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Lewis Acid Mediated Nucleophilic Ring-Opening of 1-Benzhydryl Azetidine-3-ol with Aryl Alcohols: A Formal Synthesis of Carvedilol

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Lewis acid mediated nucleophilic azetidine ring opening of 1-benzhydrylazetidine-3-ol with phenolic oxygen as nucleophile is reported. This approach was also utilized successfully to synthesize, carvedilol a β-adrenergic blocking agent.

Key Words: 1-Benzhydrylazetidin-3-ol, Lewis acid, Substituted phenols, Azetidine ring opening, Carvedilol, β-Adrenergic blocking agent.

INTRODUCTION

β-Amino alcohols play increasingly important role in the treatment of a wide variety of human disorders and also serve as chiral auxiliaries in organic synthesis[1,2]. Among those, 1-alkylamino-3-aryloxy-2-propanol is a main constituent in various α and β-adrenergic blocking agents (Fig. 1)[1].

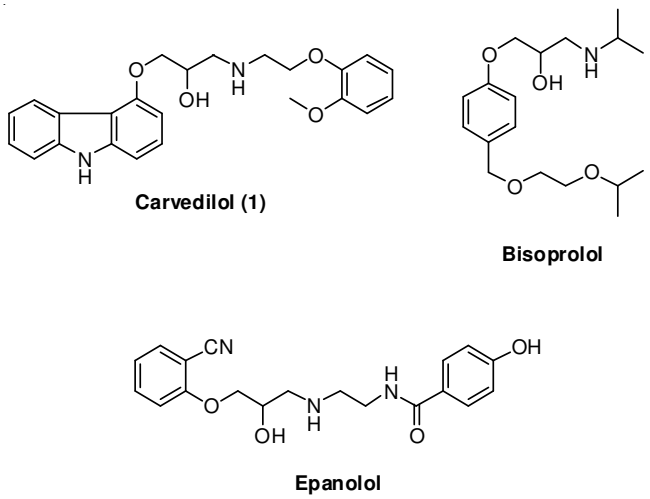


Fig. 1. Structures of various drugs consisting β-aminoalcohol moiety

The regular practice in pharmaceutical industry to synthesize 1-alkylamino-3-aryloxy-2-propanol constituent, relies on opening of oxirane ring, such as 2-(aryloxymethyl) methyloxirane with amine counterpart (Fig. 2)[3]. However, this synthetic strategy successfully works only for commercially available low boiler amines and may not be applicable in case of high boiler amine or an amine attached to bulkier moiety, because it is difficult to remove high boiler amine from the product. However, 3-hydroxyazetidine, could be utilized to prepare the targeted structural constituent, 1-alkylamino-3-aryloxy-2-propanol. The formation of C-O bond through the cleavage of sp^3-sp^3 hybridized C-N single bond was not much documented except in case of cyclic amines, especially three member nitrogen heterocycle (azeridines)[4]. Though, few reports are available on ring opening of azetidines with oxygen nucelophiles[5], much attention did not receive on study of this topic using either Brønsted acid or Lewis acid as catalysts. Since, 3-hydroxyazetidine hydrochloride is not a stable moiety, its synthetic precursor 1-benzhydrylazetidine-3-ol has been chosen for our research. Recently, we have published industrially applicable synthetic process for 1-benzhydrylazetidin-3-ol[6].

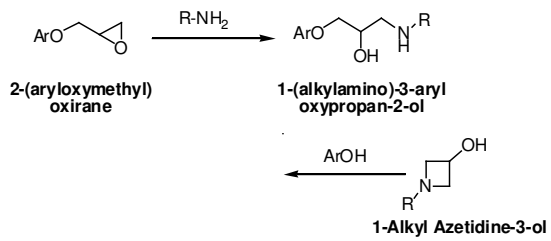


Fig. 2. Schematic representation of general method to synthesize 1-alkylamino-3-aryl oxy-2-propanol constituent

EXPERIMENTAL

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 ºC. All the organic extracts were dried over anhydrous 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's were run on precoated silica-gel plates, which were visualized using UV light and ninhydrin in ethanol (10 % solution) charring. Flash column-chromatography was carried out over silica gel (230-400 mesh) unless otherwise stated.

