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A FACILE SYNTHESIS OF (*S*) – (-) – PROPRANOLOL

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Abstract

A one-pot synthesis of (*S*)-(-)-propranolol is reported. $Zn(NO_3)_2$/(+)-tartaric acid catalyzed enantioselective synthesis of (*S*)-(-)-propranolol via kinetic resolution of key intermediate α-naphthyl glycidyl ether with high optical and chemical yield.

Keywords: Propranolol; Enantioselective synthesis; Kinetic resolution

Introduction

As stereochemistry in a drug molecule governs its biological activity [1], chirality is emerging as a key issue in pharmaceutical research [2]. β-Blockers of the 3-(aryloxy)-1-(alkylamino)-2-propanol type, *e.g.* propranolol **1**, are one such class of drugs where the activity resides mainly in the *S* isomers [3,4]. For instance, the activity of (*S*)-(-)-propranolol is 98 times higher than that of its *R* enantiomer. Moreover, (*R*)-**1** 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 of enantiomerically pure compounds have been used, resolution, asymmetric 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 syntheses have been published in which the enzymatic resolution of intermediate compounds has successfully been applied [5,11]. In spite of the excellent selectivity shown by lipase toward the intermediates used, these methods do not 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 $Zn(NO_3)_2$/(+)-tartaric acid-catalyzed kinetic resolution of key intermediate α-naphthyl glycidyl ether **4**.

Results and Discussion

Condensation of α-naphthol **2** with epichlorohydrin **3** in the presence of KOH in DMSO at room temperature for 6 h gives α- naphthyl glycidyl ether **4** in 95% yield. Treatment of this ether with excess of isopropylamine (reflux, 24 h), yielded the required (±)-propranolol **1** in 90% yield (Scheme).

However, when $Zn(NO_3)_2$ and (+)-tartaric acid allowed to stirred with α-naphthyl-glycidyl ether for 15 min in DMSO, 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 [5a] $[\alpha]_D$ = -10.2 (C = 1.02,

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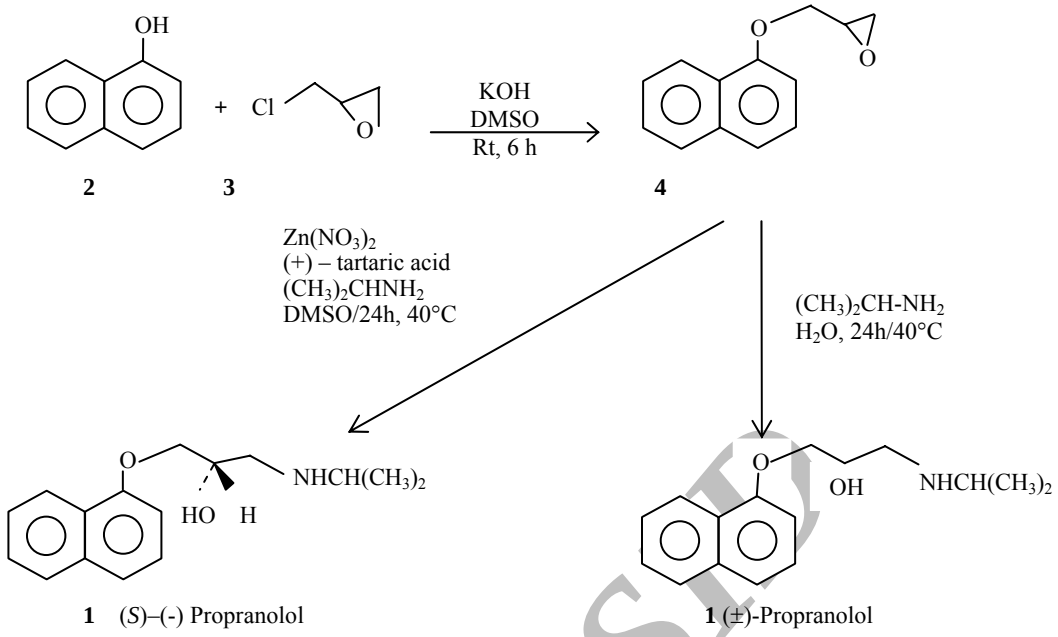

Scheme

EtOH). The results of the kinetic resolution ring opening of epoxide were listed in Table. Mole 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 55% isolated yield of crude product which showed 89% ee of (*S*)-enantiomer (94% yield of the theoretical (*S*)-isomer). In comparison with literature reports [5-11] we have shown that (*S*)-propranolol with high purity (89% ee) and chemical yield (84% overall yield) can be obtained in only two steps without any purification or resolution of intermediate. We suggested a preliminarily chiral complex, which kinetically favored for (*S*) enantiomer responsible for this optical purity. 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.

