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A convenient synthetic route to 2-aryl-*N*-tosylazetidines and their ZnX_2 (X = I, OTf) mediated regioselective nucleophilic ring opening reactions: synthesis of γ-iodoamines and tetrahydropyrimidines

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Abstract—A general and convenient synthetic route to various 2-aryl-*N*-tosylazetidines has been described. Their ZnX_2 (X = I, OTf) mediated nucleophilic ring opening with halides and [4+2] cycloaddition reactions with various nitriles have been achieved to afford γ-iodoamines and substituted tetrahydropyrimidines, respectively, in good to excellent yields. A mechanism for the cycloaddition reaction is proposed.
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Synthetic organic chemistry has witnessed extensive research activity in nucleophilic ring opening and ring expansion reactions of N-activated aziridines[1] over the years. However, the similar chemistry of N-activated azetidines has not been explored extensively probably due to the lack of availability of easy methods for their preparation. In the course of our studies on ZnX_2 (X = Cl, Br, I) mediated regioselective ring opening and [3+2] cycloaddition of *N*-tosylaziridine with nitriles,[2] we were attracted towards the regioselective nucleophilic ring opening of *N*-tosylazetidine with a variety of nucleophiles. There are only a few reports on regioselective ring opening of azetidines[3] and azetidinium ions[4] in the literature, and so far, there has been no report on regioselective nucleophilic ring opening of *N*-tosylazetidine with halide ions to give γ-haloamines. Such haloamines could be utilized as important precursors in organic synthesis, for example, as alkylating agents for the synthesis of antimalarial drugs.[5] The synthesis of six-membered nitrogen-containing heterocycles is of immense research interest as these frameworks are found in various natural products.[6] Though azetidines are less reactive in ring opening reactions due to their exceptional stability,[7] *N*-tosylazetidines have been used as 1,4 masked dipoles for cycloaddition reactions,[8] and ring opening reactions with allylsilane[9] to synthesize *N*-heterocycles. Azetidines have been used for cycloaddition reactions with various dipolarophiles using a Pd(II) complex as the catalyst.[10] In spite of the broad range of pharmacological and biological applications of tetrahydropyrimidines,[11] only a limited number of methods are available for their direct synthesis via the [4+2] cycloaddition reaction of azetidines with nitriles employing $BF_3{\cdot}OEt_2$ as the catalyst.[12]

In most of these cases the reaction suffers from several disadvantages such as the use of a highly moisture sensitive catalyst, poor yield, etc. Hence, it is desirable to develop an easy and economically viable method for the [4+2] cycloaddition of *N*-tosylazetidines with nitriles.

Herein, we report the ZnX_2 (X = I, OTf) mediated nucleophilic ring opening of a number of 2-aryl-*N*-tosylazetidines with halides and their [4+2] cycloaddition reactions with various nitriles to produce γ-iodoamines and tetrahydropyrimidines, respectively. For our study it was necessary to develop a general and convenient method for the synthesis of 2-aryl-*N*-tosylazetidines. Although a few procedures exist for the syntheses of *N*-tosylazetidines,[12a,13] those methods are not suitable because of poor yields and formation of undesired

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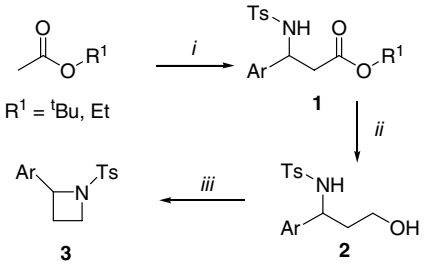
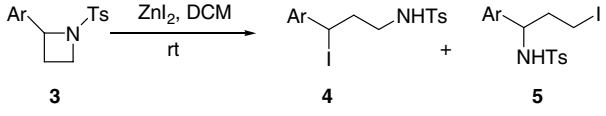


Ar = **a**: Ph; **b**: 2-ClC$_6$H$_4$; **c**: 4-ClC$_6$H$_4$; **d**: 3-BrC$_6$H$_4$; **e**: 4-MeOC$_6$H$_4$

Scheme 1. Synthesis of various 2-aryl-*N*-tosylazetidines from *tert*-butyl acetate and aryl-*N*-tosylaldimines. Reagents and conditions: (i) LDA/THF, −78 °C, 1 h, Ar–CH=N–Ts, THF, −78 °C, 2 h, 100% (**1**); (ii) LAH, THF, 0 °C–rt, 1 h, 100% (**2**); (iii) TsCl/KOH, THF, reflux, 30 min, 92–98% (**3**).

