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Active Copper Catalyzed Regioselective Ring Opening of Epoxides by Heterocyclic Amines: An Efficient Protocol for Synthesis of β-Amino Alcohols

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ABSTRACT

The regioselective epoxide ring opening at less substituted carbon atom of epoxide were reported by nucleophiles like heterocyclic amines which gives well known 1,2-difunctionalized amino alcohols. These are present in many synthetic as well as natural products. The ring opening of epoxide is achieved by cleavage with amines in presence of copper(0) as a catalyst. It is observed that the lithium napthalenide reduction of copper(I) produces a highly reactive form of copper(0) that acts as a catalyst for ring opening of epoxides with an amine.

KEYWORDS

Lithium, Napthalenide, Copper(0), Amino alcohol, Biological activity, Activity spectra.

INTRODUCTION

β-Amino alcohols are versatile intermediates in the synthesis of biologically active natural products, unnatural amino acids, β-blockers as well as insecticidal agent and chiral auxillaries [1-6]. Classically β-amino alcohols were synthesized by aminolysis of epoxides through heating with an excess of amine. This classical method has number of limitations, such as the requirement of an excess amine, inorganic base, longer reaction times, low nucleophilicity in the case of deactivated aromatic amines [7]. Generally, in the classical method the cleavage is achieved by treatment with excess amine at suitable temperature. However, the lack of appreciable selectivity, the requirement of high temperature and the need of excess amine in the classical methods have led to the necessity for activation of the epoxides so as to increase their susceptibility to nucleophilic attack by amine. Various methodologies have been developed for this include the use of alumina [8], metal amides [9-11], metal alkoxides [12], metal triflates [13-15], transition metal halides [16,17], alkali metal perchlorates [18], rare earth metal halides [19-21] and silica [22] under high pressure. However, these methodologies suffer from one or more disadvantages such as long reaction times, elevated temperatures and moderate yield. Hydroxy amino acids is the most common class of naturally occurring compounds containing the β-amino alcohol

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subunit. For example, the vancomycin [23] class of antibiotics contains an arylserine moiety and the antifungal agent sphingofungin contains a hydroxyl amino acid moiety in the polar head group. Another large group of biologically active natural products is the cyclic amino alcohols, for example quinine which is used for malaria treatment. One important class of cyclic amino alcohols is the polyhydroxylated alkaloids, also known as azasugars, for example castanospermine [24] that was found to be a potent inhibitor of α and β-glucosidases. β-Amino alcohols also plays an important role as chiral ligands and chiral auxillaries in asymmetric catalysis most commonly derived natural sources. The amino alcohols are generally derivatized to improve their chelating ability or to increase their steric directing effect [25,26]. 1,2-Amino alcohols are important intermediates in the preparation of many biologically active compounds. The preparation of these compounds are obtained by different routes but the most important route is by ring opening of epoxide with an amine. 1,2-Amino alcohols are the versatile intermediates for many organic compounds [27-30]. These 1,2-amino alcohols or β-amino alcohols constitutes a range of β-blockers used to treat cardiovascular diseases like hypertension [31-36]. β-Amino alcohols attracted a large number of researchers in the synthesis of good amount of biologically active natural and synthetic products [37,38]. These plays an increasingly vital role in the medicinal chemistry, pharmaceuticals and organic synthesis. β-Blockers are used in the treatment of a wide variety of human disorders, like sympathetic nervous system disorders, heart failure and cardiac arrhythmias [39] and also as insecticidal agents [4]. The ring opening of epoxides represents one of the most important and straightforward methods of preparing these compounds [40].

EXPERIMENTAL

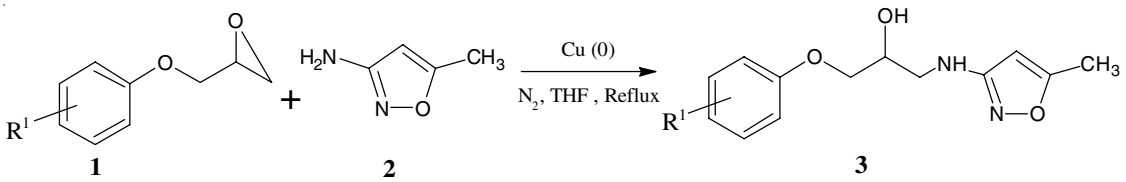
The boiling points were determined are uncorrected. I.R. spectra were determined on a Shimadzu Miracle 10 ATR instrument. ^{1}H NMR spectra were recorded on a Bruker 500 MHz spectrometer with $CDCl_3$ as a solvent and TMS as the internal standard. ^{13}C NMR spectra were recorded on Bruker 125 MHz spectrometer with $CDCl_3$ as the solvent. Column chromatography was conducted on silica gel 60 (70-230) mesh. Thin layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel.