Experimental Section

All melting points recorded are uncorrected open capillary measurements. Infrared spectra were recorded on a Shimadzu – IR 470 spectrophotometer. ^{1}H-NMR Spectra were recorded on a Brucker-80 MHz instrument using tetramethylsilane (TMS) as internal standard. Optical rotation values were noted on Bellingham + Stanly (B + S) polarimeter.

Preparation of Glycidyl-α-Naphthyl Ether (4)

Powdered KOH (5 g) was added to a solution of 1-naphthol (0.05 mol, 7.2 g) in DMSO (20 ml) and the mixture was stirred for 30 min at room temperature. Then the epichlorohydrin (0.15 mol, 12 ml) was added slowly in 45 min and stirring was continued at room temperature for 6 h. The reaction was quenched with H_2O (50 ml) and extracted with chloroform (2×75 ml). The combined organic layers were washed with sodium hydroxide solution (2×30 ml), and water (5×100 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure to give the glycidyl-α-naphthyl ether **4** in 95% yield: bp = 201 – 203°C (lit. [12] 203 – 5°C] 1H-NMR ($CDCl_3$): δ: 2.5 – 2.9 (m, 2H), 3.3 (m, 1H), 3.8 – 4.3 (m, 2H) 6.4 – 6.8 (m. 1H), 6.9 – 7.7 (m, 5H), 7.9 – 8.2 (m, 1H). IR (Neat): 3050, 2980, 1580, 1540, 1500, 1460, 1390, 1340, 1310, 1270, 1240, 1180, 1100, 1080, 1020, 960, 870, 790, 770, 750, 700, 670, 640, 570 cm^{-1}.

(±)-Propranolol (1)

A solution of glycidyl-α-naphthyl ether **4** (2.0 g, 10 mmol) in excess isopropylamine (20 ml) and water (1 ml) was stirred and heated to reflux for 24 h. Removal of solvent yielded crude (±)-propranolol (2.33 g, 90%), which could be purified by recrystalization in hexane. mp= 95°C (lit[9] 96°C), ^{1}H-NMR ($CDCl_3$): δ: 1.2 (d, 6H), 2.4 – 3.1 (m, 4H), 6.8 – 8.3 (m, 7H). IR (Neat): 3450, 3200, 3050, 2980, 1630, 1590, 1580, 1500, 1460, 1400, 1340, 1320, 1270, 1240, 1180, 1160, 1100, 1070, 1020, 960, 870, 790, 770, 760, 640, 620, 570, 520 cm^{-1}.

Table. $Zn(NO_3)_2$/(+)-tartaric acid catalyzed enantioselective synthesis of (*S*)-propranolol via kinetic resolution of racemic epoxide **4**

Entry	Mole ratio[a]	Yield %[b]	ee %[c]
1	1: 0.5: 2	65	69
2	1: 0.5: 1	55	89
3	1: 0.5: 0.5	81	38
4	1: 0.5: 0.14	82	36
5	1: 1: 1	93	15
6	1: 0: 1	92	15
7	1: 0.07: 0.07	94	10
8	1: 0: 0	90	0

a) Mole ratio corresponding to epoxide **4**: $Zn(NO_3)_2$: (+)-tartaric acid. b) Isolated yield. c) Calculated by correlation of optical rotation [α] (C = 1.0, EtOH) with literature values [5a], $[\alpha]_D$ = -10.2 (C = 1.02, EtOH).

(S)-(-)-Propranolol (1)

A solution of glycidyl-α-naphthyl ether **4** (8 mmol, 1.6 g), L-(+)-tartaric acid (8 mmol, 1.2 g) and $Zn(NO_3)_2$. $6H_2O$ (4 mmol, 2.37 g) in DMSO (20 ml) was stirred for 15 min. The isopropylamine (16 mmol, 1.2 ml) was added and stirred at ambient temperature for 24 h. The reaction mixture was cooled and filtered. The solid was washed with dichloromethane and then treated with aqueous 10% sodium hydroxide solution (10 ml), and extracted with dichloromethane (2×50 ml). The combined organic layer was washed with water (5×50 ml) and dried over sodium sulfate. The solvent was removed under reduced pressure to give crude product (1.14 g, 55% yield), that showed 89% ee for (*S*)-propranolol that equal with 94% yield of the theoretical (*S*)-isomer. mp = 72°C [α] = -9.08 (C = 1.0, EtOH), lit[9] $[\alpha]_D$ = -10.2 (C = 1.02 EtOH).

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