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Do aziridines require Lewis acids for cleavage with ionic nucleophiles?

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Abstract—A variety of activated aziridines were cleaved by sodium azide and sodium cyanide in aqueous acetonitrile at reflux, in the absence of any Lewis acid, to provide ring-opened products in quantitative yields. However, the reaction was sluggish in the ring opening of unactivated aziridines with sodium azide where the yields could be increased by adding 50 mol% $CuCl_2 \cdot 2H_2O$. The reaction was used to synthesize chiral diamines.

Aziridines are versatile intermediates for the synthesis of nitrogen containing biologically active compounds.[1] The reactivity of this strained heterocyclic ring system is dependent upon the substitution on the nitrogen atom. Electron withdrawing groups on nitrogen enhance the reactivity of the ring and these are termed as activated azidirines. A number of nucleophilic ring-opening reactions have been studied on activated and nonactivated aziridines (*N*-alkyl or aryl). The ring-opening reaction of aziridines with nitrogen nucleophiles such as the azide ion has special significance because the products are precursors for vicinal diamines which have varied applications in organic synthesis.[2] This is usually done using $TMSN_3$[3] as the classical protocol (NaN_3 and NH_4Cl)[4] requires a longer reaction time. Recently, cleavage of activated aziridines and epoxides with NaN_3 in the presence of cerium(III) chloride has been reported.[5] Although this is a useful procedure, we discovered that cerium(III) chloride is not required for opening activated aziridines and epoxides.[6] In fact, the reaction is faster in the absence of this Lewis acid. In view of this observation, we carried out a detailed study and now report our results.

A solution of *N*-tosylcyclohexyl aziridine (1 mmol) and NaN_3 (1.5 mmol) in acetonitrile:water (5 mL; 9:1) was refluxed for 40 min. After completion of the reaction, the flask was cooled and the majority of the MeCN was removed in vacuo. The crude reaction mixture was then partitioned between EtOAc and water. Work-up and purification by silica gel column chromatography gave the 1,2-azidoamine in quantitative yield (Table 1, entry 1). In a similar fashion, the reaction of the above aziridine with sodium cyanide gave the 1,2-cyanoamine in 92% yield (Table 1, entry 2). The reactions were extended to several activated aziridines and in all cases, a high yield of the product was obtained (Table 1).

A phenyl substituted aziridine underwent the reaction in a regioselective manner whereby the azide and cyanide ions attacked the benzylic position (Table 1, entries 10 and 11). Acyclic terminal aziridines gave products resulting from terminal attack (Table 1, entries 12–16). It was observed that the reaction of unactivated aziridines with sodium azide was sluggish. For example, the yield from the cleavage of *N*-phenylcyclohexyl aziridine with NaN_3 was only 40% at reflux temperature for 12 h. The reaction yield and rate were improved by adding 50 mol% of $CuCl_2 \cdot 2H_2O$ under the above conditions (Table 2, entry 1). Similar results were obtained in the cases of other *N*-arylcyclohexyl aziridines (Table 2, entries 2–6). It was observed that these unactivated aziridines could not be cleaved with sodium cyanide in absence of Lewis acids.[7] In order to increase the scope of this reaction, it was extended to epoxides (Table 2, entries 7–9), which behaved like unactivated aziridines. The epoxides were cleaved with NaN_3 in the absence of cerium chloride, but the reactions were sluggish. However, as expected, the reaction was very facile upon addition 50 mol% $CuCl_2 \cdot 2H_2O$.

The reaction was also extended to the cleavage of the chiral aziridines **1**. In the case of **1a** ($n=1$), an inseparable mixture (diastereomeric ratio = 1:3) of cleaved product **2a** was obtained in 80% yield. However, **1b** ($n=2$) provided a separable mixture of **2b** in a

