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Original article

Highly efficient regioselective ring openings of *N*-tosylaziridines to haloamines using ferric (III) halides

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ABSTRACT

FeX_3 (X = Cl, Br) were found to be very effective reagents and powerful catalysts for regioselective ring openings of a variety of *N*-tosylaziridines with them to afford the corresponding β-haloamines in good to excellent yields with high regioselectivity under mild conditions. At the same time, **13** new compounds were obtained firstly. Moreover, the β-bromoamine prepared could be transferred into β-nitroamine with $NaNO_2$ in moderate yield.

1. Introduction

Aziridines have been demonstrated to be valuable building blocks in organic synthesis due to their reactivity and versatility [1–9]. Their high ring strain energy endows them with high reactivity and enables easy ring cleavage with various nucleophiles. The use of halides as nucleophiles leads to the formation of β-haloamines, which are versatile synthetic intermediates for the synthesis of functional materials and biologically active compounds. The direct conversion of aziridines into the corresponding β-haloamines has previously been reported with a variety of halides. They are HCl [10–13], ZnX_2 (X = Cl, Br, I) [14], $MgBr_2$ [15,16], NaX (X = Br, I) [16], $CeCl_3{\cdot}7H_2O$/NaI [17], indium trihalides [18], LiX/Amb15 (X = Cl, Br, I) [19], $BF_3{\cdot}OEt_2$ as a fluorine source [20], iodine/thiophenol [21], zirconyl chloride [22], PPh_3/halogenating agent [23], tetrabutylammonium halides in the presence of β-cyclodextrin [24], an activated DMF complex [25] and $BF_3{\cdot}OEt_2$/tetraalkylammonium halides, respectively [26]. Although these limited synthetic approaches have made significant progress and provided some value in the past few years, most of these methodologies suffer from disadvantages such as narrow substrate scope, low regioselectivity, long reaction times, formation of other inseparable regioisomers, and high temperature. Hence, the study of efficient, highly regioselective and stereoselective ring openings of aziridines still remains important and challenging. At the same time, the discovery of novel catalysts and the development of new methods that make use of mild experimental conditions and readily available and inexpensive halides are highly desirable. Iron is one of the most abundant metals on earth, and consequently one of the most inexpensive and environmentally friendly ones to use. Its salts are more practical catalysts compared to traditional Lewis acids in several carbon-carbon bond forming reactions and have found wide applications in organic synthesis [27,28]. Herein, we will report a highly regioselective and efficient Fe(III) halide-promoted ring-opening reactions of *N*-tosylaziridines with readily available Fe(III) halides to give β-haloamines in good to excellent yields with better substrate scope.

2. Experimental

Typical procedure for the synthesis of chloroamines: A reaction mixture of well-stirred *N*-tosylaziridine **1** (0.2 mmol) and $FeCl_3$ (40 mol% or 50 mol%) in CH_2Cl_2 (2.5 mL) was stirred at the specified temperature for a period of time under air atmosphere (Scheme 1). After the reaction was completed, which was monitored by TLC, the reaction mixture was concentrated under vacuum, and the resultant crude mixture was purified by column chromatography on silica gel with petroleum ether/ethyl acetate to give the corresponding pure chloroamines **2** and **3**.

The experimental procedure for the synthesis of bromoamines is the same as that for the synthesis of chloroamines.

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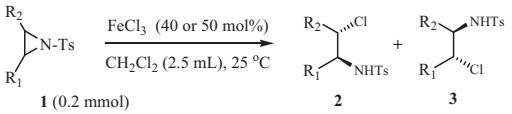
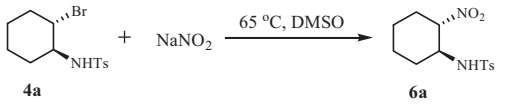


Scheme 1. Ring openings of *N*-tosylaziridines **1** with $FeCl_3$.



Scheme 2. Nucleophile substitution of **4a** with $NaNO_2$.

Typical procedure for the synthesis of **6a**: A mixture of *β*-bromoamine **4a** (0.2 mmol) and $NaNO_2$ (0.3 mmol, 1.5 equiv.) in DMSO (1.2 mL) was stirred under air atmosphere at 65 °C for 4 h (Scheme 2). After the complete conversion monitored by TLC, the reaction mixture was diluted with water (10 mL) and extracted with ether (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum and the resulting product was purified by column chromatography on silica gel (200–300 mesh, ethyl acetate/petroleum ether, 1:4) to afford pure **6a**.

