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Full Paper

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

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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 $Zn(NO_3)_2$ 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.

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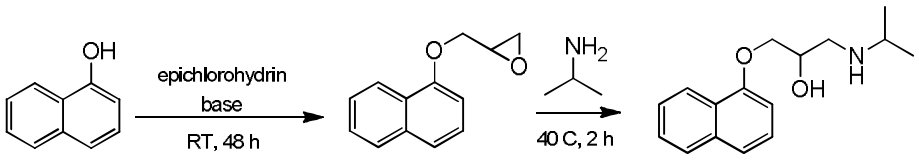
In pharmaceutical manufacturing, racemic propranolol is synthesised using epichlorohydrin (scheme 1) [14b]. A straightforward method for the preparation of racemic propranolol and atenolol as an inexpensive procedure is reported.



Scheme 1. Industrial synthesis of racemic propranolol

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. Thin-layer chromatography (TLC) was utilised on silica plates 60 F_{264} and column chromatography was carried out on 0.063-0.20 mm silica gel.

Melting points were determined on MEL-TEMP Laboratory Devices INC., USA and have not been corrected. 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 Bruker Avance 400 MHz NMR spectrometer, using trimethylsilane as an internal standard.

t-Butyl Allyl Carbamate (2)

To a stirred solution of allyl amine **1** (3.00 g, 52.5 mmol) and triethylamine (9.5 mL, 68.0 mmol) in dichloromethane (10 mL) at 0°C, Boc_2O (15.6 mL, 68.0 mmol) was added. The mixture was warmed to room temperature and stirred overnight. The reaction was washed with 10% NaOH and then extracted 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 allyl carbamate **2** (8.1 g, 98%) as a colorless solid. mp. 35-36° C. IR (neat), ν_{max} 3347, 2979, 1690, 1244; ^{1}H-NMR (400 MHz , $CDCl_3$) 1.43 (9H, s), 3.66-3.78 (2H, m), 4.54-4.72 (1H, br), 5.05-5.20 (2H, m), 5.76-5.88 (1H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 155.8, 134.9, 115.6, 79.3, 43.0, 28.4; HRMS calcd for $C_8H_{15}NO_2Na$ $[M+ Na]^+$ 180.1000, found 180.0997.

t-Butyl Oxiran-2-ylmethylcarbamate (3)

t-Butyl allyl carbamate **2** (3.00 g, 19.0 mmol) was dissolved in dichloromethane (10 mL) and *m*-chloroperbenzoic acid (6.59 g, 38.0 mmol) was added at 0°C and the reaction mixture was warmed to room temperature. After heating at reflux for 5 hr, the mixture was cooled and saturated sodium thiosulphate was added dropwise. The mixture was washed with saturated sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic phase was dried, concentrated under reduced pressure and purified by column chromatography to give *t*-butyl oxiran-2-ylmethylcarbamate **3** (3.3 g, 88%) as a pale yellow liquid. IR (neat) , ν_{max} 3352, 2980, 1700, 1249; ^{1}H-NMR (400 MHz ,$CDCl_3$) 1.42 (9H, s), 2.56-2.59 (1H, m), 2.75-2.78 (1H, m), 3.04-3.10 (1H, m),

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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 calcd for $C_8H_{16}NO_3$ $[M+H]^+$ 174.1130, found 174.1132.

_t_-Butyl 2-Hydroxy-3-(naphthalen-1-yloxy)propylcarbamate (4a)

α-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-yloxy) propylcarbamate **4a** (0.40 g, 77%) as a pale brown solid. mp. 80-82°C. IR (KBr), ν_{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 calcd for $C_{18}H_{23}NO_4Na$ $[M+Na]^+$ 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), ν_{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 calcd for $C_{16}H_{24}N_2O_5Na$ $[M+Na]^+$ 347.1583, found 347.1581.

