June 2010 ISSN: 0974 - 7516 Volume 6 Issue 2

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 6(2), 2010 [171-177]

A new and facile synthesis of 5-((9H-carbazol-4-yloxy) methyl)oxazolidin-2-one intermediate towards the synthesis of carvedilol, a β-adrenergic blocking agent

K.Chinnam Naidu[1,2], V.Kiran Kumar[1], E.Naresh[1], Ch.Kameswararao[1,2], G.Madhusudhan[1]*, K.Mukkanti[2]

[1]Inogent Laboratories Pvt. Ltd., A GVK BIO Company, 28A, IDA, Nacharam, Hyderabad - 500 076, Andhra Pradesh, (INDIA)

[2]Centre for Pharmaceutical Sciences, Institute of Science and Technology, J.N.T. University, Hyderabad - 500 072, Andhra Pradesh, (INDIA)

E-mail : madhusudhan.gutta@inogent.com; madhusudhan.gutta@yahoo.com

Received: 6th March, 2010 ; Accepted: 16th March, 2010

ABSTRACT

A facile synthesis of 1-(9H-carbazol-4-yloxy)-3-halopropan-2-ol, **(6)** and 5-((9H-carbazol-4-yloxy) methyl)oxazolidin-2-one, **(5)** intermediates is described. These intermediates are utilized for the synthesis of Carvedilol. While synthesizing the new intermediate **(5)**, observed formation of major impurity characterized as 4-((9H-carbazol-4-yloxy)methyl)-1,3-dioxolan-2-one, **(9)** and confirmed by its preparation. Reaction conditions were identified to minimize the impurity 9 formation to achieve good reaction conversion while making **(5)**. This approach avoids the formation of *bis* compound (disclosed in EUROPEAN PHARMACOPOEIA 6.0, volume 2.0 as impurity B). This approach could be useful for the preparation of many β-amino alcohols without formation of *bis* impurity.

KEYWORDS

Carvedilol;
2-oxazolidinone;
Halohydrin;
Potassium cyanate.

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 syntheses of Carvedilol are reported. The innovator, Boehringer Mannheim GmbH, synthetic approach for the preparation of Carvedilol describes the opening of oxirane ring of 4-(oxiran-2-yl methoxy)-9H-carbazole, **(3)** with 2-(2-methoxyphenoxy)ethanamine[8]. In the innovator process, the formation of impurity B (Figure 1) is observed about 35-40% in the reaction mixture and even after isolation, it is about 10-15%. A major concern in this is the formation of impurity B in considerable levels and significant amount of yield loss was observed during purification of carvedilol.

We altered various parameters to the innovator approach such as solvent, temperature, reaction time, mole ratio and mode of addition to minimize the formation of impurity B. None of these parameters played significant role to minimize the formation of impurity B which would be understandable while opening of epoxides with primary amine.

