International Journal of Chemical, Materials and Biomolecular Sciences
ISSN: 2415-6620
Vol:6, No:7, 2012

Stereoselective Reduction of Amino Ketone with Sodium Borohydride in the Presence of Metal Chloride. A Simple Pathway to *S*-Propranolol

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***Abstract*—**Propranolol is worldwide hypertension drug that is active in *S*-isomer. Patients must use this drug throughout their lives, and this action employsa significant level of expenditure. A simpler synthesis and lower cost can reduce the price for the patient. A simple synthesis pathway of *S*-propranolol starting from protection of (*R,S*)-propranolol with di-*t*-butyldicarbonate and then the product is oxidized with pyridiniumchlorochromate. The selective reduction of ketone occurrs with sodiumborohydride in the presence of metal chloride provided *S*-propranolol.

Keywords*—S*-propranolol, selective reduction, sodium borohydride, metal chloride

I. Introduction

PROPRANOLOL is a prescribed medicines belonging to a class of compounds known as beta-blockers, which are used to treat hypertension, angina pectoris, glaucoma,anxiety, obesity and other cardiovascular diseases [1,2].Nowadays, these drugs are available in the market in racemate form, in which only the *S*-enantiomer has beta-adrenergic blocking activity[3-6], while the *R*-form merely has a membrane stabilizing effect and is 130 times less active thanthe *S*-analogue[3]. While reports of various methods have been published for synthesizing *S*-propranolol including usage of enzymes for resolution [7], asymmetric hydrogenation with chiral metal complex catalyst [8], asymmetric epoxidation of allyl alcohol [9] and sorbitol [10], employing a polymer supported reagent [11], as well as using $Zn(NO_3)_2$ and (+)-tartaric acid induction in the ring opening step [12]. Several researchers have reported on the synthesis of *(S)*-propranolol *via*a lipase catalyse reaction [13-16] and in the presence of cyclodextrins [17]. However, the multiple steps in each procedure and high cost of the initial materials have increased the cost of manufacturing. In pharmaceutical manufacturing, racemic propranolol is synthesized usingepichlorohydrin (Fig. 1) [7b] as a substrate.

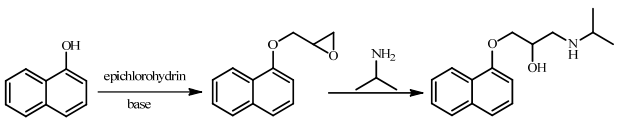

Fig. 1 Synthesis of racemic propranolol in the industrial sector

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Herein we report a straightforward method for preparation of *S*-propranololfrom the recemate*via*selective reduction, which is considered both a simple and inexpensive procedure (Fig. 2).

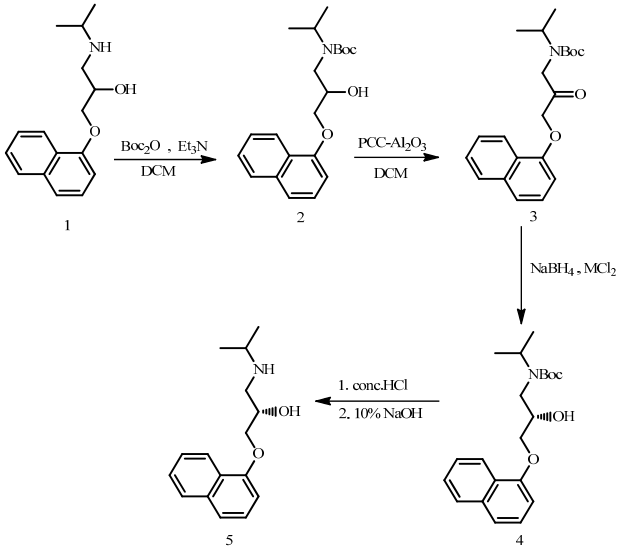

Fig. 2 Synthesis of *S*-propranolol from racemate

II. Experimental Methods

A. Materials

(*R,S*)-propranolol was extracted from propranolol that is available in the market. Pyridiniumchlorochromate and metal chloride were purchased from Aldrich Chemistry. Sodium borohydride was purchased from Labchem. All chemicals and reagents were of analytical reagent grade. Thin-layer chromatography (TLC) was utilized on silica plates 60 $F_{264}$and column chromatography was carried out in 0.063-0.20 mm. silica gel.HRMS analysis was performed on ESI-Q-TOF-MS (Micromass, Manchester, UK). IR spectra were reported on a FT-IR spectrometer (Tensor 27). ^{1}H-NMR spectra were recorded on a BrukerAvance 400 MHz NMR spectrometer, using trimethylsilane as an internal standard. Specific rotation was measured on a ADP 220 polarimeter (Bellingham + Stanley Limited, Tunbridge wells, England).

