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Ceric ammonium nitrate (CAN) catalyzed ring cleavage of *N*-tosyl aziridines: a potential tool for solution phase library generation†

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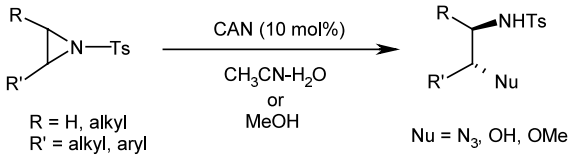
Abstract—A range of *N*-tosylaziridines is cleaved with NaN_3, H_2O, MeOH to synthesize vicinal azidoamines, aminols and amino ethers in good to excellent yields catalyzed by ceric ammonium nitrate and used in solution phase library synthesis.

Vicinal diamines and aminols are medicinally important compounds.[1] These compounds are usually prepared by ring opening of epoxides or/and *N*-substituted aziridines with appropriate nucleophiles. The nucleophiles include halogen,[2] nitrogen,[3] carbon[4] and hydrogen[5] which permit the generation of diverse combinatorial libraries.

The ring opening of activated aziridines with oxygen nucleophiles is reported with mineral acids[6] and recently Lewis acids, $BF_3{\cdot}OEt_2$ and $Sn(OTf)_2$[7] have been used with water and alcohols under very mild conditions. Surprisingly, however, other Lewis acids such as $Cu(OTf)_2$, $CuCl_2$, $SnCl_2$, $AlCl_3$, $FeCl_3$, $LiClO_4$, $CoCl_2$ and $ZnCl_2$ did not perform this transformation efficiently.[7] As part of a long term programme addressing the development of new methods[8] for the synthesis of bioactive amines[9] and aminols, we desired a general method for the opening of *N*-tosylaziridines with nucleophiles viz, OH, OR and N_3.



Scheme 1.

The screening of several reagents and catalysts allowed us to shortlist ceric ammonium nitrate (CAN) as a versatile catalyst to effect this transformation. The results pertaining to this study are presented herein (Scheme 1). This protocol allowed us to synthesize a library of 24 compounds.

Initially, our efforts began with cyclohexyl-*N*-tosylaziridine (Table 1, entry 1) which was treated with 10 mol% CAN in acetonitrile–water (9:1) and after 8 h, clean formation of the aminol derivative **1a** was obtained in 95% yield after a simple workup. To explore the usefulness of this transformation, the same aziridine was treated with 1.5 equiv. of NaN_3 in acetonitrile/water (9:1) mixture for 3 h (at 60°C, as the reaction was sluggish at rt) to yield the azidoamine **1c** in 95% yield. The nucleophilic opening of the substrate with NaN_3 did proceed in the absence of CAN, with about 60% conversion in 36 h.

Encouraged by this finding, a phenyl-*N*-tosylaziridine derivative (entry 4) was treated with CAN in acetonitrile/water (9:1) both in the absence and presence of NaN_3 to yield 2-phenyl-2-hydroxy-*N*-tosylamino ethane **4a** and 2-phenyl-2-azido-*N*-tosylamino ethane **4c** in 92% and 93% yields, respectively. As expected in methanol as a solvent, OCH_3 added as the nucleophile in both the cases studied (**1b** and **4b**). To prove the usefulness of this methodology, a series of eight aziridines was prepared and subjected to the three nucleophiles namely H_2O, MeOH and NaN_3 in a combinatorial fashion[10] using a multiple synthesizer to yield 24 compounds in acceptable purities and yields in two operations following a simple workup and filtra-

Keywords: *N*-substituted aziridines; ceric ammonium nitrate; cleavage; NaN_3; H_2O; MeOH; vicinal azidoamines; solution phase library.

