An alternative synthesis of (+)-propranolol and (+)-atenolol

Rachaneebhorn Inkum, Aphiwat Teerawutgulrag*, Pakawan Puangsombat and Nuansri Rakariyatham

Department of Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai 50200 Thailand

* Corresponding author, e-mail: aphiwattee@yahoo.co.uk

Received: 14 February 2012 / Accepted: 12 October 2012 / Published: 15 October 2012

Abstract: Herein, a simple synthesis pathway of beta-blockers starting from allyl amine is presented. This synthesis features the opening of an epoxide ring with phenol derivatives followed by N-alkylation with iso-propylbromide to produce racemic propranolol and atenolol.

Keywords: beta-blockers, propranolol, atenolol

INTRODUCTION

Propranolol and atenolol are 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 racemic form, in which only the S-enantiomer possesses 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 various methods have been published for the purpose of synthesising racemic propranolol [7-11], the disadvantages are employing harsh conditions, multiple steps synthesis or complicated catalyst preparation, while the atenolol synthesis pathway requires a high temperature [12,13]. Several methods have been reported on the synthesis of (S)-propranolol and (S)-atenolol including the use of enzymes for resolution [14], asymmetric hydrogenation with chiral metal complex catalysts [15], asymmetric epoxidation of allyl alcohol [16] and sorbitol [17], employing a polymer supported reagent [9], as well as using Zn(NO₃)₂ and (+)-tartaric acid induction in the ring opening step [18]. Several researchers have reported on the synthesis of (S)-propranolol via lipase catalysed reaction [19-22] and in the presence of cyclodextrins [23]. However, the multiple steps in each procedure and the high cost of starting materials have increased the expense of manufacturing.
In pharmaceutical manufacturing, racemic propranolol is synthesised using epichlorohydrin (scheme 1) [14b]. A straightforward method for the preparation of racemic propranolol and atenolol as an inexpensive procedure is reported.

![Scheme 1. Industrial synthesis of racemic propranolol](image)

**MATERIALS AND METHODS**

Molecular sieves (4A, Fluka) were activated by heating in an oven at 120°C for 12 hr. α-Naphthol (May&Baker Ltd Dagenham England), was purified by sublimation. p-Hydroxyphenyl acetamide was purchased from Aldrich. Allyl amine and isopropyl bromide were distilled and stored in a desiccator. All solvents were distilled prior to use.

The reaction mixture was washed with 10% NaOH and then concentrated under reduced pressure. The residue was purified by column chromatography with an eluent to give t-butyl oxiran-2-ylmethylcarbamate (3) as a pale yellow liquid. IR (neat) , νmax 3352, 2980, 1700, 1249; 1H-NMR (400 MHz ,CDCl3) 1.42 (9H, s), 2.56-2.59 (1H, m), 2.75-2.78 (1H, m), 3.04-3.10 (1H, m), 3.78 (2H, m), 5.76 (1H, m); 13C-NMR (100 MHz, CDCl3) 155.8, 134.9, 115.6, 79.3, 43.0, 28.4; HRMS calcd for C₈H₁₃NO₂Na [M+ Na]+ 180.1000, found 180.0997.
3.15-3.23 (1H, m), 3.45-3.57 (1H, m), 4.70-4.85 (1H, br); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)) 155.9, 79.6, 50.7, 44.9, 41.8, 28.3; HRMS calcld for C\(_{16}\)H\(_{16}\)NO\(_3\) [M+H]\(^+\) 174.1130, found 174.1132.

**t-Butyl 2-Hydroxy-3-(naphthalen-1-loylo)propylcarbamate (4a)**

\(\alpha\)-Naphthol (0.28 g, 1.98 mmol) was added to the solution of potassium hydroxide (0.11g, 1.98 mmol) in water (3 mL) and epoxide 3 (0.28 g, 1.65 mmol) in tetrahydrofuran at 0°C. The reaction mixture was stirred at room temperature overnight. After neutralisation with 2 N HCl at 0°C, the resulting mixture was extracted with ethyl acetate (3x20 mL). The obtained layer was evaporated to dryness to give a crude product. The resulting crude product was purified by column chromatography eluted with a gradient of ethyl acetate-hexane (3% -30%) to give \(t\)-butyl 2-hydroxy-3-(naphthalen-1-loylo) propylcarbamate 4a (0.40 g, 77%) as a pale brown solid. mp. 80-82°C. IR (KBr), \(\nu_{\text{max}}\) 3367, 3055, 2978, 1694, 1270, 1170; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) 1.46 (9H, s), 3.30-3.48 (1H, m), 3.48-3.63 (2H, m), 4.12-4.17 (2H, m), 4.25-4.35 (1H, br), 5.00-5.10 (1H, br), 6.82 (1H, d, \(J=7.2\) Hz), 7.37 (1H, \(t, J=7.2\) Hz), 7.44-7.52 (3H, m), 7.81 (1H, d, \(J=8.0\) Hz), 8.18 (1H, d, \(J=8.0\) Hz); \(^{13}\)C-NMR (100 MHz CDCl\(_3\)) 157.3, 154.1, 134.5, 127.6, 126.5, 125.8, 125.4, 121.7, 120.8, 105.0, 80.0, 70.0, 69.7, 43.9, 28.4; HRMS calcld for C\(_{18}\)H\(_{23}\)NO\(_4\)Na [M+Na]\(^+\) 340.1525, found 340.1519.