B. Synthesis of S-propranolol

t-butyl(2-hydroxy-3-(naphthalen-1-yloxy)propyl) (isopropyl)carbamate (2)

To(*R,S)*-propranolol **1** (2.19 g, 8.46mmol) and triethylamine (1.41 ml, 10.1mmol) in dichloromethane (25 ml)

at 0 ◦C, Boc_2O (2.20 ml, 10.1mmol) was added by stirring. The mixture was warmed to room temperature and stirred overnight. The reaction was washed with 10% NaOH and extraction was done with ethyl acetate (3x50 ml). The organic layer was dried with anhydrous sodium sulphate then concentrated under reduced pressure. The residue was purified by column chromatography with neat hexane as an eluent to give*t*-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl)carbamate (2) (2.96 g, 98%) as a pale yellow oil.

t-butylisopropyl(3-(naphthalen-1-yloxy)-2-oxopropyl)carbamate (3)

t-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl)carbamate (2) (0.2 g, 0.56mmol) was dissolved in dichloromethane (10 ml) and pyridiniumchlorochromate(0.24 g, 1.12mmol) was added at 0 ◦C and warmed to room temperature. After refluxing overnight, the mixture was cooled and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography eluted with gradient 5% ethylacetate-hexaneto give t-butyl isopropyl(3-(naphthalen-1-yloxy) -2-oxopropyl) carbamate (3)(0.16 g, 81%) as a paleyellow oil.

S-t-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl) (isopropyl) carbamate (4)

A solution of *t*-butyl isopropyl(3-(naphthalen-1-yloxy) -2-oxopropyl) carbamate (3) (0.20 g, 0.56 mmol), and magnesium chloride(0.23 g, 1.12mmol)in methanol (4 ml) was stirred at room temperature for 30 min. Then sodium borohydride(0.021 g, 0.56mmol) was added proportionately. After the reaction was completed, water was added and extracted with ethyl acetate (3x20 ml). The organic layer was dried with anhydrous sodium sulphate and concentrated under reduced pressure. The crude mixture was purified by column chromatography eluted with 20% ethylacetate-hexane to give *S*-t-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl) (isopropyl) carbamate(4)(0.194 g, 96%) as a pale yellow oil.

S-propranolol (5)

S-t-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl) (isopropyl) carbamate(4) (0.194 g, 0.54mmol) was dissolved in ethanol (3 ml) andconcentrated HCl(excess) was added drop wise at 0 ◦C and stirred for 2 h. After the reaction was completed, water was added and basicified with 10% sodium hydroxide, the resulting mixture was extracted with ethyl acetate (3x20 ml).The organic layer was dried with anhydrous sodium sulphateand concentrated under reduced pressure. The product was purified by recrystallization with hexane to give *S*-propranolol (5)(0.1357 g, 97%) as a white solid.

C. Selective Reduction of t-butyl isopropyl(3-(naphthalen-1-yloxy) -2-oxopropyl) carbamate (3)

The reduction of the compound (3) with sodium borohydride in the presence of various forms of metal chloride at 0 ◦C in methanol was examined.

D. Deprotection of S-t-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl) (isopropyl) carbamate (4)

The deprotection of the compound (4), which was obtained from selective reduction in the presence of various forms of metal chloride, occurred by concentrated hydrochloric acid. The absolute configuration $[\alpha]_D$ and enantiomeric excess (%ee) of selective reduction were determined by correlating the data with those reported in the literature [7b].

III. Results and Discussion

A. Selective Reduction of t-butyl isopropyl(3-(naphthalen-1-yloxy) -2-oxopropyl) carbamate (3)

Togetherness of metal chloride accelerated the reaction and increased the formation of alcohol product (compound 4). The reaction required 30 min at 0 ◦C. The yields of this step are shownin Table I.

TABLE I
Selective Reduction Of (3) In A Presence Of Metal Chloride

Entry	MCl_2	%YIELD
1	-	95
2	$MgCl_2$	96
3	$CaCl_2$	88
4	$SrCl_2$	91
5	$BaCl_2$	93

B. Deprotection of S-t-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl) (isopropyl) carbamate (4)

Going down the periodic table of alkaline earth metallic chlorides, enantiomeric excess (%ee) decreased. The result might be explained by the formation of the rigid transition state for the metal chloride which has a small ionic radius as schematically described in Fig. 3[18].

