Convenient synthesis of Carvedilol utilizing 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl phenyl carbonate as a key intermediate

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Convenient synthesis of pharmaceutically important moiety Carvedilol, a (β-adrenergic blocking agent) has been reported utilizing 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl phenyl carbonate as a key intermediate. The synthetic scheme involves the reaction of intermediate with 2-(2-methoxy phenoxo)ethanamine by using \textit{N,N}-Dimethyl-4-aminopyridine (DMAP) in \textit{N,N}-dimethylformamide (DMF) which yield 3-(2-(2-methoxyphenoxy)ethyl)-5-(9H-carbazol-4-yloxy)methyl)oxazolidin-2-one via 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yl 2-(2-methoxyphenoxy)ethylcarbamate. The resulted compound has further been converted to the required Carvedilol and this approach could be useful for the preparation of many β-amino alcohols without formation of Impurity B.

Keywords: Carvedilol, 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl phenyl carbonate, 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl2-(2-methoxyphenoxy) ethanamine, impurity B, β-adrenergic blocking agent, β-amino alcohol

Carvedilol (Figure 1) is a non-selective β-adrenergic blocking agent with α\textsubscript{1}-blocking activity. 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 including hypertension, angina pectoris, cardiac arrhythmias and other disorders related to the sympathetic nervous system.

Several syntheses of Carvedilol are been reported in the literature. The innovator’s (Boehringer Mannheim GmbH) synthetic approach for the preparation of Carvedilol describes the opening of oxirane ring of 4-(oxiran-2-ylmethoxy)-9H-carbazole, with 2-(2-methoxyphenoxy)ethanamine. In the innovator’s process, impurity B (Figure 1) formation was observed about 35-40% of the product in the reaction mixture. After isolation, it was about 10-15%. The major concerns are formation of impurity B (at higher level) and significant amount of yield loss during the purification of Carvedilol.

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, \textit{p}-methoxybenzyl and others. But all of them suffer from few of the 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 for Carvedilol to avoid impurity B in the synthetic process.

Results and Discussion

In continuation of our research on development of syntheses of Carvedilol\textsuperscript{10}, retro-synthetic analysis of the oxazolidione has been altered from path A to path B. In path A, the amidic nitrogen in compound was involved in inter-molecular reaction with respective alkyl halide whereas in path B, the chlorofomate or phenyl carbonate was involved in inter-molecular reaction with respective alkyl amine to achieve targeted compound.

Previously, synthesis of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol 3a was reported by the conventional method which involves the reaction of 9H-carbazol-4-ol with 2-(chloromethyl)oxirane (epichlorohydrin) in presence of strong base such as NaOH in DMSO gave 4-((oxiran-2-yl)methoxy)-9H-carbazole 3b followed by opening of oxirane ring with HCl (65% yield over two steps). Attempts were extended to achieve respective chlorohydrin 3a directly by reacting 9H-carbazol-4-ol with epichlorohydrin instead of reported two step synthesis. Since strength of the base impacts enough to achieve selectivity between chlorohydrin 3a and epoxide 3b (Scheme 1). We started investigation on minimizing the base strength from NaOH to NaHCO\textsubscript{3}. In majority of the reaction conditions, formation of excess % of epoxide 3b was observed over chlorohydrin 3a even utilizing catalytic amount of mild base such as NaHCO\textsubscript{3}. Reaction conditions have been altered to organic bases such as Et\textsubscript{3}N, pyridine, DMAP and others utilizing inorganic bases such as NaOH,
NaHCO₃ and others. Among all attempts, pyridine (0.5 eq.) yielded the respective chlorohydrin 3a from corresponding 9H-carbazol-4-ol (Scheme II). The attempts were summarized in Table I.

Since chlorohydrin 3a was successfully synthesized directly from 9H-carbazol-4-ol efforts were extended further to achieve Carvedilol 1 starting from chlorohydrin 3a. Compound 3a was treated with triphosgene in dichloromethane to give 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-yl chloroformate 4 which was found to be highly unstable upon isolation. However, compound 4 reacted in-situ with 2-(2-methoxyphenoxy)ethanamine 5 using K₂CO₃ in DMF to give 3-(2-(2-methoxyphenoxy)ethyl)-5-(9H-carbazol-4-yloxy)methyl)oxazolidin-2-one 7 via 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl 2-(2-methoxyphenoxy)ethylcarbamate 6. The instability of chloroformate 4 prompted to use one-pot reaction,
starting from chlorohydrin 3a to compound 7 followed by basic hydrolysis (NaOH, EtOH) provided Carvedilol 1. However, the major concern in this synthetic approach is de-chloroformylation of compound 4 and converting back to chlorohydrin 3a during its reaction with 2-(2-methoxyphenoxy)ethanamine 5. This has been observed in both the cases either step-wise version or one-pot reaction.