General procedure for the preparation of lithium naphthalenide: In a 50 mL two necked round bottom flask previously dried by using heating gun and flushed with nitrogen gas were added naphthalene (10 mmol) and lithium metal (10 mmol) to which added 10 mL dry THF and continued stirring for about 4 h under atmosphere of nitrogen gas at room temperature, the green coloured homogeneous solution has been formed which is stable under anhydrous conditions for several days.

General procedure for the preparation of active copper catalyst: In a 50 mL two necked round bottom flask previously dried by using heating gun and flushed with nitrogen gas were added solution of copper complex ($CuI.PPh_3$) (10 mmol) followed by addition of lithium naphthalenide solution (10 mmol) by syringe through septum under magnetic stirring and continued stirring for about 30 min at 0 °C in the atmosphere of nitrogen gas. The reactive form of reduced copper is formed from copper(I) to copper(0).

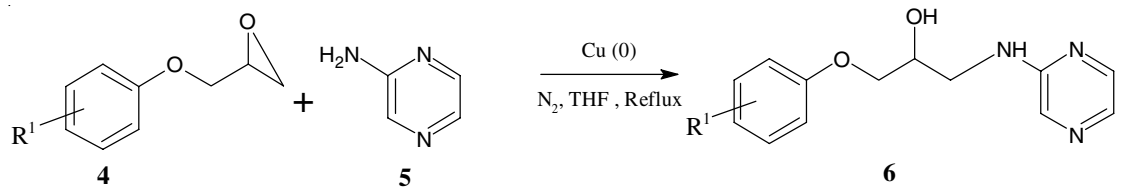
General procedure for synthesis of β-amino alcohols form epoxide with an heterocyclic amine: In a 50 mL two necked round bottom flask previously dried by using heating gun and flushed with nitrogen gas were added epoxide (10 mmol) followed by addition of active copper catalyst (5 mol %) to which drop-wise addition of heterocyclic amine in THF (10 mmol) by syringe through septum under the atomosphere of nitrogen gas at reflux temperature. After completion of reaction product were isolated by extraction with ethyl acetate (3 × 10 mL) and combine product layers were dried over anhydrous sodium sulphate (**Schemes I** and **II**).

1-[(5-Methyl-1,2-oxazol-3-yl)amino]-3-phenoxypropan-2-ol (3a): Liquid, m.f.: $C_{13}H_{16}N_2O_3$, IR (KBr, ν_{max}, cm^{-1}): 2970, 1590, 1050, 3600, 1640, 3200, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 6.95 (m, *J* = 8, 2.5 & 1 Hz, 2H), 7.22 (m, *J* = 8, 2.5 & 1 Hz, 2H), 7.01 (m, *J* = 8 & 2.5 Hz, 1H), 4.1 (d, *J* = 7 Hz, 2H), 4.3 (m, *J* = 7.0 Hz, 1H), 3.6 (d, *J* = 7 Hz, 2H), 5.7 (S, 1H), 2.3



R^1= H, *p*-Cl, *o*-Cl, *p*-NO_2, *o*-NO_2

Scheme-I: Reaction of heterocyclic amine with epoxide



R^1= H, *p*-Cl, *o*-Cl, *p*-NO_2, *o*-NO_2

Scheme-II: Reaction of heterocyclic amine with epoxide

(S, 3H), 1.7 (S, 1H), 2.03 (S, 1H), ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm, 158.9, 115.6, 129.6, 121.3, 72.1, 68.9, 42.3, 165, 99.9, 169.8, 14.1, Anal. calcd. (found) % for $C_{13}H_{16}N_2O_3$, C, 62.89 (62.87), H, 6.50 (6.52), N, 11.26 (11.28), O, 19.35 (19.33).

