$InCl_3$-Catalyzed Alkylation of Indoles with Epoxides

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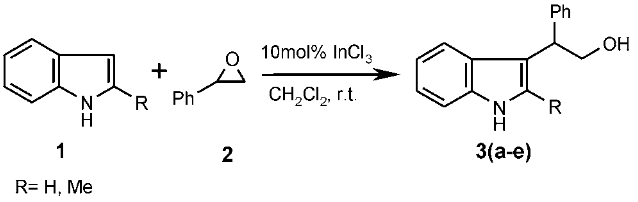
Received 15 July 2002

Abstract: Indoles react smoothly with terminal epoxides in the presence of catalytic amount of $InCl_3$ under mild conditions to afford the corresponding 3-alkyl indole derivatives in high yields with high regioselectivity.

Key words: indium reagents, epoxides, indoles, tryptophol derivatives

Epoxides are versatile building blocks for the synthesis of many bioactive natural products.[1] 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.[2] The epoxide ring opening with certain nucleophiles is generally carried out with acid or base catalysis to produce ring opened products. In particular the epoxide ring opening with indoles has been reported using lanthanide triflate catalysis[3] or high pressure conditions.[4] However these methods often involve the use of expensive reagents, drastic conditions, longer reaction times, unsatisfactory yields especially in case of aliphatic epoxides and entail undesirable side reactions due to polymerization or rearrangement of oxiranes. Thus there is a need to develop a convenient and efficient protocol for the regioselective ring opening of epoxides with indoles to produce 3-alkyl indole derivatives of biological importance.[5] In recent years, indium reagents have emerged as mild and water-tolerant Lewis acids imparting high regio- and chemoselectivity in various chemical transformations.[6] These reagents can be conveniently used either in aqueous or in non-aqueous media and can be recovered and reused in subsequent reactions.

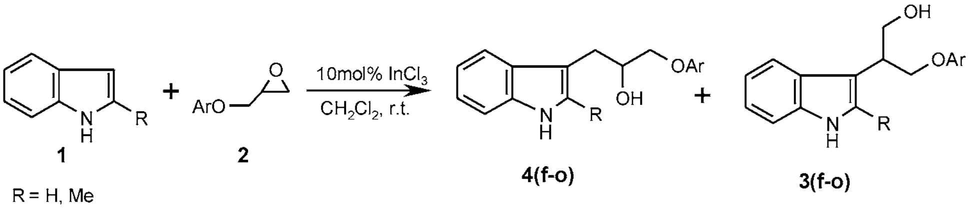
In continuation of our interest in the use of indium halides as efficient Lewis acids in various transformations,[7] we herein report another remarkable catalytic activity of $InCl_3$ in the regioselective ring opening of oxiranes with indoles. Thus treatment of indole with styrene oxide in the presence of a catalytic amount of $InCl_3$ under mild conditions afforded 2-(3-indolyl)-2-phenylethanol in 85% yield (Scheme 1).



Scheme 1

Aryl epoxides underwent cleavage by indole with preferential attack at the benzylic position resulting in the formation of primary alcohol. Since 3-position of indole is the preferred site for electrophilic substitution reactions 3-alkyl indole derivatives were obtained exclusively in all reactions. In case of aryl epoxides, a single regio isomer **3** was formed in each reaction, the structure of which was characterised by ^1H NMR, IR and mass spectroscopic data. Similarly, glycidyl aryl ethers reacted smoothly with indole and methyl indole to afford the corresponding tryptophol derivatives in high yields (Scheme 2).

The reactions proceeded efficiently at ambient temperature with high regioselectivity.[8] This method is even effective with aliphatic oxiranes, which is lacking in the existing procedures. This method does not require anhydrous solvents or any stringent reaction conditions. No precautions need to be taken to exclude moisture from the reaction media. The reactions are clean and highly regio-



Ar = phenyl, Cl-C_6H_4, F-C_6H_4, ^tBu-C_6H_4, 3,4-$(Me)_2$-C_6H_3, tolyl, Napthyl

