Glycerine and $CeCl_3 \cdot 7H_2O$: An Efficient and Recyclable Reaction Medium for Ring Opening of Epoxides with Thioamides and Amines

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Abstract: Oxiranes undergo rapid ring-opening reaction with a range of thioamides and amines to afford the corresponding β-amino alcohol derivatives. The reactions were carried out using glycerine and cerium(III) chloride as a recyclable reaction medium. All the reactions were carried out at room temperature and the products were obtained in excellent yields.

Key words: epoxides, amines, thioamides, amino alcohols, glycerine, cerium chloride.

Oxiranes are widely utilized as versatile synthetic intermediates and are considered to be 'spring-loaded' rings for nucleophilic ring opening. Their reactions are dominated by the electrophilic nature of these heterocycles, which generally involve cleavage of the three-membered rings with a variety of nucleophiles to give β-substituted alcohols and amines.[1] The resultant β-amino alcohols represent a wide range of β-adrenergic blockers, such as naptofidil (**1**), betaxolol (**2**), atenolol (**3**), and dopamine (**4**), which are used in the management of cardiovascular disorders, including hypertension, angina pectoris, cardiac arrhythmias and for disorders related to the sympathetic nervous system (Figure 1).[2]

One of the most straightforward synthetic approaches to the preparation of β-amino alcohols involves treating an epoxide with an excess of amine at elevated temperature. Since some functional groups are sensitive to high temperature, a variety of activators, such as alkali metal halides,[3] metal perchlorates,[4] metal triflates,[5] Bu_3P, ionic liquids, and hexafluoro-2-propanol[6] have been introduced. However, many of these methods involve the use of expensive catalysts, stoichiometric amounts of reagents and also require extended reaction times. Therefore, the development of an efficient and environmentally friendly, green protocol is still in demand.

The use of solvents such as water, supercritical fluids, ionic liquids, and solvent-free conditions under microwave irradiation has received much attention in recent years in the area of green synthesis. In this respect, glycerine has emerged as a green solvent with unique properties, such as high polarity, thermal stability, immiscibility with a number of organic solvents, negligible vapor pressure, low-toxicity, and recyclability.[7] Accordingly, glycerine represents a novel substitute for volatile organic solvents in organic transformations. Moreover, glycerine is inexpensive, readily available, and recyclable. Recently, Silvera et al. reported glycerine–cerium(III) chloride hydrate as a new and efficient recyclable reaction medium for the synthesis of bis(indole)methanes, and we also reported the successful synthesis of Hantzsch pyridines and quinoxalines in a similar manner.[8] In this communication, we wish to demonstrate the use of glycerine–$CeCl_3 \cdot 7H_2O$ as a recyclable reaction medium for the ring opening of

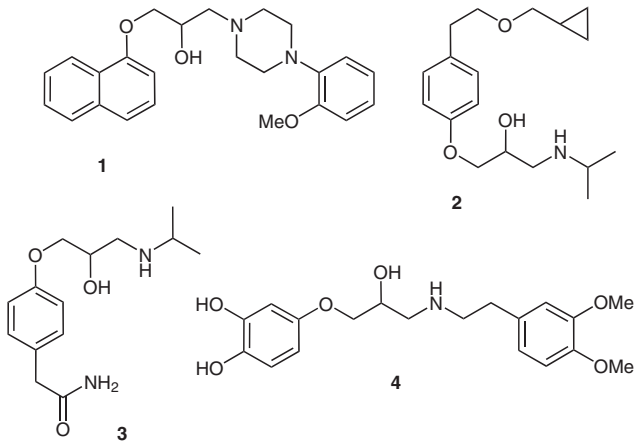
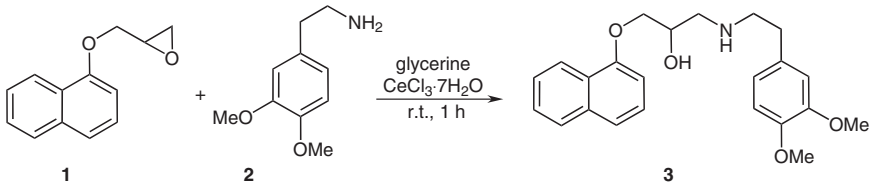


Figure 1



Scheme 1

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various epoxides with a variety of amines under mild conditions.

