

Zn(OAc)₂/Podand Catalyzed Ring Opening of Epoxides By Aromatic Amines under Solvent-Free Conditions

H. Eshghi^{a,b,*} M. Rahimizadeh^a and A. Shoryabi^b

^a Department of Chemistry, Ferdowsi University of Mashhad, Mashhad 91775-1436, Iran

^b Department of Chemistry, Sistan and Baluchestan University Zahedan 98135-674 Iran

(Received 27 February 2005, Accepted 26 April 2005)

A highly regioselective ring opening of epoxides with aromatic amines in the presence of a catalytic amount of Zn(OAc)₂ and a recently synthesized podand under solvent-free conditions is described. The yields of the amino alcohols are uniformly good and the recovered catalyst could be used in new attempts without any purification.

Key words: Epoxide, Ring opening, Amines, Solvent-free, Amino-alcohols

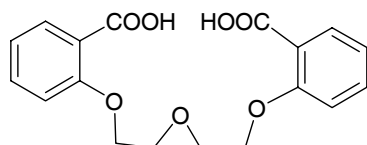
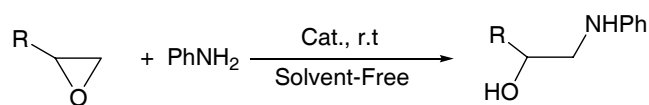
INTRODUCTION

The β-amino hydroxyl is a major class of functional group in many important biologically active natural and synthetic products and unnatural amino acids [1]. Several clinically useful skeletons, which exhibit a broad range of biological activities as anti-obesity [2] and anti-hypertensives [3], contain the β-amino alcohol functionality. The classical method for the preparation of β-amino alcohol involves heating of an epoxide in a protic solvent with excess amine. Although this non-catalytic reaction is satisfactory in many cases, it has a number of limitations. For example, the cleavage of epoxides by anilines using classical procedures are difficult [4] and the reaction requires an excess of strong inorganic base or a long reaction time, or both and the yields of the corresponding secondary alcohols are low [5]. Recently, new methods using activators/promoters have been reported. These include Lewis acids such as BiCl₃ [6], CeCl₃·7H₂O-NaI [7], TaCl₅ [8], SmCl₃ [9], diisopropoxyaluminium

trifluoroacetate [10], Cu(OTf)₂, or Sn(OTf)₂ [11] and other activating agents such as alumina [12], polyoxometalate (K₅CoW₁₂O₄₀·3H₂O) [13] and trifluoroethanol, hexafluoro-2-propanol [14]. However, there are still some limitations with these methods including the failure of deactivated aromatic amines and some sterically hindered aromatic amines to open the epoxides, the need for an excess of reagents and reflux temperature and sluggish reactions.

In conjunction with ongoing work in our laboratory on the macrocyclic crown ethers including synthesis [15], formation of complexes [16] and catalysis of regioselective ring opening of epoxides [17], we found out that 2-{2-[2-(2-carboxyphenoxy)ethoxy]ethoxy}-benzoic acid (CPEEBA, a podand) efficiently catalyzed the ring opening of epoxides with anilines under mild conditions with high regioselectivity. Recently, we have prepared CPEEBA [15a] and used it as a starting dicarboxylic acid material for the preparation of corresponding macrocyclic diamides. In this study, we wish to report the results of the reactions of some epoxides with anilines in the presence of a catalytic amount of Zn(OAc)₂ and CPEEBA (ZnCPEEBA, for short), (Scheme 1, Table 1).

* Corresponding Author. E-mail: heshghi@ferdowsi.um.ac.ir



CPEEBA

Scheme 1

EXPERIMENTAL

All melting points recorded are uncorrected open capillary measurements. IR spectra were recorded on a Shimadzu -IR 470 spectrophotometer. ^1H NMR spectra were recorded on Bruker-80 and 100 MHz instruments using tetramethylsilane (TMS) as an internal standard. Mass Spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument at 70 eV. Elemental analyses were performed at the Research Institute of Petroleum Industry of Iran. Column chromatography was carried out on short columns of silica gel 60 (230-400 mesh) in glass columns (2-3 cm diameter) using 15-30 g of silica gel per 1 g of crude mixture. CPEEBA was prepared according to literature [15a].

