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An efficient route to regioselective opening of *N*-tosylaziridines with zinc(II) halides

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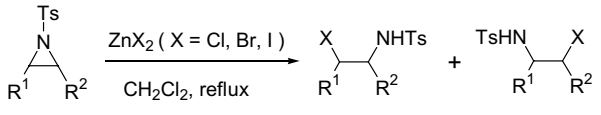
Dedicated to Dr. Ganesh Pandey on the occasion of his 50th birthday

Abstract—An efficient route for the regio- and stereoselective ring opening of *N*-tosylaziridines with zinc dihalides (ZnX_2, X = Cl, Br, I) is described. Depending on the solvent and Zn(II) halide, β-halo amines or imidazolines are obtained selectively in good to excellent yields.

Aziridines are attractive as well as versatile building blocks, widely used for the syntheses of various natural products and bioactive molecules.[1] Regio- and stereoselective ring opening reactions of aziridines with various nucleophiles have been exploited by several groups for chemical transformations of contemporary interest.[2] Although, several methods are known for the cleavage of aziridines with a range of heteroatom[3] and carbon nucleophiles,[4] only a limited number of methods for regioselective nucleophilic ring opening by halide anions have been reported. These methods include using HCl,[5] metal halides,[6] Amberlyst-15/LiCl,[7] cerium(III) chloride,[8] indium trihalides,[9] $BF_3{\cdot}OEt_2$ as a fluorine source,[10] tetrabutylammonium halides in the presence of β-cyclodextrin[11] and an activated DMF complex.[12] Most of these methodologies suffer from disadvantages such as long reaction times, formation of other inseparable regioisomers, high temperature and pH dependence, etc. Hence, it is desirable to develop a mild and efficient method for the regiospecific opening of substituted aziridines to afford β-halo amines. Such halo amines are precursors for the syntheses of various biologically active molecules and also exhibit several biological activities.[13] Herein, we describe a highly regioselective opening of activated aziridines by readily available Zn(II) halides to give β-halo amines in good to excellent yields.

To test our methodology, we synthesized *N*-tosylaziridines (**1a**–**c**, Scheme 1) following known literature methods.[14] As shown in Scheme 1, *N*-tosylaziridine **1** when subjected to our reaction conditions,[15] gave ring opened **2** as the major product in very good yield. The results of the ring opening studies with various *N*-tosylaziridines and ZnX_2 (X = Cl, Br and I) are listed in Table 1. In the case of *N*-tosyl-2-phenylaziridine **1a** (entries 1, 5 and 9) only one regioisomer **2a** was formed[16] where the halide ion attacked at the benzylic position and formation of the other regioisomer **3** (Scheme 1) was not observed. In the case of *N*-tosylcyclohexene aziridine **1b** (entries 2, 6 and 10), the corresponding *trans*-halo amine **2b** was formed in excellent yield. The trans stereochemistry of the product from **1b** was established from the coupling constants of the ring protons. All the *N*-tosylaziridines shown in Table 1 underwent nucleophilic



a : R^1 = Ph, R^2 = H; **b** : R^1, R^2 = -$(CH_2)_4$-
c : R^1 = Ph, R^2 = $CH_2OTBDMS$; **d** : R^1 = CH_2Ph, R^2 = H

Scheme 1. Reaction of *N*-tosylaziridines with zinc dihalides.

Keywords: Aziridine; Zinc(II) halide; β-Halo amine; [3+2] Cycloaddition.
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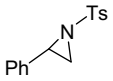
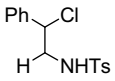
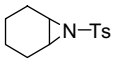
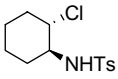
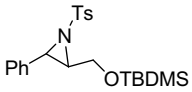
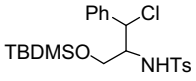
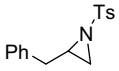
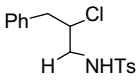
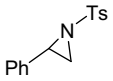
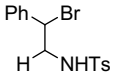
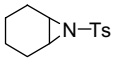
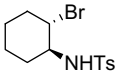
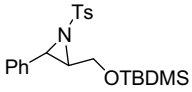
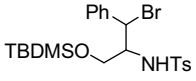
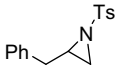
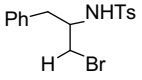
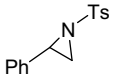
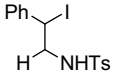
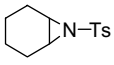
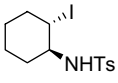
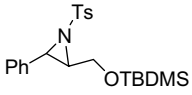
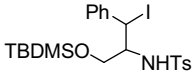
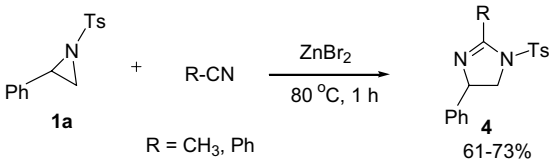
Table 1. Regioselective opening of various *N*-tosylaziridines with Zn(II) halides

