ZINC PERCHLORATE-ALUMINA: A MILD, EFFICIENT CATALYST FOR RING OPENING OF EPOXIDES WITH AMINES: AN IMPROVED PROTOCOL FOR THE SYNTHESIS OF B-AMINO ALCOHOLS

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ABSTRACT: The epoxides undergo smoothly ring-opening reaction with various amines catalyzed by zinc perchlorate on alumina under mild reaction conditions. All the reactions were carried out at room temperature to afford the corresponding β-amino alcohols in excellent yields. The catalyst was recovered and reused further reactions with very good efficiency.

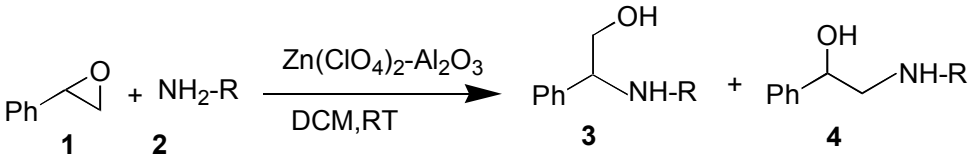
Keywords: Epoxides, amines, alumina, zinc perchlorate, 2-amino alcohols.

Introduction

The β-amino alcohols are versatile intermediates for the synthesis of various biologically active natural and synthetic products, unnatural amino acids, β-blockers, insecticidal agents, chiral auxiliaries and oxazolines.[1-6] The classical approach and the most straight forward synthetic route for the preparation of β-amino alcohols, involve the heating of epoxide with an excess of amines at elevated temperature.[7-11] Since some functional groups are sensitive to high temperature, a variety of activators such as alkali metal halides,[12-16] metal perchlorates, metal tetrafluoroborates[17] and metaltriflates[18-23] have been reported to carry out this reaction. In similar manner non-conventional methods like ionic liquids, microwave irradiation, heteropoly acids and hexafluoro-2-propanol[24-29] have also been developed for this conversion. However, many of these methods involve the use of expensive and stoichiometric amounts of reagents, suffer from poor regioselectivity and also require extended reaction times. Therefore, the development of a new and efficient protocol for this transformation under mild and more convenient conditions is still needed. Zinc perchlorate [Zn $(ClO_4)_2$] belongs to the class of Lewis acids and the catalyst doped on solid supports is the field of growing interest. Among the solid supports such as silica gel, alumina, ion exchange resin and active carbons,[30-34] we selected the neutral alumina as a solid support to dope the catalyst Zn $(ClO_4)_2$ due to its neutral nature.

RESULTS AND DISCUSSIONS

In this communication, we wish to exploit the catalyst system, zinc perchlorate doped on neutral alumina as an efficient reaction medium for the ring opening of various epoxides with nitrogen nucleophiles under mild reaction conditions as shown in the schemes 1, 2 and 3.

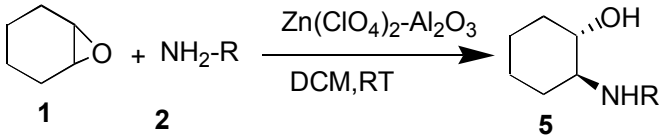


Scheme 1

In a typical experiment, styrene oxide and aniline were treated in presence of zinc perchlorate-neutral alumina, at room temperature to obtain the corresponding β-amino alcohol in 94% yield (entry **a**). The reaction was carried out in methylenedichloride and the reaction was completed within 1 hour. The epoxide opening takes place in a regioselective manner with the attack of nucleophile at benzylic position. The catalyst was separated by simple filtration, then washed with the methylenedichloride, dried and reused for further reactions with good efficiency. To evaluate the generality of the catalyst system, the reactions of different epoxides were carried out with various aromatic and aliphatic amines and the obtained results were shown in the table 1.

