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Concise synthesis of (S)-(-)-Propranolol: Using acid catalysed kinetic resolution

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ABSTRACT

Enantiomerically pure (S)-propranolol was prepared by using $Zn(NO_3)_2$/ (+)-tartaric acid for the resolution of terminal epoxide. This process is carried out at 75℃ temperature in excellent enantioselectivity via kinetic resolution of key Intermediate α-naphthyl glycidyl ether.

Key words: Propranolol, Glycidyl Ether and Kinetic resolution

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INTRODUCTION

β-blockers are among the most prescribed drugs in the world [1]. As stereochemistry in a drug molecule governs its biological activity, chirality is emerging as a key issue in pharmaceutical research [2]. β-Blockers of the 3-(aryloxy)-1-(alkylamino)-2-propanol type e.g. propanolol are one such class of drugs where the activity resides mainly in the S-isomers [3, 4]. For instance, the activity of (S)-(-)-propanolol is 98 times higher than that of its R-enantiomer. Moreover, R-isomer is known to act as a contraceptive. Methods reported for the synthesis of (S)-propranolol involved the use of enzymes for resolution of intermediate [5], asymmetric hydrogenation using chiral metal complex of the intermediate [6], asymmetric epoxidation of allyl alcohol [7] from sorbitol [8] and also by employing polymer supported reagent [9]. The three main strategies that can be applied for the synthesis using an external chiral auxiliary or *via* a chiral synthon. Direct resolution of racemic propranolol itself has been reported to be unsuccessful [10] but several synthesis have been published in which the enzymatic resolution of intermediate compounds has successfully been applied [11]. Inspite of the excellent selectivity shown by lipase toward the intermediates used, these methods donot show any promise for industrial exploitation because of several disadvantages like multisteps (more than six steps), low overall yields (10-30%) and use of hazardous and expensive reagents. We report herein a method for efficient synthesis of S-isomer of propranolol *via* $Zn(NO_3)_2$/(+)-tarteric acid-catalyzed kinetic resolution of key intermediates α–naphthyl glycidyl ether.

EXPERIMENTAL SECTION

The chemicals and reagents used in the present project were of AR and LR grade, procured from Aldrich, Hi-media, Merck, Ranbaxy, sigma and S.D-Fine Chem Ltd. Melting points were measured on Digital melting point apparatus. ^{1}H NMR spectra were recorded on a Bruker Avance II 400 MHz instrument using tetramethylsilane (TMS) as internal standard. Chemical shifts were given in parts per million (ppm). Spectra were obtained in $CDCl_3$. IR Spectra were recorded on Perkin Elmer-spectrum RX1-FTIR spectrometer (neat). Monitoring of reactions was carried out

using TLC plates Merck silica gel in Ethylacetate and Petroleum ether solution in 15:85 ratio and visualization with uv light (254 and 365 nm).

(a) Synthesis of Glycidyl-α-Naphthyl Ether: To a stirred solution of α-naphthol (0.025 mol, 3.6g) and K_2CO_3 (0.073 mol, 10.08 g) in anhydrous 2-butanone (50 mL) was added (±)-epichlorohydrin refluxed until all of the α-naphthol has been consumed (3 hours) which is confirmed by TLC (Petroleum ether/EtOAc, 85/15). The reaction mixture was filtered, solvent was removed under vacuum, and the residue was purified by column chromatography (silica gel, Petroleum ether/ EtOAc, 95/5) to give the glycidyl-α-naphthyl ether in 95% yield boiling point – 200-202°C.

^{1}H NMR ($CDCl_3$): 2.5-2.9 (m, 2H), 3.2 (m, 1H), 3.6-4.1 (m, 2H), 6.5-6.8 (m, 1H), 6.9-7.8 (m, 5H), 7.9-8.4 (m, 1H).