To overcome the above hurdles to achieve 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl 2-(2-methoxyphenoxy)ethylcarbamate 6 followed by Carvedilol 1, the leaving (Cl\(^{-}\)) group in compound 4 has been modified to phenoxy (PhO\(^{-}\)) (Scheme II). Accordingly, chlorohydrin 3a was treated with phenyl chloroformate to yield corresponding unsymmetrical carbonate 8 which was involved in nucelophilic substitution reaction upon treatment with (2-(2-methoxyphenoxy)ethylamine) 5 yielding the required carbamate 6. Employing an intra-molecular substitution reaction under mild conditions such as K\(_2\)CO\(_3\),

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Base or Resin</th>
<th>Temp. (°C)</th>
<th>9H-carbazol 4-ol (%)</th>
<th>% of 3a</th>
<th>% of 3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K(_2)CO(_3) (catalytic)</td>
<td>50-60</td>
<td>~ 20</td>
<td>~ 20</td>
<td>~ 60</td>
</tr>
<tr>
<td>2</td>
<td>NaHCO(_3)</td>
<td>50-60</td>
<td>~ 35</td>
<td>~ 15</td>
<td>~ 50</td>
</tr>
<tr>
<td>3</td>
<td>Na(_2)CO(_3)</td>
<td>50-60</td>
<td>~ 20</td>
<td>~ 20</td>
<td>~ 60</td>
</tr>
<tr>
<td>4</td>
<td>Et(_3)N</td>
<td>50-60</td>
<td>~ 45</td>
<td>~ 10</td>
<td>~ 45</td>
</tr>
<tr>
<td>5</td>
<td>Acidic resin</td>
<td>25-30</td>
<td>~ 75</td>
<td>~ 10</td>
<td>~ 15</td>
</tr>
<tr>
<td>6</td>
<td>Basic resin</td>
<td>25-30</td>
<td>~ 75</td>
<td>~ 10</td>
<td>~ 15</td>
</tr>
<tr>
<td>7</td>
<td>Pyridine (catalytic)</td>
<td>50-60</td>
<td>~50</td>
<td>~40</td>
<td>~10</td>
</tr>
<tr>
<td>8</td>
<td>Pyridine (0.5 eq.)</td>
<td>50-60</td>
<td>~10</td>
<td>~80</td>
<td>~10</td>
</tr>
<tr>
<td>9</td>
<td>DMAP</td>
<td>50-60</td>
<td>~50</td>
<td>~10</td>
<td>~40</td>
</tr>
</tbody>
</table>

*All reactions were monitored by TLC and all the described results are after 12 hr*
in DMF afforded respective oxazolidinone 7 followed by hydrolysis of carbamate functionality using alkali yielded targeted compound Carvedilol 1. The usage of a mild base such as K₂CO₃ in DMF (on reaction with carbamate 6) led to dephenoxylation (~30%) and provided chlorohydrin 3a as major by-product (~50%). To address this issue various bases (both kinds of inorganic and organic bases) have been attempted in an individual account to get the compound 6 in high yield and DMAP was identified as the best among those. By employing DMAP, the dephenoxylation has been minimized and this has proportionally improved the yield of carbamate 6 to 70%.

The amine has been either in the form of carbamate 6 or 2-oxazolidione 7 which reduced its involvement further to form Bis impurity, here with we have successfully achieved the synthesis of Carvedilol 1 through avoiding Impurity B (bis impurity).

In conclusion, a non-selective β-adrenergic blocking agent Carvedilol has been synthesized in 2 steps from commercially available raw materials by avoiding Bis impurity (impurity B) strategically by locking the amine counterpart of carvedilol into respective 2-oxazolidinone. The minimum steps (2 steps) and good overall yield (18%) proves the efficacy of the synthesis.

**Experimental Section**

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). ¹H and ¹³C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d₆ and CDCl₃ 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 and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.

**Preparation of 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol, 3a.** To a stirred solution of IPA (30.0 mL) and pyridine (1.74 g, 0.022 mol), 9H-carbazol-4-ol (10.0 g, 0.0546 mol) was added over for 10 min followed by dropwise addition of epichlorohydrin (10.02 g, 0.108 mol) at 15°C over 1 hr. The suspension was placed at a constant temperature at 20°C and the mixture was stirred for 15.0 hr. After completion of the reaction, excess epichlorohydrine and IPA were removed by evaporation under reduced pressure and the obtained crude product was extracted thrice with DCM. The combined organic layers were washed with water, dried over Na₂SO₄, filtered and the solvent was removed by evaporation. The obtained residue was purified by flash column chromatography to give 3a as a pale brown solid (10.0 g); yield 68.0 %.