In a typical experiment, 2-[(naphthalen-1-yloxy)methyl]oxirane (**1**) and 2-(3,4-dimethoxyphenyl)ethanamine (**2**) were stirred in glycerine at room temperature in the presence of $CeCl_3 \cdot 7H_2O$ (10 mol%) for one hour, to afford the corresponding product, 1-(3,4-dimethoxyphenylamino)-3-(naphthalen-1-yloxy)propan-2-ol (**3a**) in excellent yield (Scheme 1). Upon completion of the reaction, ethyl acetate (10 mL) was added to reaction mixture, which was then stirred for 15 minutes and the glycerine was separated from the ethyl acetate layer by decantation. This process was repeated three times and the residue was used for further reactions. The separated ethyl acetate layers were combined, washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the required product, which was purified by column chromatography. Encouraged by the result obtained with the above reaction, we applied this methodology to the reaction of a variety of epoxides with amines and amides. In another experiment, 2-[(naphthalene-1-yloxy)methyl]oxirane and benzothioamide were reacted under similar reaction conditions. This reaction was complete within one hour to afford the corresponding product *N*-[2-hydroxy-3-(naphthalen-1-yloxy)propyl]benzothioamide (**3h**) in very good yield. In a similar manner, 2-[(naphthalen-1-yloxy)methyl]oxirane successfully reacted with *N*-Boc-piperazine, isopropyl amine, pyrrole, morpholine, aniline, ethane thioamide and 1-phenylthiourea (Table 1, entries 2–8) to afford the corresponding derivatives with high yields.

Table 1 Ring Opening of Epoxides Mediated by Glycerine–$CeCl_3 \cdot 7H_2O$

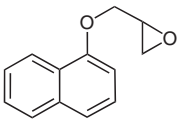
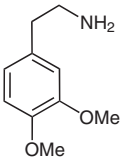
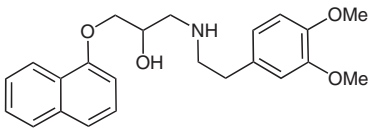
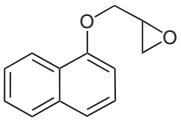
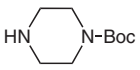
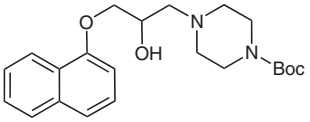
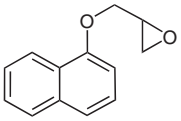
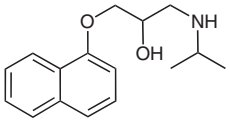
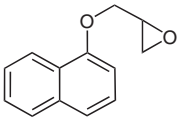
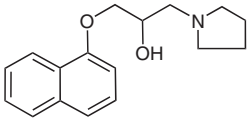
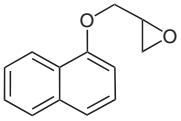
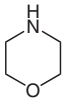
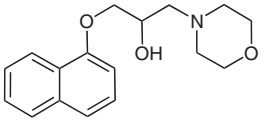
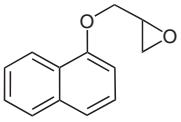
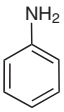
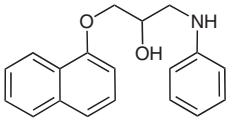
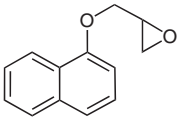
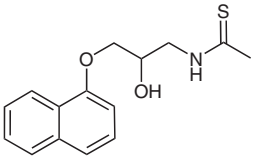
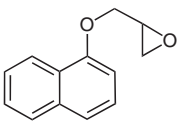
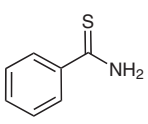
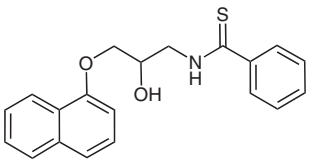
Entry	Epoxide	Amine	Product		Time (min)	Yield (%)
1				**3a**	60	90
2				**3b**	45	89
3				**3c**	30	90
4				**3d**	45	88
5				**3e**	49	92
6				**3f**	30	95
7				**3g**	60	84
8				**3h**	60	86