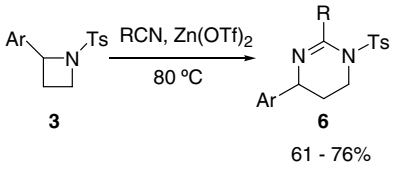
products. We also introduce in this report an easy method for the syntheses of various 2-aryl-*N*-tosylazetidines using an imino aldol reaction[14] as the key step.

We synthesized a variety of 2-aryl-*N*-tosylazetidines (**3a–e)** using simple chemistry from easily available starting materials in almost quantitative yields (Scheme 1). Ester enolates were generated from *tert*-butyl acetate upon treatment with one equivalent of LDA in THF at −78 °C and were reacted with an *N*-tosylarylaldimine to afford substituted *N*-tosyl-β-aminoesters **1** in quantitative yields (Scheme 1). When ethyl acetate was used as the enolate source, lower yields of **1** (65–70%) were observed. *N*-Tosyl-β-aminoesters **1** were reduced to the corresponding γ-amino alcohols **2** by treatment with LAH. Subsequently, compounds **2** were easily converted to 2-aryl-*N*-tosylazetidines **3a–e** in excellent yields by treatment with TsCl/KOH in THF at reflux for 30 min.



Ar = **a**: Ph; **b**: 2-ClC$_6$H$_4$; **c**: 4-ClC$_6$H$_4$; **d**: 3-BrC$_6$H$_4$

Scheme 2. Regioselective ring opening of 2-aryl-*N*-tosylazetidines **3a–d** with ZnI_2.

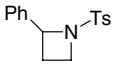
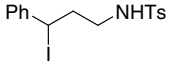
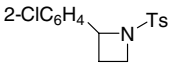
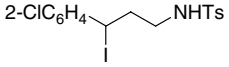
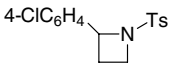
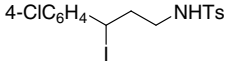
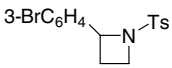
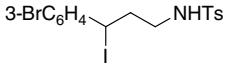


Scheme 3. Zn(OTf)$_2$ mediated [4+2] cycloaddition of 2-aryl-*N*-tosylazetidines **3a–c** with nitriles.

Our study began with the nucleophilic ring opening reaction of 2-phenyl-*N*-tosylazetidine **3a** in the presence of Zn(II) halides in DCM at room temperature. However, $ZnCl_2$ or $ZnBr_2$ gave a very complex mixture as indicated by the ^{1}H NMR spectrum of the crude reaction mixture. Compound **3a**, when subjected to our reaction conditions[15] employing ZnI_2 as the halogen source gave ring opened product **4a** as the only product in good yield. In order to generalize this approach, a number of *N*-tosylazetidines **3b–d** were studied and all of them underwent regioselective ring opening with ZnI_2 to produce γ-iodoamines[16] **4b–d** smoothly; the other possible regioisomers **5** (Scheme 2) were not been observed. The results of the ring opening studies are listed in Table 1. The azetidines are activated towards nucleophilic ring opening by iodide ions when the nitrogen atom of the ring is coordinated to ZnI_2. Regioselectivity in all these cases probably arises due to preferential intramolecular nucleophilic attack of the iodide ion at the benzylic position as it is more electrophilic in nature compared to the less substituted position.

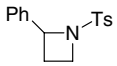
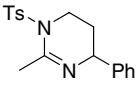
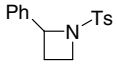
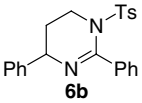
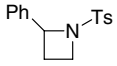
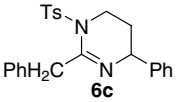
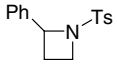
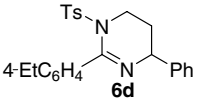
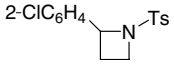
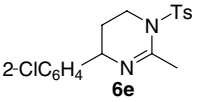
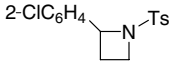
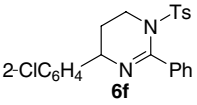
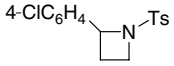
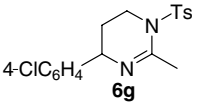
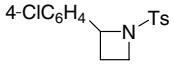
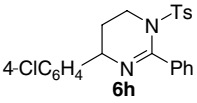
Similar to our earlier report on ZnX_2 mediated ring opening reaction of aziridines[2] in acetonitrile as a solvent, when 2-phenyl-*N*-tosylazetidine **3a** was treated with ZnX_2 (X = Cl, Br, I) at reflux in acetonitrile, a [4+2] cycloaddition reaction was observed to furnish substituted tetrahydropyrimidine **6a**, however, the reaction was found to be very slow. To overcome this problem we performed the same reaction in the presence of 1 equiv of Zn(OTf)$_2$, and obtained **6a** rapidly and in excellent yield (Scheme 3, Table 2). It was found that the use of 1 equiv of catalyst and a nitrile as the solvent were necessary for completion of the reaction. The pro-

