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$InCl_3$-catalyzed regioselective opening of aziridines with heteroaromatics

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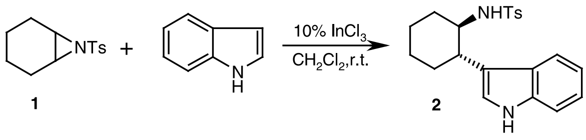
Abstract—A variety of *N*-tosylaziridines undergo ring opening with pyrrole, furan, thiophene and indole in the presence of a catalytic amount of indium trichloride at ambient temperature to afford the corresponding β-aminoheterocycles in good yields with high regioselectivity. © 2002 Elsevier Science Ltd. All rights reserved.

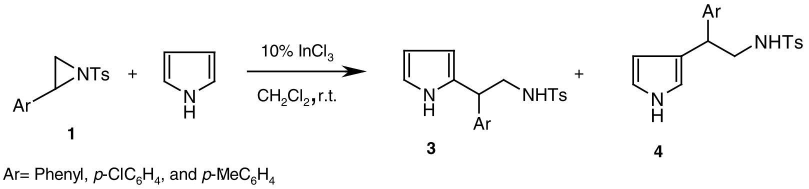
Aziridines are important precursors for the synthesis of many nitrogen containing biologically interesting molecules.[1] They are known to react with various nucleophiles and their ability to undergo regioselective ring opening reactions contribute largely to their synthetic value.[2] As a result, several procedures have been developed for the ring opening of aziridines with various nucleophiles such as organometallic reagents,[3] silyl nucleophiles,[4] Wittig reagents,[5] amines[6] and hydroxyl compounds.[7] To date, the reactions of pyrrole and furan remain a challenge for synthetic chemists because of their sensitivity to acids and air. The acid-catalyzed reactions of pyrrole and furan are limited and require the careful control of acidity to prevent side reactions.[8] As such, there is no report on the regioselective ring opening of aziridines with pyrrole, furan and other heterocycles. Recently, $InCl_3$ has attracted much attention as a mild Lewis acid with potential, imparting high regio-, chemo- and diastereoselectivity in various chemical transformations because of its unique reactivity and exceptional stability.[9]



Scheme 1.

In this report we wish to highlight our results on the regioselective ring opening of aziridines with heteroaromatics using catalytic quantities of indium trichloride. Treatment of cyclohexene *N*-tosylaziridine with indole in the presence of 10% $InCl_3$ resulted in the formation of a β-indolyl cyclohexyl amine derivative in 75% yield (Scheme 1).

Similarly, cyclopentene and styrene *N*-tosylaziridines underwent cleavage with indole to give 3-substituted indole derivatives in high yields (entries **b** and **e**). Under these conditions, pyrrole reacted smoothly with cyclohexene and cyclopentene *N*-tosylaziridines to give the corresponding 2-alkylated pyrrole derivatives.[11] In the case of cycloalkyl *N*-tosylaziridines, the stereochemistry of the ring opened products was found to be *trans* from the coupling constants of the ring protons (entry **a**). The reaction is highly regioselective with cycloalkylaziridines affording the product as a single isomer in high yield. However, the reaction of styrene *N*-tosylaziridine with pyrrole in the presence of 10% $InCl_3$ gave the corresponding ring opened product **3** with a minor amount of **4** (Scheme 2).



Scheme 2.

Keywords: indium reagents; aziridines; heterocycles; regioselectivity.

