$InCl_3$-Catalyzed Highly Regioselective Ring Opening of Epoxides with Thiols

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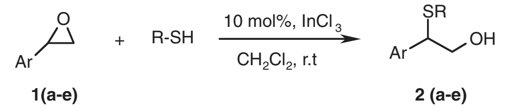
(Received May 9, 2002; CL-020401)

Epoxides react smoothly with thiols in the presence of 10 mol% $InCl_3$ under very mild conditions to afford the corresponding β-hydroxy sulfides in high yields with high regioselectivity. Similar yields and selectivity are also obtained with catalytic amount of indium triflate under these reaction conditions.

The ring opening process of epoxides with thiols to yield β-hydroxy sulfides is of great importance in the field of pharmaceuticals[1] and natural products,[2] particularly for the synthesis of leukotrienes such as LTC_4 and LTD_4. Epoxides are well known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo regioselective ring opening reactions contribute largely to their synthetic value.[3,4] One of the most straightforward synthetic procedures for the preparation of β-hydroxy sulfides is the ring opening of epoxides with thiols in the presence of base in a protic solvent.[5] Subsequently, several methods have been developed using Lewis acid catalysis to perform these epoxide ring-opening reactions under mild conditions.[6,7] However, many of these methods often involve the use of stoichiometric amounts of the reagents,[7a] drastic reaction conditions, poor regioselectivity, extended reaction times,[6a] unsatisfactory yields and entail undesirable side reactions[6b] due to oxidation of thiol or rearrangement of oxiranes. Since organic sulfur compounds have become increasingly useful and important in organic synthesis, the development of convenient and efficient methods for the preparation of appropriate sulfides, especially those, which carry other functional groups, are well appreciated. In recent years, indium reagents have emerged as mild and water-tolerant Lewis acids imparting high regio- and chemoselectivity in various chemical transformations.[8] In addition, they can be conveniently used either in aqueous or in non-aqueous medium and can be recovered *via* aqueous work-up.

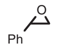
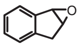
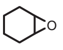
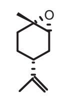
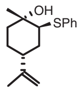
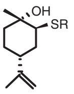
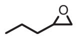
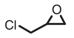
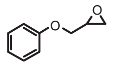
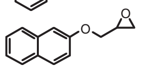
In continuation of our interest on the use of indium halides as mild and efficient Lewis acids in promoting various transformations,[9] we herein describe another remarkable catalytic activity of indium chloride in the regioselective ring opening of oxiranes with thiols. Thus treatment of styrene oxide with thiophenol in the presence of 10 mol% $InCl_3$ under mild conditions afforded the corresponding 2-phenylthio-2-phenylethanol **2** in 90% yield (Scheme 1).



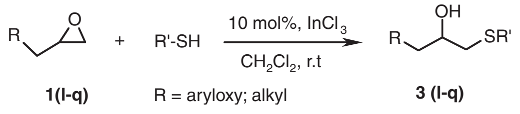
Scheme 1.

Aryl oxiranes underwent cleavage by a variety of thiols in a regioselective manner with preferential attack at benzylic position (see Table 1). Only a single product was obtained in this reaction the structure of which was confirmed by ^{1}H-NMR spectrum of the crude product. The method is highly regioselective affording exclusively the ring-opened product **2**. In a similar fashion, glycidyl aryl ethers reacted smoothly with thiols to afford the corresponding β-hydroxy sulfides **3** in high yields (entries p, q). Alkyl oxiranes such as limonene oxide, epichlorohydrin and pentene oxide underwent cleavage with thiols to produce respective thioethers in high yields (Scheme 2).

Table 1. $InCl_3$-Catalyzed regioselective opening of epoxides with thiols

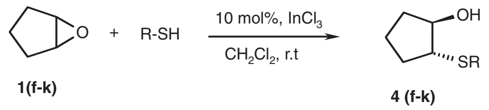
Entry	Epoxide	Thiol	Product [a]	Yield/%[b]	Time/h
a		Phenyl	2a	90	3.0
b	"	n-Decyl	2b	87	4.5
c	"	2-Naphthyl	2c	82	3.5
d		Phenyl	2d[c]	75	3.0
e	"	4-MeC_6H_4	2e[c]	80	3.5
f		Phenyl	4f	90	4.5
g	"	n-Decyl	4g	87	6.0
h	"	2-Naphthyl	4h	80	5.0
i		Phenyl	4i	88	4.5
j	"	2-Naphthyl	4j	81	5.5
k	"	n-Decyl	4k	85	6.0
l		Phenyl	3l 	75	4.0
m	"	R = n-Decyl	3m 	70	4.5
n		Phenyl	3n	87	3.0
o		4-BrC_6H_4	3o	85	4.5
p		Phenyl	3p	89	3.5
q		4-$MeOC_6H_4$	3q	87	4.5

[a]All products were characterized by ^{1}H NMR, IR and mass spectroscopy. [b]isolated and unoptimized yields. [c]Isomer 3 was also obtained in 15-20% yield.



