

EUROPIUM (II) TRIFLATE CATALYZED RING OPENING OF OXIRANES: AN IMPROVED METHOD FOR THE SYNTHESIS OF β -AMINO ALCOHOLS

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ABSTRACT: Epoxides undergo rapidly ring-opening reaction with various amine nucleophiles in the presence of Europium triflate. The catalyst was very active and used in 10% mole only. All the reactions were carried out at room temperature in methylene dichloride to afford the corresponding β -amino alcohols in very good yields.

Keywords: Epoxides, amines, Europium triflate, 2-amino alcohols

INTRODUCTION

2-Amino alcohols are versatile intermediates for the synthesis of various biologically active natural products, unnatural amino acids, β -blockers (Atenolol, Propranolol, etc), insecticidal agents, chiral auxiliaries and oxazolines.¹⁻⁶ One of the most straightforward synthetic approaches for the preparation of β -amino alcohols involves the heating of an epoxide with an excess of amines at elevated temperature.⁷⁻¹¹

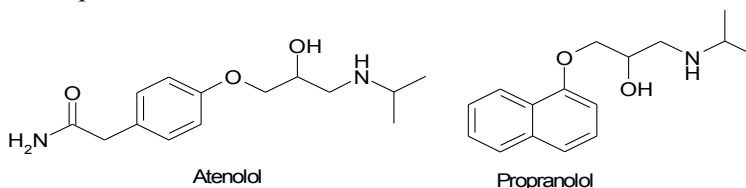


Figure 1

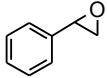
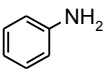
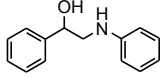
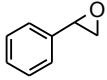
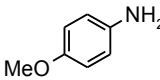
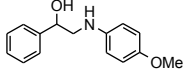
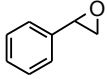
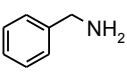
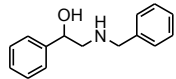
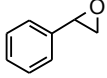
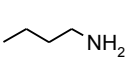
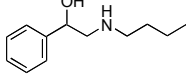

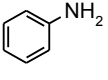
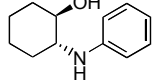

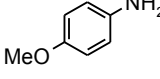
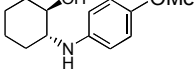

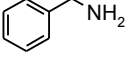
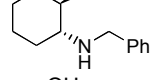

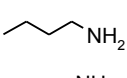
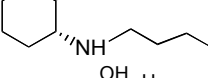
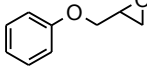
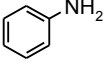
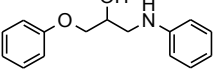
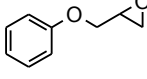
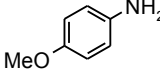
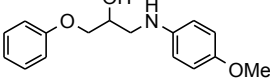
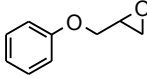
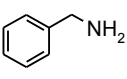
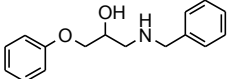
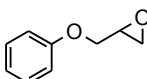
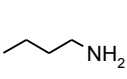
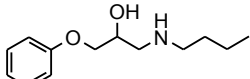
Since some functional groups are sensitive to high temperature, a variety of activators such as alkali metal halides,¹²⁻¹⁵ metal perchlorates,¹⁶ metal triflates¹⁷⁻²² ionic liquids²³ and hexafluoro-2-propanol,²⁴ metal complexes²⁵⁻³⁰ have been developed for this conversion. However, many of these methods involve the use of expensive and stoichiometric amounts of reagents, suffer from selectivity and also require extended reaction times. Therefore, the development of a new and efficient protocol for this transformation under mild reaction conditions is still needed. During the past decade, rare-earth metal triflates have been found to be unique Lewis acids. They are water-tolerant, reusable catalysts, and they can effectively promote several carbon-carbon and carbon-heteroatom bond formation in good yields.³¹

Experimental Section

General procedure: To a mixture of epoxide (2 mmol) and amine (2 mmol) in methylenedichloride (10 ml) was added the catalyst Europium triflate (0.2 mmol) and the resulting reaction mixture was stirred at room temperature for a specified period (Table 1).

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Table 1: Eu(OTf)₂ Catalyzed synthesis of 2-amino alcohols:

Entry	Epoxide (1)	Amine (2)	Product(3a-3l) ^a	Reaction Time (h)	Yield (%) ^b
a				2.5	90
b				2.5	88
c				3.0	89
d				2.5	95
e				3.0	90
f				3.0	88
g				3.5	85
h				3.0	84
i				2.5	89
j				2.5	87
k				3.0	85
l				3.5	84

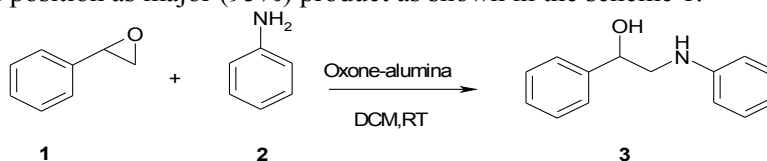
^aAll the products were characterized by their ¹H NMR, IR and Mass spectrum ^bYields were isolated and unoptimized

The progress of the reaction was monitored by TLC. After complete conversion of the starting material, as indicated by TLC, the reaction mixture was extracted with methylene dichloride (2x10 ml).

