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Synthesis of carvedilol *via* 1-(9*H*-carbazol-4-yloxy)-3-(*N*-(2-(2-methoxy phenoxy)ethyl)-N-(4-methoxybenzyl) amino) propan-2-ol

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ABSTRACT

Synthesis of carvedilol is described to avoid the formation of bis impurity (disclosed in EUROPEAN PHARMACOPOEIA 6.0, Volume 2.0 as Impurity B) by choosing a simple 2-(2-methoxyphenoxy)-*N*-(4-methoxybenzyl) ethanamine to open the oxirane ring of 4-((oxiran-2-yl) methoxy)-9*H*-carbazole gave the tertiary amine, 1-(9*H*-carbazol-4-yloxy)-3-(*N*-(2-(2-methoxyphenoxy)ethyl)-*N*-(4-methoxybenzyl)amino) propan-2-ol. Removal of the *N*-*p*-methoxybenzyl (PMB) group in the tertiary amine is achieved easily and completely to get the targeted carvedilol with high purity.

KEYWORDS

Carvedilol;
Impurity B;
Secondary amine;
p-methoxybenzyl (PMB) group;
Oxirane.

INTRODUCTION

Carvedilol (Figure 1) is a third-generation, nonselective β-blocker that also possesses α_1-adrenergic blocking[1], antioxidant[2] and calcium antagonist properties[3]. Carvedilol blocks both the β_1- and β_2-adrenergic receptors, resulting in improved myocardial function and attenuation (or reversal) of adverse myocardial remodeling in heart failure[4]. Carvedilol also reduces peripheral vascular resistance *via* vasodilation caused by antagonism of α_1-adrenergic receptors[3]. Several syntheses of carvedilol are reported in the literature[5]. Major draw back in all the approaches is the formation of impurity B (Figure 1). In order to avoid the formation of impurity B, various attempts were performed in the literature[6-8]. Eventhough the formation of impurity B was avoided, the preparation is multi step and tedious.

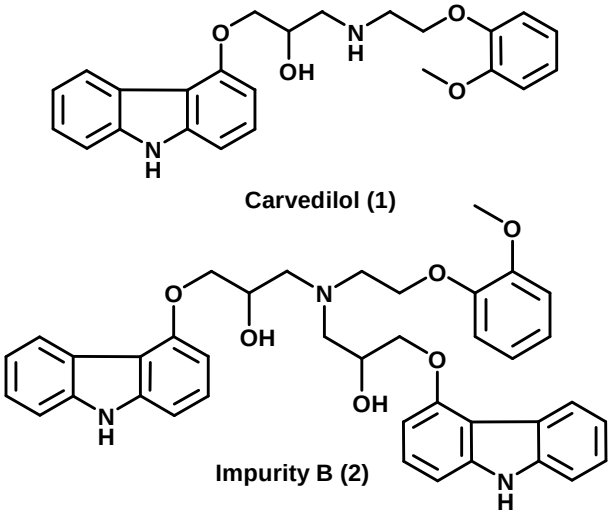

Figure 1 : Structures of carvedilol (1) and impurity B (2)

EXPERIMENTAL

Melting points were determined on Buchi 540 melt-

ing point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR Instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H NMR spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6 as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C.

Preparation of 1-(2-chloroethoxy)-2-methoxy benzene (4)

To a stirred solution of aqueous sodium hydroxide (145.5g NaOH in 750mL water) and tetrabutylammoniumbromide (TBAB) (10.5g, 0.0326 mol), 2-methoxyphenol (150g, 1.2 mol) was added at room temperature. The reaction mixture was heated to 50°C and added 1,2-dichloroethane (750.0mL) at 50°C for 30 min. The reaction mixture was heated to reflux and maintained at the same temperature for 4 h. Then the reaction mixture was cooled to 25°C and separated the dichloroethane layer. The separated dichloroethane layer was washed with 10% NaOH solution and distilled under reduced pressure at 80°C gave syrupy mass. Yield: 210g (93%).

^{1}H NMR (DMSO-d_6): δ 3.7 (s, 3H), 3.9 (t, 2H), 4.2 (t, 2H), 6.8-7.0 (m, 4H).IR (KBr)cm^{-1}: 2947, 2361, 1510, 1227, 1125 733; MS (m/e): 186 [M$^+$].