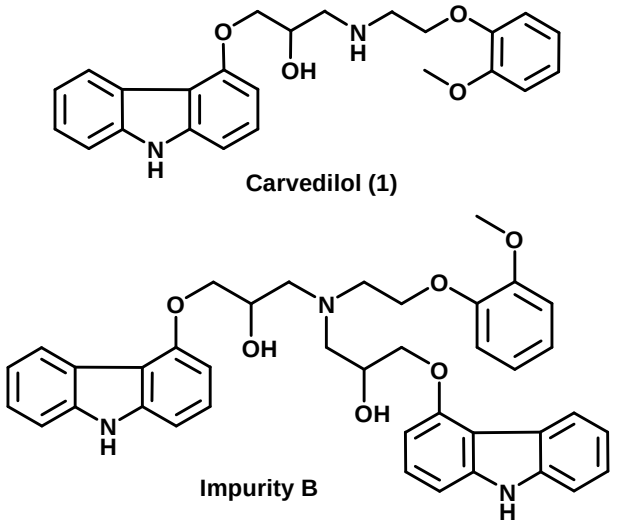


Figure 1 : Structures of Carvedilol (1), and Impurity B

In order to avoid the formation of impurity B, other attempts are performed and documented in the literature. One of the report describes the opening of oxirane ring of 4-(oxiran-2-ylmethoxy)-9*H*-carbazole, 3 with N-benzyl-2-(2-methoxyphenoxy) ethanamine instead of 2-(2-methoxyphenoxy) ethanamine followed by debenzylation[9]. This process produces no impurity B and also involves the catalytic N-debenzylation at the final stage. According to the literature knowledge, N-debenzylation reaction never goes for 100% completion, leading the traces of *N*-benzyl Carvedilol as major impurity in final product. European pharmacopoeia has covered the limit of this N-benzyl carvedilol impurity not more than 0.02% due to its toxic nature and practically it is very difficult to achieve this level. As well as the process also suffers from the usage of an expensive palladium catalyst for N-debenzylation. As an alternative, the opening of oxirane ring of 3 with 2-(2-methoxyphenoxy)ethanamine which is used in an excess to reduce the formation of impurity B[10]. This process could not remove or avoid complete formation of impurity B. In addition, this process suffers from the low price competitiveness due to the excess usage of expensive ethylamine compound and difficult to remove the amine compound while isolation of Carvedilol. Another approach also described to prepare Carvedilol without formation of impurity B *via* oxazolidinone intermediate[11]. Even though the formation of Impurity B was not observed, but the preparation of this intermediate is multi step and tedious.

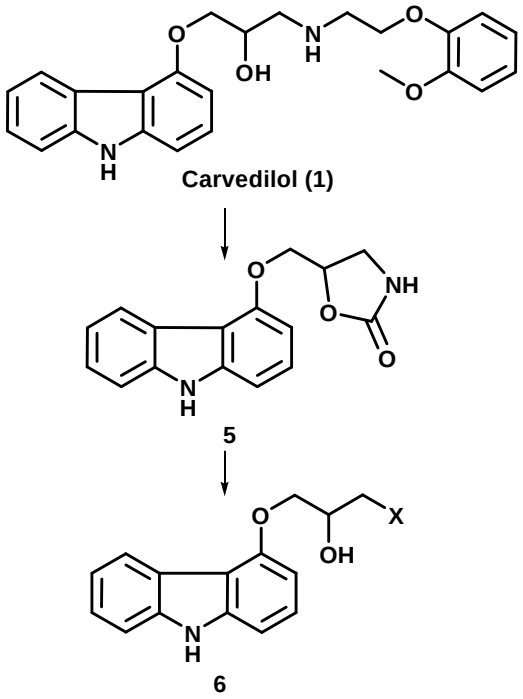


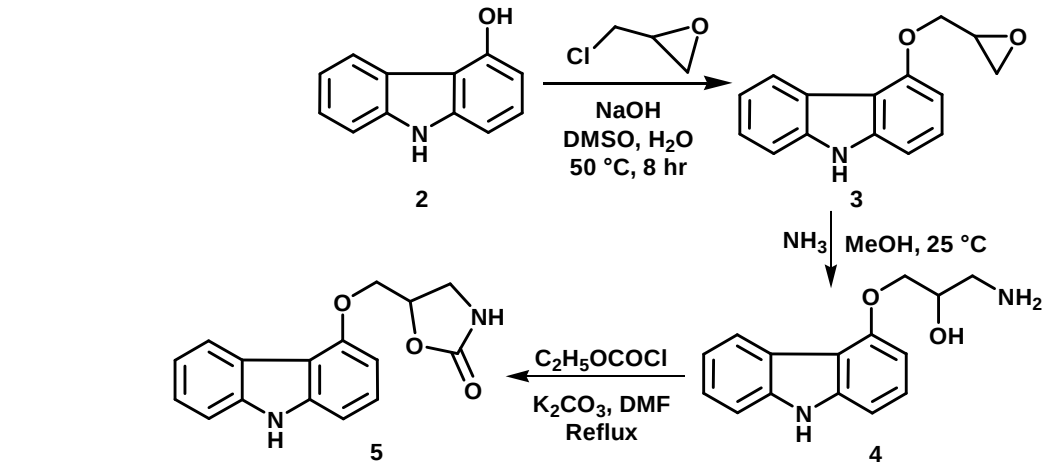
Figure 2 : Retro synthesis of Carvedilol (1)