General procedure for the synthesis of 1-(benzhydrylamino)-3-(aryloxy) propan-2-ol: To a stirred solution of 1-benzhydrylazetidin-3-ol (100 mmol), aryl alcohol (110 mmol) and Lewis acid (10 mmol) in *o*-xylene (50 mL) was heated to reflux temperature for 24 h. After completion of the reaction *o*-xylene was removed under reduced pressure, diluted with water (10 mL) and extracted thrice with EtOAc (50 mL). The combined organic layer was dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure to dryness. The obtained crude product was purified by using flash column chromatography (Silica gel, EtOAc: *n*-hexane 1:9) to give respective 1-(benzhydrylamino)-3-(aryloxy)propan-2-ol.

1-(Benzhydrylamino)-3-phenoxypropan-2-ol: ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 7.40-7.37 (m, 4H, Ar-H), 7.19-7.33 (m, 8H, Ar-H),6.93-6.98 (t, 1H, OH) 6.86-6.89 (d, 2H, Ar-H), 4.86 (s, 1H, -$CHPh_2$), 4.06-4.12 (m, 1H, -CHOH), 3.98-3.99 (d, 2H, -CH_2OPh), 3.0 (bs, 1H, NH), 2.73-2.88 (m, 2H, -CH_2NH); ES-MS: m/z 334.1 (M^+ + 1); IR (KBr, ν_{max}, cm^{-1}): 3289, 3062, 3030, 2926, 1494, 1247, 1077, 1038, 750.

1-(4-Chlorophenoxy)-3-(benzhydrylamino)propan-2-ol: ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 7.2-7.39 (m, 12H, Ar-H), 6.77-6.83 (d, 2H, Ar-H), 4.85 (s, 1H, -$CHPh_2$), 4.7 (bs, 1H, OH), 4.03-4.08 (m, 1H, -CHOH), 3.94-3.96 (d, 2H, CH_2OPh), 2.71-2.871 (m, 2H, -CH_2NH), 2.0-2.5 (bs, 1H, NH); ES-MS: m/z 368 (M^+ + 1), 370 (M^+ + 3); IR (KBr, ν_{max}, cm^{-1}): 3285, 2926, 1596, 1500, 1455, 1244, 1028, 824, 704.

1-(4-Methoxyphenoxy)-3-(benzhydrylamino)propan-2-ol: ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 7.19-7.40 (m, 10H, Ar-H), 6.82 (s, 4H, Ar-H), 4.85 (s, 1H, $CHPh_2$), 4.04-4.07 (m, 1H, -CHOH), 3.92-3.94 (d, 2H, CH_2OAr), 3.76 (s, 3H, -OCH_3), 2.73- 2.84 (m, 2H, -CH_2NH), 2.2-2.5 (bs, 2H, NH and OH); ES-MS: m/z 364 (M^+ + 1), 365; IR (KBr, ν_{max}, cm^{-1}): 3292, 2927, 2850, 1593, 1508, 1462, 1235, 1031, 824, 746, 702.

Methyl 3-(3-(benzhydrylamino)-2-hydroxypropoxy)-benzoate: ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 7.62-7.65 (d, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.09-7.46 (m, 13H, Ar-H, OH and NH), 7.06-7.07 (m, 1H, Ar-H), 4.87 (s, 1H, -$CHPh_2$), 4.07-4.1 (m, 1H, -CHOH), 4.02-4.04 (d, 2H, CH_2OAr), 3.907 (s, 3H, -$COOCH_3$), 2.74-2.89 (m, 2H, -CH_2NH); ES-MS: m/z 392 (M^+ + 1); IR (KBr, ν_{max}, cm^{-1}): 3322, 3026, 2923, 1721, 1490, 1447, 1228, 1078, 1023, 701.