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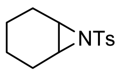
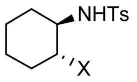
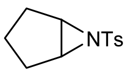
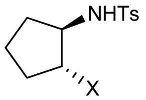
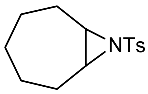
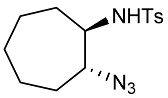
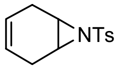
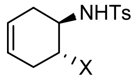
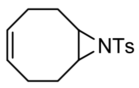
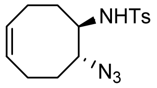
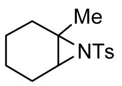
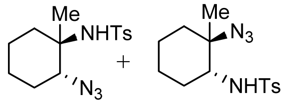
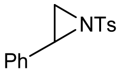
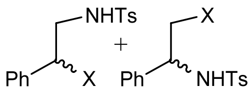
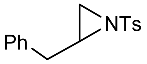
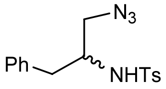
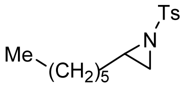
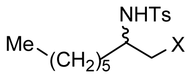
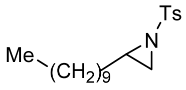
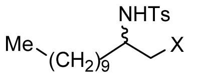
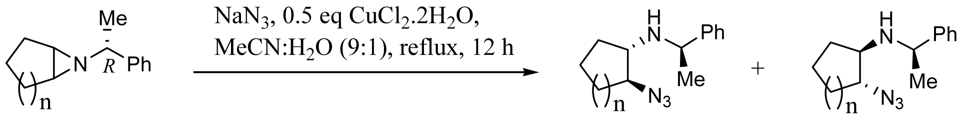
Table 1. Cleavage of activated aziridines with NaN_3 or NaCN in $MeCN:H_2O$ (9:1) at 80°C

Entry	Aziridine	1,2-Azidoamine		Time	Isolated Yield
1			$X = N_3$	40 min	99%
2			X = CN	3 h	92%
3			$X = N_3$	2.5 h	99%
4			X = CN	5 h	90%
5				12 h	93%
6			$X = N_3$	50 min	98 %
7			X = CN	4 h	85%
8				12 h	86%
9		 (ratio: 9 : 1)		80 min	98%
10			$X = N_3$	75 min	98%[a]
11			X = CN	2 h	83%[b]
12				75 min	98%
13			$X = N_3$	1.7 h	92%
14			X = CN	4 h	88%
15			$X = N_3$	1.5 h	93%
16			X = CN	4 h	85%

[a]Ratio of prodcucts = 89:11. [b]Ratio of products = 77:23.



1

NaN_3, 0.5 eq $CuCl_2.2H_2O$, $MeCN:H_2O$ (9:1), reflux, 12 h

(*S*,*S*,*R*)-**2** + (*R*,*R*,*R*)-**2**

a, n = 1 Yield = 80 % ratio = 1 : 3 (inseparable)
b, n = 2 Yield = 97 % ratio = 1 : 4.5 (separable)

Scheme 1.

diastereomeric ratio of 1:4.5. The major diastereomer (*R*,*R*,*R*)-**2b** was converted to the (*R*)-enantiomer of *trans*-1,2-cyclohexanediamine by a known method (Scheme 1).[3e]

Acknowledgements

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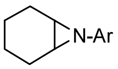
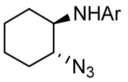
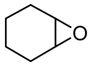
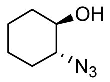
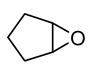
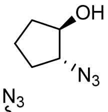
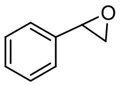
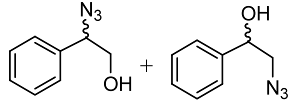
Table 2. Cleavage of unactivated aziridines and epoxides with NaN_3 in MeCN:H_2O (9:1) at 80°C

Entry	Substrate	Product	Isolated Yield (time)	
			without catalyst	with $CuCl_2.2H_2O$
1		 Ar = Ph	40% (12 h)	73% (2 h)
2		Ar = C_6H_4-*m*-Cl	42% (12 h)	78% (2 h)
3		Ar = C_6H_4-*p*-Cl	49% (12 h)	73% (3 h)
4		Ar = C_6H_4-*p*-OMe	45% (12 h)	66% (1.5 h)
5		Ar = 2-naphthyl	39% (12 h)	61% (2 h)
6		Ar = Benzyl	80% (20 h)	95% (4 h)
7			78% (6 h)	94% (3 h)
8			55% (6 h)	82% (4 h)
9		 ratio: 7 : 3	90% (6 h)	92% (3 h)

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6. For some more papers in this area, see: (a) Yadav, J. S.; Reddy, B. V. S.; Parimala, G.; Reddy, P. V. *Synthesis* **2002**, 2383; (b) Babu, R. S.; Reddy, M. S. K.; Yadav, J. S. *Synthesis* **2002**, 2254.
7. It was observed that unactivated aziridines could also not be cleaved with nucleophiles such as NaCl and LiBr even in the presence of $CuCl_2·2H_2O$. However, activated aziridines could be cleaved with NaCl in aqueous MeCN at reflux upon addition of $CuCl_2·2H_2O$.