1-(4-Chlorophenoxy)-3-[(5-methyl-1,2-oxazol-3-yl)-amino]propan-2-ol (3b): Pale yellow liquid, m.f.: $C_{13}H_{15}N_2O_3Cl$, IR (KBr, ν_{max}, cm^{-1}): 2974, 1600, 1100, 650, 3600, 1650, 3230, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 6.9 (d, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.5 Hz, 2H), 3.8 (d, *J* = 7 Hz, 2H), 4.34 (m, *J* = 7 Hz, 1H), 3.4 (d, *J* = 7 Hz, 2H), 5.8 (S, 1H), 2.42 (S, 1H), 1.77 (S, 1H), 2.4 (S, 1H), ^{13}C NMR, (125 MHz, $CDCl_3$), δ ppm, 157.1, 115.7, 129.3, 126.9, 72.12, 68.6, 46.3, 164, 101, 170.2, 14.4, Anal. calcd. (found) % for $C_{13}H_{15}N_2O_3Cl$, C, 55.23 (55.21), H, 5.33 (5.35), Cl, 12.54 (12.52), N, 9.89 (9.91), O, 16.98 (16.96).

1-(2-Chlorophenoxy)-3-[(5-methyl-1,2-oxazol-3-yl)-amino]propan-2-ol (3c): Pale yellow liquid, m.f.: $C_{13}H_{15}N_2O_3Cl$, IR (KBr, ν_{max}, cm^{-1}): 2972, 1610, 1050, 540, 3610, 1650, 3200, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 7.26 (m, *J* = 7.5, 2.0 & 1.0 Hz, 1H), 6.87 (m, *J* = 7.5 & 2.0 Hz, 1H), 7.13 (m, *J* = 7.5 & 2. 0 Hz, 1H), 6.84 (m, *J* = 7.5, 2 & 1 Hz, 1H), 3.91 (d, *J* = 7 Hz, 2H), 4.41 (m, *J* = 7 Hz, 1H), 3.42 (m, *J* = 7 Hz, 2H), 5.77 (S, 1H), 2.3 (S, 1H), 1.42 (S, 1H), 2.01 (S, 1H), ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm, 155.3, 124.8, 131, 123.7, 124.8, 116.8, 72, 69.7, 46.2, 99, 170, 14.5, Anal. calcd. (found) % for $C_{13}H_{15}N_2O_3Cl$, C, 55.21 (55.23), H 5.33 (5.35), Cl, 12.54 (12.52), N, 9.91(9.89), O, 16.98 (16.96).

1-[(5-Methyl-1,2-oxazol-3-yl)amino]-3-(4-nitrophenoxy)-propan-2-ol (3d): Yellow liquid, m.f.: $C_{13}H_{15}N_3O_5$, IR (KBr, ν_{max}, cm^{-1}): 2970, 1600, 1110, 3600, 1640, 1350, 3214, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 7.16 (d, *J* = 7 Hz, 2H), 8.16 (d, *J* = 7 Hz, 2H), 4.13 (d, *J* = 7 Hz, 2H), 4.46 (m, *J* = 7 Hz, 1H), 3.8 (d, *J* = 7 Hz, 2H), 5.8 (S, 1H), 2.34 (S, 1H), 2.2 (S, 1H), 1.5 (S, 1H), ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm, 164.4, 114.9, 127.3, 142.1, 72.1, 68.4, 46.12, 165.6, 100.1, 171, 15.03, Anal. calcd. (found) % for $C_{13}H_{15}N_3O_5$, C, 53.24 (53.22), H, 5.14 (5.16), N, 14.33 (14.31), O, 27.26 (27.28).

1-[(5-Methyl-1,2-oxazol-3-yl)amino]-3-(2-nitrophenoxy)-propan-2-ol (3e): Yellow liquid, m.f.: $C_{13}H_{15}N_3O_5$, IR (KBr, ν_{max}, cm^{-1}): 2971, 1600, 1050, 3650, 1640, 1350, 3210, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 8.1 (m, *J* = 7.5, 2.0 & 1 Hz, 1H), 7.18 (m, *J* = 7.5 & 2 Hz, 1H), 7.60 (m, *J* = 7.5 & 2 Hz, 1H), 7.15 (m, *J* = 7.5, 2 & 1 Hz, 1H), 3.93 (d, *J* = 7 Hz, 2H), 4.37 (m, *J* = 7 Hz, 1H), 3.6 (d, *J* = 7 Hz, 2H), 6.1 (S, 1H), 2.33 (S, 1H), 1.46 (S, 1H), 4.10 (S, 1H), ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm, 155.2, 137.6, 127.9, 121.7, 135, 118.1, 72.1, 68, 46.2, 164, 98.9, 171, 15.2, Anal. calcd. (found) % for $C_{13}H_{15}N_3O_5$, C, 53.24 (53.22), H, (5.14 (5.16), N, 14.33 (14.31), O, 27.26 (27.28).