Methyl 4-(3-(benzhydrylamino)-2-hydroxypropoxy) benzoate: ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 7.9-8.0 (d, 2H, Ar-H), 7.2-7.4 (m, 10H, Ar-H), 6.85-6.9 (d, 2H, Ar-H), 4.85 (s, 1H, -$CHPh_2$), 4.1-4.15 (m, 1H, -CHOH), 4.0-4.1(d, 2H, CH_2OAr), 3.9 (s, 3H, -$COOCH_3$), 2.7-2.9 (m, 2H, -CH_2NH); ES-MS: m/z 392 (M^+ + 1); IR (KBr, ν_{max}, cm^{-1}): 3322, 3026, 2923, 1721, 1496, 1450, 1228, 1078, 1025, 705.

1-(9*H*-Carbazol-4-yloxy)-3-(benzhydrylamino)-propan-2-ol: ^{1}H NMR (400 MHz) (DMSO-d_6) δ (ppm): 11.3-11.18 (s, 1H, NH), 8.05-7.95 (d, 1H, Ar-H), 7.50-7.00 (m, 15H, Ar-H), 6.62-6.60 (d, 1H, Ar-H), 5.20-5.15 (m, 1H, -OH), 4.85-4.80 (s, 1H, -$CHPh_2$), 4.24-4.18 (m, 3H, CH_2OAr), 2.84-2.62 (m, 2H, -CH_2NH); ES-MS: m/z 423.5 (M^+ + 1); IR (KBr, ν_{max}, cm^{-1}): 3317, 3055, 3025, 2921, 1626, 1505, 1261, 1211, 1108, 784, 667.

1-(9*H*-Carbazol-4-yloxy)-3-aminopropan-2-ol 4: To a stirred solution of 1-(9*H*-carbazol-4-yloxy)-3-(benzhydrylamino)propan-2-ol (**3)** (5 g) in methanol (20 mL) was added 10 % Pd-C (0.2 g). The reaction mixture was stirred under 60-70 psi of hydrogen pressure for 6 h. The heterogeneous reaction mixture was filtered through celite, washed with methanol (50 mL) and dried over Na_2SO_4. Solvent was removed from the filtrate under reduced pressure to dryness and the obtained residue was triturated with *n*-hexane (20 mL) to give compound **4** as a white coloured solid (1.67 g, 55 % yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 11.3 (s, 1H, Ar-H), 8.21-8.19 (d, 1H, Ar-H), 7.42-7.45 (d, 1H, Ar-H), 7.05-7.36 (m, 5H, Ar-H), 6.67-6.70 (d, 1H, Ar-H), 5.0 (bs, 1H), 4.1-4.17 (m, 2H, -CH_2OAr), 3.9-3.94 (m, 1H, -CH_2OH), 2.5-2.9 (m, 2H, -CH_2NH_2), 2.5-2.8 (m, 1H, -CH_2NH_2); ES-MS: m/z 257 (M^+ + 1); IR (KBr, ν_{max}, cm^{-1}): 3358, 3245, 2919, 2865, 2361, 1595, 1507, 1506, 1448, 1341, 1260, 1217, 1102, 789, 725.

Preparation of 5-((9*H*-carbazol-4-yloxy)methyl) oxazolidin-2-one (5): To a stirred solution of amino alcohol compound **4** (10 g, 0.039 mol), K_2CO_3 (13.5 g, 0.097 mol) and N,N-dimethylformamide (50 mL), ethyl chloroformate (6.4 g, 0.058 mol) was added slowly at 0 ºC. The reaction mixture was heated to reflux temperature. After completion of the reaction, reaction mixture was cooled to 25 ºC, filtered and the filtrate was evaporated under reduced pressure to dryness. The obtained residue was triturated with isopropanol gave required 2-oxazolidinone **3** as a white solid (5.2 g, yield 47.2 %), m.p. 247-249 ºC; ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 11.3 (s, -NH), 8.16 (d, Ar-H), 7.7 (s, -NHCO), 7.4 (d, Ar-H), 7.3 (m, Ar-H), 7.18 (t, Ar-H), 7.1 (d, Ar-H), 6.7 (d, Ar-H), 5.1 (s, 2H, -CHOAr), 4.42-4.30 (d, -CHOH), 3.7-3.56 (t, 2H, -CHNH); ES-MS: m/z 283 (M^+ + 1).