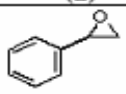
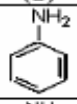
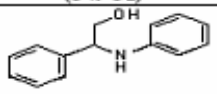
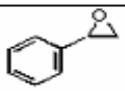
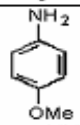
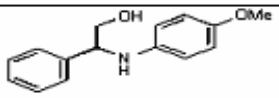
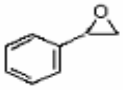
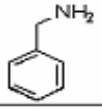
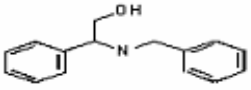
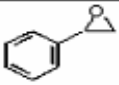
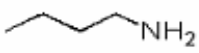
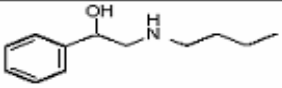
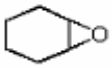
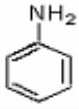
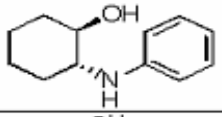
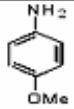
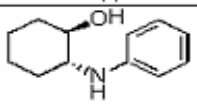
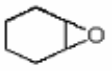
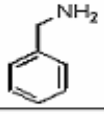
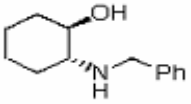
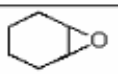
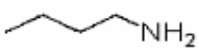
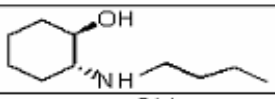
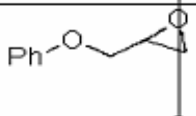
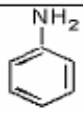
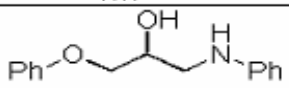
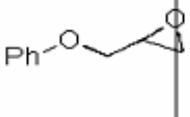
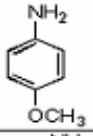
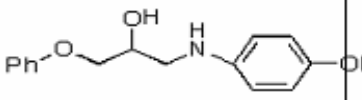
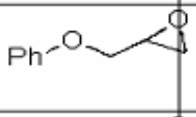
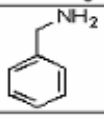
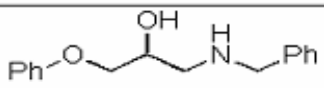
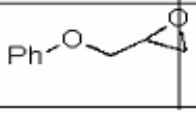
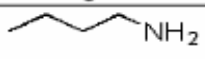
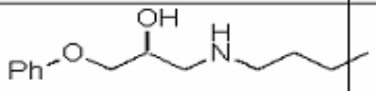
The region selectivity of the products, in the case of styrene oxide with aromatic and benzyl amines gave the benzylic opening products (entry **a**, **b**, **c**). However, the region selectivity with styrene oxide and aliphatic amines, the terminal opening products of β-amino alcohol was obtained as a single isomer in very good yields (entry **d**). The product thus obtained was identified by its ^{1}H NMR spectrum.

In a similar manner, cyclohexene oxide was treated with various amines such as aromatic, benzylic and aliphatic amines. In these cases also, the reactions takes place smoothly at room temperature while giving the corresponding products in very good yields. The stereo chemistry of the ring opening products was found to be *trans* from the coupling constants of the ring protons in ^{1}H NMR spectrum (Scheme 2).



Scheme 2

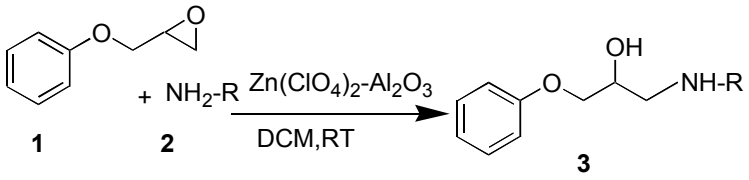
Table 1; Zinc perchlorate-alumina catalyzed epoxide opening with amines

Entry	Epoxide (1)	Amine (2)	Product (3a-3l)[a]	Reaction Time (h)	Yield[b] (%)
a				1.0	94
b				1.5	92
c				2.0	91
d				2.5	89
e				1.5	91
f				2.0	89
g				2.5	87
h				3.0	85
i				1.5	92
j				2.0	90
k				2.5	87
l				3.0	85

[a]All the products were characterized by their ^{1}H NMR, IR and Mass spectroscopy data

[b]Yields were isolated and un-optimized.

In a similar manner, glycidyl aryl ethers reacted smoothly with aromatic, benzylic and aliphatic amines to afford the corresponding β-amino alcohols in very good yields with high regioselectivity. In these cases also, the epoxide opening took place in regioselective manner, preferentially by terminal attack of the nucleophile (Scheme 3). In general, all the reactions were completed with in 1-3 hours of reaction time. The obtained yields of β-amino alcohols were in very good to excellent (85-94%). The catalyst system of zinc perchlorate-alumina was conveniently separated from reaction mixture by simple filtration.