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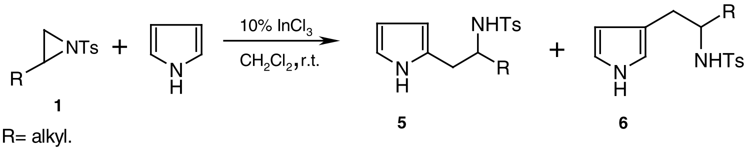
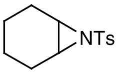
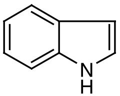
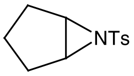
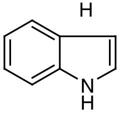
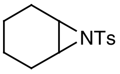
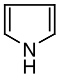
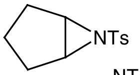
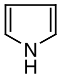
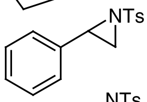
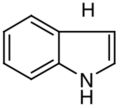
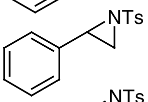
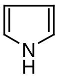
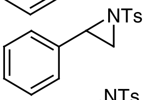
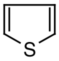
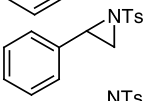
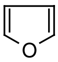
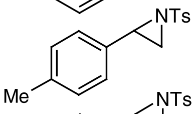
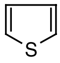
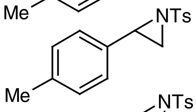
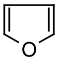
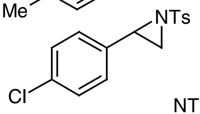
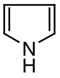
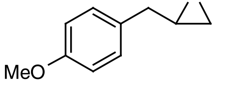
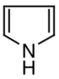
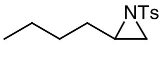
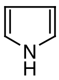
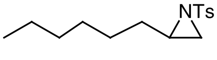
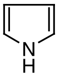
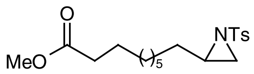
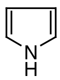


Scheme 3.

Table 1. $InCl_3$-catalyzed opening of aziridines with heteroaromatics

entry	aziridine	nucleophile	time (h)	yield[a] (%)	ratio of products
a			12	75	—
b			10	70	—
c			5.5	72	—
d			6.5	74	—
e			5.5	85	60:40[b]
f			2.5	90	87:13[c]
g			5.0	87	90:10[b]
h			4.0	80	70:30[b]
i			5.5	85	80:20[b]
j			4.5	83	85:15[b]
k			3.5	87	85:15[c]
l			4.5	85	75:25[c]
m			2.5	85	70:30[c]
n			3.0	80	75:25[c]
o			2.0	83	70:30[c]

a: Isolated and unoptimised yields
b: Ratio of products resulting from benzylic attack vs terminal attack of nucleophile
c : Ratio of 2- and 3-alkylated pyrrole products

Aryl *N*-tosylaziridines underwent cleavage by pyrrole with preferential attack at the benzylic position resulting in the formation of 2- and 3-alkylated pyrrole derivatives. The ring opening of aryl *N*-tosylaziridines with furan and thiophene gave the products resulting from benzylic as well as terminal attack of the nucleophile (entries **g**, **h**, **i** and **j**). Furthermore, alkyl substituted *N*-tosylaziridines underwent cleavage smoothly with pyrrole to afford the corresponding 2- and 3-alkylated pyrrole derivatives (Scheme 3).

The ratio of products in each reaction was determined by ^{1}H NMR spectroscopic analysis. The position of the substitution on the heteroaromatic ring was assigned on the basis of ^{1}H NMR spectra and also by comparison with 2- and 3-alkylated pyrrole and indoles.[10] In the case of alkyl substituted *N*-tosylaziridines, the regioisomers were isolated by column chromatography. In all cases the reactions proceeded efficiently in high yields at ambient temperature. The reaction conditions are mild so that no decomposition of the products or polymerization of the starting materials was observed. The method is clean and the products were obtained in high yields without the formation of any side products. However, products are obtained in low yields in the presence of metal triflates such as $Sc(OTf)_3$, $In(OTf)_3$ and $Yb(OTf)_3$, because of the rapid decomposition of the pyrrole and furan. Among various metal halides such as $BiCl_3$, $ZrCl_4$, $YbCl_3$, YCl_3 and $CeCl_3$ used for this reaction, $InCl_3$ was found to be more effective in terms of conversion and reaction time. Finally, the catalyst was recovered during work-up and recycled in subsequent reactions without any decrease in activity. Several examples illustrating this novel and convenient method for regioselective ring opening of aziridines with heteroaromatics are listed in Table 1.

In summary, we have found that $InCl_3$ is a mild and highly efficient Lewis acid catalyst for the regioselective ring opening of aziridines with heterocycles. Due to its efficiency, simplicity and compatibility with acid sensitive pyrrole and furan this new procedure will find wide applications in organic synthesis.

