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INDIUM TRICHLORIDE PROMOTED REGIOSELECTIVE RING OPENING OF AZIRIDINES WITH TMS AZIDE

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ABSTRACT

N-Tosylaziridines are opened regioselectively with trimethylsilyl azide in the presence of indium trichloride to afford the corresponding azido amines in high yields.

Aziridines are useful precursors for the synthesis of many biologically active molecules.[1] They are well known electrophiles capable of reacting with a wide variety of nucleophiles[2] such as Grignard, Wittig, organolithium or cuprate reagents to generate ring opened products. Particularly, the ring opening reaction of aziridines with TMS azide has special interest because the resultant products can be easily transformed to *vic*-diamines, which have wide applications in asymmetric synthesis.[3] As a result, there have been some reports on the ring opening of aziridines with TMS azide which utilize imidochromium complex,[4] rare earth metal complexes[5] tetrabutylammonium fluoride[6] and tin triflate[7] as promoters. However, many of these procedures have limitations in terms of yields, reaction

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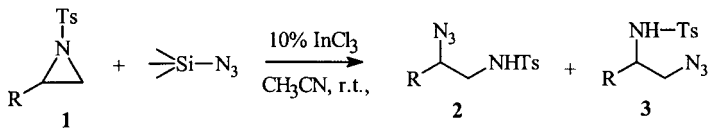
times, regioselectivities and incompatibility with other functional groups present in the substrate. Therefore, there is still a scope to develop a potentially practical method for this transformation. Recently, indium trihalides have emerged as powerful Lewis acids imparting high regio- and chemoselectivity in various chemical transformations[8] due to their exceptional stability, reactivity, and recoverability from water. The unique catalytic properties inherent to $InCl_3$ prompted us to investigate the use of this reagent for the azidolysis of aziridines.

In this report we describe the ring opening of aziridines with TMS azide using $InCl_3$ as promoter. The treatment of phenyl substituted *N*-tosyl aziridines with trimethylsilyl azide in acetonitrile in the presence of 10% $InCl_3$ at ambient temperature gave the corresponding azidoamines as a mixture of regioisomers **2** and **3** in 85–92% yield (Table 1).

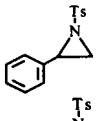
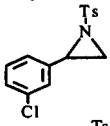
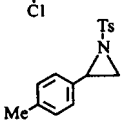
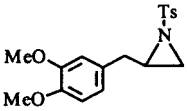
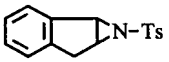
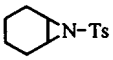
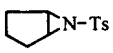
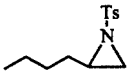
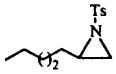
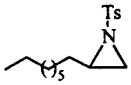
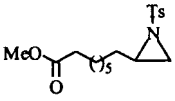
In a similar fashion, substituted styrene *N*-tosylaziridines underwent cleavage in a regioselective manner, whereby azide ion is attacked at the bezylic as well as at the terminal positions led to the formation of azido products as a mixture of **2** and **3**. The ratio of **2** and **3** was determined by ^{1}H NMR spectrum of the product. The ring opening reaction proceeded smoothly at room temperature in the presence of 10% $InCl_3$, however, no reaction took place in the absence of catalyst. Acyclic *N*-tosyl aziridines gave predominantly the ring-opened product **3** with a trace amount of **2** (entry d and h-1) whereas cyclic aziridines afforded the product as a single isomer (entry f and g). The substrate (entry d) also gave the product as a mixture of **3** and **2**. Acyclic terminal aziridines gave the products resulting from terminal attack as well as internal attack of azide ion as has been observed by others in most of the aziridine opening reactions.[6] All the products were fully characterized by ^{1}H NMR, IR and mass spectral data and also by comparison with the known compounds.[4a] Further the reaction of cyclic aziridines with TMS azide in the presence of 20 mol.% $InCl_3$ gave the corresponding azido products in 70–90% yield (Scheme 2, Table 1).

In the case of cyclic aziridines, the stereochemistry of the ring-opened product was found to be *trans* from the coupling constants of ring protons. The method is clean and completely regioselective, affording the corresponding azidoamines in high yields. Several examples illustrating this

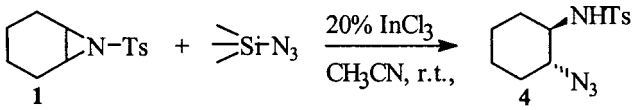


Scheme 1.

Table 1. $InCl_3$-Promoted Ring Opening of Aziridines with TMS Azide

Entry	Aziridine	Method	Reaction Time (h)	Yield[a] (%)	Selectivity 2 : 3[b]
a)		A	6	92	82 : 18
b)		A	5	87	88 : 12
c)		A	7	85	77 : 23
d)		B	10	78	15 : 85
e)		A	8	90	92 : 8
f)		B	14	78	2 : 98
g)		B	16	71	2 : 98
h)		B	10	80	4 : 96
i)		B	8	85	2 : 98
j)		B	12	87	2 : 98
k)		B	18	87	2 : 98
l)		B	18	78	7 : 93

[a]Isolated and unoptimized yields after purification.
[b]Ratio of 2 and 3 was determined by ^1H NMR spectra (400 MHz).