Entry	Aziridine **1**	ZnX_2	Product **2**	Time (h)	Yield[a] (%)	Ratio[b] **2**:**3**
1		$ZnCl_2$		1	86	>99:1
2		$ZnCl_2$		5	82	>99:1
3		$ZnCl_2$		3	65 (58:42)[c]	86:14
4		$ZnCl_2$		12	87[d]	28:72
5		$ZnBr_2$		1	83	>99:1
6		$ZnBr_2$		5	78	>99:1
7		$ZnBr_2$		2	52 (55:45)[c]	82:18
8		$ZnBr_2$		12	73[d]	18:82
9		ZnI_2		1	88	>99:1
10		ZnI_2		1	86	>99:1
11		ZnI_2		1	56 (81:19)[c]	>99:1

[a] Isolated yield after column chromatographic purification.
[b] The ratio was determined by ^1H NMR analysis of the crude reaction mixture.
[c] Isolated yield of **2** as a diastereomeric mixture and the diastereomeric ratio is given in parentheses.
[d] Combined yield of isolated **2** and **3**.

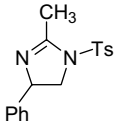
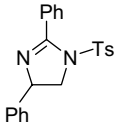
ring opening with halide ions smoothly except for *N*-tosyl-2-benzylaziridine (entries 4 and 8), derived from chiral L-phenylalanine, which reacted slowly and gave a low yield of **2**. This can be attributed to the reduced electrophilic nature at the homobenzylic position. In the case of *N*-tosyl-2-phenylaziridine, the more stable carbocation type intermediate facilitates attack by the nucleophile at the benzylic position. In **1b** ring strain may be the driving force for the easy attack by the nucleophile. When ZnI_2 was used as the halogen source (entries 9–11), ring opening took place at room temperature within 1 h.

We also studied the reaction in DCM, THF, $CHCl_3$ and CH_3CN. Excellent yields of the product, with high regioselectivity were found in DCM as the solvent. Interestingly, the reaction of *N*-tosyl-2-phenylaziridine **1a** with ZnX_2 was very sensitive to solvent. In acetonitrile, β-chloro- or iodo- amines were isolated as the only products when $ZnCl_2$ or ZnI_2 was used. Surprisingly, substituted imidazoline **4** was obtained (Scheme 2, Table 2) in good yield by a [3+2] cycloaddition reaction when using $ZnBr_2$ at reflux in acetonitrile.[17] Similar cyloadditions of aziridines with nitriles but using boron complexes have been reported earlier.[18] The β-halo amines



Scheme 2. $ZnBr_2$ promoted [3+2] cycloaddition of *N*-tosyl-2-phenylaziridine with nitriles.

Table 2. $ZnBr_2$ promoted [3+2] cycloaddition of *N*-tosyl-2-phenylaziridine with nitriles

Entry	RCN	ZnX_2	Product	Time (h)	Yield (%)
1	CH_3CN	$ZnBr_2$		1	61
2	PhCN	$ZnBr_2$		1	73

and cycloaddition products were characterized by ^1H NMR, ^{13}C NMR and mass spectral data. Our strategy is significant, compared to earlier reports, as we can control the direction taken by the reaction to produce either β-halo amines or substituted imidazolines simply by selecting a particular Zn(II) halide and solvent.

The mechanism for formation of the cycloaddition product is rationalized in Scheme 3, where the aziridine nitrogen is coordinated to $ZnBr_2$ generating a highly reactive intermediate **5**, which would then undergo a [3+2] cycloaddition reaction with nitriles to provide the substituted imidazoline **4**. To support the mechanism, we carried out the ring opening reaction of a chiral aziridine, *R*-(−)-2-phenyl-1-(toluene-4-sulfonyl)aziridine. When it was treated with ZnX_2 (X = Cl, Br and I) in DCM, nonracemic β-halo amines were formed. Similarly, the same reaction in CH_3CN as solvent in the presence of $ZnBr_2$ also produced a nonracemic imidazoline. Based on these observations it is clear that the reaction proceeds through a cationic intermediate **5** (Scheme 3) not via a stable benzylic carbocation intermediate **6** from which a racemic product could be expected.

In conclusion, we believe that the described methodology using Zn(II) halides represents an important as well as a convenient approach for the regiospecific opening of *N*-tosylaziridines to give β-halo amines under extremely mild reaction conditions. We have also demonstrated that $ZnBr_2$ is a selective reagent for [3+2] cycloaddition of *N*-tosylaziridines with nitriles. Further applications of our methodology are under active investigation.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.04.006.

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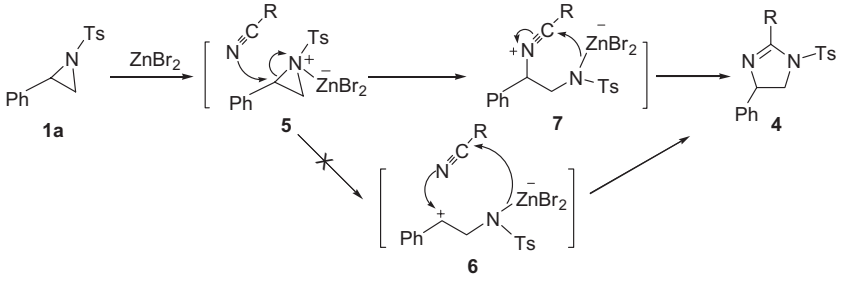

Scheme 3. Proposed mechanism for the [3+2] cycloaddition of *N*-tosyl-2-phenylaziridine with a nitrile in the presence of $ZnBr_2$.