Scheme 3

The filtered catalyst was washed with the solvent and dried under reduced pressure. The recovered catalyst was used further reactions up to three cycles without any problem. In a blank experiment, epoxide and amine were stirred in methylenedichloride without catalyst for a period of 10 hours but no product was observed. This experiment very clearly shows the role of catalyst for the synthesis of β-amino alcohols. All the reactions were carried out at room temperature in methylenedichloride solvent.

Conclusion

In conclusion, the present methodology describes a simple and efficient procedure for the regioselective ring opening of various epoxides with different amines like aromatic, benzylic and aliphatic to afford the corresponding amino alcohols in excellent yields. The catalyst system zincperchlorate adsorbed on neutral alumina worked very efficiently in repeating cycles. The notable features of this procedure are mild reaction conditions, excellent regioselectivity, cleaner reaction profiles, improved yields, enhanced reaction rates, reusability of the catalyst and simplicity in operation for the isolation of products.

Experimental Section

General procedure: To a mixture of epoxide (2mmol) and amine (2mmol) in methylene dichloride (10 ml) was added the catalyst zinc perchlorate-alumina (200 mg). The resulting reaction mixture was stirred at room temperature for a specified period (Table 1). The progress of the reaction was monitored by TLC. After complete conversion of the starting material, as indicated by TLC, the reaction mixture was filtered and the catalyst washed with ethylene dichloride (2x10 ml).

The combined filtrates were dried over Na_2SO_4 and directly adsorbed on silica gel (60-120 mesh) and eluted with ethyl acetate and hexane mixture to afford the corresponding pure 2-amino alcohol in excellent yields. All the products were confirmed by their H NMR, IR and Mass spectrometry and compa red with literature data.

Spectral data for the products:

2-(Phenylamino)-2-phenylethanol (3a).[25] Light yellow oil. IR (neat): ν 3341, 3267, 3047, 3051, 2972, 2847, 1605, 1543, 1511, 1438, 1361, 1232, 1128, 1045, 1005, 986, 878, 746 cm^{-1}. ^{1}HNMR ($CDCl_3$). δ 3.78 (dd, 1H, *J* = 5.0 & 10.5 Hz), 3.90 (dd, 1H, *J* = 4.0 &10.5 Hz), 4.55 (dd, 1H, *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).

2-(4-Methoxyphenylamino)-2-Phenylethanol (3b).[27] Solid. MP, 52-53 ^{0}C.IR (KBr): ν 3385, 3271, 3049, 2937, 2851, 1614, 1546, 1513, 1438, 1361, 1310, 1293, 1202, 1138, 1045, 1065, 986, 878, 741 cm^{-1}. ^{1}H NMR ($CDCl_3$). δ 3.76 (dd, 1H, *J* = 4.5 & 10.0 Hz), 3.90 (dd, 1H, *J* = 4.0 & 10.0 Hz), 3.93 (s, 3H), 4.50 (dd, 1H, *J* = 6.0 & 10.5 Hz), 6.45 (d, 2H, *J* = 7.0 Hz), 6.80 (t, 1H, *J* = 7.8 Hz), 6.90 (d, 4H, *J* = 8.0 Hz), 7.35-7.45 (m, 5H). EIMS: *m/z* (%). 243 (m^+ 25), 212 (15), 195 (18), 185 (10), 107 (100), 91 (35), 77 (28), 57 (40).

2-(Benzylamino)-2-Phenylethanol (3c).[23] Solid. MP, 100-101 ^{0}C. IR (K Br): ν 3293, 3057, 2941, 2858, 1606, 1580, 1510, 1452, 1373, 1308, 1256, 1208, 1182, 1106, 1025, 974, 859, 736 cm^{-1}.^{1}H NMR ($CDCl_3$). δ 2.70-2.85 (m, 2H), 3.30 (brs, 2H), 3.75-3.85 (m, 2H), 4.75-4.82 (m, 1H), 7.35-7.48 (m, 10H). EIMS: *m/z* (%). 227 (m^+ 45), 209 (10), 185 (10), 136 (65), 118 (25), 91 (100), 77 (22), 57 (35), 51 (18).