Preparation of 5-((9*H*-carbazol-4-yloxy)methyl)-3-(2-(2-methoxyphenoxy)ethyl) oxazolidin-2-one (7): To a stirred solution of compound **5** (10.0 g, 0.035 mol) and N,N-dimethylformamide (50 mL), K_2CO_3 (12.0 g, 0.087 mol), 1-(2-chloroethoxy)-2-methoxybenzene (8.9 g, 0.053 mol) and KI (0.2 g, 0.001 mol) were added at 25 ºC. The reaction mixture was heated to 100 ºC for 25 h. After completion of the reaction,

the reaction mixture was cooled to 25 ºC and filtered. The solvent was removed from the filtrate under the reduced pressure. The obtained crude compound was purified by flash column chromatography (Silica gel, dichloromethane: *n*-hexane 3:2) to give compound **8** as a pale yellow coloured solid (6.8 g, 45 % yield). ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 3.55-3.79 (m, 3H, -NCH_2, -NCH), 3.70 (s, 3H, -OCH_3), 4.02 (t, 1H, -NCH), 4.15 (t, 2H, -OCH_2), 4.32-4.45 (m, 2H, -OCH_2), 5.04-5.14 (m, 1H, -OCH), 6.71 (d, 1H, Ar-H), 6.82-6.97 (m, 4H, Ar-H), 7.08-7.12 (m, 2H, Ar-H), 7.28-7.35 (m, 2H, Ar-H), 7.45 (d, 1H, Ar-H), 8.06 (d, 1H, Ar-H); ^{13}C NMR (100 MHz) ($CDCl_3$) δ (ppm): 43.29, 46.8, 55.5, 66.7, 68.2, 71.2, 100.4, 104.3, 110.4, 111.4, 112.3, 114.1, 118.6, 120.6, 121.6, 121.5, 122.1, 124.6, 126.4, 138.9, 141.1, 147.6, 149.3, 154.3, 157.2; ES-MS: m/z 431.4 (M^+ + Na); IR (KBr, ν_{max}, cm^{-1}): 3366, 1746, 1504, 1450, 1115, 1044.

Preparation of 1-(9*H*-carbazol-4-yloxy)-3-(2-(2-methoxyphenoxy)ethylamino) propan-2-ol (8) (carvedilol): To a stirred solution of compound **8** (10.0 g, 0.023 mol) and EtOH (100 mL), 5 N NaOH solution (4.0 g in 20 mL H_2O) was added. The reaction mixture was maintained at reflux temperature for 12 h. After completion of the reaction, the reaction mixture was cooled to room temperature and extracted with EtOAc (2 × 50 mL). A mixture of toluene and THF followed by water (100 mL) are added to the reaction mixture. The phases are separated and the aqueous phase is extracted thrice with 1:1 mixture of toluene and THF. The organic layers are combined, dried over Na_2SO_4, filtered and the solvent is removed by evaporation under reduced pressure to dryness. The crude product was recrystallized from EtOAc to give carvedilol **1** as a white solid (6.58 g, 70 % yield), m.p. 114-116 ºC. ^{1}H NMR (400 MHz) ($CDCl_3$) δ (ppm): 1.95-2.05 (br s, -OH), 2.80-2.85 (m, 2H, -NCH_2), 2.94 (t, 2H, -NCH_2), 3.73 (s, -OCH_3), 4.01 (t, 2H, -OCH_2), 4.10-4.18 (m, 3H, -OCH_2, -OCH), 5.18 (d, 1H, -NH), 6.68 (d, Ar-H), 6.82-6.96 (m, 4H, Ar-H), 7.05-7.15 (m, -2H, Ar-H), 7.26-7.35 (m, 2H, Ar-H), 7.44 (d, 1H, Ar-H), 8.22 (d, 1H, Ar-H), 11.2 (s, -NH); ^{13}C NMR (100 MHz) ($CDCl_3$) δ (ppm): 48.5, 52.5, 55.4, 68.4, 70.4, 100.4, 103.7, 110.3, 111.5, 112.2, 113.6, 118.5, 120.6, 121.0, 121.7, 122.4, 124.4, 126.4, 138.8, 141.0, 148.0, 149.1, 154.9; ES-MS: m/z 407 (M^+ + 1); IR (KBr, ν_{max}, cm^{-1}): 3344, 2923, 1590, 1504, 1452, 1217, 1099.

