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A New and Alternate Synthesis of Carvedilol: An Adrenergic receptor

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ABSTRACT

A New and alternate synthesis of carvedilol, β-adrenergic blocking agent is reported and finalized the meritorious one. The key step in this approach is synthesis of o-protected 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol ***6a, 6b****, by protecting the alcohol group with acetyl and tertiarybutyldimethylsilylychloride protecting the group it is wished to report towards synthesis of Carvedilol* **1** *this approach is more efficient , improved overall yield, easy process and to avoid the process impurity like bis impurity Impurity B*

Keywords: Carvedilol, β-adrenergic blocking agent, *o-protected 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol, Impurity B.*

INTRODUCTION

Carvedilol (**Figure 1**) is a non-selective β-adrenergic blocking agent with α_1-blocking activity β-Adrenergic blocking agents [1-4], mostly comprising of β-amino alcohols, are of pharmaceutical significance and have received major attention due to their utility in the management of cardiovascular disorders [5] including hypertension [6], angina pectoris, cardiac arrhythmias and other disorders [7] related to the sympathetic nervous system.

Several methods have been reported in the literature for synthesis of Carvedilol **1**. The innovator, Boehringer Mannheim GmbH, synthetic approach for the preparation of Carvedilol describes the opening of oxirane ring of 4-(oxiran-2-yl methoxy)-9*H*-carbazole **4**, with 2-(2-methoxyphenoxy) ethanamine [8]. In this process, it is observed that the formation of impurity **B** is about 35-40 % of the product in the reaction mixture. After isolation, it is about 10-15 %.

In order to avoid the formation of impurity **B**, various methods were performed and documented in the literature such as protecting the amine counterpart with benzyl, *p*-methoxybenzyl [9] and others. Despite their extensive success, many of the methods suffer from drawbacks such as incompletion of the reactions during deprotection, lower yields and others. Our research group has been extensively working on identifying and improving new synthetic methods specially protecting the aminoalchol functionality estabilished a new and efficient method for the synthesis of Carvedilol [10].

Generally halohydrines react with amines to form corresponding aminoalcohols via formation of epoxides. The formation of bis impurity is very general in these reactions. Hence, we thought that to protect halohydrine with relative substance like acetyl, *t*-butyldimethylsilyl (TBDMS) etc. Since epoxide is more reactive species, it immediately reacts with the intentional product i.e. Carvedilol and leading to the formation of undesired bis impurity in major portion. Most of the research has been carried out on synthesis of carvedilol using two strategies i) removal of bis Impurity; ii) minimization of formation of bis impurity. Removal of this impurity could be achieved with major loss of required product even though it is difficult to achieve pharmacopic grade the select the minimization of formation of Bis impurity till to day, major research work has been done through with protecting the amine or lowering the reactivity of amine We would like to work on lowering reactivity of halohydrine, generally, halohydrine react through epoxide, intermediate to react with neuclophiles preferably amines.Since epoxide is a reactive species due to its strain ring system, may be on of the parameter for the formation of bis impurity. To justify the above assumption and address the “Bis Imp” is through protecting the halohydrine such a way that, it could not form respective epoxide, Acetyl, TBDMSCl were chosen as protecting groups for the present study.

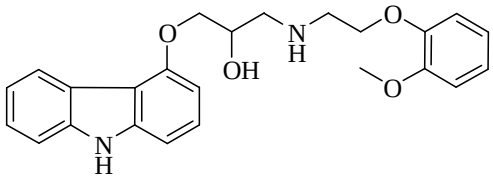


Figure 1

MATERIALS AND METHODS

Melting points were determined on Buchi 540 melting 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 and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6 and $CDCl_3$ 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. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light. Flash column-chromatography was carried out on silica gel (100-200 mesh) unless otherwise stat

Preparation of 4-(oxiran-2-ylmethoxy)-9*H*-carbazole, (4). To a stirred solution of (300 mL)water and sodium hydroxide (22.9 g, 0.573 Mole), 9*H*-carbazol-4-ol, 3 (100 g, 0.546 Mole) was added over 10 min followed by drop wise addition of (150 mL) DMSO over 30 min at 15 °C. After 10 min, to this solution is added epichlorohydrin (75.7 g, 0.818 mole) at 15 °C over 1 hr. The suspension is placed in a constant temperature bath at 50 °C and the mixture is stirred for 8.0 hr. After completion of the reaction, water (400 mL) was added, filtered and washed with water. The crude product was recrystallised in isopraponal gave glycidyl aryl ether, **4** as a pale brown solid; yield 76.6%; mp 121-126°C; **^{1}H NMR (DMSO):** δ 11.3 (s, 1H), 8.16 (d,1H), 7.3 (m, 1H), 7.3 (m, 1H), 7.46 (d,1H), 7.18 (t, 1H), 7.1 (d, 1H), 6.9 (d, 1H), 4.1 (m, 2H), 3.3 (m, 1H), 3.0 (m, 2H). MS: *m/z* (M^++1) 240; IR (KBr): ν 3296, 2928, 1609, 1509, 1099, 725 cm^{-1}.