Cleavage of Epoxides with Aromatic Amines

General procedure. A mixture of the $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ (0.2 mmol) and 2-{2-[2-(2-carboxyphenoxy)ethoxy]ethoxy}-benzoic acid (CPEEBA) (0.2 mmol) was ground in a mortar for 5 min. Then, epoxide (2 mmol) and aniline (2 mmol) were added to the catalyst and the mixture was grounded for 15 min at room temperature and stand over night. Chloroform (15 ml) was added and the catalyst filtered off. The filtrate was washed with water (2×15 ml), passed through anhydrous MgSO_4 and the solvent was distilled off to give the respective amino alcohol. These were further purified by column chromatography (silica gel, petroleum ether/EtOAc (9:1)). Physical properties of the products thus obtained were in good

unknown compounds are given below.

1-(2-Methoxy-phenoxy)-3-phenylamino-propan-2-ol

(2). Viscous liquid. IR (neat): $\nu = 3500, 3400, 1250, 1120$ cm^{-1} . ^1H NMR (80 MHz, CDCl_3): $\delta = 3.2$ -3.4 (m, 2H), 3.4-3.7 (m, 2H), 3.8 (s, 3H), 3.9-4.3 (m, 3H), 6.5-6.8 (m, 3H), 6.9 (s, 4H), 7.0-7.3 (m, 2H). MS: m/z 273 (M^+). Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.35; H, 7.04; N, 5.32.

1-Phenylamino-3-o-tolyloxy-propan-2-ol

(3). Viscous liquid. IR (neat): $\nu = 3450, 1250, 1120$ cm^{-1} . ^1H NMR (80 MHz, CDCl_3): $\delta = 2.2$ (s, 3H), 2.8-3.4 (m, 2H), 3.4-3.7 (m, 2H), 3.7-4.4 (m, 3H), 6.3-6.9 (m, 5H), 6.9-7.3 (m, 4H). MS: m/z 257 (M^+). Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.71; H, 7.50; N, 5.48.

1-Phenylamino-3-m-tolyloxy-propan-2-ol

(4). Viscous liquid. IR (neat): $\nu = 3500, 3400, 1250, 1150$ cm^{-1} . ^1H NMR (80 MHz, CDCl_3): $\delta = 2.3$ (s, 3H), 3.0 (b, 2H), 3.1-3.6 (m, 2H), 3.8-4.4 (m, 3H), 6.4-6.8 (m, 5H), 6.9-7.3 (m, 4H). MS: m/z 257 (M^+). Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.70; H, 7.47; N, 5.47.

1-Phenylamino-3-p-tolyloxy-propan-2-ol

(5). Viscous liquid. IR (neat): $\nu = 3550, 3400, 1240, 1100$ cm^{-1} . ^1H NMR (80 MHz, CDCl_3): $\delta = 2.2$ (s, 3H), 3.0 (b, 2H), 3.1-3.6 (m, 2H), 3.8-4.44 (m, 3H), 6.6-6.9 (m, 5H), 7.0-7.3 (m, 4H). MS: m/z 257 (M^+). Anal. Calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.68; H, 7.44; N, 5.44. Found C, 74.72; H, 7.46; N, 5.47.