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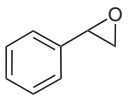
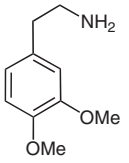
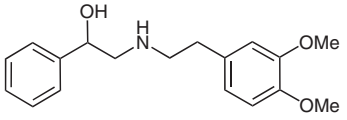
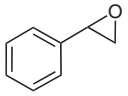
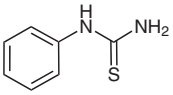
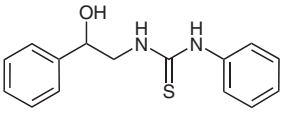
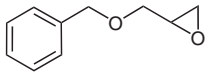
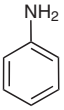
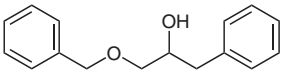
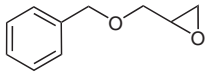
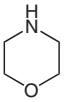
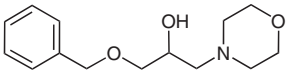
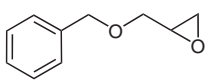
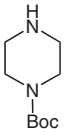
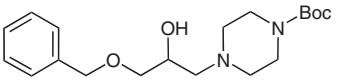
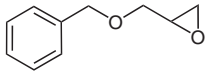
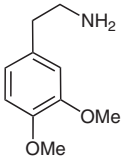
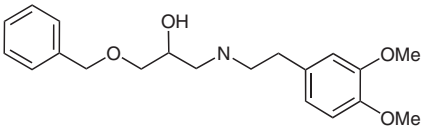
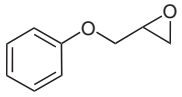
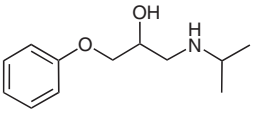
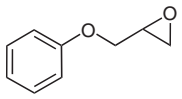
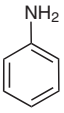
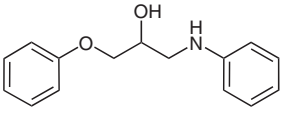
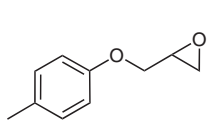
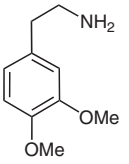
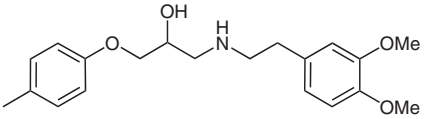
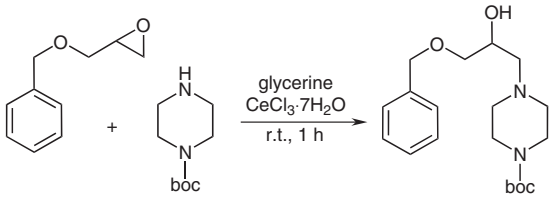
Table 1 Ring Opening of Epoxides Mediated by Glycerine–$CeCl_3 \cdot 7H_2O$ (continued)

Entry	Epoxide	Amine	Product		Time (min)	Yield (%)
9				**3i**	45	92
10				**3j**	60	87
11				**3k**	60	88
12				**3l**	45	90
13				**3m**	60	87
14				**3n**	60	89
15				**3o**	60	86
16				**3p**	45	90
17				**3q**	60	87

In a continuation of the series of reactions, 2-(benzyloxymethyl)oxirane was reacted with *N*-Boc-piperazine using the reaction conditions established above. The epoxide ring opening took place very efficiently within one hour to afford the corresponding product *tert*-butyl-4-[3-(benzyloxy)-2-hydroxypropyl]piperazine-1-carboxylate (**3m**) in very good yields as shown in Scheme 2.