2-(4-Methoxyphenylamino)-2-Phenylethanol (3d).[24] Low melting solid. IR (KBr). ν 3379, 3246, 3051, 2943, 2862, 1634, 1589, 1512, 1473, 1410, 1396, 1318, 1295, 1211, 1169, 1086, 1015, 982, 868, 749 cm^{-1}.; ^{1}H NMR ($CDCl_3$). δ 0.95 (t, 3H, *J* = 6.5 Hz), 1.30-1.40 (m, 2H), 1.45-1.55 (m, 2H), 2.35 (brs, 2H), 2.55-2.65 (m, 2H), 3.80-3.90 (m, 2H), 4.25 (d, 1 H, *J* = 6.0 Hz), 7.30-7.45 (m, 5H). EIMS: *m/z* (%). 193 (m^+ 15), 175 (28), 164 (20), 146 (42), 136 (10), 107 (15), 103 (100), 91 (35), 78 (22), 53 (35).

***Trans*-2-(phenylamino)-cyclohexanol (3e)**.[25] Solid. MP, 61-62 ^{0}C. IR (KBr): ν 3352, 3295, 3068, 2935, 2857, 1604, 1543, 1502, 1498, 1450, 1430, 1321, 1243, 1156, 1102, 1031, 976, 891, 743 cm^{-1}. ^{1}HNMR (CD Cl_3). δ 1.02-1.43 (m, 4H), 1.50 (brs, 1H), 1.70-1.75 (m, 2H), 2.12-2.18 (m, 2H), 3.05 (brs, 1H), 3.15 (ddd, 1H, *J* = 3.5, 10.0 & 10.0 Hz), 3.40 (ddd, 1H, *J* = 4.0, 10.5 & 10.5 Hz), 6.65-7.10 (m, 5H). EIMS: *m/z* (%). 191 (m^+ 38), 173 (10), 147 (10), 131 (15), 117 (20), 105 (12), 92 (20), 81 (100), 77 (31), 52 (41), 41 (18).

***Trans*-2-(4-methoxyphenylamino)-cyclohexanol (3f)**.[21] Solid. MP, 59-60 ^{0}C. IR (KBr): ν 3361, 3274, 3052, 2943, 2851, 1608, 1569, 1506, 1452, 1315, 1243, 1122, 1062, 1015, 987, 857, 743 cm^{-1}. ^{1}HNMR (CD Cl$_3$). 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* (%). 221 (m$^+$ 22), 206 (18), 190 (56), 174 (10), 114 (100), 99 (10), 92 (25), 82 (15), 77 (68), 63 (18), 51 (24), 43 (20).

***Trans*-2-(benzylamino)-cyclohexanol (3g)**.[22] Low-melting solid. IR (KBr): ν 3487, 3261, 3124, 2963, 2847, 1605, 1581, 1508, 1462, 1325, 1246, 1215, 1120, 1059, 1005, 981, 853, 736 cm^{-1}. ^{1}H NMR (CDCl$_3$). δ 1.06-1.28 (m, 1H), 1.35-1.45 (m, 3H), 1.73-1.82 (m, 2H), 2.21-2.30 (m, 2H), 3.24 (ddd, 1H, *J* = 3.5, 10.0 & 10.0 Hz), 3.41 (ddd, 1H, *J* = 4.0, 10.0 & 10.0 Hz), 3.85 (brs, 1H), 3.91 (s, 3H), 4.10 (brs 1H), 4.80 (s, 2H), 7.20-7.50 (m, 5H). EIMS: *m/z* (%). 205 (m$^+$ 18), 187 (12), 174 (10), 114 (100), 107 (25), 99 (10), 92 (25), 82 (15), 77 (60), 63 (18), 51 (28), 43 (20).

***Trans*-2-(butylamino)-cyclohexanol(3h)**.[24] Yellow oil. IR (neat): ν 3386, 3271, 2845, 1684, 1610, 1573, 1508, 1491, 1426, 1395, 1321, 1276, 1208, 1169, 1124, 1081, 1012, 993, 915, 874, 831, 786, 734 cm^{-1}. ^{1}H NMR (CDCl$_3$). δ 0.95 (t, 3H, *J* = 7.0 Hz), 0.98-1.05 (m, 2H), 1.25-1.45 (m, 8H), 1.72-1.76 (m, 2H), 2.20-2.40 (m, 1H), 2.50-2.60 (m, 1H), 2.80 (ddd, 1H, *J* = 11.5, 9.0 & 3.0 Hz), 3.20 (ddd, 1H, *J* = 11.5, 9.0 & 3.0 Hz), 4.05 (brs, 2H). EIMS: *m/z* (%). 171 (m$^+$ 20), 153 (10), 142 (15), 114 (10), 99 (100), 69 (12), 56 (45), 43 (20).