¹H NMR (CDCl₃): δ 11.3 (s, 1H), 8.16 (d, 1H), 7.3 (m, 2H), 7.46 (d, 1H), 7.18 (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: 3401, 2933, 1585,1499 cm⁻¹

**Preparation of 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl phenyl carbonate, 8.** To a stirred solution of DCM (50.0 mL) in pyridine (2.8 g, 0.036 mol) was added 1-(9H-carbazol-4-yloxy)-3-chloropropan-2-ol 3a (5.0 g, 0.018 mol). The reaction mass was cooled at 5°C, phenyl chloro formate (4.0 g, 0.025 mol) was added slowly. The suspension was placed at a constant temperature at 20°C and the mixture was stirred for 12.0 hr. After the completion of the reaction, 50.0 mL water was added and stirred for 30 min. The organic layer was separated, washed with water and dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue obtained was purified by flash column chromatography to give 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl phenyl carbonate 8 as a white solid (5.2 g); yield 73.0%; ¹H NMR (CDCl₃): δ 8.2 (d, 1H), 8.16 (s, 1H), 7.46 (m, 5H), 6.7-7.27 (m, -6H), 5.5 (m, 1H), 4.5 (d, 2H), 4.0 (m, 2H); MS: m/z. (M⁻1) 394; IR (KBr): 3410, 1762 cm⁻¹

**Preparation of 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl 2-(2-methoxyphenoxy) ethyl carbamate, 6.** To a stirred solution of 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl phenyl carbonate 8 (5.0 g, 0.012 mol) and DMAP (0.72 g, 0.0059 mol) in 15.0 mL DMF, 2-(2-methoxyphenoxy) ethanamine 5 (0.92g, 0.0055 mol) was added at 15°C. The reaction temperature was raised to 30°C, and maintained for 6.0 hr. After completion of the reaction, DMF was removed by evaporation under reduced pressure and the obtained crude product was extracted thrice with ethylacetate. The combined organic layers were
washed with brine and dried over Na₂SO₄. The solvent was removed by evaporation. The obtained residue was purified by flash column chromatography to give carbamylate 6 as a light white coloured solid (4.1 g); yield 70.0%; m.p. 60-63°C; ¹H NMR (CDCl₃): δ 8.2 (t, 1H), 8.05 (m, 1H), 6.6-7.45 (m, 10H), 5.6 (s, 1H), 5.5 (m, 1H), 4.5 (m, 2H), 4.0-4.2 (m, 4H), 3.8 (s, 3H), 3.6 (t, 2H); MS: m/z (M⁺+1) 469; IR (KBr): 3409, 2930, 1713, 1109 cm⁻¹.

One step synthesis of 3-(2-(2-methoxyphenoxy)ethyl)-5-((9H-carbazol-4-yloxy)methyl)oxazolidin-2-one, 7. To a stirred solution of 3-(9H-carbazol-4-yloxy)-1-chloropropan-2-yl phenyl carbonate 8 (5.0 g, 0.012 mol) and DMAP (0.72g, 0.0055 mol) in 15.0 mL DMF, 2-(2-methoxyphenoxy)ethanamine 5 (0.92g, 0.0055 mol) was added at 15°C. The reaction temperature was raised to 30°C, and was maintained for 3 hrs. The solid was filtered and washed with water. The crude product was recrystallised from ethyl acetate to give Carvedilol as a white solid (6.6 g); yield 54.9%; m.p. 156.3-58°C; ¹H NMR (DMSO-d₆): δ 11.25 (s, 1H), 8.06 (d, 1H), 6.7-7.45 (m, 10H) 5.1 (m, 1H), 4.1-4.45 (m, 4H) 4.02 (t, 1H), 3.7 (s, 3H), 3.55-3.79 (m, 3H); ESI-MS: m/z (M⁺+1) 431.4; IR (KBr): 3237, 1726 cm⁻¹.

Preparation of 1-(9H-carbazol-4-yloxy)-3-(2-(methoxyphenoxy)ethylamino)propan-2-ol, (Carvedilol, 1). The compound 7 (10.0 g, 0.023 mol) was refluxed in 100 mL 96% ethanol containing sodium hydroxide (4.0 g, 0.10 mol) under a nitrogen atmosphere. After completion of the reaction, reaction mixture was cooled to RT and 50 mL 1:1 mixture of toluene and THF was added followed by 100 mL water to the reaction mixture. The organic phase was separated and the aqueous phase was extracted thrice with 1:1 mixture of toluene and THF. The organic layers were combined and dried over Na₂SO₄. The solvent was removed by evaporation under reduced pressure. The crude product was recrystallised from ethyl acetate to give Carvedilol as a white solid (6.6 g); yield 70%; m.p. 114-16°C; ¹H NMR (CDCl₃): δ 11.2 (s, -NH), 8.2 (s, -CH), 7.4 (d, -CH), 7.3 (m, -CH), 7.3 (m, -CH), 7.1 (m, -CH), 7.1 (m, -CH), 6.9 (m, -CH), 6.9 (m, -CH), 6.9 (m, -CH), 6.7 (d, -CH), 5.2 (s, -OH), 4.2 (d, -OCH₂), 4.1 (m, -CH₂), 4.0 (s, -CH), 3.75 (s, -OCH₃), 2.97 (m, -CH₂), 2.8 (m, -CH₂), 2.0 (s, -NH); MS: m/z (M⁺+1) 407. IR (KBr): 3344, 2923, 1590, 1504, 1452, 1217, 1099 cm⁻¹.

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