Scheme 2

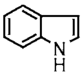
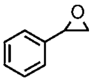
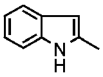
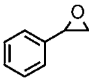
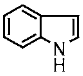
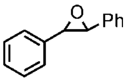
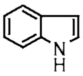
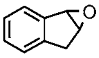
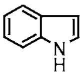
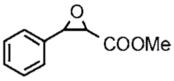
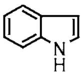
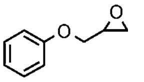
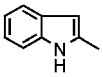
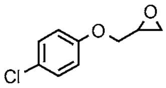
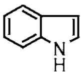
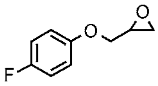
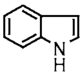
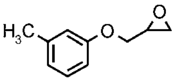
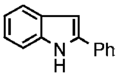
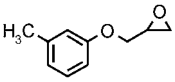
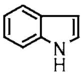
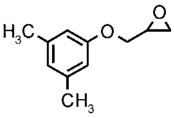
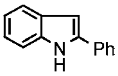
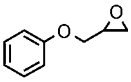
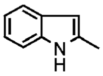
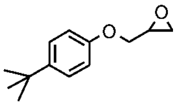
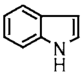
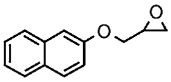
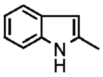
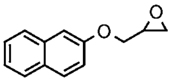
Synlett 2002, No. 9, Print: 02 09 2002.
Art Id.1437-2096,E;2002,0,09,1550,1552,ftx,en;D01602ST.pdf.

ISSN 0936-5214

selective affording high yields of products in a short period. The scope and generality of this process is illustrated with respect to various epoxides and indoles and the results are presented in the Table. Among various Lewis acids such as YCl_3, $YbCl_3$, $ZrCl_4$, $BiCl_3$ and $CeCl_3$ studied for this transformation $InCl_3$ was found to be more effective in terms of yields and selectivity.

In summary this paper describes a simple, convenient and efficient protocol for the alkylation of indoles with epoxides using a novel catalyst $InCl_3$. The notable features of this procedure are mild reaction conditions, greater selectivity, cleaner reaction profiles, improved yields, enhanced rates and simplicity in operation which make it a useful and attractive process for the synthesis of 3-alkyl

Table $InCl_3$-Catalyzed Alkylation of Indoles with Epoxides

Entry	Nucleophile	Epoxide	Time[a] (h)	Yield (%)	Ratio[b] (**4**:**3**)
a			3.0	85	–
b			2.5	80	–
c			4.0	87	–
d			4.5	80	–
e			5.0	70	–
f			3.5	82	85:15
g			2.5	84	85:15
h			3.5	72	78:22
i			3.0	78	90:10
j			4.0	82	92:8
k			3.5	76	89:11
l			5.5	80	90:10
m			4.0	74	95:5
n			3.5	73	91:9
o			3.0	75	93:7

[a] Isolated and unoptimised yields.

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

indoles. This method also provides a useful procedure to prepare tryptophol derivatives that are of interest as intermediates towards the synthesis of antibiotics such as indolmycin.

Acknowledgement

SA and BVS thanks CSIR, New Delhi for the award of fellowships.

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(8) **Experimental procedure**: A mixture of epoxide (5 mmol), indole (5 mmol) and $InCl_3$ (10 mol%) in dichloromethane (15 mL) was stirred at ambient temperature for an appropriate time (Table). 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. Spectral data for selected compounds **3a** : Solid, mp 121–122 °C; IR (KBr): 3520, 3050, 1640, 1500, 1240, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.13 (br s, 1 H, OH), 4.10 (dd, *J* = 10.5, 6.7 Hz, 1 H), 4.20 (dd, *J* = 10.5, 6.7 Hz, 1 H), 4.45 (t, 1 H, *J* = 6.7 Hz), 7.03 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.07 (d, *J* = 1.8 Hz, 1 H), 7.16 (dd, *J* = 8.0, 1.8 Hz, 1 H), 7.21 (m, 1 H), 7.26–7.36 (m, 5 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 8.05 (brs, NH, 1 H); EIMS *m/z*: 237 (M^+); Anal. Calcd for $C_{16}H_{15}NO$ (237.30): C, 80.98; H, 6.37; N, 5.90. Found: C, 80.95; H, 6.44; N, 5.95.
4f : Solid, mp 83–84 °C; IR (KBr): 3420, 2980, 1597, 1481,1240, 770 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (br s, 1 H, OH), 3.10 (d, *J* = 6.4 Hz, 2 H), 3.90 (dd, *J* = 13.5, 6.2 Hz, 1 H), 3.97 (dd, *J* = 13.5, 4.0 Hz, 1 H), 4.30 (m, 1 H), 6.80–7.35 (m, 9 H), 7.60 (d, *J* = 8.1 Hz, 1 H), 8.10 (br s, 1 H, NH); EIMS *m/z*: 267 (M^+); Anal. Calcd for $C_{17}H_{17}NO_2$ (267.32): C, 76.38; H, 6.41; N, 5.24. Found: C, 76.41; H, 6.43; N, 5.30.