1-Phenoxy-3-phenylaminopropan-2-ol (3i).[25] Colorless oil. IR (neat): ν 3392, 3261, 3057, 2926, 2871, 1612, 1542, 1505, 1495, 1456, 1356, 1312, 1296, 1110, 1015, 972, 841, 743 cm^{-1}. ^{1}H NMR (CDCl$_3$). δ 3.22-3.26 (m, 1H), 3.38-3.42 (m, 1H), 3.60-3.65 (m, 2H), 3.98-4.05 (m, 2 H), 4.25 (brs, 1H), 6.64-6.68 (m, 2H), 6.70-6.75 (m, 2H), 6.88-6.91 (m, 2H), 7.05-7.25 (m, 2H), 7.30-7.40 (m, 2H). EIMS: *m/z* (%). 243 (m$^+$ 22), 195 (10), 166 (42), 133 (28), 106 (61), 94 (100), 77 (30), 65 (20), 57 (40), 51 (15).

1-(*N*-4-Methoxyphenyl) amino-3-phenoxy-2-propanol (3j).[23] Solid. MP, 79-80 ^{0}C. IR (KBr): ν 3260, 3054, 2939, 2865, 1638, 1605, 1596, 1508, 1495, 1446, 1352, 1302, 1269, 1235, 1170, 1079, 1016, 982, 823, 751 cm^{-1}.; ^{1}HNMR (CDCl$_3$). δ 3.20-3.28 (m, 1H), 3.35-3.45 (m, 1H), 3.63 (brs, 2H), 3.75 (s, 3 H), 4.05-4.10 (m, 2H), 4.28 (brs, 1H), 6.70 (d, 2H, *J* = 8.5 Hz), 6.85 (d, 2H, *J* = 8.5 Hz), 6.90-7.10 (m, 3H), 7.30-7.40 (m, 2H). EIMS: *m/z* (%). 273 (m$^+$ 20), 258 (10), 242 (35), 195 (10), 166 (23), 137 (36), 107 (41), 93 (40), 91 (68), 77 (22), 65 (20), 57 (40), 51 (25).

1-(*N*-Benzyl) amino-3-phenoxy-2-propanol (3 k).[23] Solid. MP, 68-69 ^{0}C. IR (KBr): ν 3305, 3272, 3061, 2953, 2846, 1632, 1598, 1583, 1510, 1490, 1453, 1368, 1305, 1246, 1215, 1126, 1078, 1012, 983, 869, 751 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 2.75-2.85 (m, 2H), 2.95 (brs, 2H), 3.80 (d, 2H, *J* = 2.0 Hz), 3.95 (d, 2H, *J* = 5.0 Hz), 4.05-4.15 (m, 1H), 6.85-6.95 (m, 3H), 7.30-7.40 (m, 7H). EIMS: *m/z* (%): 257 (M$^+$ 18), 180 (100), 160 (34), 142 (20), 117 (56), 91 (42), 88 (10), 77 (62), 65 (20), 57 (28), 51 (10).

1-(*N*-Butyl)-Amino-3-phenoxy-2-propanol (3l):[23] Solid. MP, 90-91 ^{0}C IR (KBr): ν 3312, 3256, 3072, 2967, 2853, 1605, 1586, 1508, 1492, 1446, 1358, 1315, 1296, 1241, 1173, 1109, 1085, 1035, 1026, 986, 873, 749 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.05 (t, 3H, J = 6.0 Hz), 1.85-1.95 (m, 4H), 2.70-2.90 (m, 4H), 3.90 (s, 2H), 4.01-4.05 (m, 1H), 6.80-6.90 (m, 3H), 7.25-7.35 (m, 2H). EIMS: *m/z* (%): 223 (M^+ 22), 194 (10), 166 (15), 146 (20), 137 (18), 130 (100), 93 (42), 91 (42), 88 (10), 77 (25), 74 (10), 65 (20), 57 (28), 51 (18).

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