Encouraged by the result obtained with 2-(benzyloxymethyl)oxirane and *N*-Boc-piperazine, we extended this procedure to successfully react the same oxirane with aniline (Table 1, entry 11), morpholine (entry 12) and 2-(3,4-dimethoxyphenyl)ethanamine (entry 14) to afford the corresponding products in very good yields. In a similar manner, styrene oxide was reacted smoothly with 2-(3,4-dimethoxyphenyl)ethanamine (entry 9) and 1-phenylthiourea (entry 10) to afford the corresponding derivatives in very good yields. In another series of experiments, 2-(phenoxymethyl)oxirane was reacted with isopropyl amine (entry 15) and aniline (entry 16) to afford the cor-



Scheme 2

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responding products in very good yields. In a similar manner, the 2-(*p*-tolyloxymethyl)oxirane reacted well with 2-(3,4-dimethoxyphenyl)ethanamine to afford the corresponding product 1-(3,4-dimethoxyphenethylamino)3-(*p*-tolyloxy)propan-2-ol (**3q**) in very good yields; the reaction was also complete within one hour.

In general, all the reactions were carried out at room temperature, using the catalyst cerium(III) chloride (10% mol) in glycerine as solvent. All the reactions were completed within one hour and the products were obtained in 84–95% yield. In all cases, the epoxide ring opening took place in a regioselective manner that favored terminal ring-opening. All the products were confirmed by analysis of their respective IR, ^{1}H NMR and mass spectroscopic data.

In conclusion, the present methodology provides a simple and efficient green protocol for ring opening of various epoxides with amides and amines. The reaction medium, glycerine–$CeCl_3 \cdot 7H_2O$, was recycled and reused up to five times without loss of activity. The notable features of this procedure are mild reaction conditions, cleaner reactions, improved yields, enhanced reaction rates, and simplicity of operation, which makes it a useful and attractive process for the synthesis of β-amino alcohols.

IR spectra were recorded with a Perkin–Elmer FT-IR 240-c spectrophotometer. ^{1}H NMR spectra were recorded with a Gemini-300 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded with a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General Procedure

To a stirred mixture of epoxide (1 mmol) in glycerine (2 mL) was added amine (1 mmol) and the catalyst $CeCl_3 \cdot 7H_2O$ (0.1 mmol) at r.t. The resulting reaction mixture was stirred for the specified time (Table 1). The progress of the reaction was monitored by thin-layer chromatography (TLC). After complete conversion of the starting material, as indicated by TLC, the reaction mixture was extracted with EtOAc (3×10 mL). The combined organic layers were washed with H_2O (2×5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude products, which was purified by column chromatography (silica gel 60–120 mesh; EtOAc–petroleum ether, 3:7). The identities of the products were confirmed by analysis of their ^{1}H NMR, IR and mass spectroscopic data.

1-(3,4-Dimethoxyphenethylamino)-3-(naphthalen-1-yloxy)propan-2-ol (3a)

Yellow syrup.

