Lithium Perchlorate Catalyzed Regioselective Ring Opening of Aziridines with Sodium Azide and Sodium Cyanide

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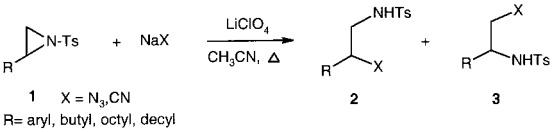
Abstract: Aziridines react smoothly with sodium azide and sodium cyanide in the presence of catalytic amount of lithium perchlorate under essentially mild and neutral reaction conditions to afford the corresponding β-azido and β-cyanoamines in high yields with high regioselectivity.

Keywords: lithium perchlorate, aziridines, regioselective, β-azidoamines

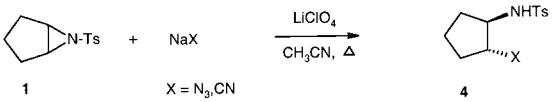
Aziridines are useful precursors for the synthesis of many biologically interesting molecules such as amino acids,[1] heterocycles[2] and alkaloids.[3] They are well known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo regioselective ring opening reactions contributes largely to their synthetic value.[4] In particular, the cleavage of aziridines with azide nucleophile has special interest because the resultant azidoamines can be easily transformed into *vic*-diamines, which have widespread applications in asymmetric synthesis.[5] As a result, there have been some reports on the ring opening of aziridines with silyl nucleophiles which utilize imidochromium complex,[6] rare earth metal complexes[7] and tetrabutylammonium fluoride[8] as promoters. However, many of these procedures have limitations in terms of yields, reaction times, selectivity, availability and quantity of the reagents used. Therefore, the development of neutral reaction conditions like solutions of lithium perchlorate in acetonitrile would extend the scope of this transformation. In addition, there are no reports on the regioselective ring opening of aziridines with sodium azide and sodium cyanide using lithium perchlorate as catalyst. In recent years, lithium perchlorate in diethyl ether has emerged as mild Lewis acid for effecting various organic transformations.[9] This medium provides a convenient procedure to carry out the reactions under neutral reaction and work-up conditions.[10]

In this report we wish to describe a simple and convenient method for the synthesis of β-azidoamines from aziridines using a catalytic amount of lithium perchlorate under mild reaction conditions. Thus, treatment of styrene *N*-tosyl aziridine with sodium azide or sodium cyanide in the presence of 10 mol% $LiClO_4$ in acetonitrile at reflux temperature resulted in the formation of β-azido- or β-cyano amines **2** and **3** respectively in high yields (Scheme 1).



Scheme 1

In a similar fashion, *p*-tolyl-*N*-tosyl aziridine also reacted smoothly with sodium azide to afford the corresponding β-azidoamine in high yield (Table 1, entry g). Aryl-*N*-tosyl aziridines underwent cleavage by an azide or cyano nucleophile with preferential attack at the benzylic position resulting in the formation of product **2** with a trace amount of **3** (Table 1, entries f–h). However, the treatment of alkyl-*N*-tosyl aziridines with sodium azide and sodium cyanide gave predominantly the ring-opened product **3** with a minor amount of **2** (Table 1, entries i–l). The ratios of products **2** and **3** were determined from the ^{1}H NMR spectrum of the crude products. The products could not be separated by column chromatography on silica gel. In all cases, the reactions proceeded efficiently in high yields. Furthermore, the treatment of cycloalkyl-*N*-tosyl aziridines with azide or cyanide nucleophile afforded the corresponding ring opened products in high yields (Scheme 2).



Scheme 2

In case of cycloalkyl aziridines, the stereochemistry of the ring opened product **4b** was found to be *trans* from the coupling constants of the ring hydrogens at δ = 3.05 (ddd, *J* = 10.0, 9.5, 4.0 Hz, 1 H), for (NCH) in ^{1}H NMR spectrum. Similarly the peak at δ = 3.25 ppm for (CHN) showed the similar splitting pattern (ddd, *J* = 9.5, 9.5, 3.8 Hz, 1 H). The method is clean and highly regioselective, affording β-azido- and β-cyano amines in excellent yields. The reaction conditions are mild and no side products or decomposition of the products was observed. All the products were fully characterized by ^{1}H NMR, IR, and mass spectroscopic data. However, in the absence of catalyst, the reaction did not yield any product even at reflux

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temperature. The efficacy of other Lewis acids, such as $InCl_3$, YCl_3 and $YbCl_3$ was studied for this transformation. Among these catalysts, lithium perchlorate was found to be an excellent catalyst in terms of conversion and reaction time. This is because of the mild Lewis acidity of the lithium ion, which coordinates the nitrogen atom of the aziridine and facilitates the ring opening reaction with nucleophile. The *N*-tosyl aziridines underwent cleavage by azide and cyanide nucleophiles in an S_N2 manner to produce ring opened products under neutral conditions. The scope and generality of this process is illustrated with respect to various aziridines and nucleophiles such as azide and cyanide and the results are presented in Table 1.