RESULTS AND DISCUSSION

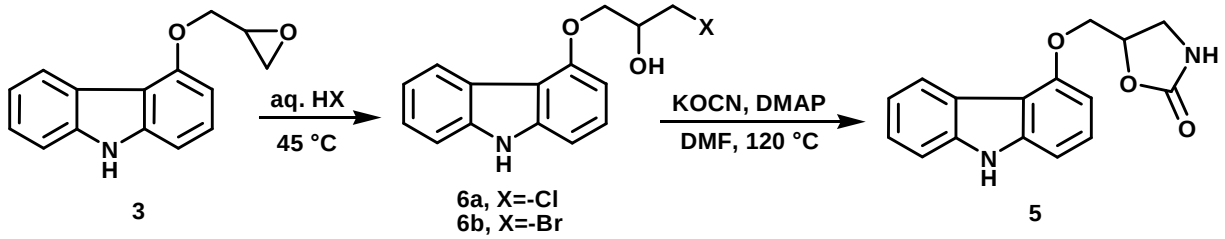
As a summary, practical preparation of Carvedilol consists of various hurdles such as impurity B formation, purification, poor yields and usage of excess amount of substrates.

In continuation of our research on development on syntheses of 1,3-oxazolidi-2-nones[12a] and Carvedilol[12b] and 5-substituted-2-oxazolidinones[12c], synthesized 5-((9H-carbazol-4-yloxy)methyl)oxazolidin-2-one 5 as a key intermediate towards the synthesis of Carvedilol 1 without formation of impurity B (Figure 2).

Initially, the synthesis of 5-((9H-carbazol-4-yloxy)methyl)oxazolidin-2-one **(5)** is achieved by conventional method which involves the reaction of 9H-Carbazol-4-ol 2 with epichlorohydrin to yielded corresponding epoxide **(3)**. Opening of oxirane ring of 4-(oxiran-2-ylmethoxy)-9H-carbazole **(3)** with aqueous ammonia gave the corresponding amino alcohol **(4)**. This amino alcohol **(4)** on reaction with ethyl chloroformate, which is used as one carbon source in bridging the hydroxyl and amino functions of amino alcohol, gave required oxazolidinone intermediate **(5)** (Scheme 1). In this process, the formation of series of



Scheme 1



Scheme 2

impurities was observed while opening of oxirane ring in **(3)** by using ammonia.

To achieve good yield and purity of the oxazolidinone intermediate **(5)**, alternative relevant synthetic approaches were searched in the literature. Among those, it has been identified that the α-hydroxy isocyantes could serve as an *in-situ* intermediate in the preparation of 2-oxazolidinones. Cyanate ion is accepted as nucleophile to react with halohydrins to yield 2-oxazolidonones *via* α-hydroxy isocyantes[13]. This method is applied to prepare 2-oxazolidione intermediate **(5)** from halohydrin **(6)**.

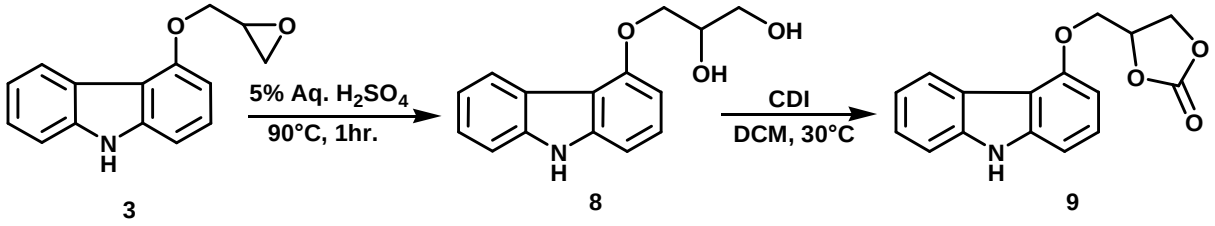
The epoxide of 4-(oxiran-2-yl methoxy)-9H-carbazole **(3)** is opened with aqueous hydrochloric acid to produce corresponding chlorohydrin **(6a)** with good yield. The halohydrin **(6)** was further treated with KOCN in DMF to yield corresponding 2-oxazolidinone **(5)** (Scheme 2).

