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

R. Inkum, A. Teerawutgulrag, P. Puangsombat, N. Rakariyatham

Abstract—Propranolol is worldwide hypertension drug that is active in S-isomer. Patients must use this drug throughout their lives, and this action employs a 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-tert-butyl dicarbonate and then the product is oxidized with pyridinium chlorochromate. The selective reduction of ketone occurs with sodium borohydride in the presence of metal chloride provided S-propranolol.

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

I. INTRODUCTION

PROPRANOLOL is a prescribed medicine 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 stabilising effect and is 130 times less active than the 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(NO₃)₂ and (+)-tartaric acid induction in the ring opening step [12]. Several researchers have reported on the synthesis of (S)-propranolol via lipase catalyse reaction [13-16] and in the presence of cycloexdetrins [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 using pichlorohydrin (Fig. 1) [7b] as a substrate.

Herein we report a straightforward method for preparation of S-propranolol from the racemate 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. Pyridinium chlorochromate 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 F254 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). ¹H-NMR spectra were recorded on a Bruker Avance 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-buty1(2-hydroxy-3-(napthalen-1-yl oxy) propyl) (isopropyl) carbamate (2)

To (R,S)-propranolol 1 (2.19 g, 8.46 mmol) and triethylamine (1.41 ml, 10.1 mmol) in dichloromethane (25 ml)
at 0 °C, Boc₂O (2.20 ml, 10.1 mmol) 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 hexane as an eluent to give t-butyl isopropyl (3-(naphthalen-1-ylxyo)-2-oxopropyl) carbamate (2) (2.96 g, 98%) as a pale yellow oil.

\[ t\text{-butyl isopropyl}(3\text{-(naphthalen}-1\text{-ylxyo})\text{-2-oxopropyl})\text{carbamate} \]

A solution of t-butyl isopropyl(3-(naphthalen-1-ylxyo))-2-oxopropyl carbamate (2) (0.2 g, 0.56 mmol) was dissolved in dichloromethane (10 ml) and pyridinium chlorochromate (0.24 g, 1.12 mmol) 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% ethyl acetate-hexane to give t-butyl isopropyl(3-(naphthalen-1-ylxyo))-2-oxopropyl carbamate (3)(0.16 g, 81%) as a pale yellow oil.

**Selectivity Reduction or (3) in a Presence of Metal Chloride**

<table>
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<th>MCl₂</th>
<th>%Yield</th>
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<tr>
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<tr>
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<tr>
<td>4</td>
<td>BaCl₂</td>
<td>93</td>
</tr>
</tbody>
</table>

**C. Selective Reduction of t-butyl isopropyl(3-(naphthalen-1-ylxyo))-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-ylxyo)(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 [α]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-ylxyo)-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 shown in Table I.

**B. Deprotection of S-t-butyl (2-hydroxy-3-(naphthalen-1-ylxyo)(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].

The data of Table I was compared with those reported in the literature [7b].

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

The ionic radius of metal and were as follows: Mg²⁺ 0.86 Å; Ca²⁺ 1.14 Å; Sr²⁺ 1.32 Å; Ba²⁺ 1.49 Å. The %ee of products (5) are shown in Table II.
The selective reduction of ketone compound (3) with sodium borohydride in the presence of various forms of metal chloride can produce S-propranolol. This method is considered both convenient and economical enough to proceed with.

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REFERENCES


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