In conclusion, we have developed a simple, convenient and efficient method for the preparation of β-azido- and β-cyanoamines from aziridines using a catalytic amount of lithium perchlorate under neutral reaction and work-up conditions. The notable features of this method are high yields of products, mild reaction conditions, high regioselectivity, cleaner reaction profiles, simplicity in operation and ready availability of the catalyst at low cost, which makes it a useful and attractive process for the synthesis of β-azido- and β-cyanoamines of synthetic importance.

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a Vario EL analyzer.

β-Azido or β-Cyano Amines; General Procedure

A mixture *N*-tosyl aziridine (5 mmol), NaN_3 or NaCN (7.5 mmol) and $LiClO_4$ (10 mol%) in MeCN (10 mL) was stirred at reflux temperature for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over anhyd Na_2SO_4, concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc –hexane, 2:8) to afford pure β-azido or β-cyano amine.

4a

Liquid.

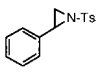
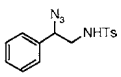
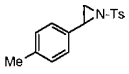
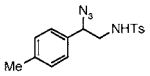
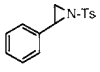
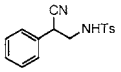
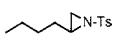
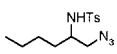
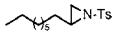
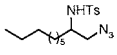
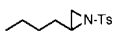
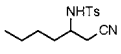
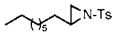
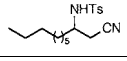
IR (KBr): 3275, 2960, 2105, 1600 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.27–1.50 (m, 1 H), 1.55–1.75 (m, 3 H), 1.90–2.05 (m, 2 H), 2.45 (s, 3 H), 3.30 (ddd, 1 H, *J* = 10.0, 9.5, 4.0 Hz), 3.65 (ddd, 1 H, *J* = 9.5, 9.5, 3.8 Hz), 4.95 (br s, NH), 7.40 (d, 2 H, *J* = 8.1 Hz), 7.80 (d, 2 H, *J* = 8.1 Hz).

MS-EI: *m*/*z* = 281 [M$^+$], 251, 238, 155, 133, 91.

HRMS: *m*/*z* calcd for $C_{12}H_{16}NO_2S$ (M – N_3)$^+$, 238.09; found, 238.09.

Table 1 $LiClO_4$-Catalyzed Synthesis of β-Azido- and β-Cyanoamines

Entry	Aziridine	Product	NaX	Time (h)	Yield[a] (%)	Ratio **2**:**3**[b]
a			NaN_3	6.0	90	–
b			NaN_3	5.5	85	–
c			NaN_3	5.5	85	–
d			NaCN	7.0	80	–
e			NaCN	6.5	82	–
f			NaN_3	4.0	90	92:8
g			NaN_3	3.5	92	95:5
h			NaCN	5.5	86	92:8
i			NaN_3	6.0	90	13:87
j			NaN_3	6.5	85	12:88
k			NaCN	8.0	87	15:85
l			NaCN	9.5	83	10:90

[a] Isolated and unoptimized yields.

[b] Ratio of products from internal attack vs terminal attack.

4b
Liquid.

IR (KBr): 3270, 2940, 2870, 2100, 1600 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.15–1.50 (m, 4 H), 1.60–1.80 (m, 2 H), 1.95–2.20 (m, 2 H), 2.45 (s, 3 H), 3.05 (ddd, 1 H, *J* = 10.0, 9.5, 4.0 Hz), 3.25 (ddd, 1 H, *J* = 9.5, 9.5, 3.8 Hz), 4.80 (br s, NH), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 295 [M^+], 252, 210, 155, 111, 91.

HRMS: *m*/*z* calcd for $C_{13}H_{18}NO_2S$ $(M - N_3)^+$, 252.10; found, 252.10.

4c
Solid.

Mp 147–148 °C.

IR (KBr): 3270, 2935, 2870, 2098, 1598 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.20–1.40 (m, 6 H), 1.42–1.70 (m, 4 H), 1.80–1.90 (m, 1 H), 2.42 (s, 3 H), 3.05–3.10 (m, 1 H), 4.65 (br s, NH), 7.33 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 307 [M^+], 266, 210, 155, 125, 91.

Anal. Calcd for $C_{14}H_{20}N_4O_2S$ (308.39): C, 54.53; H, 6.54; N, 18.17; S, 10.40. Found: C, 54.40; H, 6.57; N, 18.37; S, 10.43.