RESULTS AND DISCUSSION

1-Benzhydrylazetidin-3-ol (**1**) was initially treated with phenol in *o*-xylene at elevated temperature (130-140 ºC). Oxygen nucleophile of phenol was reacted with compound **1** at α-carbon to nitrogen and opened the cyclic azetidine ring and provided the corresponding compound **2** with 10-15 % yield. Incompletion of the reaction was observed during initial development of the reaction even after continuing it for more than 100 h. To improve the yield, we thought of protonating tertiary nitrogen of 1-benzhydrylazetinine-3-ol to weaken the C-N bond by employing mild acidic agents such as acidic resin (H^+ amberlyte) or silica gel, but did not improve the product formation in the reaction. Addition of strong acids (6N HCl or H_2SO_4) either stoichiometric or catalytic amount didn't serve the purpose. All the reaction conditions and observations were depicted in Table-1.

TABLE-1
REACTION CONDITIONS ATTEMPTED TO OPEN THE AZETIDINE RING OF 1-BENZHYDRYLAZETIDIN-3-OL

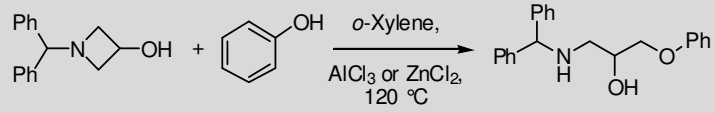
Reaction condition	Remarks
o-Xylene, 140 ºC	In completion of the reaction
Acetic acid, *o*-xylene, 140 ºC	In completion of the reaction and formation of various impurities
Acidic resin (H^+ Amberlyte), *o*-xylene, 140 ºC	In completion of the reaction and gummy nature was observed in reaction
Silica gel, *o*-xylene, 140 ºC	In completion of the reaction
6.0 N HCl (1.0 eq.), *o*-xylene, 140 ºC	Formation of various impurities
H_2SO_4 (0.1 eq), *o*-xylene, 140 ºC	Formation of various impurities

Since Brønsted acids were not useful, impact of Lewis acids on reaction progress was studied on mentioned reaction, initially using BF_3:etherate, which did not led to success. Employing other Lewis acids such as $SnCl_2$, $FeCl_3$ didn't make much effect on reaction progress. However, $AlCl_3$ made better impact on reaction, ie the reactant was almost completed in the reaction and yield was also improved significantly. Further, attempts were made on reaction temperature and found that 120 ºC could be the optimum for better conversion, but looking for an alternate solvent ie toluene didn't succeeded. Versatility of this reaction was studied by utilizing various phenols substituted with electron donor (-OCH_3) and electron withdrawers (-CO_2Me and -Cl) were selected for this purpose and succeeded. But, difficulty during aqueous work-up of the reaction mixture was observed and to overcome the problem, $ZnCl_2$ was planned ($ZnCl_2$ is nearly 90 times more aq. soluble than $AlCl_3$). Employing $ZnCl_2$ gave similar results as compared with $AlCl_3$ and the results are summarized in Table-2. In case of phenol (entry 1, Table-2), $ZnCl_2$ made high impact on yield of the product. Reaction time and isolated yields of all conversions in both the methods ($AlCl_3$/$ZnCl_2$) were consolidated and compared in Table-2.