The physical and spectral data and spectra of ^1H NMR, ^{13}C NMR and HRMS of all products are given in Supporting information.

3. Results and discussion

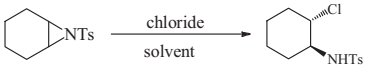
Initially, our aim was to identify the best halides through screening metal halides in terms of the ring openings of *N*-tosylaziridines [29], and we began our research by choosing *N*-tosylcyclohexylaziridine **1a** as the model substrate. Subsequently, a series of halides was screened under air atmosphere at room temperature, and the results are summarized in Table 1. When $AlCl_3$ was used, the trace amount of product was detected (Table 1, entry 1). Compared with $MgCl_2$ (75%), $FeCl_3$ provided a better result (81%) (Table 1, entry 3). So, $FeCl_3$ was selected as a better nucleophile that also served as an excellent catalyst for the ring openings.

Then, a series of experimental parameters was examined. Different solvents such as CH_2Cl_2, THF and CH_3CN were screened. No product was detected when this reaction was performed in THF or CH_3CN (Table 1, entries 4,5). CH_2Cl_2 was identified as the best solvent for this reaction (Table 1, entry 3). The investigation of the temperature indicated that room temperature was suitable (Table 1, entry 3 *vs.* 6, 7). Subsequently, the screening of the amount of $FeCl_3$ was carried out. 81% yield was obtained when 2.0 equiv. of $FeCl_3$ was adopted (Table 1, entry 3). Decreasing the amount of $FeCl_3$ from 2.0 to 0.5 equiv. can dramatically increase the yield to 94% (Table 1, entry 10). Further improvement of the yield was not observed by using 0.4 equiv of $FeCl_3$ (Table 1, entry 11). Besides, it was found that the reaction time can be reduced by increasing the solvent dosages from 2.0 to 2.5 mL (Table 1, entry 12 *vs.* 11). At last, extensive screening showed the optimal reaction conditions were 0.2 mmol *N*-tosylcyclohexylaziridine **1a** and 50 mol% $FeCl_3$ in 2.5 mL CH_2Cl_2 under air atmosphere at room temperature for 1.5 h (Table 1, entry 14).

Having established the optimal conditions of this ring-opening reaction, we turned to a survey of the substrate scope and generality of this method. Similarly, $FeCl_3$ and $FeBr_3$ reacted well to give the corresponding chloro and bromo amines, and this reaction worked equally well with both aliphatic and aromatic *N*-tosylaziridines, and the corresponding products were provided in good to excellent yields with high regioselectivity (Table 2). The important feature of the reaction is its high regioselectivity. Both cyclic and acyclic alkenes-derived aliphatic *N*-tosylaziridines proceeded smoothly with $FeCl_3$ and $FeBr_3$ affording only one regioisomer **2** or **4,** respectively, in excellent yields, and the formation of the other regioisomers **3** or **5** was not observed (Table 2, entries 1–4). The ring opening reactions of cyclic *N*-tosylaziridines were completely *anti*-stereoselective, giving only the *trans* isomers. Acyclic terminal *N*-tosylaziridines gave high regioselectivity with the formation of only one product, which demonstrates the predominant attack of the nucleophile at the less hindered terminal carbon [17,18]. In terms of mono-substituted aromatic *N*-tosylaziridines, neither the electronic properties of the substituents on the aromatic ring nor the steric hindrance had obvious influence on the yields. Except for **1n** which gave two isomers with high regioselectivity (94/6) about $FeBr_3$, other *N*-tosylaziridines provided the single regioisomer **3** or **5** by nucleophilic attack of the halide ion ($FeCl_3$ and $FeBr_3$) at the benzylic position, and up to 99% yields were obtained within 0.5 h (Table 2, entries 5–12). It was possible that electronic factors predominated over the steric factors in this process. In addition, moderate yields and high regioselectivity could also be obtained with condensed-ring *N*-tosylaziridines (Table 2, entries 13–14). Unfortunately, it can be seen that disubstituted aromatic *N*-tosylaziridines provided the two regioisomer products in good yields with bad regioselectivity due to the effect of spatial structure and the fact that the regioisomers could not be separated by column chromatography on silica gel (Table 2, entries 15,16).