**t-Butyl 3-(4-(2-Amino-2-oxoethyl)phenoxy)-2-hydroxypropylcarbamate (4b)**

\(p\)-Hydroxyphenyl acetamide (0.21 g, 1.38 mmol) was added to the solution of potassium hydroxide (0.08 g, 1.38 mmol) in water (2.2 mL) and epoxide 3 (0.20 g, 1.16 mmol) at 0°C. The reaction mixture was stirred at room temperature overnight. After neutralisation with 2N HCl at 0°C, the resulting mixture was extracted with ethyl acetate (3x20 mL). The obtained layer was evaporated to dryness to give a crude product. The resulting crude product was purified by column chromatography eluted with a gradient of ethyl acetate-hexane (10%-50%) to give \(t\)-butyl 3-(4-(2-amino-2-oxoethyl)phenoxy)-2-hydroxypropylcarbamate 4b (0.37 g, 84%) as a white solid. mp. 128-130°C. IR(KBr), \(\nu_{\text{max}}\) 3361, 3179, 2978, 1694, 1246; \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)) 1.37 (9H, s), 2.94-3.14 (2H, m), 3.27 (2H, s), 3.74-3.90 (3H, m), 5.08-5.14 (1H, br), 6.82 (2H, d, \(J=8.3\) Hz), 7.15 (2H, d, \(J=8.3\) Hz), 7.32-7.40 (1H, br); \(^{13}\)C-NMR (100 MHz, DMSO-\(d_6\)) 172.6, 157.3, 155.8, 129.9, 128.5, 114.2, 77.7, 70.4, 68.2, 43.5, 41.4, 28.2; HRMS calcld for C\(_{16}\)H\(_{24}\)N\(_2\)O\(_2\)Na [M+Na]\(^+\) 347.1583, found 347.1581.

**1-Amino-3-(naphthalen-1-loylo)propan-2-ol (5a)**

Trifluoroacetic acid (2 mL) was added to a solution of \(t\)-butyl 2-hydroxy-3-(naphthalen-1-loylo) propylcarbamate 5 (0.40 g, 1.28 mmol) in dichloromethane (2 mL) at 0°C. After the solution was stirred for 2 hr, the mixture was concentrated under reduced pressure. Then the resulting crude mixture was basified with 10% NaOH, and was extracted with ethyl acetate (3x20 mL). The organic layer was dried with anhydrous sodium sulphate and was concentrated in vacuo to give 1-amino-3-(naphthalen-1-loylo) propan-2-ol 5a (0.32 g, quantitative yield) as a pale yellow solid. mp. 78-80°C. IR (KBr), \(\nu_{\text{max}}\) 3363, 3275, 1581, 1265; \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)) 2.68-2.76 (1H, m), 2.80-2.88 (1H, m), 3.87-3.94 (1H, m), 4.02-4.14 (2H, m), 6.95 (1H, d, \(J=7.3\) Hz), 7.37-7.55 (4H, m), 7.85 (1H, d, \(J=7.3\) Hz), 8.22 (1H, m); \(^{13}\)C-NMR (100 MHz, DMSO-\(d_6\)) 154.7, 134.5, 127.8, 126.9, 126.7, 125.6, 122.3, 120.3, 106.0, 70.9, 70.8, 45.2; HRMS calcld for C\(_{13}\)H\(_{16}\)NO\(_2\) [M+H]\(^+\) 218.1180, found 218.1181.
2-(4-(3-Amino-2-hydroxypropoxy)phenyl) Acetamide (5b)

HCl gas was bubbled through a solution of t-buty 3-(4-(2-amino-2-oxoethyl)phenoxy)-2-hydroxypropylcarbamate 4b (0.40 g, 1.23 mmol) in methanol (2 mL) at 0°C. After the reaction was completed, the mixture was concentrated under reduced pressure. Then, the product was basicified with triethylamine and the solution was concentrated in vacuo. The resulting crude mixture was purified by column chromatography with a gradient of dichloromethane-methanol (10-30%) to give 2-(4-(3-amino-2-hydroxypropoxy)phenyl) acetamide 5b (0.29 g, quantitative yield) as a pale yellow solid. mp. 218-220 C. IR (KBr), ν_max 3356, 3176, 1639, 1247; 1H-NMR (400 MHz, DMSO-d_6) 2.76-2.84 (1H, dd, J=12.9 Hz), 2.99 (1H, dd, J= 12.9 Hz), 3.29 (2H, s), 3.90-3.94 (2H, m), 3.98-4.06 (1H, m), 6.80-6.84 (1H, br), 6.87 (2H, d, J= 8.6 Hz), 7.17 (2H, d, J= 8.6 Hz) 7.40-7.46 (1H, br); 13C-NMR (100 MHz, DMSO-d_6) 172.7, 156.9, 130.1, 128.8, 114.3, 69.6, 65.9, 41.9, 41.3; HRMS calcd for C_{21}H_{23}N_3O_3 [M+H]^+ 225.1239, found 225.1240.