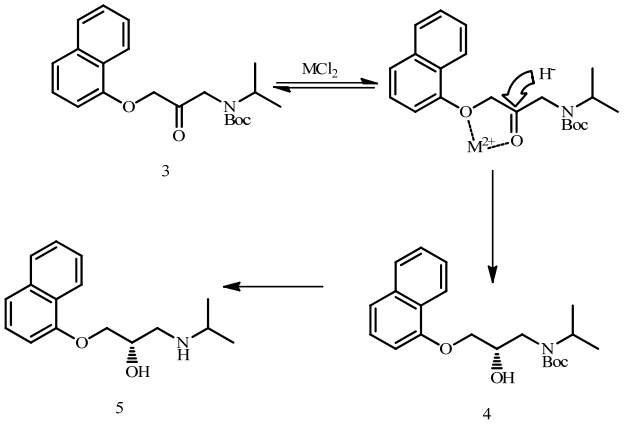

Fig. 3 The formation of a rigid transition state for metal chloride

The ionic radius of metal and were as follows:Mg^{2+} 0.86 A°Ca^{2+} 1.14 A°; Sr^{2+} 1.32 A°; Ba^{2+} 1.49 A°. The %ee of products (5) are shown in Table II.

TABLE II
DEPROTECTION OF (4) IN A PRESENCE OF METAL CHLORIDE

Entry	MCl_2	%YIELD	%ee
1	-	95	27.46
2	$MgCl_2$	97	68.65
3	$CaCl_2$	93	36.62
4	$SrCl_2$	93	27.76
5	$BaCl_2$	94	27.30

t-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl)(isopropyl)carbamate (2)

IR (neat), ν_{max}, 3379, 3056, 2973, 1685, 1403;^{1}H-NMR (400 MHz,$CDCl_3$) 1.20 (6H, dd, *J*= 6.821 Hz, 6.568 Hz), 1.52 (9H, s), 3.46-3.60 (2H, m), 4.00-4.13 (1H,m),4.14-4.32 (3H,m), 5.02-5.24 (1H, br), 6.85 (1H, d, *J*= 7.579 Hz),7.38(1H, t, *J* = 7.579 Hz), 7.42-7.54 (3H, m), 7.78-7.85 (1H,m), 8.20-8.28 (1H, m); ^{13}C-NMR (100 MHz ,$CDCl_3$) 154.1, 134.4, 127.5, 126.3, 125.8, 125.1, 121.6, 120.5, 104.7, 80.6, 71.9, 69.8, 49.5, 48.6, 47.0, 28.4, 20.9; HRMS calcd for $C_{21}H_{29}NO_4$[M+ Na]$^+$382.1994, found 382.2003.

t-butylisopropyl(3-(naphthalen-1-yloxy)-2-oxopropyl)carbamate (3)

IR (neat) , ν_{max}, 3058, 2976, 2930, 1692, 1399, 1166;^{1}H-NMR (400 MHz,$CDCl_3$) 1.20 (6H, dd, *J*= 6.821 Hz),1.40 (9H, s),4.20 (1H, s), 4.45-4.58 (1H, m), 4.80 (1H, s),6.73 (1H, d, *J*= 7.831 Hz), 7.36 (1H, t, *J* = 7.831 Hz),7.45-7.60 (3H, m), 7.78-7.88 (1H,m), 8.29-8.36 (1H, m);^{13}C-NMR (100 MHz ,$CDCl_3$) 202.9, 154.6, 153.4, 134.6, 127.6, 126.7, 125.7, 125.5, 121.6, 121.3, 104.9, 80.1, 72.2, 49.1, 48.7, 28.2, 20.4;HRMS calcd for $C_{21}H_{27}NO_4$ [M+Na]$^+$ 380.1838, found 380.1826.

S-t-butyl (2-hydroxy-3-(naphthalen-1-yloxy)propyl) (isopropyl) carbamate (4)

All data are accordance with compound (2).

S-propranolol (5)

IR (KBr) , ν_{max}, 3477, 3275, 2964, 1628, 1265; ^{1}H-NMR (400 MHz,$CDCl_3$) 1.03 (6H, d, *J*= 6.316 Hz), 2.73-2.82 (2H, m), 2.89-2.95 (1H,m), 4.03-4.14 (3H,m), 6.75 (1H, d, *J*= 6.568 Hz), 7.29 (1H, t, *J*= 7.579 Hz), 7.35-7.45 (3H, m), 7.70-7.75 (1H,m), 8.15-8.19 (1H, m); ^{13}C-NMR (100 MHz ,$CDCl_3$) 154.4, 134.5, 127.5, 126.4, 125.8, 125.2, 121.8, 120.6, 104.9, 70.7, 68.6, 49.5, 48.9, 23.2, 23.0; HRMS calcd for $C_{16}H_{21}NO_2$ [M+1]$^+$ 260.1650, found 260.1651. mp. 90-92 °C.; %ee 68.65 %

IV. CONCLUSION

The selective reduction of ketone compound (3)with sodium borohydride in the presenceof various forms of metal chloride can produce *S*-propranolol. This method is considerd both convenient and economical enough to proceed with.

ACKNOWLEDGMENT

Financial assistance for this work was provided by Rajamangala University of Technology Lanna Nan. We thank The Graduate School and Department of Chemistry, Faculty of Science, Chiang Mai University for the provision of chemical substances and facilities.

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