Br-substituted organic compounds have versatile applications in organic synthesis. Some new functional groups can be smoothly introduced by nucleophilic substitution of a bromo group. Furthermore, we examined the substitution reactions of the *β*-haloamines obtained through the ring openings of *N*-tosylaziridines. The Br group in the product **4a** could be conveniently substituted by the nitro group (-NO_2) using $NaNO_2$, and the desired product **6a** was obtained in 55% yield (see Scheme 2).

Table 1
Screening of reaction conditions for ring openings of *N*-tosylcyclohexylaziridine 1a with anhydrous chloride source.[a]



1a 2a

Entry	Chloride source	Solvent	*T* (°C)	Amount of chloride (equiv.)	Solvent dosage (mL)	*t* (h)	Yield (%)[b]
1	$AlCl_3$	CH_2Cl_2	25	2.0	2.0	12	Trace
2	$MgCl_2$	CH_2Cl_2	25	2.0	2.0	16	75
3	$FeCl_3$	CH_2Cl_2	25	2.0	2.0	0.5	81
4	$FeCl_3$	THF	25	2.0	2.0	12	N.D.[c]
5	$FeCl_3$	CH_3CN	25	2.0	2.0	12	N.D.
6	$FeCl_3$	CH_2Cl_2	35	2.0	2.0	0.5	83
7	$FeCl_3$	CH_2Cl_2	Reflux	2.0	2.0	0.5	86
8	$FeCl_3$	CH_2Cl_2	25	1.5	2.0	0.5	89
9	$FeCl_3$	CH_2Cl_2	25	1.0	2.0	0.5	92
10	$FeCl_3$	CH_2Cl_2	25	0.5	2.0	1.5	94
11	$FeCl_3$	CH_2Cl_2	25	0.4	2.0	7.5	93
12	$FeCl_3$	CH_2Cl_2	25	0.4	2.5	3	94
13	$FeCl_3$	CH_2Cl_2	25	0.4	1.5	5	88
14	$FeCl_3$	CH_2Cl_2	25	0.5	2.5	1.5	98

[a] Unless otherwise noted, all reactions were performed with *N*-tosylcyclohexylaziridine **1a** (0.2 mmol) under specified conditions.
[b] Isolated yields after column chromatographic purification.
[c] N.D. = not detected.

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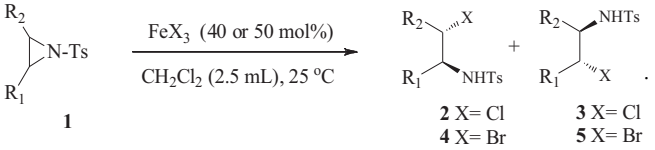
Table 2
Regioselective ring openings of various *N*-tosylaziridines with anhydrous FeX_3.[a]