1-[2-(2-Hydroxy-1-phenyl-ethylamino)-phenyl]-ethanone

(12). m.p.: = 74-75 °C. IR (neat): $\nu = 3400, 3300, 1630, 1240, 1160$ cm^{-1} . ^1H NMR (100 MHz, CDCl_3): $\delta = 2.5$ (s, 3H), 3.0 (b, 1H), 3.8-4.06 (m, 2H), 4.6 (dd, 1H, $J_1 = 12$ Hz, $J_2 = 5.5$ Hz), 6.4-6.6 (m, 2H), 7.0-7.4 (m, 6H), 7.8 (dd, 1H, $J_1 = 8.7$ Hz, $J_2 = 1.7$ Hz), 9.52 (d, 1H, $J = 6$ Hz). MS: m/z 255 (M^+). Anal. Calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_2$: C, 75.27; H, 6.71; N, 5.49. Found C, 75.50; H, 6.75; N, 5.52.

RESULTS AND DISCUSSION

The results of the reactions of cyclohexene oxide with aniline in the presence of ZnCPEEBA catalyst are summarized in Table 1, and compared with the corresponding results obtained by other applied catalysts. In each case, cleavage of the epoxide ring occurs and the corresponding amino alcohol was obtained upon simple workup. In comparison, the

Table 1. Ring Opening of Cyclohexene Oxide with Aniline^a

Entry	Catalyst	Reaction conditions	Yield (%) ^b [lit]
1	-	CH ₂ Cl ₂ /7 days	0
2	Zinc tartarate	CH ₂ Cl ₂ /28 days	53 [18]
3	Zinc tartarate	CH ₂ Cl ₂ /7 days	95 [18]
4	Zinc acetate	CH ₂ Cl ₂ /7 days	40
5	Zinc acetate, CPEEBA	CH ₂ Cl ₂ /7 days	96
6	Zinc acetate, CPEEBA	Solvent-Free/15 min	94

^a All reactions were carried out using 2 mmol of epoxide, 2 mmol of aniline, and 10 mol% of catalyst (Only except entry 3 with 50 mol%). ^b Yields refer to isolated yield.

agreement with reported data [10-12,18-21]. Spectral data of cleavage behavior of cyclohexene oxide with aniline in the absence of catalyst is given in entry 1. As shown in Table 1, the yields of ring opening with this methodology are quite good and ZnCPEEBA is a more effective catalyst under solvent-free conditions than in solution; short reaction time and lower catalyst loading (10 mol% versus 50 mol%) could be used. The catalyst was easily recovered and could be reused several times. Generally, the optimum amounts of the catalyst were found to be 0.1 mol per 1 mol of epoxide and aniline.

The results obtained with some representative epoxides in the presence of ZnCPEEBA as the catalyst are summarized in Table 2. With the only exception of styrene oxide (entries 10-12), when unsymmetric epoxides were allowed to react in the presence of ZnCPEEBA, the ring opening takes place in a completely regioselective fashion. The attack at the less substituted oxirane carbon affording the desired compound as the only product. However, when styrene oxide was used in CH₂Cl₂, two regioisomer were formed in 60 : 40 ratio whereas, in solvent-free condition mainly one isomer was obtained (90: 10) by attacks to the benzylic carbon of the epoxide. Such a reverse regioselectivity could be attributed to ionic nature of styrene oxide reactions. This is further confirmed by the observation that the reaction of sterically hindered aromatic amine; for example, in the case of 2-acetylaniline with styrene oxide, the ring opening takes place

in a completely regioselective fashion, by attack at the benzylic carbon.

The stereoselectivity of the aminolysis reactions was *anti* as demonstrated by the reaction of cyclohexane oxide with 2-acetylaniline which gave exclusively corresponding *trans* amino alcohol (**9**) by the coupling constants of the peaks at 3.35 ppm (CHNHAr) (ddd, J = 10.3, 10.1 and 5.5 Hz) and 3.55 ppm (CHOH) (ddd, 10.1, 8.5 and 4.1 Hz) in ¹H NMR spectra. All the compounds are fully characterized by ¹H-NMR, IR and mass spectral data, by comparison with the known compounds [10-12,18,19]. It is interesting to note that in the above studies, aliphatic amines such as *n*-butyl amine, benzylamine and *iso*-propylamine failed to react with epoxides at room temperature even for 3 days in the presence of a catalytic amount of ZnCPEEBA in solvent-free condition. This may be due to stronger complexation of aliphatic amines with the catalyst due to their higher basicity (highly exothermic reactions were observed). This type of behavior has already in reported for metal catalysts [6-9,11].

