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Facile Synthesis of Carvedilol from Corresponding N-Sulfonamide

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ABSTRACT

The synthesis of Carvedilol (1) was achieved from 2-(2-methoxyphenoxy)-N tosylethanamine (6) in a three steps. 2-(2-methoxyphenoxy)-N-tosylethanamine(6)1-(9H-carbazol-4-yloxy)-3-(N-(2-(2-methoxyphenoxy)ethyl)-N tosylamino)propan-2-ol (7) are intermediates. This1-(9H-carbazol-4-yloxy)-3-(N-(2-(2-methoxyphenoxy) ethyl)-N-tosylamino) propan-2-ol were conveniently desulfonylated with Mg in methanol. The followed synthetic sequence avoids/minimize the formation of impurity B (bis impurity). This approach could be useful for the preparation of pharmaceutically important moieties containing β-amino alcohols without formation of bis impurity.

Keywords: Carvedilol; Bis impurity; Facile method; N-sulfonamide

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INTRODUCTION

Carvedilol is a non-selective β-adrenergic blocking agent with α_1 blocking activity. β-adrenergic blocking agents mostly comprising of β-amino alcohols are of pharmaceutical significance, Major concern in the preparation of carvedilol is formation of Bisimpurity. Several methods have been reported in the literature for synthesis of Carvedilol [1]. The innovator, approach for the preparation of Carvedilol describes the opening of oxirane ring of 4-(oxiran-2-yl methoxy)-9H-carbazole 4, with 2-(2-methoxyphenoxy) ethanamine 3. In this process, it is observed that the formation of impurity B. 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 and others [2-5]. Despite their extensive success, many of the methods suffer from drawbacks such as incompletion of the reactions during deprotection, lower yields, usage of expensive catalysts (Pd/C) and others. Our research group has been extensively working on identifying and improving new synthetic methods. Specially protecting the aminoalchol functionality established a new and efficient method for the synthesis of Carvedilol.

The preparation of N-sulfonamides constitutes a common method of amine protection in synthesis [6]. The resultant sulfonamides are often crystalline and more resistant to nucleophilic attack than carbamates. N-sulfonamides group has served as a highly effective protecting group for nitrogen because it is readily introduced and significantly lowers the basicity of nitrogen.

In addition, sulfonamides derived from primary amines can be readily deprotonated and the resultant anion can serve as a nucleophile for reaction with e.g. Alkyl or acyl halides [7]. Deprotection of the resulting N-alkyl or acylsulfonamides produce secondary amines or amides respectively. However, sulfonamides are amongst the most stable of the nitrogen protecting groups and drastic deprotection conditions are required which often limit the scope of the procedures. Thus aryl sulfonamides are cleaved by sodium in liquid ammonia,sodium naphthalenide or anthracenide and by heating to reflux in strong acid (e.g. 48% HBr in the presence of phenol). These harsh conditions have led to recent interest in the development of new deprotection methods which have included SmI_2deprotection of N-acyl sulfonamides can be achieved under neutral reaction conditions using the radical generating agent Bu_3SnH. Moreover, sulfonamides derived from primary amines can be easily deprotonated and the

anions serve as nucleophiles in reactions with alkylating reagents. Previously reported methods for deprotection required drastic conditions (lengthy reaction times, strongly basic conditions) e.g. sodium naphthalenide, sodium in liquid ammonia and refluxing in strong acid. Therefore, there is much interest in the development of new deprotection methods which include SmI_2, Mg in methanol [8] and TBAF [9].

EXPERIMENTAL SECTION

General

The melting points were determined in an open capillary tube using a Büchi B-540 melting point instrument and were uncorrected. The IR spectra were obtained on a Nicolet 380 FT-IR instrument (neat for liquids and as KBr pellets for solids). NMR spectra were recorded with a Varian 300 MHz Mercury Plus Spectrometer at 300 MHz (^{1}H) and at 75 MHz (^{13}C). Chemical shifts were given in ppm relative to trimethylsilane (TMS). Mass spectra were recorded on Waters quattro premier XE triple quadrupole spectrometer using either electron spray ionisation (ESI) or atmospheric pressure chemical ionization (APCI) technique.