1-Phenoxy-3-(pyrazin-2-ylamino)propan-2-ol (6a): Liquid, m.f.: $C_{13}H_{15}N_3O_2$, IR (KBr, ν_{max}, cm^{-1}): 2900, 1610, 1100, 3600, 1625, 3200, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 6.8 (m, *J* = 8, 2.5 & 1.5 Hz, 2H), 7.21 (m, *J* = 8, 2.5 & 1.5 Hz, 2H), 6.90 (m, *J* = 8 & 2.5 Hz, 1H), 4.01 (d, *J* = 7 Hz, 2H), 4.21 (m, *J* = 7 Hz, 1H), 3.32 (d, *J* = 7 Hz, 2H), 7.6 (S, 1H), 7.74 (d, *J* = 6 Hz, 1H), 7.91 (d, *J* = 6 Hz, 1H), 1.8 (S, 1H), 1.62 (S, 1H), ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm, 158.8, 115.6, 129.4, 121.2, 72.1, 68.3, 46.2, 149, 131.8, 141.2, 128.2, Anal. calcd. (found) % for $C_{13}H_{15}N_3O_2$, C, 63.66 (63.64), H, 6.14 (6.16), N, 17.13 (17.11), O, 13.03 (13.05).

1-(4-Chlorophenoxy)-3-(pyrazin-2-ylamino)propan-2-ol (6b): Pale yellow liquid, m.f.: $C_{13}H_{14}N_3O_2Cl$, IR (KBr, ν_{max}, cm^{-1}): 2976, 1600, 1050, 3610, 1630, 3240, 650, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 6.92 (m, *J* = 8 Hz, 2H), 7.30 (m, *J* = 8 Hz, 2H), 4.11 (d, *J* = 7 Hz, 2H), 4.27 (m, *J* = 7 Hz, 1H), 3.23 (m, *J* = 7 Hz, 2H), 7.64 (S, 1H), 7.89 (d, *J* = 6 Hz, 1H), 7.88 (d, *J* = 6 Hz, 1H), 1.30 (S, 1H), 1.59 (S, 1H), ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm, 157.1, 115.7, 129.2, 126.8, 72.1, 68.9, 46.8, 148.7, 131.9, 142.2, 128.3, Anal. calcd. (found) % for $C_{13}H_{14}N_3O_2Cl$, C, 55.82 (55.80), H, 5.02 (5.04), Cl, 12.67 (12.65), N, 15.0 (15.02), O, 11.44 (11.42).

1-(2-Chlorophenoxy)-3-(pyrazin-2-ylamino)propan-2-ol (6c): Pale yellow liquid, m.f.: $C_{13}H_{14}N_3O_2Cl$, IR (KBr, ν_{max}, cm^{-1}): 2972, 1590, 1100, 3600, 1640, 3200, 540, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 7.22 (m, *J* = 7.5, 2 & 1.5 Hz, 1H), 6.86 (m, *J* = 7.5 & 2 Hz, 1H), 7.13 (m, *J* = 7.5 & 2 Hz, 1H), 6.82 (m, *J* = 7.5, 2 & 1.5 Hz, 1H), 3.92 (d, *J* = 7 Hz, 2H), 4.27 (m, *J* = 7 Hz, 1H), 3.63 (d, *J* = 7 Hz, 2H), 7.65 (S, 1H), 7.77 (d, *J* = 6 Hz, 1H), 7.93 (d, *J* = 6 Hz, 1H), 2.01 (S, 1H), 1.68 (S, 1H), ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm, 155.4, 124.9, 130.8, 123.7, 128.4, 116.3, 72.03, 69.4, 46.3, 149, 132, 142, 128.3, Anal. calcd. (found) % for $C_{13}H_{14}N_3O_2Cl$, C, 55.82 (55.80), H, 5.02 (5.04), CL, 12.67 (12.65), N, 15.0 (15.02), O, 11.44 (11.42).

