products and relevant compounds.[1,2] Due to their synthetic value and pharmacological properties, considerable interest and effort have been focused on the construction of β-aminoalcohols and their derivatives.[3] In recent years, some attractive methods for the synthesis of them have been developed.[4-9] Among these methods, the ring openings of *N*-tosylaziridines with H_2O provides direct access to them, and several catalysts and activators have been employed and identified for this transformation, respectively.[10] Despite these creative efforts and significant progress, the discovery of new catalysts or activators which are cheaper and more efficient and the development of new methods which are more effective remain urgent. $NaHSO_3$ has been applied to the ring-opening reactions of nonactivated aziridines as a nucleophilic reagent.[11] Herein, we will describe another new and successful application of $NaHSO_3$ as a promoting reagent in the ring opening.

We began with our studies by selecting the ring opening of *N*-tosylcyclohexylaziridine[12] **1a** with H_2O as the model reaction and $NaHSO_3$ as a promoting reagent. Initially, the survey of solvents clearly highlighted the beneficial effect of mixture solvents (Table 1, entries 2-4 *vs.* 1). It was observed that the mixture solvent of acetone and H_2O (1:1) was the most suitable for this transformation (Table 1, entry 4).[13] No ring-opening product was detected when H_2O was used as a kind of solvent at 25 °C (Table 1, entry 1).

Table 1. Screening of reaction conditions for ring opening of *N*-tosylcyclohexylaziridine **1a** with H_2O[a]



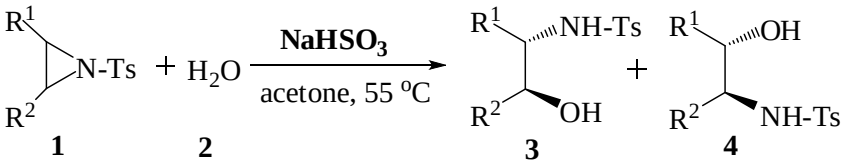
1a **2** **3a**

Entry	Solvent	T (°C)	Yield[b] (%)
1	H_2O	25	trace
2	DMSO/H_2O=1:1	25	trace
3	MeCN/H_2O=1:1	25	22
4	acetone/H_2O=1:1	25	33
5[c]	acetone/H_2O=1:1	55	99

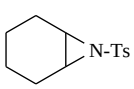
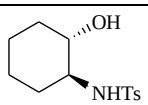
[a] Unless otherwise noted, all reactions were carried out with *N*-tosylcyclohexylaziridine **1a** (50 mg, 0.2 mmol) and 1.1 equiv. of $NaHSO_3$ in 1.0 mL solvent under identified conditions for 24 h. [b] Isolated yield. [c] 2.0 equiv. of $NaHSO_3$ and 3.0 mL solvent were used.[14]

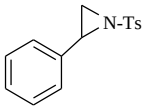
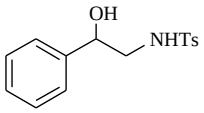
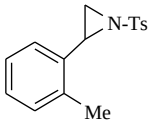
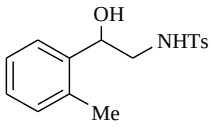
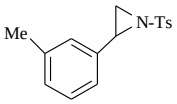
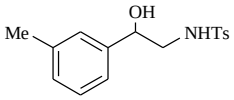
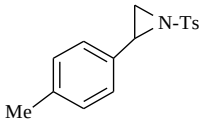
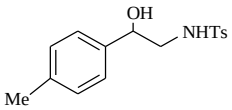
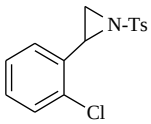
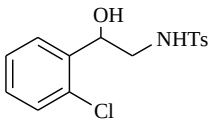
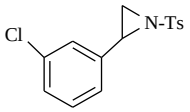
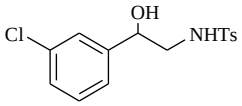
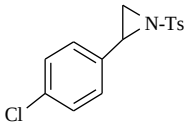
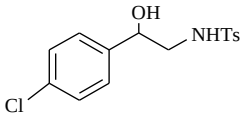
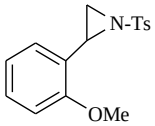
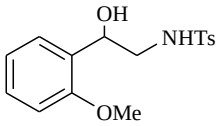
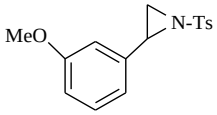
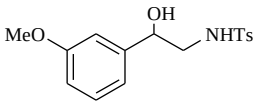
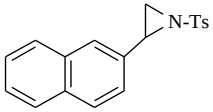
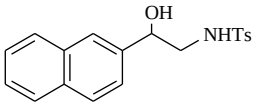
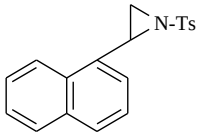
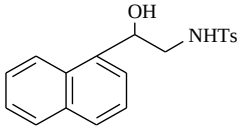
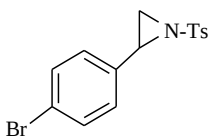
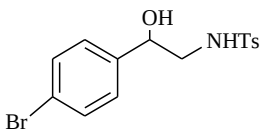
Under these optimized reaction conditions,[14] a wide variety of *N*-tosylaziridines such as aromatic, aliphatic (cyclic and acyclic), and condensed-ring ones could be smoothly transformed into the desired ring-opening products in good to excellent yields with high regioselectivity and the results are listed in Table 2. Except for the *N*-tosylaziridine **1q** which afforded the two corresponding isomers (**3q**:**4q** = 9:2) (Table 2, entry 16), all other *N*-tosylaziridines showed the remarkable regioselectivity and provided only single regioisomers **3** (Table 2, entries 2-13). In addition, it was observed that steric hindrance of the substituent groups at the aromatic ring of *N*-tosylaziridines played an important role on the reactivity of this reaction. The *para*-substituted *N*-tosylaziridines indicated higher reactivity than those substituted in *ortho*- and *meta*-position (Table 2, entry 5 *vs.* 3, 4 and entry 8 *vs.* 6, 7). Excitedly, the *N*-tosylaziridines **1n** could give the desired ring-opening product with the moderate yield (Table 2, entry 14).