Preparation of 2-(2-Methoxyphenoxy)-n-Tosylethanamine

To a stirred solution of Paratouluene sulphonyl chloride (2.5 g, 0.4 eq) and dichloromethane (50.0 mL), Cool the reaction mass to -5 to10°C and add 2-(2-methoxyphenoxy)ethanamine (5.0 g 1.0 eq), Cool the mass to -5 to -10°C and add to prepared solution of triethylamine (21.0 ml g, 5.0 eq) and dichloromethane (50.0 mL) at -10°C, maintain the reaction mass to -10°C for 1.0 h and slowly raise the temperature to 0-5°C, maintain the reaction mass for 1.0 hr. check the TLC, after completion of the reaction and slowly quench the reaction mass with chilled water (100 mL) and separate the both layers, extract the compound from aqueous layer with dichloromethane (20.0 mL). Combined the both organic layers and wash with water (20.0 mL) and dry over on anhydrous sodium sulphate, distil the organic layer under reduced pressure to get 2-(2-methoxyphenoxy)-N-tosylethanamine with 80% yield.

^{1}H NMR (DMSO):

δ 7.7 (d, 2H), 7.4 (d, 2H), 6.8-7.0 (m, 4H), 4.0 (m, 2H), 3.9 (t, 2H), 3.7(s, 3H), 3.1 (t, 2H), 2.3(s, 3H). MS: *m/z* (M^++1) 320; IR (KBr): ν 3413, 2927, 1594, 1508 and 653 cm^{-1}.

2-(2-methoxyphenoxy)-P-nitrotosylethanamine:

^{1}H NMR (DMSO): δ 8.4 (d,1H), 8.16 (d,1H), 7.3-7.5 (s, 1H), 6.8-7.0 (m, 5H), 4.0 (m, 2H), 3.9 (1H), 3.8 (s, 3H), 3.3 (m, 2H). MS: *m/z* (M^++1) 351; IR (KBr): ν 3296, 2928, 1609, 1509, 1099, 725 cm^{-1}.

2-(2-methoxyphenoxy)-P-flourotosylethanamine:

^{1}H NMR (DMSO): δ 7.9 (d, 2H), 7.4 (d, 2H), 6.8-7.0 (m, 5H), 4.0 (t, 2H),3.7(s, 3H), 3.1 (t, 2H),2.3(s, 3H). MS: *m/z* (M^+-1) 324; IR (KBr): ν 3286, 2934, 1590 and 741 cm^{-1}.

Preparation of 1-(9H-carbazol-4-yloxy)-3-(N-(2-(2-methoxyphenoxy)ethyl)-N-tosylamino)Propan-2-ol:

To a stirred solution of toluene with 2-(2-methoxyphenoxy)-N-tosylethanamine (2.0 g 1.0 eq), cool the mass to 0-5°C, add 40% sodium hydroxide solution (5.0 ml), charge 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol (1.7 g, 1.0 eq) and TBAB (0.01 eq), slowly heat the reaction mass 80-85°C, maintain the reaction mass to 80°C for 4hrs, check the TLC, after completion of the reaction cool the reaction mass to 20-25°C and separate the both layers, extract the compound from aqueous layer with Ethyl acetate (20.0 mL). Dry over on anhydrous sodium sulphate, distil the organic layer under reduced pressure to get crude compound, this compound was purified with coloumn to get required compound 65.0%.

^{1}H NMR (DMSO-d6, 300 MHz): δ: 2.3 (s, 3H), 3.1 (dd, 1H),3.3 (m, 1H),3.73 (s,3H), 3.58 (m,2H) 4.1-4.3 (m, 5H),5.49(s,1H) 6.6 (d,1H), 6.82 (m, 4H,), 7.0-7.2 (m, 7H,), 7.7(d, 2H), 8.28 (d, 1H), 11.2 (s, 1H); δ; ESI-MS: *m/z* (%) 559 (100, M-1); IR (KBr): 3399(OH), 2924, 1592, 1507, 1107 cm^{-1}.