Table 1. Regioselective ring opening of 2-aryl-*N*-tosylazetidines **3a–d** with ZnI_2

Entry	Azetidine **3**	Product **4**	Time (h)	Yield[a] (%)
1			1.5	74
2			14	72
3			2	67 (84)[b]
4			12	62

[a] Isolated yield after column chromatographic purification.
[b] Yield was determined by ^{1}H NMR analysis of the crude reaction mixture.

Table 2. $Zn(OTf)_2$ mediated [4+2] cycloaddition of 2-aryl-*N*-tosylazetidines **3a–c** with nitriles[a]

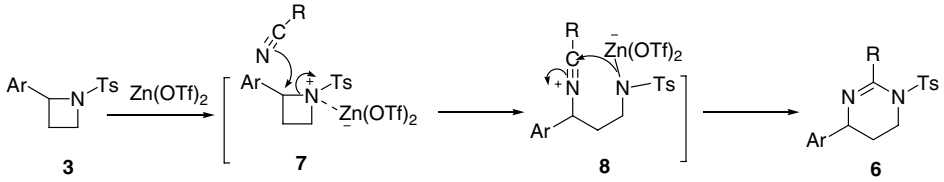
Entry	Azetidine **3**	Nitrile	Product **6**	Time	Yield[b] (%)
1		CH_3CN	 **6a**	1.5 h	76 (90%)[c]
2		PhCN	 **6b**	1 h	72
3		$PhCH_2CN$	 **6c**	20 min	65
4		4-EtC_6H_4CN	 **6d**	20 min	62
5		CH_3CN	 **6e**	18 h	67
6		PhCN	 **6f**	18 h	61
7		CH_3CN	 **6g**	3 h	71
8		PhCN	 **6h**	2.5 h	69

[a] In all the cases the nitrile served as the solvent.
[b] Isolated yield after column chromatographic purification.
[c] Yield was determined by ^1H NMR analysis of the crude reaction mixture.

gress of the reaction was comparatively slow when the reaction was performed at room temperature or when using 0.3–0.5 equiv of catalyst. We also studied the reaction with 1 equiv of acetonitrile in DCM, THF, $CHCl_3$ and benzene, in all cases **3a** gave a poor yield of **6a**. When the reaction of **3a–c** with different nitriles was carried out under optimal conditions,[17] tetrahydropyrimidines **6a–c** were obtained in good yields and the results are summarized in Table 2.

Interestingly, the ring opening and cycloaddition reactions were found to be very dependent on the substituent pattern of the azetidine ring. 2-(2-Chlorophenyl)-1-tosylazetidine **3b** (entries 5 and 6, Table 2) reacted very slowly with different nitriles compared to **3a** or **3c** (entries 1–4, 7 and 8, Table 2). Typically, arylnitriles reacted faster with azetidines than acetonitrile presumably because the intermediate **7** (Scheme 4) is more stabilized in an arylnitrile solvent compared to acetonitrile.

To investigate the mechanism of the cycloaddition reaction we carried out the reaction with chiral (*R*)-2-phenyl-1-(toluene-4-sulfonyl)-azetidine **3a**. When this substrate was reacted with acetonitrile as solvent non-racemic tetrahydropyrimidine **6a** (R = Me) was obtained. From this observation we have proposed a mechanism for the cycloaddition reaction as shown in Scheme 4 where $Zn(OTf)_2$ is coordinated to the nitrogen atom of the heterocycle **3a** and activates the ring generating a highly reactive species **7**. Subsequently, it undergoes a [4+2] cycloaddition reaction with the nitrile to provide non-racemic tetrahydropyrimidine **6a**. We have proposed a similar mechanism for the [3+2] cycloaddition of *N*-tosylaziridine with nitriles using $ZnBr_2$ as the Lewis acid.[2]



Scheme 4. Proposed mechanism for the [4+2] cycloaddition of 2-aryl-*N*-tosylazetidines with nitriles in the presence of $Zn(OTf)_2$.