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

Trifluoroacetic acid (2 mL) was added to a solution of *t*-butyl 2-hydroxy-3-(naphthalen-1-yloxy) 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-yloxy) propan-2-ol **5a** (0.32 g, quantitative yield) as a pale yellow solid. mp. 78-80°C. IR (KBr), ν_{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 calcd for $C_{13}H_{16}NO_2$ $[M+H]^+$ 218.1180, found 218.1181.

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2-(4-(3-Amino-2-hydroxypropoxy)phenyl) Acetamide (5b)

HCl gas was bubbled through a solution of *t*-butyl 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 dichlorimethane-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; ^{1}H-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); ^{13}C-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 $C_{11}H_{17}N_2O_3$ $[M+H]^+$ 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 dichlorimethane-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; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.14 (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); ^{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 $C_{16}H_{22}NO_2$ $[M+H]^+$ 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; ^{1}H-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); ^{13}C-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 $C_{14}H_{23}N_2O_3$ $[M+1]^+$ 267.1709, found 267.1707.

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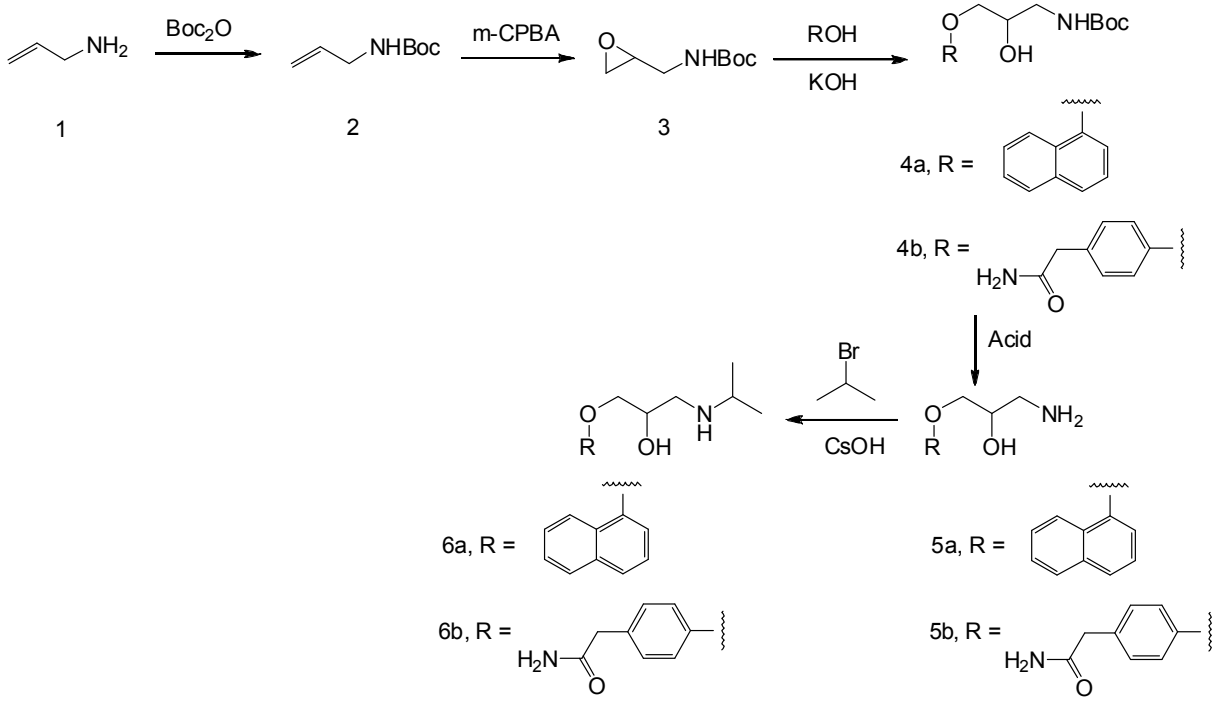
RESULTS AND DISCUSSION

Treatment of allyl amine **1** with *t*-butyl dicarbonate (Boc_2O) 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).



Scheme 2. A synthetic route to beta-blockers

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.

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