1-(4-Nitrophenoxy)-3-(pyrazin-2-ylamino)propan-2-ol (6d): Yellow liquid, m.f.: $C_{13}H_{14}N_4O_4$, IR (KBr, ν_{max}, cm^{-1}): 2960, 1600, 1100, 3650, 1640, 3300, 1350, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 7.10 (d, *J* = 7.5 Hz, 2H), 7.97 (d, *J* = 7.5 Hz, 2H), 3.88 (d, *J* = 7 Hz, 2H), 4.34 (m, *J* = 7 Hz, 1H), 3.65 (d, *J* = 7 Hz, 2H), 7.56 (S, 1H), 7.77 (d, *J* = 6 Hz, 1H), 7.88 (d, *J* = 6 Hz, 1H), 1.44 (S, 1H), 1.66 (S, 1H), ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm, 164.3, 114.9, 127.3, 142.1, 72.4, 69.2, 46.12, 149.1, 131.6, 142, 129.1, Anal. calcd. (found) % for $C_{13}H_{14}N_4O_4$, C, 53.79 (53.77), H, 4.84 (4.86), N, 19.30 (19.28), O, 22.03 (22.05).

1-(2-Nitrophenoxy)-3-(pyrazin-2-ylamino)propan-2-ol (6e): Yellow liquid, m.f.: $C_{13}H_{14}N_4O_4$, IR (KBr, ν_{max}, cm^{-1}): 2971, 1610, 1100, 3600, 1640, 3250, 1350, ^{1}H NMR (500 MHz, $CDCl_3$), δ ppm, 8.01 (m, *J* = 7.5, 2.5, 1.5 Hz, 1H), 7.2 (m, *J* = 7.5 & 2.5 Hz, 1H), 7.62 (m, *J* = 7.5, & 2.5 Hz, 1H), 7.14 (m, *J* = 7.5, 2.5 & 1 Hz, 1H), 3.90 (d, *J* = 7 Hz, 2H), 4.11 (m, *J* = 7 Hz, 1H), 3.4 (d, *J* = 7 Hz, 2H), 7.73 (S, 1H), 7.89 (d, *J* = 6 Hz, 1H), 7.77 (d, *J* = 6 Hz, 1H), 1.31 (S, 1H), 3.10 (S, 1H), ^{13}C NMR (125 MHz, $CDCl_3$), δ ppm, 155.2, 137.6, 127.9, 121.7, 135, 118.1, 72.9, 68.4, 46.2, 148, 131.4, 142.1, 128.3, Anal. calcd. (found) % for $C_{13}H_{14}N_4O_4$, C, 53.79 (53.77), H, 4.84 (4.86), N, 19.30 (19.28), O, 22.03 (22.05).

RESULTS AND DISCUSSION

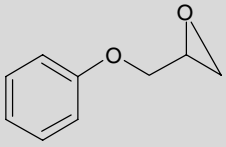
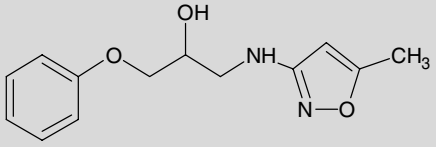
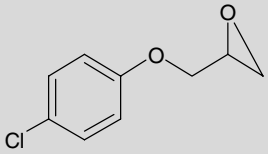
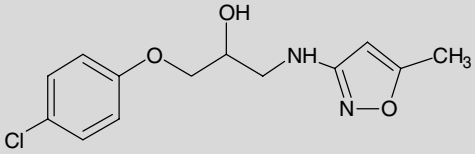
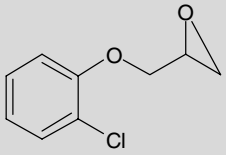
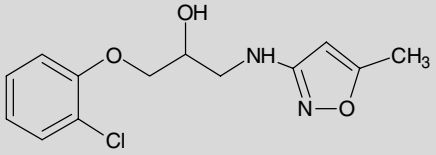
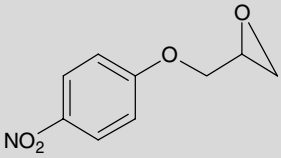
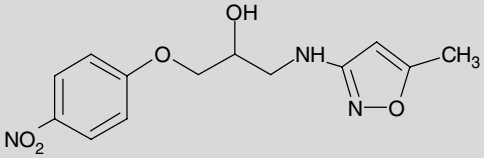
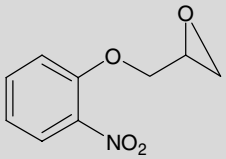
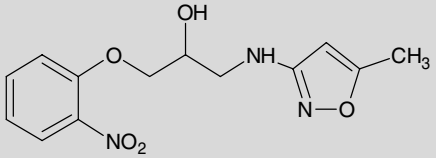
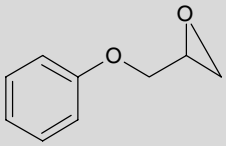
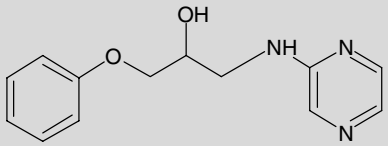
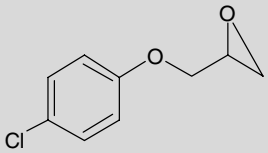
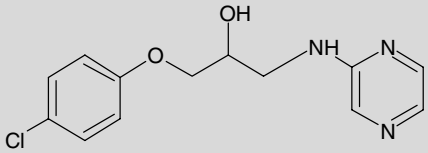
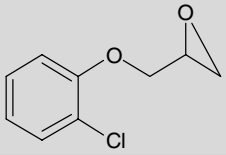
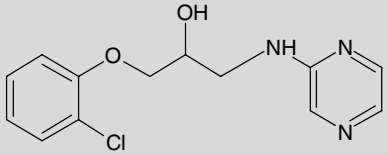
The chemicals for the reaction were purchased from Merck and used after purification. These chemicals were purified by using distillation technique. The solvents used for reaction were dried by different techniques like Na-benzophenone method for THF drying. All the starting compound epoxides were synthesized by alkylation of phenols and substituted phenol derivatives with epichlorohydrin. The lithium naphthalenide