In conclusion, we have developed a general and convenient synthetic route to various 2-aryl *N*-tosylazetidines using simple reagents and conditions in excellent overall yields. We have reported for the first time a novel ZnX_2 (X = I, OTf) mediated nucleophilic ring opening and [4+2] cycloaddition reaction of a series of *N*-tosylazetidines with halides and nitriles, respectively. A mechanism for the cycloaddition reaction is also proposed. We believe that the present work will be very useful for constructing nitrogen-containing biologically and synthetically important molecules. Further work in this area is under investigation in our laboratory.

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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.2006.05.058.

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15. General procedure for the regioselective ring opening of *N*-tosylazetidines with ZnI_2: A solution of 2-phenyl-*N*-tosylazetidine (0.174 mmol) in DCM (1.0 ml) was added to anhydrous ZnI_2 (0.348 mmol) under argon and stirred for the appropriate amount of time at rt until complete consumption of the substrate (monitored by TLC). The reaction mixture was quenched with saturated aq NH_4Cl solution (1.0 ml) and extracted with DCM three times. The organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel (using ethyl acetate/petroleum ether eluent) to provide the corresponding γ-iodoamines. All products were characterized by ^1H NMR, ^{13}C NMR and mass spectral analysis.
16. Spectral data of **4a**: ^1H NMR (400 MHz, $CDCl_3$): δ 2.06–2.14 (m, 1H), 2.33–2.42 (m, 1H), 2.36 (s, 3H), 2.90–3.04 (m, 2H), 4.46 (t, $J = 6.36$ Hz, 1H, NH), 5.05 (dd, $J = 6.36$, 8.8 Hz, 1H), 7.16–7.25 (m, 7H), 7.65 (d, $J = 8.32$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 29.4, 40.8, 42.9, 127.0, 127.1, 128.2, 128.8, 129.8, 136.5, 142.9, 143.6; ESI mass: m/z 416 (M^++1).

17. The procedure described in Ref. 15 was followed except, (a) the nitrile was used as the solvent instead of DCM, (b) $Zn(OTf)_2$ was used as the Lewis acid. The crude product was purified by flash column chromatography using ethyl acetate/petroleum ether as eluent to provide the tetrahydropyrimidines. All products were characterized by ^1H NMR, ^{13}C NMR, and mass spectral analysis. The tetrahydropyrimidines isolated were sensitive to moisture and may give hydrolyzed products. In cases where higher boiling nitriles were used, a modified purification method was followed. The reaction mixture was directly charged on a deactivated basic alumina column followed by washing with petroleum ether to remove and recover excess nitriles. Pure compounds were obtained using ethyl acetate/petroleum ether as eluent.

Spectral data of **6a**[12a] (R = CH_3) ^1H NMR (400 MHz, $CDCl_3$): δ 1.65–1.74 (m, 1H), 2.06–2.13 (m, 1H), 2.35 (d, $J = 1.48$ Hz, 3H), 2.38 (s, 3H), 3.65–3.78 (m, 2H), 4.40 (m, 1H), 7.07–7.29 (m, 7H), 7.66 (d, $J = 8.28$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 25.2, 30.2, 44.0, 57.4, 126.4, 126.8, 126.9, 128.4, 130.0, 137.1, 143.1, 144.4, 149.2; FAB mass: m/z 329 (M^++1).

Spectral data of **6b**[12a] (R = Ph) ^1H NMR (400 MHz, $CDCl_3$): δ 1.56–1.61 (m, 1H), 2.03–2.08 (m, 1H), 2.35 (s, 3H), 3.70–3.76 (m, 1H), 3.84–3.90 (m, 1H), 4.39 (dd, $J = 5.12$ Hz, 9.04, 1H), 7.06 (d, $J = 6.84$ Hz, 2H), 7.13–7.36 (m, 8H), 7.45 (d, $J = 8.32$ Hz, 2H), 7.50 (d, $J = 7.08$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 31.3, 44.1, 58.6, 126.5, 126.8, 127.4, 127.6 128.3, 128.6, 129.6, 129.8, 136.4, 137.7, 142.9, 144.3, 152.9; FAB mass: m/z 391 (M^++1).