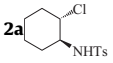
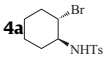
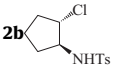
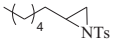
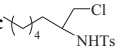
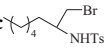
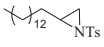
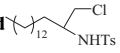
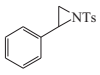
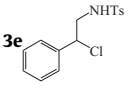
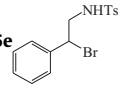
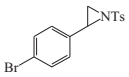
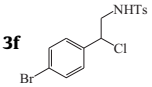
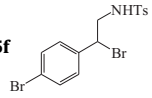
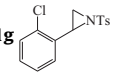
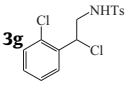
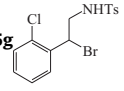
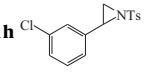
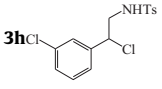
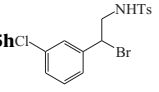
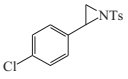
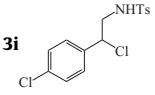
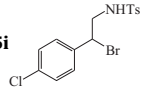
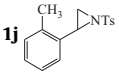
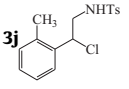
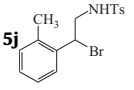
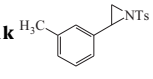
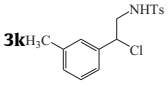
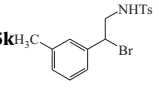
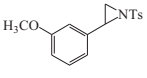
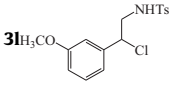
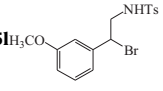
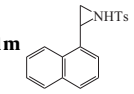
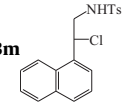
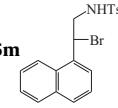
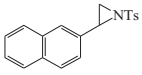
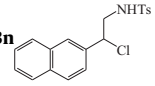
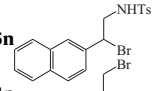
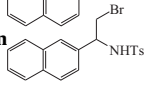
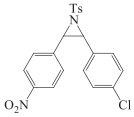
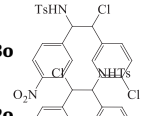
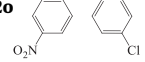
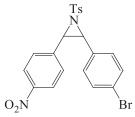
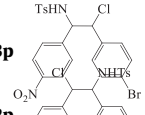
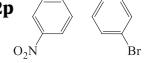
Entry	*N*-tosylaziridine **1**	X = Cl			X = Br		
		Product[b]	Time (min)	Yield (%)[c]	Product[b]	Time (min)	Yield (%)[c]
1	**1a** 	**2a** 	90	98	**4a** 	135	98
2	**1b** 	**2b** 	480	94	**4b** 	135	96
3	**1c** 	**2c** 	480	91	**4c** 	135	90
4	**1d** 	**2d** 	270	93	–	–	–
5[d]	**1e** 	**3e** 	10	93[d]	**5e** 	10	89
6[e]	**1f** 	**3f** 	20	85	**5f** 	20	90
7[e]	**1g** 	**3g** 	20	96	**5g** 	40	96
8[e]	**1h** 	**3h** 	15	90	**5h** 	25	91
9[e]	**1i** 	**3i** 	10	84	**5i** 	20	84
10[d]	**1j** 	**3j** 	25	95[d]	**5j** 	25	84
11[e]	**1k** 	**3k** 	5	79	**5k** 	30	89
12[e]	**1l** 	**3l** 	10	86	**5l** 	20	91

Table 2 (*Continued*)

Entry	*N*-tosylaziridine **1**	X = Cl			X = Br		
		Product[b]	Time (min)	Yield (%)[c]	Product[b]	Time (min)	Yield (%)[c]
13[e]	**1m** 	**3m** 	5	19	**5m** 	15	46
14[e]	**1n** 	**3n** 	15	67	**5n**  **4n** 	15	70[f] (**5n:4n** = 94:6)
15[e]	**1o** 	**3o**  **2o** 	30	89 (**3o:2o** = 59:41)[g]	–	–	–
16[e]	**1p** 	**3p**  **2p** 	30	86 (**3p:2p** = 64:36)[g]	–	–	–

[a] Unless otherwise noted, all reactions were performed with *N*-tosylaziridines **1** (0.2 mmol) and 50 mol.% anhydrous FeX_3 (X = Cl or Br) under air atmosphere in CH_2Cl_2 (2.5 mL) at 25 °C.
[b] Products **2** and **4** were formed through terminal attack and products **3** and **5** were formed through internal attack.
[c] Isolated yield after column chromatographic purification.
[d] 40 mol% anhydrous FeX_3 and 0 °C were adopted.
[e] 40 mol% anhydrous FeX_3 was used about all aromatic *N*-tosylaziridines.
[f] Combined yield of isolated **4n** and **5n**.
[g] The ratio was determined by ^1H NMR spectrum.

4. Conclusion

In summary, we have developed a simple, practical, and highly efficient method for the synthesis of β-haloamines through the ring-opening reactions of various *N*-tosylaziridines with readily available FeX_3 (X = Cl, Br). More importantly, good to excellent yields and single regioisomers could be provided for a wide variety of mono-substituted substrates under extremely mild conditions. In addition, β-haloamines can be easily transferred into nitro compounds through the nucleophilic substitution of the Br group by $NaNO_2$.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.03.033.

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