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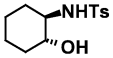
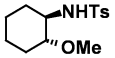
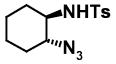
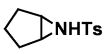
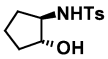
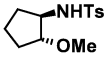
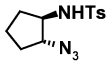
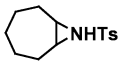
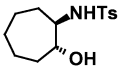
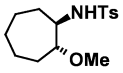
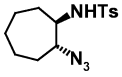
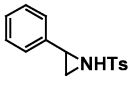
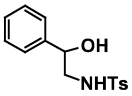
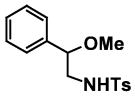
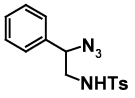
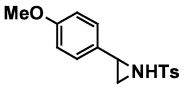
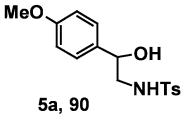
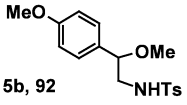
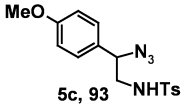
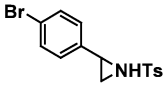
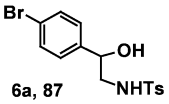
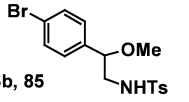
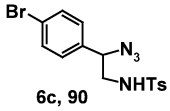
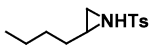
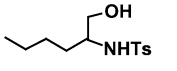
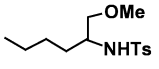
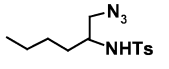
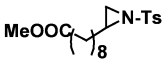
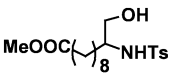
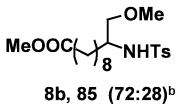
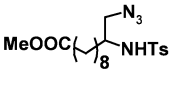
Table 1. Ring opening of *N*-tosylaziridines

S.No	Substrate	Nu = H_2O (product,yield%)[a]	Nu = MeOH (product, yield%)[a]	Nu = NaN_3 (product, yield%)[a]
1		 1a, 95	 1b, 93	 1c, 95
2		 2a, 90	 2b, 94	 2c, 92
3		 3a, 75	 3b, 77	 3c, 70
4		 4a, 92	 4b, 90	 4c, 93
5		 5a, 90	 5b, 92	 5c, 93
6		 6a, 87	 6b, 85	 6c, 90
7		 7a, 90 (70:30)[b]	 7b, 87 (77:23)[b]	 7c, 83 (75:25)[b]
8		 8a, 75 (68:32)[b]	 8b, 85 (72:28)[b]	 8c, 82 (82:18)[b]

[a] Yields calculated after column chromatography

[b] Ratio of products from terminal attack *vs* internal attack as determined by ^{1}H NMR

tion. With reference to regiochemistry of the ring opening, as expected, it was observed that in the case of benzylic aziridines, electronic factors controlled the ring opening whereas in the case of unsymmetrical terminal aziridines, steric factors controlled the regioselectivity. Some of the functionalities studied, which were stable to CAN, included the aryl bromide group (entry 6), the aromatic methoxy group (entry 5), and the ester functionality (entry 8). The vicinal *N*-tosylaminols (**1a**–**8a**), methoxy-*N*-tosylamines (**1b**–**8b**) and azido-*N*-tosylazidoamines (**1c**–**8c**) synthesized are being explored as building blocks for new chemical entities.

In conclusion, a mild protocol has been developed for the ring opening of *N*-tosylaziridines with H_2O, MeOH and NaN_3 as nucleophiles which should find applicability in medicinal chemistry and complex natural product synthesis.[11,12]

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10. The tabletop organic synthesizer 'Carousel' stirring hot plate was used. While synthesizing the compounds on the organic synthesizer, the initial reactions were kept at room temperature for 8 h after which the completed reactions with MeOH and H_2O were taken out of reaction block. The remaining tubes were heated at 60°C for 2 h to allow the NaN_3 reactions to be completed.
11. Representative procedures: *Method A:* To *N*-tosylaziridine (2 mmol) in 5 mL of acetonitrile/water (9:1) was added CAN (0.2 mmol) and the mixture left stirring at room temperature (1–6 samples placed in a multiple synthesizer). After 8 h the reaction mixture was diluted with water and extracted with ether (3×10 mL). The combined organic layers were dried over Na_2SO_4, concentrated in vacuo and purified by column chromatography.
Method B: To *N*-tosylaziridine (2 mmol) in 5 mL of methanol was added CAN (0.2 mmol) and the mixture left stirring at room temperature (1–8 samples placed in a multiple synthesizer). After 8 h the solvent was removed, the reaction mixture was diluted with water and extracted with ether (3×10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo and purified by column chromatography.
Method C: To *N*-tosylaziridine (2 mmol) in 5 mL of acetonitrile/water (9:1) was added NaN_3 (3 mmol), CAN (0.2 mmol) and the mixture left stirring at room temperature (1–6 samples placed in a multiple synthesizer). After 8 h the reaction mixture was diluted with water and extracted with ether (3×10 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo and purified by column chromatography.
12. All products were characterized by ^1H NMR and mass spectral analysis, and also by comparing with authentic samples wherever available.