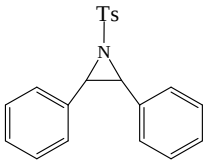
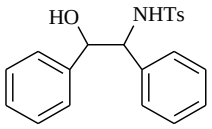
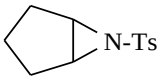
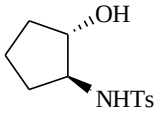
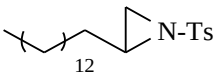
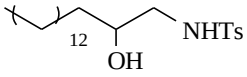
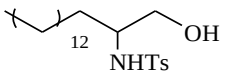
Table 2. Ring-opening reactions of various *N*-tosylaziridines **1** with H_2O[a]



1 **2** **3** **4**

Entry	*N*-Tosylaziridine **1**	Product	*t* (h)	Yield[b] (%)
1	 **1a**	 **3a**	24	99

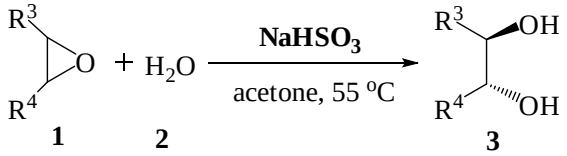
2	 **1b**	 **3b**	12	99
3	 **1c**	 **3c**	10	99
4	 **1d**	 **3d**	4	96
5	 **1e**	 **3e**	2	92
6	 **1f**	 **3f**	36	97
7	 **1g**	 **3g**	24	92
8	 **1h**	 **3h**	9	81
9	 **1i**	 **3i**	4	93
10	 **1j**	 **3j**	8	97
11	 **1k**	 **3k**	21	83
12	 **1l**	 **3l**	3	96
13	 **1m**	 **3m**	12	97

14	 **1n**	 **(±)-3n**		48	53
15	 **1o**	 **3o**		48	91
16	 **1q**	 **3q**  **4q**		36	62[c] (**3q:4q** = 82:18)

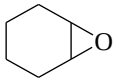
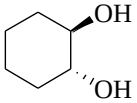
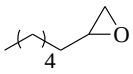
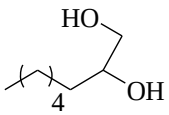
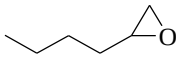
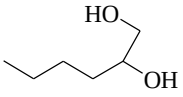
[a] Unless otherwise noted, all reactions were performed at 0.2 mmol scale of *N*-tosylaziridines **1** and 2.0 equiv. of $NaHSO_3$ (41.9 mg) in 3 mL of mixture solvent of acetone/water (1:1) under air atmosphere at 55°C within specified time. [b] Isolated yield. [c] Combined yield of isolated **3q** and **4q**.

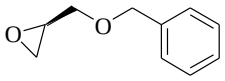
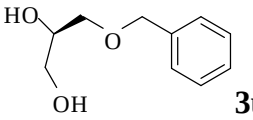
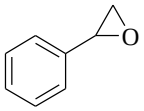
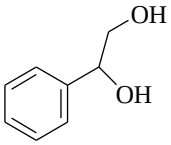
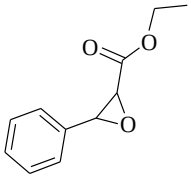
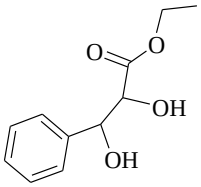
Moreover, from a practical point of view, epoxides as substrates were also tested to obtain β-diols for examining the scope of application of the reaction system under the optimal conditions. It can be seen from Table 3 that various epoxides could be hydrolyzed to give the desired 1,2-diols in good to excellent yields using $NaHSO_3$ as a catalyst. The ring-opening reaction of chiral epoxide **1u** also proceeded smoothly and provided product **3u** in 87 yield (Table 3, entry 4).

Table 3. The hydrolysis of epoxides in the presence of $NaHSO_3$[a]



1 **2** **3**

Entry	Epoxide **1**	Product	*t* (h)	Yield[b] (%)
1	 **1r**	 **3r**	36	82
2	 **1s**	 **3s**	36	86
3	 **1t**	 **3t**	40	83

4	 **1u**	 **3u**	36	87
5	 **1v**	 **3v**	28	91
6	 **1w**	 **3w**	40	68

[a] Unless otherwise noted, all reactions were performed at 0.2 mmol scale of epoxides **1** and 2.0 equiv. of $NaHSO_3$ (41.9 mg) in 3 mL of mixture solvent of acetone/water (1:1) under air atmosphere at 55 °C within specified time. [b] Isolated yield.

In summary, we have developed a single, practical and efficient method for the synthesis of β-aminoalcohols through the ring-opening reactions of *N*-tosylaziridines with H_2O using $NaHSO_3$ as a promoting reagent. All substrates gave high regioselectivity and good to excellent yields. In addition, the same experimental conditions can be successfully applied in the ring openings of epoxides with H_2O to afford the desired β-diols with good yields.

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13. The results that some other ratio of acetone to H_2O provided were relatively wore.
14. These are the optimal reaction conditions. The screening about experimental parameters can be seen in the Supporting Information.