An efficient method for the ring opening of epoxides with aromatic amines catalysed by indium trichloride†

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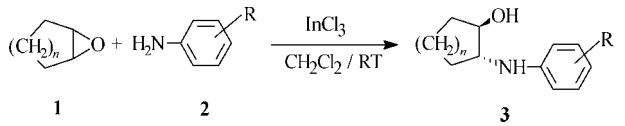
Received (in Montpellier, France) 20th September 2000, Accepted 20th November 2000
First published as an Advance Article on the web 11th January 2001

Indium trichloride catalyses for the first time the formation of β-amino alcohols from epoxides and aromatic amines in dichloromethane at room temperature.

β-Amino alcohols are an important class of organic compounds, which have found much use in medicinal chemistry and organic synthesis.[1] The classical synthesis of *β*-amino alcohols consists heating an epoxide with an excess of amine at elevated temperatures.[2] Since some functional groups may be susceptible to high temperatures, a variety of activators have been introduced for the cleavage of epoxides at room temperature.[3] However, there are still some limitations with the literature methods; for example, deactivated aromatic amines and some sterically hindered aromatic amines fail to open up these epoxides or still require high temperatures. To overcome these limitations, we report herein an efficient, simple and practical method for the ring opening of epoxides with aromatic amines catalysed by indium trichloride ($InCl_3$) in dichloromethane at room temperature.

The use of indium trichloride as a catalyst in various organic transformations,[4] such as transmetallation with organotin compounds,[4a–c] Mukaiyama aldol reactions,[4d] imino Diels–Alder reactions,[4e] Barbier reactions,[4f] *etc.*, is well documented. The opening of epoxides with indium trichloride is known to give either the corresponding carbonyl compounds or chlorohydrins.[4g] But this reaction has not so far been attempted in the presence of amines, which can give rise to versatile *β*-amino alcohols of great utility in medicinal and organic chemistry. Herein, we have attempted for the first time the cleavage of epoxides with aromatic amines using indium trichloride as a catalyst since this is one of the most useful synthetic transformations with varied applications.

The reaction was carried out by adding indium trichloride to a mixture of epoxide (**1**) and amine (**2**) in dichloromethane at room temperature (Scheme 1). The optimum ratio of indium trichloride was found to be 0.20 mol.%. The reaction mixture was stirred at room temperature for 12 h to give the corresponding amino alcohols (**3**) in almost quantitative yields (Table 1). All the compounds were fully characterised by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data by comparison with the known compounds.[3a,b] The *trans* stereochemistry of the amino alcohols, for compound **3c** as an example, was determined from the coupling constants of the peaks at 3.31 ppm (CH–OH) (ddd, J = 9.8, 9.2, 4.5 Hz) and 3.07 ppm (CH–NHPh) (ddd, J = 9.8, 9.2, 3.9 Hz) in the ^{1}H NMR spectra.[3h]



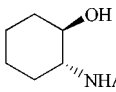
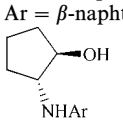
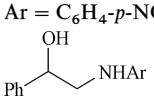
1 **2** **3**

Scheme 1

† IICT Communication no. 4580.

With the present methodology, even sterically hindered amines such as *o*-methyl (**3b**, **3m**, **3q**), *o*-methoxyaniline (**3d**, **3n**, **3r**) and α-naphthylamine (**3j**, **3o**) react smoothly at room temperature. The noteworthy feature of the present methodology is that highly deactivated amines such as *p*-nitroaniline (**3i**, **3p**) also opened the epoxides in a reasonable yield at room temperature. The unusual feature of this reaction is that only aromatic amines opened the epoxides, whereas aliphatic amines such as diethylamine, benzylamine and pyrrolidine failed to react with these epoxides at room temperature after 48 h under the reaction conditions. The reaction of these epoxides with diethylamine also did not take place even under dichloromethane reflux conditions. The lack of reactivity of aliphatic amines may be due to stronger complexation with the catalyst as a consequence of their higher basicity.

Table 1 Indium trichloride catalysed epoxide opening with aromatic amines

	Amino alcohol[a]	Yield[b] (%)
		
3a	Ar = Ph[c]	90
3b	Ar = C_6H_4-*o*-CH_3[c]	88
3c	Ar = C_6H_4-*p*-CH_3[c]	94
3d	Ar = C_6H_4-*o*-OCH_3[c]	90
3e	Ar = C_6H_4-*p*-OCH_3[c]	96
3f	Ar = C_6H_4-*m*-Br[d]	92
3g	Ar = C_6H_4-*p*-Br[d]	94
3h	Ar = C_6H_4-*p*-F[c]	95
3i	Ar = C_6H_4-*p*-NO_2[d]	80
3j	Ar = α-naphthyl[c]	84
3k	Ar = *β*-naphthyl[c]	92
		
3l	Ar = Ph[c]	78
3m	Ar = C_6H_4-*o*-CH_3[e]	81
3n	Ar = C_6H_4-*o*-OCH_3[e]	80
3o	Ar = α-naphthyl[e]	76
3p	Ar = C_6H_4-*p*-NO_2[d]	75
		
3q	Ar = C_6H_4-*o*-CH_3[e]	86
3r	Ar = C_6H_4-*o*-OCH_3[e]	84

[a] Substrates **1** and **2** were mixed in a 1 : 1 ratio with 0.2 mol.% of $InCl_3$. Substrates and catalyst were stirred in CH_2Cl_2 at r.t. for 12 h. [b] Isolated yields. [c] Ref. 3*h*. [d] Ref. 3*b*. [e] New compound.