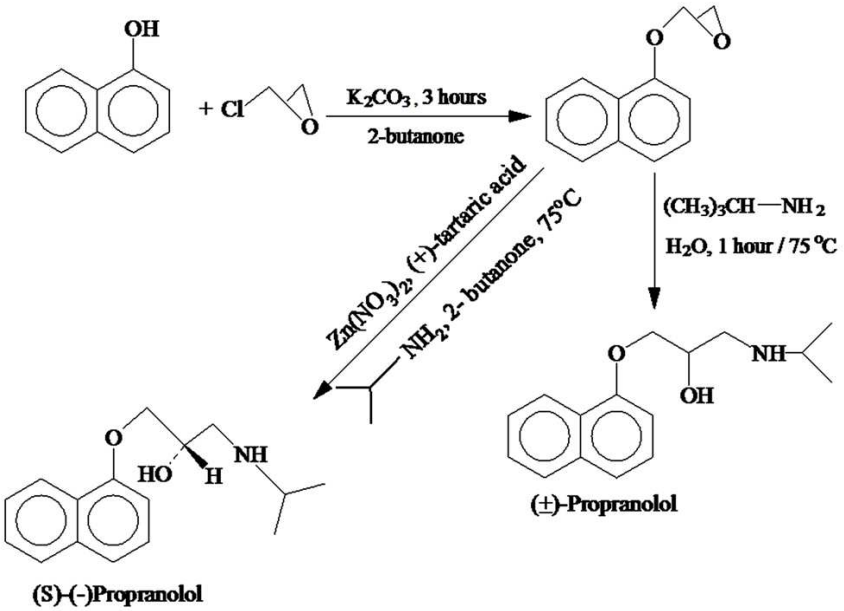
IR (Neat): 3048, 2985, 1585, 1545, 1500, 1460, 1388, 1340, 1310, 1270, 1240, 1180, 1080, 1020, 870, 780, 770, 750, 700, 670, 640, 570 cm^{-1}.

(b) Synthesis of (±)-Propranolol

A solution of glycidyl-α-napthyl ether (2g, 10 mmol) in excess isopropylamine (20mL) and water (1 mL) was stirred and heated to reflux for 1 hour. Removal of solvent yielded crude (±)-propranolol (2.2g, 89%) which could be purified by recyrstallization in hexane m.p. 95 °C.

^{1}H NMR ($CDCl_3$): 1.2 (d, 6H), 2.3-3.2 (m, 4H), 6.8-8.3 (m, 7H).

IR (Neat): 3450, 3200, 3055, 2980, 1630, 1595, 1580, 1500, 1465, 1400, 1345, 1320, 1270, 1240, 1180, 1160, 1100, 1070, 1020, 960, 870, 790, 770, 640, 620, 570,520 cm^{-1}.



Scheme 1. Synthesis of (S) - isomer of Propranolol using acid catalysed resolution.

(c) Synthesis of (S)-(-)-Propranolol

A solution of glycidyl-α-napthyl ether (10 mmol, 2g) L-(+)-tartaric aid (10 mmol, 1.5g) and $Zn(NO_3)_2.6H_2O$ (5 mmol, 2.96 g) in 2-butanone was stirred for 15 minutes. The isopropylamine (20 mmol, 1.5 mL) was added and stirred at ambient temperature for 1 hour. The mixture was cooled and filtered. The solid was washed with dichloromethane and then treated with sodium hydroxide solution and extracted with dichloromethane. The combined organic layer was washed with water and dried over sodium sulphate. The solvent was removed under

reduced pressure to give crude product (1.5g, 60% yield) that showed 90% ee for (S)-propranolol that equal with 95% yield of the theoretical (S)-isomer m.p. - 73 °C

RESULTS AND DISCUSSION

Condensation of α-naphthol with (±)-epichlorohydrin in anhydrous 2-butanone in the presence of K_2CO_3 at 75 °C temperature for 3 hours gives α-naphthyl glycidyl ether in 96% yield. Treatment of this ether with excess of isopropylamine (reflux, 1 hour) yielded the required (±)-propranolol in 92% yield.

However, when $Zn(NO_3)_2$ and (±)-tartaric acid allowed to stirred with glycidyl-α- naphthyl ether for 15 min in 2-butanone followed by addition of Isopropylamine to the same reaction vessel gave (S)-propranolol in good chemical yield and optical purity. The enantiomeric excess was calculated by correlation of optical rotation [α] with literature values $[\alpha]_D$ = -10.2 (C = 1.02, EtOH).

Molar ratios of epoxide: $Zn(NO_3)_2$ (+)-tartaric acid was affected on chemical and optical yields. The best mole ratio is 1:0.5:1 with 60% isolated yield of crude product which showed 90% ee of (S)-enantiomer (94% yield of the theoretical (S)-isomer.

In comparison with literature reports we have shown that (S)-propranolol with high purity and chemical yield can be obtained in only two steps without any purification or resolution of intermediate we suggested a preliminary chiral complex. Which kinetically favoured for (S)- enantiomer responsible for this optical purity.

CONCLUSION

Finally, we can concluded that enantioselective ring opening by using $Zn(NO_3)_2$/(+)- tartaric acid is an efficient alternative short route, with simple work up and high enantiomeric excess for synthesis of (S)-propranolol.

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