Preparation of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol, (5).
A mixture 4-(oxiran-2-ylmethoxy)-9*H*-carbazole **4** (50.0 g) and 5 N hydrochloric acid (250.0 mL) was stirred for 5 hrs at 40-45 °C until to get complete conversion as indicated by TLC. The reaction mixture was cooled to room temperature. The obtained solid was filtered and washed with water to gave product **5** as off -white solid. Yield 86.0 %; **^{1}H NMR (DMSO):** δ 11.28 (s, 1H), 8.17 (d, 1H), 7.3 (m, 2H), 7.4 (d, 1H), 7.2 (t, 1H), 7.1 (d, 1H), 6.9 (d, 1H), 5.8 (s,1H), 4.2 (m,2H.),3.8-4.0 (m,2H); MS: *m/z* (M^++1) 276; IR (KBr): ν 3401, 2933, 1585,1499 cm^{-1}.

Preparation of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yl acetate (6a).
To a stirred solution of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol **5** (10.0 g, 0.036 Mole) and DCM (50.0 ml), Triethylamine (5.5 g, 0.0545 Mole) was added, cool to 0-5 °C. Charge acetic anhydride (4.4 g, 0.043) to slowly to the reaction mass at 0-5 °C, maintain the reaction mass to 30 °C for 4hrs, check the TLC, after completion of the reaction cool the reaction mass to 0-5 °C and slowly quench the reaction mass with chilled water (100 mL) and separate the both layers, extract the compound from aqueous layer with DCM (20.0 mL). combined the both organic layers and wash with saturated sodium carbonate solution and dry over on anhydrous sodium sulphate , distil the organic layer under reduced pressure to get 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yl acetate 6a with 70 % yield **.**

Preparation of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yl acetate (6a):
To a stirred solution of dichloromethane (50.0 ml), hydroxycarbazole **3** (10.0 g, 0.0545 Mole), epichlorohydrin (10.02 g, 0.108 Mole) and pyridine (2.0 mL) was added and maintain the reaction mass to 4 hrs. check the TLC, after completion of the reaction, cool the mass to 0-5 °C, charge the acetic anhydride slowly to the mass, maintain the reaction mass to 6 hrs at 28 °C, check the TLC, after completion of the reaction, cool the mass to 0-5 °C, quench the reaction mass with sodium bicarbonate solution and separate the layers and extract the compound from aqueous layer with DCM (2X 20.0 mL). combined the both organic layers and wash with saturated sodium carbonate solution and dry over on sodium sulphate , distil the organic layer under reduced pressure to get 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yl acetate **6a** with 59.2 % yield .
^{1}H NMR ($CDCl_3$): δ 8.2 (s, 1H), 8.16 (d, 1H), 7.4 (m, 2H), 7.3 (m, 2H), 7.18 (t, 1H), 6.7 (d, 1H), 5.6(s,1H), 4.5 (dd,2H.),3.9-4.0 (dd,2H), 2.20 (s,3H); MS: *m/z* (M^++1) 318; IR (KBr): ν 3401, 2933, 1585,1499 cm^{-1}.

Preparation of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yloxy (tert-butyl) dimethylsilane (6b).

To a stirred solution of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol **5** (10.0 g, 0.036 Mole) and DCM (50.0 ml), Triethylamine (5.5 g, 0.0545 Mole) was added and cool to 0-5 °C. Charge teritiarybutyl dimethyl silyl chloride (6.0 g, 0.04 Mole) to slowly to the reaction mass at 0-5 °C, maintain the reaction mass to 30 °C for 4hrs, check the TLC, after completion of the reaction cool the reaction mass to 0-5 °C and slowly quench the reaction mass with chilled water (100 Ml) and separate the both layers, extract the compound from aqueous layer with DCM (20.0 Ml). Combined the both organic layers and wash with saturated sodium carbonate solution and dry over on anhydrous sodium sulphate, distil the organic layer under reduced pressure to get **6b** with 63 % yield.

^{1}H NMR ($CDCl_3$): δ 8.2 (m, 1H), 8.0 (s, 1H), 6-2-7.6 (m, 6H) 3.75 to 4.5(m, 5H), 1.0 (s, 9H) & 0.2 (s, 6H); MS: *m/z* (M^++1) 390. IR (KBr): ν 3344, 2923, 1590, 1504, 1452, 1217, 1099 cm^{-1}.