Preparation of 2-(2-(2-methoxyphenoxy) ethyl) isoindoline-1, 3-dione (5)

To the compound 4 (200.0g, 1.072 mol), potassium phthalimide (218.4g, 1.178 mol) was added at 130°C over 45 min and the reaction was maintained at 130-140°C for 90 min. The reaction mixture was cooled to 50°C, diluted with water (400mL), filtered and washed the precipitate with water (400.0mL). Isolated crude product was recrystallized from isopropanol to obtain compound 5. Yield: 210g (66%).

^{1}H NMR (DMSO-d_6): δ 3.6 (s, 3H), 3.8-4.0 (t, 2H), 4.2 (t, 2H), 6.8-7.0 (m, 4H), 7.8-8.0 (m, 4H). IR (KBr)cm^{-1}: 3460, 2360, 1714, 1505, 1126, 720; MS (m/e): 298 [M$^+$+1].

Preparation of 2-(2-methoxyphenoxy)ethanamine (6)

To a stirred solution of compound 5 (200g, 0.673 mol) in water (600mL), 40% aqueous methylamine (146mL, 1.68 mol) was added and the reaction mixture was heated to 80°C for 75 min. The reaction mixture was cooled to 25°C and acidified using conc. HCl (136mL, pH 1). The reaction mixture was washed with dichloromethane (2 × 200mL) and aqueous layer was basified using aqueous 2.5M sodium hydroxide (pH 11-12) at 25 °C. The product was extracted with dichloromethane (2 × 200mL) and combined organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure at 30 °C gave the compound 6 as a liquid. Yield: 94g (83.5%).

^{1}H NMR (DMSO-d_6): δ 1.4 (br, 2H), 2.9 (t, 2H), 3.7 (s, 3H), 3.9 (t, 2H), 6.8-7.0 (m, 4H). IR (KBr)cm^{-1}: 3446, 2872, 1508, 1257, 1119, 1018, 745; MS (m/e): 168 [M$^+$+1].

Preparation of 2-(2-methoxyphenoxy)-N-(4-methoxybenzyl)ethanamine (3)

To a stirred solution of *p*-methoxybenzaldehyde (7.3g, 0.056 mol) in ethanol (50mL), 2-(2-methoxyphenoxy)ethanamine (6) (10g, 0.059 mol) was added at 25°C and maintained the reaction at same temperature for 4 h. Then the reaction mixture was cooled to 0-5°C, $NaBH_4$ was added slowly portion wise to the reaction mixture at 0-5°C and maintained at this temperature for 6 h. The reaction mixture was quenched with cold water at same temperature. Filter the reaction mass and the filtrate was extracted with toluene (3 × 50.0mL), distill the toluene under reduced pressure gave the product 3. Yield: 13.75g (80%).

^{1}H NMR (DMSO-d_6): δ 2.2 (br, 1H), 2.8 (m, 2H), 3.7 (s, 2H), 3.8 (s, 6H), 4.0 (t, 2H), 6.9-7.3 (m, 8H). IR (KBr)cm^{-1}: 3422, 2936, 2834, 1507, 1125, 747; MS (m/e): 288 [M$^+$+1].

Preparation of 4-((oxiran-2-yl)methoxy)-9H-carbazole (8)

To a stirred solution of 2 M aqueous sodium hydroxide (225mL), 4-hydroxycarbazole (75.0g, 0.409 mole) was added at 25°C. Dimethylsulfoxide (DMSO) (112.5mL) was added to the reaction mixture at 28°C over 15 min. The reaction mixture was slowly heated to 45°C and 2-(chloromethyl)oxirane (56.8g, 0.614 mol) was added at same temperature over 45 min, followed by maintained at 45°C for 8 h. The reaction mix-

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ture was cooled to 25°C and diluted slowly with water (300mL). The reaction mass was filtered and washed with water (2 × 75.0mL) gave crude product. Crude product was crystallized from isopropanol (225.0mL) to obtain the compound 8. Yield: 70g (71.5%). M.P.: 121-126°C.

^{1}H NMR (DMSO-d_6): δ 3.0 (m, 2H), 3.3 (m, 1H), 4.1 (dd, 1H), 4.6 (dd, 1H), 6.7-8.2 (m, 7H), 11.3 (s, 1H).IR (KBr)cm^{-1}: 3296, 2928, 1609, 1509, 1099, 725; MS (m/e): 240 [M$^+$+1].