Acknowledgements

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11. Experimental procedure: A mixture of aziridine (5 mmol), pyrrole (7 mmol) and $InCl_3$ (10 mol%) in dichloromethane (15 mL) was stirred at ambient temperature for the appropriate time (see Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (2×10 mL) and extracted with dichloromethane (2×15 mL). The aqueous layer was concentrated in vacuo to recover the catalyst. 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 product. ^{1}H NMR data for compound **2a** ($CDCl_3$, 200 MHz): δ 1.28–1.41 (m, 4H), 1.65–1.78 (m, 4H), 2.38 (s, 3H), 2.45 (ddd, J = 3.8, 4.0, 11.7 Hz, 1H), 2.65 (ddd J = 3.8, 6.0, 11.7 Hz, 1H), 4.45 (brs, NH, 1H), 6.80 (d, J = 1.7 Hz, 1H), 6.85–6.95 (m, 2H), 7.10–7.30 (m, 6H), 7.95 (brs, NH, 1H).

    Compound **2c** ($CDCl_3$, 200 MHz): δ 1.25–1.38 (m, 4H), 1.65–1.85 (m, 4H), 2.30 (ddd, J = 3.7, 6.0, 11.8 Hz, 1H), 2.40 (s, 3H), 3.78 (ddd, J = 4.0, 6.5, 11.8 Hz, 1H), 4.45 (m, NH, 1H), 5.70 (m, 1H), 6.00 (m, 1H), 6.48 (m, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 8.10 (brs, NH, 1H).

    Compound **3h** ($CDCl_3$, 200 MHz): δ 2.45 (s, 3H), 3.40 (ddd, J = 6.8, 7.5, 12.8 Hz, 1H), 3.55 (ddd, J = 7.5, 8.0, 12.8 Hz, 1H), 4.10 (dd, J = 6.8, 8.0 Hz, 1H), 4.45 (brs, NH, 1H), 6.05 (d, J = 2.7 Hz, 1H), 6.32 (m, 1H), 7.20 (d, J = 8.0 Hz, 2H), 7.23–7.41 (m, 6H), 7.70 (d, J = 8.0 Hz, 2H).

    Compound **5m** ($CDCl_3$, 400 MHz): δ 0.86 (t, J = 6.2 Hz, 3H), 1.15–1.30 (m, 4H), 1.48–1.61 (m, 2H), 2.45 (s, 3H), 2.70–2.95 (m, 2H), 3.10–3.26 (m, 1H), 4.63 (brs, NH, 1H), 5.80 (t, J = 3.4 Hz, 1H), 6.10 (dt, J = 2.4, 3.4 Hz, 1H), 6.30 (dd, J = 2.4, 3.4 Hz, 1H), 7.28 (d, J = 7.2 Hz, 2H), 7.70 (d, J = 7.2 Hz, 2H), 8.25 (brs, NH, 1H).

    Compound **6m** ($CDCl_3$, 400 MHz): δ 0.86 (t, J = 6.2 Hz, 3H), 1.15–1.32 (m, 4H), 1.45–1.58 (m, 2H), 2.45 (s, 3H), 2.60 (m, 1H), 2.76 (m, 1H), 3.15 (m, 1H), 4.24 (brs, NH, 1H), 5.85 (dd, J = 2.5, 3.8 Hz, 1H), 6.51 (m, 1H), 6.67 (t, J = 2.5 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H), 8.25 (brs, NH, 1H).

    Compound **5o** ($CDCl_3$, 400 MHz): δ 1.18–1.38 (m, 10H), 1.53–1.65 (m, 4H), 2.28 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 2.78–2.83 (m, 1H), 2.85–2.90 (m, 1H), 3.18–3.22 (m, 1H), 3.65 (s, 3H), 4.75 (brs, NH, 1H), 5.80 (t, J = 3.2 Hz, 1H), 6.08 (dt, J = 2.3, 3.2 Hz, 1H), 6.60 (dd, J = 2.3, 3.2 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 8.45 (brs, NH, 1H).