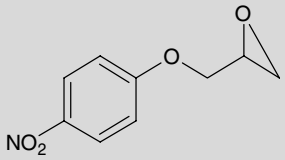
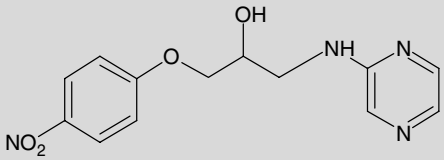
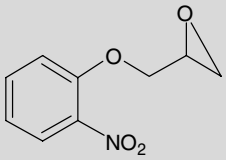
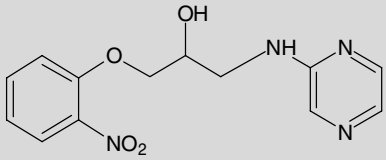
were prepared in inert atmosphere of nitrogen gas. The active copper catalyst used in this process were prepared by Rieke and Rhyne method [41]. Table-1 shows the results obtained from using different reaction conditions for the synthesis of compounds **3a-e** and **6a-e**. In order to justify the significance of the solvent in this process, the reactions were performed in the absence and presence of active copper catalyst. The reactions were performed in presence of active copper catalyst and different solvents like THF, 1,4-dioxane and DMSO where in the reaction gives different yields and good regioselectivity. It has been observed that substituted epoxide gives different results (Table-2) in absence and presence of the active copper catalyst. The nucleophilic attack of heterocyclic amines were occurred at less substituted carbon atom of epoxide to give β-amino alcohols which shows various biological activities like cardiotonic, antineurotic, antidiabetic, antianginal, antihypertensive, antiviral and antiinfective predicted by using prediction of activity spectra for substances (PASS). It has also been observed that the different regioselectivity obtained in absence of active copper catalyst and mixture of products were formed.

TABLE-2
SCREENING OF CATALYST AND SOLVENT FOR THE SYNTHESIS OF COMPOUNDS **3a** AND **6a**

Entry	Reagent	Solvent	Time (min)		Yield (%)	
			3a	**6a**	**3a**	**6a**
1	$CuI.PPh_3$	THF	40	60	82	80
2	$CuI.PPh_3$	1,4-Dioxane	55	70	77	69
3	$CuI.PPh_3$	DMSO	75	80	60	64
4	–	THF	70	75	62	59
5	–	1,4-Dioxane	80	80	58	56
6	–	DMSO	95	105	55	48

TABLE-1
SYNTHESIS OF COMPOUNDS **3a-e** AND **6a-e**

Entry	Reactant	Product	Time (min)	Yield (%)
3a			40	82
3b			35	79
3c			50	65
3d			35	74
3e			55	62
6a			60	80
6b			65	78
6c			75	64

6d			40	70
6e			80	63

Conclusion

We have used active copper catalyst as a simple and efficient catalyst for the regioselective ring opening of epoxides by heterocyclic amines. The yield obtained by method is higher and found to be effective and convinient for the synthesis of desired biologically active β-amino alcohols as described. The short reaction times, easy work up and higher yield make this catalyst a more convinient alternative to the reported methods.

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