In summary, we have demonstrated a novel, mild and efficient method for the ring opening of epoxides with aromatic amines using indium trichloride as a catalyst. This method is also compatible with deactivated and sterically hindered aromatic amines. We believe that this will be a useful addition to modern synthetic methodology.

Experimental

General procedure

To a mixture of epoxide **1** (1 mmol) and amine **2** (1 mmol) in dichloromethane (5 ml) was added anhydrous $InCl_3$ (0.2 mmol) at room temperature; the mixture was stirred at room temperature for 12 h. It was then quenched by the addition of aqueous sodium hydrogen carbonate (10%, 25 ml), extracted with dichloromethane (3 × 25 ml), dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel (100–200 mesh) using chloroform as eluent. The characterisation data for **3b** (for comparison with the literature) and for all new compounds are given below.

Compound 3b. Pale yellow viscous liquid. IR (neat): 3150–3600 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.08 (m, 1H), 1.39 (m, 3H), 1.75 (m, 2H), 2.08 (m, 2H), 2.18 (s, 3H), 2.81 (br s, 2H, NH and OH), 3.14 (ddd, J = 10.9, 9.3, 3.9, 1H, C*H*–NHPh), 3.41 (ddd, J = 10.5, 10.5, 4.8 Hz, 1H, C*H*–OH), 6.68 (m, 2H), 7.05 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 17.59, 24.23, 24.94, 31.76, 33.22, 59.91, 74.49, 111.69, 117.91, 123.11, 127.08, 130.37, 145.54. HR-MS m/z calc. for $C_{13}H_{19}NO$ (M^+): 205.147 446; found: 205.146 664.

Compound 3m. Pale yellow viscous liquid. IR (neat): 3110–3500 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.40 (m, 1H), 1.75 (m, 3H), 1.98 (m, 1H), 2.15 (s, 3H), 2.28 (m, 1H), 3.60 (m, 1H), 4.03 (m, 1H), 4.25 (br s, 2H, NH and OH), 6.69 (m, 2H), 7.02 (m, 2H). EI-MS (70 ev): m/z 191 (M^+). Anal. calc. for $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32; found: C 75.45, H 8.88, N 7.36%.

Compound 3n. Pale yellow viscous liquid. IR (neat): 3110–3550 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.45 (m, 1H), 1.80 (m, 3H), 2.05 (m, 1H), 2.30 (m, 1H), 3.60 (m, 1H), 3.85 (s, 3H), 4.00 (m, 1H), 4.15 (br s, 2H, NH and OH), 6.76 (m, 4H). EI-MS (70 ev): m/z 207 (M^+). Anal. calc. for $C_{12}H_{17}NO_2$: C 69.54, H 8.27, N 6.76; found: C 69.52, H 8.17, N 6.55%.

Compound 3o. White solid, mp 78–80 °C. IR (neat): 3120–3550 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.41 (m, 1H), 1.78 (m, 3H), 2.01 (m, 1H), 2.25 (m, 1H), 3.65 (m, 1H), 4.05 (m, 1H), 4.20 (br s, 2H, NH and OH), 7.30 (m, 2H), 7.45 (m, 2H), 7.84 (m, 3H). EI-MS (70 ev): m/z 227 (M^+). Anal. calc. for $C_{15}H_{17}NO$: C 79.26, H 7.54, N 6.16; found: C 79.12, H 7.48, N 5.98%.

Compound 3q. Pale yellow viscous liquid. IR (neat): 3100–3550 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.21 (s, 3H), 3.75 (m, 1H), 3.92 (m, 1H), 4.05 (br s, 2H, NH and OH), 4.51 (m, 1H), 6.69 (m, 4H), 7.38 (m, 5H). EI-MS (70 ev): m/z 227 (M^+). Anal. calc. for $C_{15}H_{17}NO$: C 79.26, H 7.54, N 6.16; found: C 79.48, H 7.66, N 6.28%.

Compound 3r. Pale yellow viscous liquid. IR (neat): 3050–3500 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 3.80 (m, 1H), 3.95 (m, 4H, –OCH_3, H), 4.05 (br s, 2H, NH and OH), 4.55 (m, 1H), 6.40 (m, 1H), 6.75 (m, 3H), 7.38 (m, 5H). EI-MS (70 ev): m/z 243 (M^+). Anal. calc. for $C_{15}H_{17}NO_2$: C 74.05, H 7.04, N 5.76; found: C 74.26, H 6.95, N 5.88%.

Acknowledgements

L. R. R. and M. A. R. thank CSIR, New Delhi, India for the award of Research Fellowships.

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