IR (neat): 3298, 3056, 3013, 2927, 2855, 1630, 1582, 1514, 1460, 1398, 1268, 1240, 1152, 1103, 1070, 1025, 869, 764, 666 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.75–2.81 (m, 1 H), 2.90–3.08 (m, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 3.95–4.12 (m, 5 H), 4.20–4.30 (m, 1 H), 6.58–6.71 (m, 3 H), 7.28 (t, *J* = 7.0 Hz, 1 H), 7.35–7.45 (m, 3 H), 7.71 (d, *J* = 7.0 Hz, 1 H), 8.18 (d, *J* = 7.0 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 382 (10) [M + 2], 349 (20), 318 (10), 215 (20), 186 (35), 168 (30), 143 (50), 127 (100), 103 (25), 96 (10).

***tert*-Butyl 4-[2-Hydroxy-3-(naphthalen-1-yloxy)propyl]piperazine-1-carboxylate (3b)**

Yellow syrup.

IR (neat): 3363, 3055, 3008, 2927, 2879, 2844, 1691, 1579, 1509, 1458, 1418, 1363, 1336, 1270, 1246, 1174, 1143, 1105, 1012, 984, 867, 769, 740 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.49 (s, 9 H), 2.40–2.50 (m, 2 H), 2.60–2.75 (m, 4 H), 3.40–3.55 (m, 4 H), 4.05–4.12 (m, 1 H), 4.19–4.20 (m, 2 H), 6.80 (d, *J* = 6.5 Hz, 1 H), 7.25–7.49 (m, 4 H), 7.75 (d, *J* = 6.5 Hz, 1 H), 8.18 (d, *J* = 6.5 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 388 (40) [M + 2], 331 (50), 287 (10), 243 (10), 187 (10).

1-(Isopropylamino)-3-(naphthalen-1-yloxy)propan-2-ol (3c)

IR (neat): 3298, 3056, 3013, 2927, 2855, 1630, 1582, 1514, 1460, 1398, 1268, 1240, 1152, 1103, 1070, 1025, 869, 764, 666 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 6 H), 3.15 (t, *J* = 6.0 Hz, 1 H), 3.31 (d, *J* = 6.0 Hz, 1 H), 3.35–3.42 (m, 1 H), 3.90–4.05 (m, 2 H), 4.50 (br s, 1 H), 6.48 (d, *J* = 7.0 Hz, 1 H), 7.15 (t, *J* = 7.0 Hz, 1 H), 7.30 (d, *J* = 7.0 Hz, 1 H), 7.40 (d, *J* = 7.0 Hz, 2 H), 7.70 (d, *J* = 7.0 Hz, 1 H), 8.18 (d, *J* = 7.0 Hz, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 258 (10) [M – 1], 243 (10), 214 (10), 143 (20), 114 (25), 72 (100), 57 (20), 43 (25).

1-(Naphthalen-1-yloxy)-3-(phenylamino)propan-2-ol (3f)

Yellow syrup.

IR (neat): 3404, 3053, 2126, 1601, 1506, 1459, 1398, 1318, 1268, 1240, 1101, 1069, 1021, 993, 956, 876, 767, 693 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.39 (q, *J* = 6.5 Hz, 1 H), 3.55 (dd, *J* = 5.0, 12 Hz, 1 H), 4.25 (d, *J* = 6.5 Hz, 2 H), 4.38–4.45 (m, 1 H), 6.69 (q, *J* = 7.5 Hz, 2 H), 6.80 (d, *J* = 7.5 Hz, 1 H), 7.15 (t, *J* = 7.5 Hz, 2 H), 7.32 (t, *J* = 7.5 Hz, 1 H), 7.40–7.50 (m, 3 H), 7.72–7.80 (m, 1 H), 8.18–8.25 (m, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 294 (100) [M + 1], 183 (10), 150 (15), 131 (10), 139 (15), 103 (10), 99 (10).

1-(2-Hydroxy-2-phenylethyl)-3-phenylthiourea (3j)

IR (neat): 3445, 3057, 2923, 2854, 1652, 1588, 1485, 1452, 1395, 1268, 1236, 1160, 1100, 1069, 1021, 944, 766, 694 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.55–3.72 (m, 2 H), 5.05–5.15 (m, 1 H), 6.95 (d, *J* = 6.5 Hz, 2 H), 7.09 (q, *J* = 6.5 Hz, 1 H), 7.29–7.52 (m, 8 H).