Preparation of 1-(2-(2-methoxyphenoxy)ethylamino)-3-(9H-carbazol-4-yloxy)propan-2-yl acetate (8a): To a stirred the solution of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yl acetate **6a** (10.0g, 0.03 Mole) (4), Toluene (20.0ml), potassium carbonate (8.7 g , 0.06 Mole) and 2-(2-methoxyphenoxy)ethanamine(5.7 g, 0.034 Mole) was added, stir the mass for 15 min, slowly raise the temperature to 80 °C, maintain the reaction mass until reaction was completd, after completion of the reaction cool the reaction mass to 30 °C, filter the reaction mass and wash with toluene, distil the solvent under reduced pressure at below 60 °C to get residue , this residue was dissolved in ethyl acetate and wash with water, dried the organic layer over anhydrous sodium sulphate, distil the organic layer under reduced pressure, obtained residue was purified with column to get 1-(2-(2-methoxyphenoxy)ethylamino)-3-(9H-carbazol-4-yloxy)propan-2-yl acetate **8a** with 48 % yield.

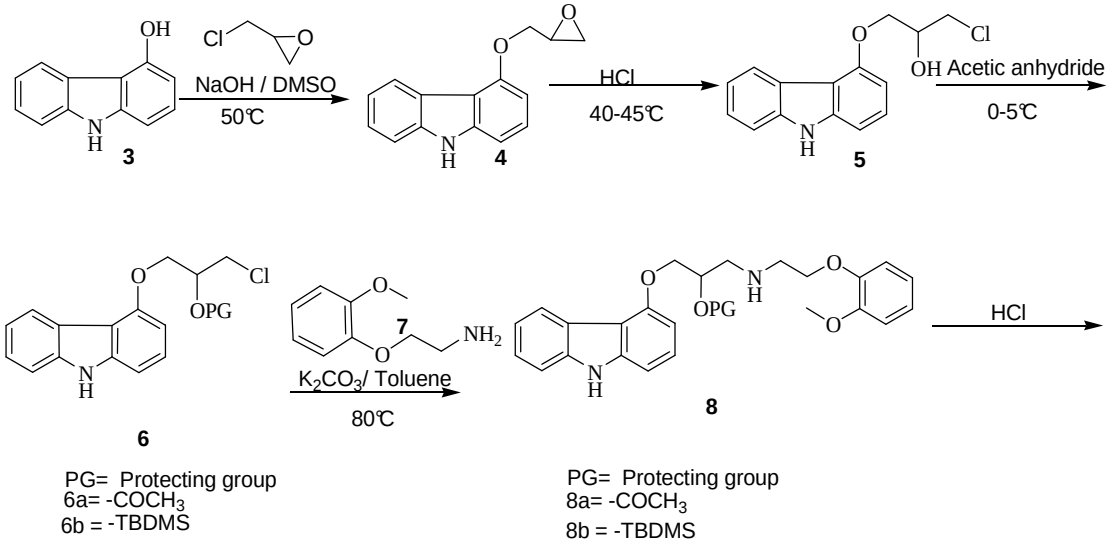
^{1}H NMR (DMSO): δ 11.2 (s, 1H), 8.2 (s, 1H), 6-7-7.5 (m, 10H), 5.2 (s, 1H), 4.2 (d, 2H), 4.1 (m, 2H), 4.0 (s, 1H), 3.75 (s, 3H), 2.7-2.97(m, 4H), 2.4(s,3H) MS: *m/z* (M^++1) 449. IR (KBr): 3344, 2923, 1590, 1504, 1452, 1217, 1099 cm^{-1}.

Preparation of 1-(2-(2-methoxyphenoxy) ethylamino)-3-(9H-carbazol-4-yloxy) propan-2-yloxy (tert-butyl) dimethylsilane (8b).

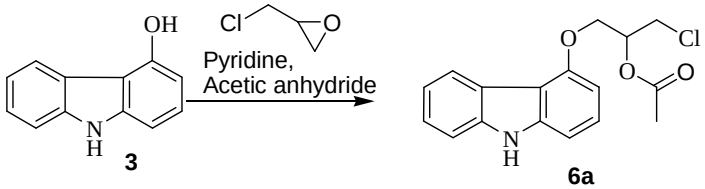
To a stirred solution of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yloxy (tert-butyl) dimethylsilane **6b** (10.0g , 0.03 Mole) and Toluene (20.0ml), potassium carbonate (8.7 g , 0.06 Mole), 2-(2-methoxyphenoxy)ethanamine (5.7 g, 0.034 Mole) was added ,stir the mass for 15 min, slowly raise the temperature to 80 °C, until reaction was completed, after completion of the reaction cool the reaction mass to 30 °C, filter the reaction mass and wash with toluene , distil the solvent under reduced pressure at below 60 °C to get residue , this residue was dissolved in ethyl acetate and wash with water, dry the organic layer with sodium sulphate , distil the organic layer under reduced pressure to get residue, obtained residue was purified with column to get silyl protected Carvedilol **8b** with 42.3 % yield.