Scheme 2.

Alkyl oxiranes (entries l–q) underwent cleavage by a range of thiols in a regioselective manner with preferential attack at the terminal position (see Table 1). In all cases the reactions proceeded efficiently at ambient temperature with high regioselectivity. Furthermore, cycloalkyl epoxides such as cyclohexene oxide and cyclopentene oxides reacted smoothly with thiols to afford the corresponding β-hydroxy sulfides **4** in high yields (Scheme 3).



Scheme 3.

In the case of cycloalkyl epoxides (entries f–k), the stereochemistry of the ring product **4f** was found to be *trans* from the coupling constants of the ring protons at δ 2.78 (ddd, $J = 4.5$, 9.8, 11.6 Hz, 1H), for (SCH) in ^{1}H NMR spectrum similarly the peak at δ 3.30 ppm for (OCH) showed the similar splitting pattern (ddd, $J = 4.5$, 9.8, 9.8 Hz, 1H). A variety of epoxides underwent cleavage with thiols to afford the corresponding β-hydroxy thioethers in high yields. All products were characterized by ^{1}H NMR, IR and mass spectroscopic data. This method does not require anhydrous solvents or any stringent reaction conditions. No precautions need to be taken to exclude moisture from the reaction medium. The reactions are clean and highly regioselective affording high yields of products in a short period. The scope and generality of this process is illustrated with respect to various epoxides and thiols. Among the various Lewis acids such as $InCl_3$, YCl_3, $YbCl_3$ and $CeCl_3$ studied for this transformation, $InCl_3$ was found to be more effective in terms of yields and selectivity. Thus, this method is superior to acid catalyzed or base catalyzed epoxide ring opening reactions with thiols. Furthermore, 10 mol% indium triflate was also found to be equally effective for the ring opening reactions of epoxides with thiols.

In summary, this paper describes a simple, convenient and efficient method for the regioselective ring opening of epoxides with thiols using a novel catalyst $InCl_3$. The notable features of this procedure are mild reaction conditions, greater regioselectivity, cleaner reaction profiles, improved yields, enhanced rates and simplicity in operation which make it a useful and attractive process for the synthesis of β-hydroxy thioethers of biological importance.

BVS thanks CSIR New Delhi for the award of fellowship.

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10 Experimental Procedure: A mixture of epoxide (5 mmol), thiol (5 mmol) and $InCl_3$ (10 mol%) in dichloromethane (10 mL) was stirred at ambient temperature for an appropriate time (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 ($2\times$ 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 product. The aqueous layer was concentrated *in vacuo* to recover the catalyst. Compared to indium trichloride, indium triflate was recovered in quantitatively and reused in subsequent reactions without loss of activity. Spectroscopic data for compounds: **2a**: 2-phenylthio-2-phenylethanol: Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.55–7.15 (m, 10H), 4.70 (t, 1H, $J = 6.8$ Hz), 3.65 (d, 2H, $J = 6.8$ Hz). EIMS: m/z: 230[M$^+$]; IR (neat) ν: 3340, 1620, 1508 1243, 1048, 710 cm.$^{-1}$ Anal. Calcd for $C_{14}H_{14}OS$ (230.324): C, 73.01; H, 6.13; S, 13.92%. Found: C, 73.1; H, 6.15; S, 13.95%. **4f**: 2-phenylthiocyclohexanol: Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.20–7.30 (m, 5H), 3.30 (ddd, 1H, $J = 9.8$, 9.8, 4.5 Hz), 3.0 (brs, 1H, OH), 2.78 (ddd, 1H, $J = 11.6$, 9.8, 4.5 Hz), 2.43–2.14 (m, 2H), 1.80–1.65 (m, 1H), 1.40–1.20 (m, 4H). EIMS: m/z: 208 [M$^+$]; IR (neat) ν: 3345, 3347, 1620, 1515 1243, 1053, 715 cm.$^{-1}$ Anal. Calcd for $C_{12}H_{16}OS$ (208.317): C, 69.19; H, 7.74; S, 15.39%. Found: C, 69.23; H, 7.75; S, 15.42%. **3p**: 3-phenoxy-1-phenylthio-propan-2-ol: Oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.80–6.77 (m, 10H), 4.20 (m, 1H), 3.80 (d, 2H, $J = 7.0$ Hz), 3.10 (d, 2H, $J = 6.8$ Hz). EIMS: m/z: 260[M$^+$]; IR (neat) ν: 3420, 1620, 1517 1245, 1058, 721 cm.$^{-1}$ Anal. Calcd for $C_{15}H_{16}O_2S$ (260.349): C, 69.20; H, 6.19; S, 12.31%. Found: C, 69.28; H, 6.21; S, 12.35%.