Preparation of Carvedilol

To a stirred solution methanol (1.0 ml), alkylated Sulphonamide (0.1 g 1.0 eq), and magnesium (0.04 g, 10.0 eq) slowly heat the reaction mass 65-68°C, maintain the reaction mass to 68°C for 10.0 hrs, check the TLC, after completion of the reaction cool the reaction mass to 20-25°C, distil the solvent by using vacuum and add water (2.0 ml) and dichloromethane (3 × 5.0 ml) and separate the both layers, dry over on anhydrous sodium sulphate

(Schemes 1 and 2) distil the organic layer under reduced pressure to get compound, the crude product is recrystallised from ethyl acetate to give Carvedilol 1 as a white solid in 67% yield. Mp; 114-16°C.

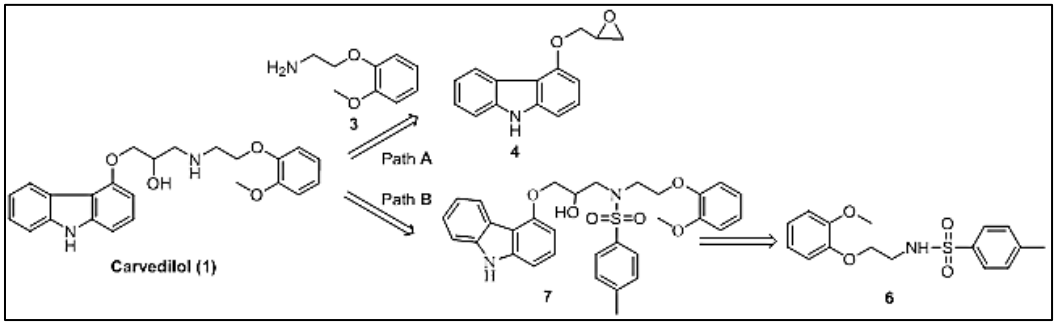
^{1}H NMR ($CDCl_3$, 300 MHz):

δ 1.95-2.05 (brs, -OH), 2.80-2.85 (m, 2H, $-NCH_2$), 2.94 (t, 2H, *J* = 5.7 Hz, $-NCH_2$), 3.73 (s, 3H $-OCH_3$), 4.01 (t, 2H, *J* = 5.3 Hz, $-OCH_2$), 4.10-4.18 (m, 3H, $-OCH_2$, -OCH), 5.18 (d, 1H, *J* = 4.4 Hz, -NH), 6.68 (d,1H, *J* = 8.0 Hz, ArH), 6.82-6.96 (m, 4H, ArH), 7.05-7.15 (m, 2H, ArH), 7.26-7.35 (m, 2H, ArH), 7.44 (d, 1H, *J* = 7.9 Hz, ArH), 8.22 (d, 1H, *J* = 8.0 Hz, ArH), 11.2 (s, NH).

^{13}C NMR (DMSO-d^6):