^{1}H NMR (DMSO): δ 11.2 (s, 1H), 8.2 (s, 1H), 6-7-7.5 (m, 10H), 5.2 (s, 1H), 4.2 (d, 2H), 4.1 (m, 2H), 4.0 (s, 1H), 3.75 (s, 3H), 2.9-3.0(m, 4H),2.0(s,1H), 0.9(s,9H),0.2(s,6H),MS: *m/z* (M^+-1) 521. IR (KBr): 3344, 2923, 1590, 1504, 1452, 1217, 1099 cm^{-1}

Synthetic Scheme



Scheme 1. Synthesis of Carvedilol



Scheme 2

Preparation of 1-(2-(2-methoxyphenoxy) ethylamino)-3-(9H-carbazol-4-yloxy) propan-2-ol (1): To a solution of 1-(2-(2-methoxyphenoxy) ethylamino)-3-(9H-carbazol-4-yloxy) propan-2-yl acetate (5.0 g, 0.011 Mole) **8a**, hydrochloric acid (10 mL)was added and stir the mass to 30-45 min at 55 °C, after completion of the reaction monitored by TLC, extract the compound with ethyl acetate (20 mL), distil the solvent under reduced pressure to get crude product, and product was purified with coloum to get pure carvedilol with 56.2 % yield. M.p. 114-116 °C;

^{1}H NMR (DMSO): δ 11.2 (s, 1H), 8.2 (s, 1H), 7.4 (d, 1H), 7.3 (m, 1H), 7.3 (m, 1H), 7.1 (m, 1H), 7.1 (m, 1H), 6.9 (m, 1H), 6.9 (m, 1H), 6.9 (m, 1H), (6.9, 1H), 6.7 (d, 1H), 5.2 (s, 1H), 4.2 (d, 2H), 4.1 (m, 2H), 4.0 (s, 1H), 3.75 (s, 3H), 2.97 (m, 2H), 2.8 (m, 2H), 2.0 (s, 1H); MS: *m/z* (M^++1) 407. IR (KBr): ν 3344, 2923, 1590, 1504, 1452, 1217, 1099 cm^{-1}.

RESULTS AND DISCUSSION

As a part of the ongoing research programme on synthesis Carvedilol, we have selected acetyl and tertiarybutyldimethylsilyly for protecting the alcohol. Which yields the 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yl acetate **6a,** 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yloxy (tert-butyl) dimethylsilane **6b** as key intermediates towards synthesis of Carvedilol **1.** The feasibility for the synthesis of this intermediate **6a, 6b** is described by the reaction of 9*H*-carbazol-4-ol, **3**; with epichlorohydrin gave glycidyl aryl ether, **4**. The opening of oxirane ring, **4** with hydrochloric acid to afford 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol **5**, it is reacted with acetic anhydride and triethylamine to gave corresponding o-protected 1-(9*H*-carbazol-4-yloxy)-3-chloropropan-2-ol, **6a, 6b**. The obtained intermediates (**6a, 6b**) are reacted with counter part amine, **7** to give 1-(2-(2-methoxyphenoxy)ethylamino)-3-(9H-carbazol-4-yloxy)propan-2-yl acetate, **8a** and 1-(2-(2-methoxyphenoxy) ethylamino)-3-(9H-carbazol-4-yloxy) propan-2-yloxy (tert-butyl) dimethylsilane **8b** and this **8a, 8b** is de protected with hydrochloric acid to form required compound, **1**. The synthetic route was outlined in (**Scheme 1**)

Scheme-2: synthesis of 1-(9*H*-carbazol-4-yloxy)-3-chloropropan-2-ol, **5** was reported by the conventional method which involves the reaction of 9*H*-carbazol-4-ol, **3** with 2-(chloromethyl)oxirane (epichlorohydrin) in presence of base such as pyridine followed by reacted with acetic anhydride to form respective 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yl acetate **6a,** 59.2 % yield over two steps). Protected chlorohydrins, **6a** reacted with 2-(2-methoxyphenoxy) ethanamine, **7** using K_2CO_3 in DMF gave O-protected carvedilol, **8a** compound followed by deprotection of the respective groups to provided Carvedilol, **1**. However, the major concern in this synthetic approach is protecting the alcohol group to avoid Impurity **B**

CONCLUSION

In conclusion, we have found that highly efficient method to prepare Carvedilol. The method offers several benefits which include time, yield and formation of single product without impurity **B**. Because of these advantages this method should be great value for process development.

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