Propranolol (6a)

A suspension of 1-amino-3-(naphthalen-1-yloxy) propan-2-ol 5a (0.10 g, 0.46 mmol), molecular sieves 4 (0.135 g) and cesium hydroxide (0.15 g, 0.92 mmol) in dimethylformamide (2.24 mL) was stirred at room temperature for 30 min. Then isopropyl bromide (0.43 mL, 4.60 mmol) was added dropwise. After the reaction was completed, 1 N HCl was added and the mixture was extracted with ethyl acetate (3x5 mL). The organic layer was dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by column chromatography and eluted with a gradient of dichloromethane-methanol (0-3%) to give propranolol 6a (0.0838 g, 70%) as a white solid. mp. 90-92 C (Lit [8] mp. 93-94 C). IR (KBr), ν_max 3477, 3275, 2964, 1628, 1265; 1H-NMR (400 MHz, CDCl_3) 1.44 (6H, d, J= 6.3 Hz), 2.85-2.96 (2H, m), 2.89-2.95 (1H, m), 4.09-4.15 (1H, m), 4.16-4.28 (2H, m), 6.75 (1H, d, J= 7.6 Hz), 7.35 (1H, t, J= 7.6 Hz), 7.42-7.52 (3H, m), 7.78-7.82 (1H, m), 8.15-8.19 (1H, m); 13C-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_{13}H_{22}NO_2 [M+H]^+ 260.1650, found 260.1651.

Atenolol (6b)

A solution of 2-(4-(3-amino-2-hydroxypropoxy) phenyl) acetamide 5b (0.20 g, 0.89 mmol), molecular sieves 4 (0.135 g) and cesium hydroxide (0.18 g, 1.07 mmol) in dimethylformamide (4.48 mL) was stirred at room temperature for 30 min. Then isopropyl bromide (0.84 mL, 8.92 mmol) was added dropwise. After completion, the mixture was filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography with a gradient of dichloromethane-methanol (10-30%) to give atenolol 6b (0.13 g, 60%) as a white solid. mp. 148-150 C (Lit [24] 148-150 C). IR (KBr), ν_max 3360, 2916, 1635, 1242; 1H-NMR (400 MHz, DMSO-d_6) 0.98 (6H, d, J= 6.3 Hz), 2.54-2.58 (1H, m), 2.64-2.74 (2H, m), 3.29 (2H, s), 3.80-3.86 (2H, m), 3.88-3.94 (1H, m), 6.84 (2H, d, J= 8.8 Hz), 7.14 (2H, d, J= 8.8 Hz), 7.38-7.42 (1H, br); 13C-NMR (100 MHz, DMSO-d_6) 172.6, 156.8, 130.1, 128.9, 114.3, 69.8, 65.4, 49.8, 46.8, 41.3, 19.1, 18.5; HRMS calcd for C_{14}H_{23}N_2O_3 [M+H]^+ 267.1709, found 267.1707.
RESULTS AND DISCUSSION

Treatment of allyl amine 1 with t-butyl dicarbonate (Boc₂O) in the presence of triethylamine at room temperature gave t-butyl allylcarbamate 2 in 98% yield. After epoxidation of 2 with m-chloroperbenzoic acid, t-butyl oxiran-2-ylmethylcarbamate 3 was attained with 88% yield. The epoxide ring opening of 3 with phenol derivatives and an aqueous solution of potassium hydroxide provided 4a and 4b in yields of 77% and 84% respectively. Deprotection of the Boc group in 4a and 4b was performed under acidic conditions (trifluoroacetic acid for 4a and HCl gas for 4b) in quantitative yields. The desired amines were reacted with iso-propylbromide and cesium hydroxide in dimethylformamide yielding propranolol 6a (70%) and atenolol 6b (60%) (Scheme 2).

CONCLUSIONS

An alternative route for the synthesis of racemic propranolol and atenolol has been developed compared to previous reports. This pathway is simple, inexpensive and mild conditions could be used.

ACKNOWLEDGEMENTS

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 chemicals and use of their facilities.

REFERENCES


© 2012 by Maejo University, San Sai, Chiang Mai, 50290 Thailand. Reproduction is permitted for noncommercial purposes.