Scheme 2.

novel and efficient protocol for the ring opening of aziridines are summarized in table. The solvent acetonitrile is one of the choices, as best results were obtained. The catalyst, $InCl_3$ was recovered during work-up and reused in subsequent reactions without decrease in activity.

In summary, $InCl_3$ is found to be a superior Lewis acid for the ring opening of aziridines with TMS azide under mild reaction conditions. The method offers several advantages including high yields of products, greater regioselectivity, operational simplicity, regeneration of the catalyst, simple experimental and work-up procedures which makes it a useful and attractive strategy for the synthesis of azidoamines.

EXPERIMENTAL

General Procedure

Method-A: A mixture of phenyl substituted *N*-tosyl aziridine (5 mmol), trimethylsilyl azide (7.5 mmol) and $InCl_3$ (10 mol%) in acetonitrile (10 ml) was stirred at room temperature for an appropriate time (table). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water (10 ml) and extracted with ethyl acetate (2×15 ml). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2 : 8) to afford pure azidoamine.

Method-B: A mixture of cyclic or acyclic *N*-tosylaziridine (5 mmol) trimethylsilyl azide (10 mmol) and $InCl_3$ (20 mol%) in acetonitrile (10 ml) was stirred at room temperature for an appropriate time (table). On completion, the reaction mixture was quenched with water (10 ml) and extracted with ethyl acetate (2×15 ml). The organic layers were dried over anhydrous $NaSO_4$, concentrated in vacuo, and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2 : 8) to afford pure azidoamine.

Spectroscopic data for product **2a:** Liquid, IR (KBr): ν 3280, 2110, 1600. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 3.05–3.10 (m, 1H), 3.15–3.30

(m, 1H), 4.50–4.60 (dd, 1H, $J = 8.7$ and 5.2 Hz), 4.80–4.90 (m, 1H), 7.10–7.35 (m, 7H), 7.80 (d, 2H, $J = 8.0$ Hz). HRMS: Calcd for $C_{15}H_{16}NO_2S$ $(M\text{-}N_3)^+$ 274.0952, found 274.0932. **3a:** Liquid, IR (KBr): ν 3280, 2110, 1600. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 3.58 (d, 2H, $J = 6.0$ Hz), 4.45–4.50 (dd, 1H, $J = 12.8$ and 6.0 Hz), 5.20 (d, 1H, $J = 7.1$ Hz), 7.15–7.40 (m, 7H), 7.60 (d, 2H, $J = 8.0$ Hz). EIMS: m/z 274 $(M\text{-}N_3)^+$, 260, 184, 155, 91. HRMS: Calcd for $C_{15}H_{16}NO_2S$ $(M\text{-}N_3)^+$ 274.0952, found 274.0932. **4f:** Liquid, IR (KBr): ν 3270, 2940, 2870, 2100, 1600. ^{1}H NMR ($CDCl_3$): δ 1.15–1.50 (m, 4H), 1.60–1.80 (m, 2H), 1.95–2.20 (m, 2H), 2.45 (s, 3H), 3.05 (ddd, 1H, $J = 10.5$, 9.2, 4.0 Hz), 3.25 (ddd, 1H, $J = 9.2$, 9.2, 3.8 Hz), 4.80 (brs, NH), 7.35 (d, 2H, $J = 8.0$ Hz), 7.80 (d, 2H, $J = 8.0$ Hz). EIMS: m/z 295 M^+, 252, 210, 155, 111, 91. HRMS: Calcd for $C_{13}H_{18}NO_2S$ $(M\text{-}N_3)^+$ 252.1058, found 252.1075. **4g:** Liquid, IR (KBr): ν 3275, 2960, 2105, 1600. ^{1}H NMR ($CDCl_3$): δ 1.25–1.50 (m, 1H), 1.55–1.75 (m, 3H), 1.90–2.05 (m, 2H), 2.45 (s, 3H), 3.30 (ddd, 1H, $J = 10.5$, 9.0, 3.9 Hz), 3.65 (ddd, 1H, $J = 9.5$, 9.5, 3.8 Hz), 4.95 (brs, NH), 7.40 (d, 2H, $J = 8.1$ Hz), 7.80 (d, 2H, $J = 8.1$ Hz). EIMS: m/z 281 M^+, 251, 238, 155, 133, 91, 62. HRMS: Calcd for $C_{12}H_{16}NO_2S$ $(M\text{-}N_3)^+$ 238.0901, found 238.0908. **4i:** Liquid, IR (KBr): ν 3280, 2105, 1595. ^{1}H NMR ($CDCl_3$): δ 0.85 (t, 3H, $J = 7.0$ Hz), 1.05–1.30 (m, 4H), 1.35–1.50 (m, 2H), 2.45 (s, 2H), 3.25–3.35 (m, 3H), 4.80 (d, 1H, $J = 7.0$ Hz), 7.40 (d, 3H, $J = 8.0$ Hz), 7.80 (d, 2H, $J = 8.0$ Hz). EIMS: m/z 240 $(M\text{-}CH_2N_3)^+$, 155, 91. HRMS: Calcd for $C_{12}H_{18}NO_2S$ $(M\text{-}CH_2N_3)^+$ 240.1115, found 240. 10935.

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