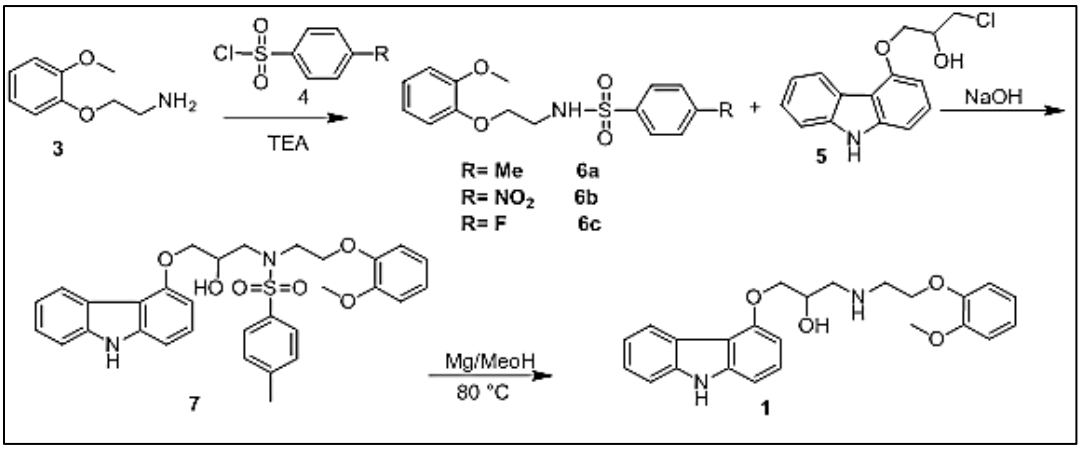
δ 48.5 ($N-CH_2$), 52.5 ($N-CH_2$), 55.4 (OCH_3), 68.4 (C-OH),68.4 (OCH_2), 70.4 (OCH_2), 100.4 (Ar), 103.7 (Ar), 110.3 (Ar), 111.5 (Ar), 112.2 (Ar), 113.6 (Ar), 118.5 (Ar), 120.6 (Ar), 121.0 (Ar), 121.7 (Ar), 122.4 (Ar), 124.4 (Ar), 126.4 (Ar), 138.8 (Ar), 141.0 (Ar), 148.0 (Ar), 149.1 (Ar), 154.9 (Ar); ESI-MS: *m/z* (%) 407 (100, M^++1); IR (KBr): 3344(OH), 2923, 1590, 1504, 1452, 1217, 1099 cm^{-1}.

RESULTS AND DISCUSSION



Scheme 1: Synthesis of carvedilol-I

As a part of the ongoing research programme on synthesis of Carvedilol, Extensively working on identifying and improving new synthetic methods for specially protecting aminoalchol functionality. Of N-sulfonamides constitutes a common method of amine protection in synthesis. N-sulfonamides group has served as a highly effective protecting group for nitrogen because it is readily introduced and significantly lowers the basicity of nitrogen which yields the 2-(2-methoxyphenoxy)-N-tosylethanamine, 6 as key intermediates towards synthesis of Carvedilol 1.



Scheme 2: Synthesis of carvedilol II

The feasibility for the synthesis of this intermediate 6 is described by the reaction of 2-(2-methoxyphenoxy) ethanamine 3; with benzene sulphonyl chlorides, 4 in triethyl amine and DCM like Para toluene benzene sulphonyl chloride, Para nitro benzene sulphonyl chloride, Para Flouro benzene sulphonyl chloride and methane sulphonyl chloride to give N-protected sulphonamides 6, These sulpohonamide are reacted with 1-(9*H*-carbazol-4-yloxy)-3-chloropropan-2-ol **5** in sodium hydroxide, TBAB at 80-85°C to give Sulphonamide protected carvedilol **7**.

This protected N-alkylated sulphonamide carvedilol is de protected is tried different conditions like 48% HBr in the presence of phenol, TBAF, sodium naphthalenide sodium in liquid ammonia, in those condition is deprotection of the sulphonamide is critical, so finally we attempted with Mg in methanol in this condition only paratoulene sulphonamide protected group is de protected other protected groups are not deprotected they give side products like nitro to amine and des flouro compound etc. The opening of oxirane ring, 4 with required N-protected sulphonamide to give afford Sulphonamide protected carvedilol, it de protected with Mg in ethanol to give required carvedilol.

CONCLUSION

In conclusion we synthesized carvedilol (1) from 2-(2-methoxyphenoxy)-N tosylethanamine (6) in 3 steps. The followed synthetic sequence avoids/minimize the formation of impurity B (bis impurity). This approach could be useful for the preparation of pharmaceutically important moieties of β-amino alcohols without formation of bis impurity.

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