Preparation of 1-(9H-carbazol-4-yloxy)-3-(N-(2-(2-methoxyphenoxy)ethyl)-N-(4-methoxy benzyl) amino) propan-2-ol (9)

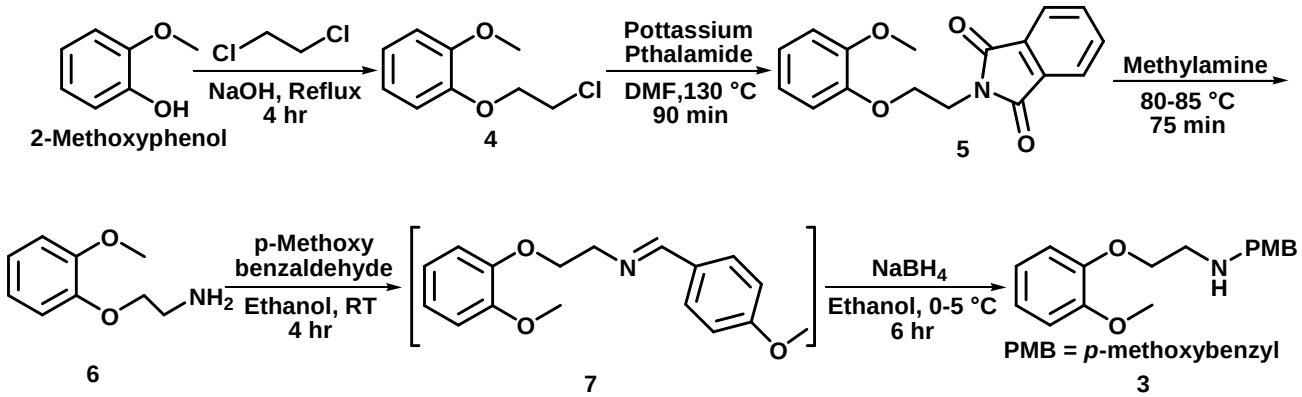
To a stirred solution of 2-(2-methoxyphenoxy)-N-(4-methoxybenzyl)ethanamine (3) (132.2g, 0.460 mol) in ethanol (100mL), 4-((oxiran-2-yl)methoxy)-9H-carbazole (100g, 0.418 mol) was added. The reaction mixture was stirred at 25°C for 12 h. The solid was filtered and washed with chilled ethanol to obtain compound 9 as a fine solid. Yield: 176g (80%). M.P.: 120-122°C.

^{1}H NMR (DMSO-d_6): δ 2.8-3.0 (m, 4H), 3.6 (s, 6H), 3.7-4.3 (m, 7H), 5.0 (s, 1H), 6.6-7.4 (m, 14H), 8.2 (d, 1H), 11.2 (s, 1H). IR (KBr)cm^{-1}: 3402, 2924, 2834, 1593, 1506, 1125, 1111, 747; MS (m/e): 527 [M$^+$+1].

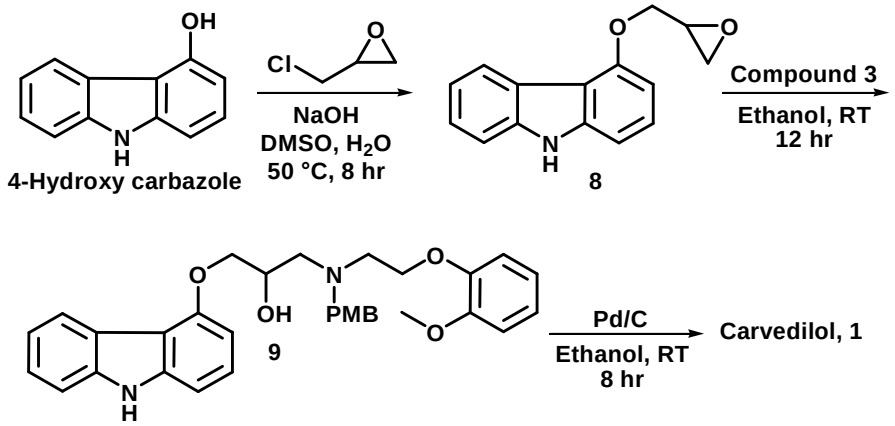
Preparation of 1-(2-(2-methoxyphenoxy)ethyl-amino)-3-(9H-carbazol-4-yloxy)propan-2-ol (carvedilol, 1)