The cleavage of epoxides with aromatic amines is unique and is highly useful in organic synthesis. To the best of our knowledge, the above catalyst has not been used in ring opening reactions of epoxides. A variety of chiral derivatives of CPEEBA can be complexed with zinc acetate for asymmetric version of these reactions; the work is in progress in our laboratory.

Table 2. Ring Opening of Various Epoxides with Amines Catalyzed by ZnCPEEBA under Solvent-Free Conditions^a

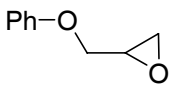
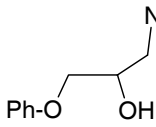
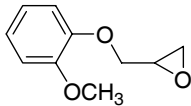
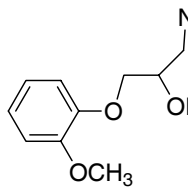
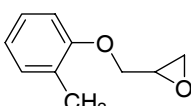
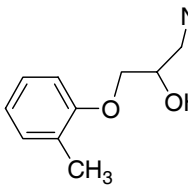
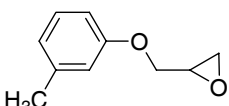
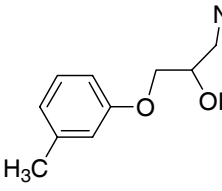
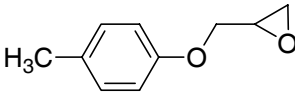
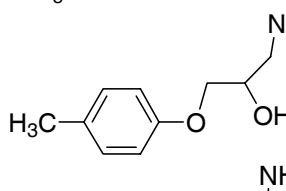
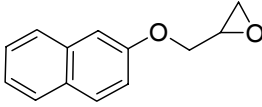
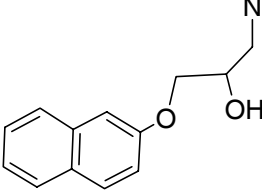
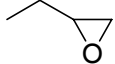
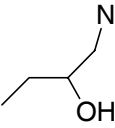
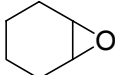
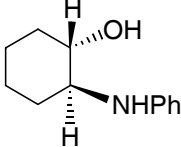
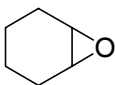
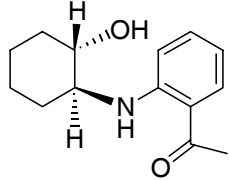
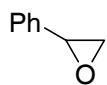
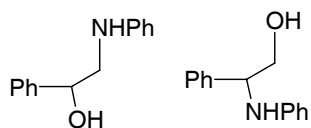
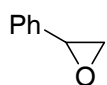
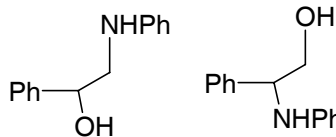
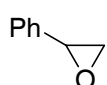
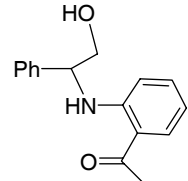
Entry/product number	Epoxides	Products	Yield (%) ^b
1			70
2			75
3			75
4			76
5			78
6			70
7			72
8			94

Table 1. Continued

9			72
10			83 ^a (40 : 60)
11			85 (10 : 90)
12			82

^a All reactions were carried out using 2 mmol of epoxide, 2 mmol of aniline, and 10 mol% of catalyst (the only exception was entry 10 in which the reaction was performed in CH₂Cl₂ for 7 days). ^b Isolated yield of pure product after column chromatography [(petroleum ether/EtOAc (9 : 1))].

ACKNOWLEDGMENTS

We are thankful to Sistan and Baluchestan University for the partial support of this work.