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15. General procedure for ring opening of aziridines with zinc dihalides: A suspension of anhydrous zinc dihalide (0.73 mmol) in DCM (2.0 mL) was refluxed for five minutes, then a solution of *N*-tosylaziridine (0.365 mmol) in anhydrous DCM (2.0 mL) was added slowly with stirring under a nitrogen atmosphere. The resulting mixture was refluxed for the appropriate time until complete consumption of the substrate (monitored by TLC). The reaction mixture was quenched with saturated aq NH_4Cl solution (2.0 mL), and extracted with DCM. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. The crude product was purified by the column chromatography on silica gel (using ethyl acetate in petroleum ether) to provide the corresponding β-halo amines.
16. ^{1}H NMR and ^{13}C NMR data of the crude reaction mixture showed the presence of only one regioisomer **2a** (X = Cl): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H, CH_3), 3.31–3.44 (m, 2H, CH_2), 4.74 (t, J = 6.6 Hz, 1H, NH), 4.79 (dd, J = 7.2, 2.2 Hz, 1H), 7.11–7.29 (m, 7H, Ar–H), 7.66 (d, J = 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 50.3, 61.6, 127.0, 127.1, 128.9, 129.1, 129.8, 136.9, 137.7, 143.5; FAB Mass: *m/z* 311 (M^++2), 310 (M^++1), 289, 274, 263, 258, 234, 233, 206, 184, 178, 155, 154, 136, 120, 119, 91, 77.
Spectral data of **2c** (X = Cl): It was isolated as an inseparable mixture of two diastereomers and was characterized by ^{1}H NMR, ^{13}C NMR, DEPT, 2D (^{1}H COSY) and mass spectral analysis. The protons of the individual diastereomer were assigned by 2D (^{1}H COSY) and D_2O exchange experiments in ^{1}H NMR to assign the NH proton.
For the major diastereomer of **2c** (X = Cl): ^{1}H NMR (400 MHz, $CDCl_3$): δ −0.18 (s, 3H), −0.21 (s, 3H) 0.87 (s, 9H), 2.38 (s, 3H, CH_3), 3.53 (dd, J = 9.5, 4.4 Hz, 1H), 3.58 (dd, J = 9.8, 6.8 Hz, 1H), 3.63–3.68 (m, 1H), 4.82 (d, J = 9.5 Hz, 1H, NH), 5.23 (d, J = 4.6, 1H), 7.12–7.26 (m, 7H, Ar–H), 7.53 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.5, 18.1, 21.4, 25.8, 60.9, 62.1, 62.5, 126.8, 127.3, 127.8, 128.3, 129.4, 137.2, 137.8, 143.1; for the other diastereomer of **2c** (X = Cl): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.07 (s, 3H), 0.88 (s, 9H), 2.39 (s, 3H, CH_3), 3.46 (dd, J = 10.3, 4.4 Hz, 1H), 3.74–3.81 (m, 1H), 4.02 (dd, J = 10.3, 2.7 Hz, 1H), 4.92 (d, J = 8.8 Hz, NH), 4.95 (d, J = 7.8 Hz, 1H), 7.12–7.26 (m, 7H, Ar–H), 7.5 (d, J = 8.3, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.5, 18.2, 21.4, 25.7, 60.1, 60.8, 61.7, 126.9, 127.3, 128.1, 128.4, 129.5, 137.2, 137.6, 143.2.
FAB Mass: *m/z* 455 (M^++2), 454 (M^++1), 438, 418, 396, 388, 341, 328, 286, 263, 228, 184, 155, 118, 91.
17. The procedure described in Ref. 15 was followed except (a) acetonitrile or benzonitrile was used as the solvent instead of DCM, (b) $ZnBr_2$ was used as the Lewis acid. The isolated imdazolines are sensitive to moisture and may give hydrolyzed products. The imidazolines were characterized by ^{1}H NMR, ^{13}C NMR, DEPT, 2D (^{1}H COSY) experiments and mass spectral data.
Spectral data of **4** (R = Me): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 3.62 (dd, J = 10, 8 Hz, 1H), 4.16 (t, J = 10 Hz, 1H), 4.98 (t, J = 8.5 Hz, 1H), 7.03–7.05 (m, 2H), 7.21–7.30 (m, 3H), 7.34 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 21.4, 55.4, 66.1, 126.3, 127.2, 127.7, 128.7, 130.1, 134.9, 141.1, 144.9, 157.1. FAB Mass: *m/z* 315 (M^++1), 313, 274, 237, 207, 193, 155, 147, 103.
18. (a) Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2073–2080; (b) Bhanu Prasad, B. A.; Pandey, G.; Singh, V. K. *Tetrahedron Lett.* **2004**, *45*, 1137–1141.