To a stirred solution of compound 9 (100g, 0.19 mol) in ethanol (500mL), 10% Pd/C (10g, dry reduced) was added. The reaction mixture was vigorously stirred under a hydrogen atmosphere (40 psi) at room temperature for 8 h. The reaction mixture was filtered, washed with ethanol (2 × 50mL) and the filtrate is evaporated under reduced pressure. The obtained solid was recrystallized from ethyl acetate gave the carvedilol 1. Yield: 73.3g (95.0%). M.P.: 114-116°C.

^{1}H NMR (DMSO-d_6): δ 2.0 (s, 1H), 2.8-3.0 (m, 4H), 3.75 (s, 3H), 4.0-4.2 (m, 5H), 5.2 (s, 1H), 6.7-7.2 (m, 10H), 8.2 (s, 1H), 11.2 (s, 1H). IR (KBr)cm^{-1}: 3344, 2923, 1590, 1504, 1255, 1099, 750; MS (m/e): 407 [M$^+$+1].



Scheme 1



Scheme 2

RESULTS AND DISCUSSION

The synthesis of 2-(2-methoxyphenoxy)-*N*-(4-methoxybenzyl)ethanamine (3) is described. 2-Methoxyphenol on reaction with 1,2-dichloroethane in the presence of sodium hydroxide at reflux condition gave 1-(2-chloroethoxy)-2-methoxybenzene (4). The obtained chloro compound (4) was converted to amine (6) by the reaction of potassium phthalimide in N,N-dimethylformamide (DMF) at 130°C followed by removal of the phthaloyl group using methylamine at 85°C to give 2-(2-methoxy- phenoxy)ethanamine (6). This ethanamine was converted to imine (7) by reaction with p-methoxy benzaldehyde in ethanol followed by *in-situ* reduction of the imine with $NaBH_4$ to give the targeted 2-(2-methoxyphenoxy)-N-(4-methoxybenzyl)ethanamine (3) (Scheme 1).

Previously, the opening of 8 by using 2-(2-methoxyphenoxy)-N-benzylethanamine followed by the deprotection of the obtained 1-(9H-carbazol-4-yloxy)-3-(N-(2-(2-methoxy-phenoxy)ethyl)-N-benzylamino) propan-2-ol using Pd/C to give carvedilol (1) was reported[6]. This approach is versatile to avoid the formation of impurity B, at the same time it also suffers the presence of trace amount of impurity C (N-benzyl impurity and its limit is 0.02 % by lc) in the carvedilol. It is very difficult to avoid or complete removal of the impurity C in the preparation of carvedilol. Although the described approach is superior, the industrial chemists are not interested to follow this approach for the preparation of carvedilol in view of lower limit of impurity C (0.02% by lc).

Herein is reported the synthesis of carvedilol (Scheme 2) by following the analogous approach by choosing the versatile secondary amine, 2-(2-methoxyphenoxy)-N-(4-methoxybenzyl) ethanamine (3), instead of 2-(2-methoxyphenoxy)-N-benzyl ethanamine while opening the oxirane ring of 8. By the selection of the 3, the obtained tertiary amine, 1-(9H-carbazol-4-yloxy)-3-(N-(2-(2-methoxy phenoxy)ethyl-N-(4-methoxybenzyl) amino) propan-2-ol (9), is completely converted to carvedilol in the deprotection reaction and no traces of 9 was observed in the isolated carvedilol. Several reaction conditions were screened for the removal of p-methoxybenzyl group in the tertiary amine. Removal of the PMB group under oxidative conditions such as ceric ammonium nitrate (CAN) was unsuccessful and this was achieved by using the standard condition, Pd/C in ethanol (Scheme 2).

CONCLUSION

In conclusion, an efficient and commercial viable preparative method is developed for carvedilol 1 with high purity (with out impurity B) by choosing a simple 2-(2-methoxyphenoxy)-N-(4-methoxybenzyl) ethanamine to open the oxirane ring of 4-((oxiran-2-yl) methoxy)-9*H*-carbazole.

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