REFERENCES

- [1] a) D.J. Ager, I. Prakash, D.R. Schaad, *Chem. Rev.* 96 (1996) 835; b) S. Kobayashi, H. Ishitani, M. Ueno, *J. Am. Chem. Soc.* 120 (1998) 431; c) E.J. Corey, F.Y. Zhang, *Angew. Chem. Int. Ed.* 38 (1999) 1931; d) G.A. Rogers, S.M. Parsons, D.C. Anderson, L.M. Nilsson, B.A. Bahr, W.D. Kornreich, R. Kaufman, R.S. Jacobs, B. Kirtman, *J. Med. Chem.* 32 (1989) 1217.
- [2] D.R. Gehlert, D.J. Goldstein, P.A. Hipskind, *Annual Reports in Medicinal Chemistry* (1999) 201.
- [3] C.W. Johannes, M.S. Visser, G.S. Weatherhead, A.H. Hoveyda, *J. Am. Chem. Soc.* 120 (1998) 8340.
- [4] F. Moller, in: E. Muller (Ed.), *Methoden der Organische Chemie (Houbenweyl)* 4th ed., Vol 11/1, Thieme-verlag; Stuttgart, 1957, pp 311-326.
- [5] a) G.H. Posner, D.Z. Rogers, *J. Am. Chem. Soc.* 99 (1977) 8208; b) G.H. Posner, *Angew. Chem. Int. Ed.* 7 (1978) 487.
- [6] T. Ollevier, G. Lavie-Compin, *Tetrahedron Lett.* 43 (2002) 7891.
- [7] L. Rajender Reddy, M. Arjun Reddy, N. Bhanumathi, K. Rama Rao, *Synthesis* (2001) 831.
- [8] S. Chandrasekhar, T. Ramachandar, S. Jaya Prakash, *Synthesis* (2000) 1817.
- [9] X.-L. Fu, S.-H. Wu, *Synth. Commun.* 27 (1997) 1677.
- [10] S. Rampalli, S.S. Chandhari, K. G. Akamanchi, *Synthesis* (2000) 78.
- [11] G. Sekar, V.K. Singh, *J. Org. Chem.* 64 (1999) 287.
- [12] Y. Harrak, M.D. Pujol, *Tetrahedron Lett.* 43 (2002) 816.
- [13] E. Rafiee, S. Tangestaninejad, M.H. Habibi, V.

- Mirkhani, *Synth. Commun.* 34 (2004) 3673.
- [14] U. Das, B. Crousse, V. Kesavan, D. Bonnet-Delpon, J. P. Be'gue', *J. Org. Chem.* 65 (2000) 6749.
- [15] a) H. Sharghi, H. Eshghi, *Tetrahedron* 51 (1995) 913;
b) M. Rahimizadeh, H. Eshghi, F. Rostami, Z. Faghihi, *Pol. J. Chem.* 79 (2005) 73.
- [16] a) M. Shamsipur, A.R. Fakhari, H. Sharghi, H. Eshghi, M.R. Ganjali, *Pol. J. Chem.* 76 (2002) 1665 and references cited therein.
- [17] a) H. Sharghi, A.R. Massah, H. Eshghi, K. Niknam, *J. Org. Chem.* 63 (1998) 1455.
- [18] H. Yamashita, *Bull. Chem. Soc. Jpn.* 61 (1988) 1213.
- [19] X.I. Hou, L. Wu, L.X. Dai, L.J. Xia, M.H. Tang, *Tetrahedron Asymmetry* 9 (1998) 1747.
- [20] G. Sabitha, G.S. Reddy, K. Kumar, K.B. Reddy, J.S. Yadav, *Synthesis* (2003) 2298.
- [21] P.-Q. Zhao, L.-W. Xu, C.-G. Xia, *Synlett* (2004) 846.
- [22] J. Iqbal, A. Pandey, *Tetrahedron Lett.* 31 (1990) 575.