The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude products which were purified by column chromatography using silica gel (60-120 mesh) and eluted with ethyl acetate and hexane mixture in 3:7 ratio to afford the pure 2-amino alcohol in excellent yields.

RESULTS AND DISCUSSIONS

To optimize the reaction conditions, equimolar amounts of styrene oxide (2 mmol) and aniline (2 mmol) were treated in presence of the catalyst europium triflate to obtain the corresponding product of 1-phenyl-2-(phenylamino)-ethanol in 90% yield (**3a**). The reaction was completed within 2.5 hours of reaction time at room temperature in methylenedichloride. The epoxide opening took place in a region selective manner with the attack of nucleophile at least hindered side of terminal position as major (95%) product as shown in the scheme 1.



Scheme 1.

Encouraged by the results obtained with styrene oxide and various amines, we turned our attention to cyclohexene oxide and different amines. In this case, the cyclohexane oxide was treated with aniline in presence of the catalyst europium triflate to obtain the corresponding 2-amino alcohol of *trans*-2-(phenylamino) cyclohexanol (**3e**) in 90% yield. The stereochemistry of the ring-opened products **5e-5h** was found to be *trans* from the coupling constants of the ring hydrogens at C-1 and C-2 positions. This reaction was completed within 3.0 hours at room temperature. In a similar manner, various amines such as *para*-ansidine, benzylamine and butylamine were reacted smoothly to afford the corresponding β -amino alcohols in very good yields with high regioselectivity. In a similar manner, glycidyl aryl ether oxirane was treated with aromatic, aliphatic and alicyclic amines to afford the corresponding β -amino alcohols in very good yields with high regioselectivity. In these cases, the epoxide opening took place in regioselective manner preferentially by terminal attack of the nucleophile. In these reactions also, the product was obtained as a single isomer and the structure of which was confirmed by their ^1H NMR spectral data. In general all the reactions were completed with in 2.5-3.5 hours and the obtained yields were very good to excellent (84-95%). The catalyst europium triflate was used in 10% mole only. All the reactions were carried out at room temperature in methylenedichloride solvent.

Spectral data for compounds:

1-Phenyl-2-(phenylamino)-ethanol (3a): IR (KBr): ν 3341, 3267, 3047, 3051, 2972, 2847, 1605, 1543, 1511, 1438, 1361, 1310, 1232, 1128, 1045, 1005, 986, 878, 746 cm^{-1} . ^1H NMR (CDCl_3): δ 3.78 (dd, 1H, $J = 5.0, 10.5$ Hz), 3.90 (dd, 1H, $J = 4.0, 10.5$ Hz), 4.55 (dd, 1 H, $J = 6.5, 10.8$ Hz), 6.40 (d, 2H, $J = 7.5$ Hz), 6.80 (t, 1H, $J = 7.8$ Hz), 6.95 (d, 2H, $J = 8.0$ Hz), 7.35-7.45 (m, 5H). EIMS: m/z (%): 213 (M^+ 25), 195 (18), 185 (10), 107 (100), 91 (35), 77 (28), 57 (40).

Trans-2-(phenylamino)-cyclohexanol (e): IR (KBr): ν 3358, 3269, 3047, 2938, 2856, 1605, 1571, 1508, 1450, 1318, 1241, 1126, 1065, 1012, 985, 863, 742 cm^{-1} . ^1H NMR (CDCl_3): δ 1.05-1.40 (m, 4H), 1.48 (brs, 1H, OH), 2.15-2.25 (m, 2H), 2.80-2.90 (m, 2H), 3.20 (ddd, 1H, $J = 3.5, 10.0, 10.0$ Hz), 3.40 (ddd, 1H, $J = 4.0, 10.0, 10.0$ Hz), 3.80 (brs, 1H), 6.80-7.10 (m, 5H). EIMS: m/z (%): 191 (M^+ 20), 174 (15), 114 (45), 92 (22), 82 (10), 77 (100), 63 (10), 51 (20), 43 (25).

Trans-2-(OMe-phenylamino)-cyclohexanol (f): IR (KBr): ν 3361, 3274, 3052, 2943, 2851, 1608, 1569, 1506, 1452, 1315, 1243, 1205, 1122, 1062, 1015, 987, 857, 743 cm^{-1} . ^1H NMR (CDCl_3): δ 1.08-1.30 (m, 1H), 1.38-1.48 (m, 3H), 1.75-1.83 (m, 2H), 2.20-2.30 (m, 2H), 3.20 (ddd, 1H, $J = 3.5, 10.0, 10.0$ Hz), 3.40 (ddd, 1H, $J = 4.0, 10.0, 10.0$ Hz), 3.80 (brs, 1H), 3.90 (s, 3H), 6.85 (d, 2H, $J = 7.0$ Hz), 7.30 (d, 2H, $J = 7.0$ Hz). EIMS: m/z (%): 206 (M^+ 20), 174 (15), 114 (45), 92 (22), 82 (10), 77 (100), 63 (10), 51 (20), 43 (25).

Conclusion

In conclusion, we have demonstrated a novel and highly efficient methodology for the ring opening of various epoxides with a variety of amines using europium triflate as catalyst. The notable features of this procedure are mild reaction conditions, excellent regioselectivity, cleaner reactions, improved yields, enhanced reaction rates and simplicity in operation, which makes it a useful and attractive process for the synthesis of β -amino alcohols.

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