4d
Solid.

Mp 107–109 °C.

IR (KBr): 3253, 2935, 2243, 1600 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.38–1.59 (m, 1 H), 1.60–1.78 (m, 3 H), 1.90–2.05 (m, 2 H), 2.45 (s, 3 H), 2.80–3.0 (m, 1 H), 3.68–3.88 (m, 1 H), 5.45 (br s, NH), 7.38 (d, 2 H, *J* = 8.1 Hz), 7.80 (d, 2 H, *J* = 8.1 Hz).

MS-EI: *m*/*z* = 264 [M^+], 237, 210, 155, 91.

Anal. Calcd for $C_{13}H_{16}N_2O_2S$ (264.34): C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 59.01; H, 6.07; N, 10.58; S, 12.15.

4e
Solid.

Mp 112–113 °C.

IR (KBr): 3278, 2940, 2245, 1600 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.20–1.50 (m, 3 H), 1.51–1.80 (m, 3 H), 1.87–2.20 (m, 2 H), 2.45 (s, 3 H), 2.61–2.87 (m, 1 H), 3.32–3.52 (m, 1 H), 5.25 (br s, NH), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 278 [M^+], 210, 155, 111, 91.

Anal. Calcd for $C_{14}H_{18}N_2O_2S$ (278.36): C, 60.41; H, 6.52; N, 10.06; S, 11.52. Found: C, 60.56; H, 6.50; N, 10.10; S, 11.55.

2f
Liquid.

IR (KBr): 3280, 2110, 1600 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 3.05–3.10 (m, 1 H), 3.15–3.30 (m, 1 H), 4.50–4.60 (dd, 1 H, *J* = 8.7, 5.2 Hz), 4.80–4.90 (br s, NH), 7.10–7.35 (m, 7H), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 316 [M^+], 274 $[M - N_3]^+$, 260, 184, 155, 91.

Anal. Calcd for $C_{15}H_{16}N_4O_2S$ (316.37): C, 56.95; H, 5.10; N, 17.71; S, 10.13. Found: C, 56.91; H, 5.13; N, 17.8; S, 10.21.

3f
Liquid.

^1H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 3.50 (d, 2 H, *J* = 6.0 Hz), 4.45 (dd, 1 H, *J* = 12.8, 6.0 Hz), 5.20 (br s, 1 H, NH), 4.80–4.90 (br s, NH), 7.10–7.40 (m, 7 H), 7.70 (d, 2 H, *J* = 8.0 Hz).

2g
Liquid.

IR (KBr): 3275, 2108, 1599 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.35 (s, 3 H), 2.43 (s, 3 H), 2.95–3.10 (m, 1 H), 3.15–3.20 (m, 1 H), 4.50 (dd, 1 H, *J* = 8.7, 5.2 Hz), 4.80–4.90 (br s, NH), 7.10–7.25 (m, 4 H), 7.30 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 330 [M^+], 288 $[M - N_3]^+$, 275, 183, 155, 91.

Anal. Calcd for $C_{16}H_{18}N_4O_2S$ (330.40): C, 58.16; H, 5.49; N, 16.96; S, 9.70. Found: C, 58.20; H, 5.50; N, 17.01; S, 9.73

3g
Liquid.

^1H NMR ($CDCl_3$): δ = 2.39 (s, 3 H), 2.45 (s, 3 H), 3.5 (d, 1 H, *J* = 5.9 Hz), 3.15–3.20 (m, 1 H), 4.50 (dd, 1 H, *J* = 12.5, 5.9 Hz), 5.25 (br s, NH), 7.10–7.29 (m, 4 H), 7.33 (d, 2 H, *J* = 8.0 Hz), 7.75 (d, 2 H, *J* = 8.0 Hz).

2h
Solid.

MP 120–122 °C.

IR (KBr): 3250, 2253, 1598 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.40 (s, 3 H), 2.80–3.0 (m, 2 H), 4.50–4.60 (m, 1 H), 5.45 (br s, NH), 7.10–7.48 (m, 7 H), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 301 [M^+], 260, 155, 91.

Anal. Calcd for $C_{16}H_{16}N_2O_2S$ (300.37): C, 64.0; H, 5.37; N, 9.33; S, 10.67. Found: C, 64.03; H, 5.36; N, 9.40; S, 10.7.

3i
Liquid.

IR (KBr): 3280, 2105, 1595 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, 3 H, *J* = 7.0 Hz), 1.05–1.30 (m, 4 H), 1.35–1.50 (m, 2 H), 2.45 (s, 3 H), 3.25–3.35 (m, 3 H), 4.80 (d, 1 H, *J* = 7.0 Hz), 7.38 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 296 [M^+], 240 $[M - CH_2N_3]^+$, 155, 91.