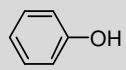
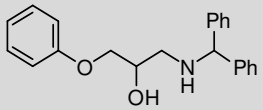
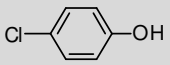
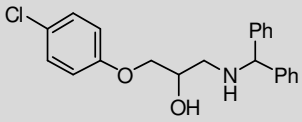
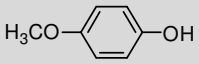
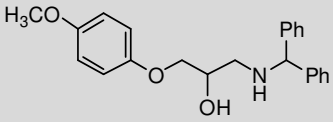
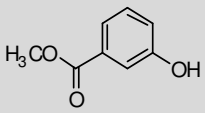
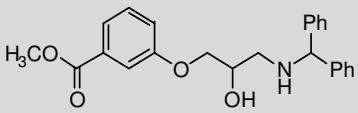
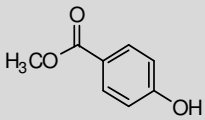
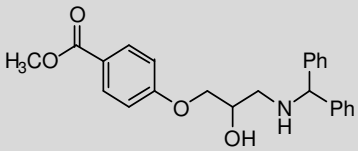
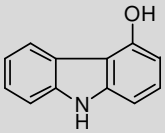
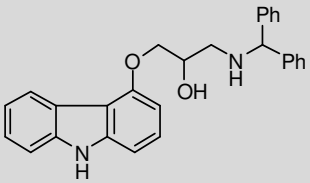
As an initial objective of the current research, we targeted on two concepts, one is Lewis acid mediated opening of azetidine ring and second one exploration of this approach into the synthesis of any α and β-adrenergic blocking agent. Hybridizing both the above concepts/purposes, we were interested to synthesize industrially important molecule and thus carvedilol was chosen for this study.

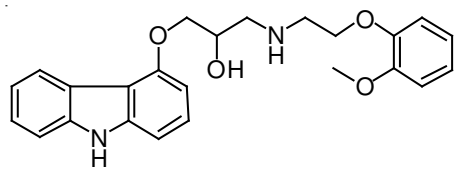
Carvedilol (Figs. 1 and 3) is a non-selective β-adrenergic blocking agent with α_1-blocking activity[7,8]. β-Adrenergic blocking agents, mostly comprising of β-amino alcohols are of pharmaceutical significance and have received major attention due to their utility in the management of cardiovascular disorders[9] including hypertension[10], angina pectoris, cardiac arrhythmias and other disorders[11] related to the sympathetic nervous system. Several syntheses of carvedilol are reported. Innovator's approach for the preparation of carvedilol describes the opening of oxirane ring of 4-(oxiran-2-yl methoxy)-9*H*-carbazole with 2-(2-methoxyphenoxy)-ethanamine[3]. In this process, the formation of impurity B (Fig. 3) was observed about 35-40 % in the reaction mixture and after isolation, it is observed at around 10-15 %. 1-Benzhydryl-azetidine-3-ol **1** was treated with 4-hydroxycarbazole **2** in presence of $AlCl_3$ in *o*-xylene at 120 ºC for 8-10 h to obtain

TABLE-2
EXAMPLES OF LEWIS ACID MEDIATED NUCLEOPHILIC RING-OPENING OF 1-BENZHYDRYLAZETIDIN-3-OL WITH ARYL ALCOHOLS

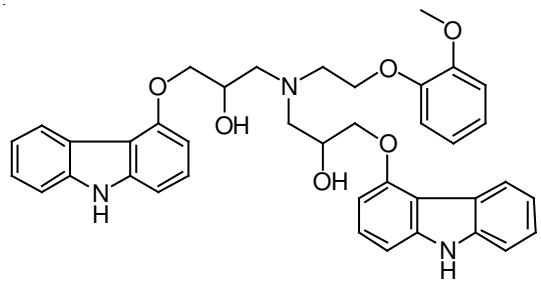


1 **2**

Entry No.	Aryl alcohol	Product	Yield (%)	
			$AlCl_3$	$ZnCl_2$
1			30	50
2			22	30
3			25	25
4			30	30
5			20	35
6			25	25



Carvedilol



Impurity B

Fig. 3. Structures of carvedilol and impurity B

the alcohol **3** with 25 % yield (Table-2). Initial attempts to alkylate benzhydryl amine functionality of **3** with an alkyl halide **6** were not successful. Probably, steric bulky benzhydryl group on amine was limiting the reaction and it was deprotected by hydrogenolysis (H_2/Pd-C) to give the β-aminoalcohol **4**. Compound **4**, was alkylated with chloro compound **6** and gave the corresponding carvedilol **8** along with unwanted impurity B, which is a major drawback even in innovators process. To overcome, this problem we have followed our approach[12] and the β-amino alcohol of **4** was protected into cyclic carbamate **5** and was alkylated with **6** to give protected carvedilol **7**, subsequent de protection of β-amino alcohol under alkali conditions, yielded the target molecule carvedilol with good yield (**Scheme-I**).