MS (EI, 70 eV): *m*/*z* (%) = 272 (10) [M]$^+$, 244 (100), 132 (10), 121 (10), 101 (15).

1-(Benzyloxy)-3-morpholinopropan-2-ol (3l)

Yellow liquid.

IR (neat): 3421, 2925, 2857, 1454, 1366, 1271, 1116, 1010, 947, 864, 745, 699 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.40–2.50 (m, 4 H), 2.60–2.69 (m, 2 H), 3.45 (d, *J* = 5.0 Hz, 2 H), 3.66–3.71 (m, 4 H), 3.85–3.92 (m, 1 H), 4.54 (s, 2 H), 5.00 (br s, 1 H, OH), 7.25–7.35 (m, 5 H).

MS (EI, 70 eV): *m*/*z* (%) = 252 (100) [M + 1].

***tert*-Butyl 4-[3-(Benzyloxy)-2-hydroxypropyl]piperazine-1-carboxylate (3m)**

^{1}H NMR ($CDCl_3$): δ = 1.98 (s, 9 H), 2.40–2.50 (m, 4 H), 2.05–2.15 (m, 2 H), 3.39–3.48 (m, 6 H), 3.88–3.95 (m, 1 H), 4.52 (s, 2 H), 7.20–7.35 (m, 5 H).

1-(Benzyloxy)-3-(3,4-dimethoxyphenethylamino)propan-2-ol (3n)

Liquid.

IR (neat): 3425, 2924, 2856, 1613, 1512, 1460, 1239, 1146, 1031, 811, 760 cm^{-1}.

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^{1}H NMR ($CDCl_3$): δ = 2.65–2.75 (m, 4 H), 2.85–2.95 (m, 1 H), 3.02–3.18 (m, 1 H), 3.35–3.45 (m, 2 H), 3.80 (s, 6 H), 3.83–3.90 (m, 1 H), 4.50 (s, 2 H), 6.65–6.73 (m, 2 H), 7.22–7.38 (m, 6 H).

MS (EI, 70 eV): *m*/*z* (%) = 346 (100) [M + 1], 258 (15), 181 (10), 167 (25), 91 (10).

1-(Isopropylamino)-3-phenoxypropan-2-ol (3o)
^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 3 H), 1.95 (s, 3 H), 2.65–2.92 (m, 2 H), 3.85–3.99 (m, 2 H), 4.05–4.18 (m, 1 H), 3.7 (m, 1 H,), 6.80–6.95 (m, 3 H), 7.18–7.28 (m, 2 H).

1-Phenoxy-3-(phenylamino)propan-2-ol (3p)
^{1}H NMR ($CDCl_3$): δ = 3.14–3.40 (m, 2 H), 3.90–4.05 (m, 2 H), 4.15–4.25 (m, 1 H), 6.55–6.70 (m, 3 H), 6.80–6.90 (m, 3 H), 7.10–7.30 (m, 4 H).

1-(3,4-Dimethoxyphenethylamino)-3-(*p*-tolyloxy)propan-2-ol (3q)
IR (neat): 3425, 2924, 2856, 1613, 1512, 1460, 1239, 1146, 1031, 811, 760 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3 H), 2.70–2.80 (m, 3 H), 2.85–2.95 (m, 1 H), 3.79–3.88 (m, 5 H), 3.98–4.06 (m, 1 H), 6.65–6.75 (m, 5 H), 7.05 (d, *J* = 7.5 Hz, 2 H).

MS (EI, 70 eV): *m*/*z* (%) = 347 (30) [M + 2], 346 (100) [M + 1], 259 (10), 181 (10), 165 (35), 150 (10).

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