Anal. Calcd for $C_{14}H_{20}N_4O_2S$ (296.38): C, 52.68; H, 6.80; N, 18.90; S, 10.82. Found: C, 52.70; H, 6.78; N, 18.87; S, 10.85.

2i
^1H NMR ($CDCl_3$): δ = 0.90 (t, 3 H, *J* = 7.0 Hz), 1.25–1.38 (m, 4 H), 1.47–1.55 (m, 2 H), 2.45 (s, 3 H), 2.75–2.82 (m, 1 H), 3.05–3.15 (m, 1 H), 3.38–3.45 (m, 1 H), 4.85 (br s, 1 H, NH), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.70 (d, 2 H, *J* = 8.0 Hz).

3j
Liquid.

IR (KBr): 3278, 2930, 2100, 1592 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.85 (t, 3 H, *J* = 7.0 Hz), 1.0–1.35 (m, 7 H), 1.37–1.60 (m, 3 H), 2.45 (s, 3 H), 3.20–3.38 (m, 3 H), 4.55 (d, 1 H, *J* = 7.0 Hz), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 325 [M^+], 282, 268, 254, 155, 91.

Anal. Calcd for $C_{15}H_{24}N_4O_2S$ (324.43): C, 55.53; H, 7.46; N, 17.27; S, 9.88. Found: C, 55.51; H, 7.50; N, 17.3; S, 9.90.

2j
^{1}H NMR ($CDCl_3$): δ = 0.90 (t, 3 H, *J* = 7.0 Hz), 1.15–1.35 (m, 6 H), 1.39–1.60 (m, 4 H), 2.45 (s, 3 H), 2.75–2.85 (m, 1 H), 3.05–3.15 (m, 1 H), 3.40–3.50 (m, 1 H), 5.0 (br s, 1 H, NH), 7.30 (d, 2 H, *J* = 8.0 Hz), 7.75 (d, 2 H, *J* = 8.0 Hz).

3k
Solid.

Mp 72–73 °C.

IR (KBr): 3265, 2241, 1595 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.80 (t, 3 H, *J* = 7.0 Hz), 1.05–1.30 (m, 4 H), 1.40–1.60 (m, 2 H), 2.41 (s, 3 H), 2.50–2.60 (m, 2 H), 3.40–3.50 (m, 1 H), 4.80 (d, 1 H, *J* = 7.5 Hz), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 281 [M^+], 240, 155, 91.

Anal. Calcd for $C_{14}H_{20}N_2O_2S$ (280.38): C, 59.97; H, 7.19; N, 10.0; S, 11.43. Found: C, 60.1; H, 7.23; N, 9.92; S, 11.5.

2k
Liquid.

IR (KBr): 3265, 2241, 1595 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.89 (t, 3 H, *J* = 7.0 Hz), 1.25–1.39 (m, 4 H), 1.42–1.65 (m, 2 H), 2.45 (s, 3 H), 2.61–2.73 (m, 2 H), 3.45–3.55 (m, 1 H), 4.85 (d, 1 H, *J* = 7.5 Hz), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.78 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 281 [M^+], 240, 155, 91.

3l
Liquid.

IR (KBr): 3278, 2930, 2245, 1597 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.85 (t, 3 H, *J* = 7.0 Hz), 1.05–1.35 (m, 7 H), 1.39–1.70 (m, 3 H), 2.41 (s, 3 H), 2.50–2.70 (m, 2 H), 3.30–3.48 (m, 1 H), 4.55 (d, 1 H, *J* = 7.7 Hz), 7.32 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 309 [M^+], 268, 224, 155, 91.

Anal. Calcd for $C_{16}H_{24}N_2O_2S$ (308.43): C, 62.31; H, 7.84; N, 9.08; S, 10.39. Found: C, 62.33; H, 7.90; N, 9.12; S, 10.43.

2l
Liquid.

IR (KBr): 3278, 2930, 2245, 1597 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 0.90 (t, 3 H, *J* = 7.0 Hz), 1.20–1.40 (m, 6 H), 1.42–1.75 (m, 4 H), 2.43 (s, 3 H), 2.65–2.85 (m, 2 H), 3.35–3.50 (m, 1 H), 4.75 (d, 1 H, *J* = 7.5 Hz), 7.35 (d, 2 H, *J* = 8.0 Hz), 7.75 (d, 2 H, *J* = 8.0 Hz).

MS-EI: *m*/*z* = 309 [M^+], 268, 224, 155, 91.

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