Conclusion

This work demonstrate application of 1-benzhydryl-azetidine-3-ol, through opening the azetidine ring and utilized as versatile precursor for the synthesis of various 1-alkylamino-3-aryloxy-2-propanol (β-amino alcohol) and the concept has been well proven in the preparation of synthetically and pharmaceutically important molecule carvedilol.

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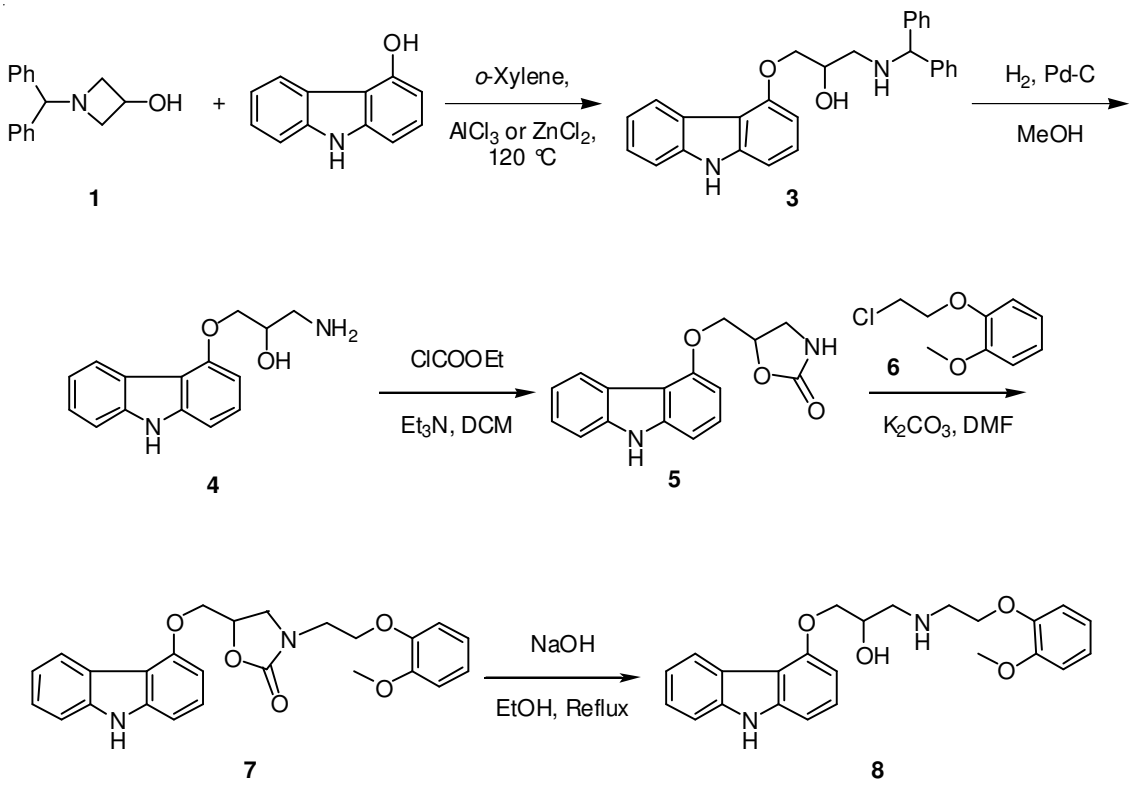

Scheme-I: Synthesis of carvedilol (**8**) using 1-benzhydrylazetidin-3-ol (**1**)

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