The reaction has slower rate at the temperature 80°C, we have attempted various other temperatures to improve the rate of reaction as well as yield. Series of reactions were conducted at a range of temperatures 80°C-120°C and the amount of product formation as well as time for reaction completion in each condition were observed at regular time intervals (TABLE 1). According to TLC, reaction didn't progressed at any temperature lower than 80°C, has the enhanced reaction rate with incremental in the temperature and there is not much further improvement beyond 120°C.

Moreover, decrease in reaction time was also observed with respect to raise in temperature. The reaction didn't complete even after 50hr. at the temperatures 80°C and 100°C, completed in 24hr. at 120°C and just within 6.0 hr at 120°C with DAMP (Table-1) and proves huge impact of temperature on rate of the reaction as well as the yield of product of formation.

Though, the reaction hasn't completed in both the cases at 80°C and 100°C, improvement in the yield was observed at 100°C (40%), over the reaction performed at 80°C (20%). In case of 120°C with DMAP, the required product 5 was obtained almost instantaneously, without much amount of time and 55% yield was obtained (TABLE 1). Further higher temperatures (>120 °C) was screened using high boiling solvent DMSO, has made much impact neither on further reaction rate nor on yield. In all the cases, observed the formation of one major impurity in these reaction conditions. However, while the reaction temperature increases lower amount of impurity formation was observed. This impurity was isolated and characterized as

Full Paper



Scheme 3

4-((9*H*-carbazol-4-yloxy)methyl)-1,3-dioxolan-2-one, 9. This was confirmed by the preparation of 9 by the opening of oxirane ring in 3 with sulfuric acid followed by carbonyl insertion between diols of 8 with carbonyldiimidazole (CDI) (Scheme 3).

To enhance reactivity of compound **(6)**, the leaving group was changed from chloro to bromo. The oxirane ring of compound **(3)** was opened with 48% aq. HBr at 40-45°C to obtain corresponding bromohydrin **(6b)** with 85% yield. The bromohydrine was also treated with KOCN at optimized conditions such as KOCN/ DMF/120°C to yield oxazolidinone **(5)**. Moreover, the reactivity of the halohydrin hasn't much differed, while comparing the reactivity of chlorohydrin **(6a)** with bromohydrin **(6b)** to form oxazolidinone **(5)**. But the reaction was completed one hour before in case of bromohydrin and much yield difference was not found. This exercise has concluded that temperature plays a key role over the leaving group ability of halo atom in halohydrin **(6)** on reaction with KOCN.

Various attempts were done to condense 2-oxazolidinone intermediate **(5)** with 1-(2-chloroethoxy)-2-methoxybenzene to yield final precursor moiety **(7)**. Initially, we have attempted K_2CO_3 in DMF at reflux temperature gave poor yields, to improve the yield Cs_2CO_3/DMF at reflux was attempted but not succeeded enough. Strong base NaH was used in THF, to alkylate the carbamate nitrogen of **(5)**, ended with formation of multiple impurities even at lower temperatures like -5°C. Among the numerous attempts, finally optimized condition to produce **(7)** from corresponding oxazolidinone **(5)** is Cs_2CO_3/ KI/DMF at reflux temperature and the isolated yield is 70%.

The condensed product **(7)** was treated with sodium hydroxide in ethanol, hydrolyzed the 2-oxazolidinone of **(7)** to provide required amino alcohol and afforded the title moiety carvedilol 1 with out formation of impurity B (Scheme 4).

CONCLUSION

In conclusion, an efficient and commercial viable preparative method is developed for carvedilol 1 with high purity (without impurity B) by choosing a simple 1-(9H-carbazol-4-yloxy)-3-halopropan-2-ol and 5-((9H-carbazol-4-yloxy) methyl)oxazolidin-2-one.

EXPERIMENTAL

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 ^{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.

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 4-(oxiran-2-ylmethoxy)-9H-carbazole (3)

To a stirred solution of 300mL water and sodium hydroxide (22.9 g, 0.573 mole), 9H-carbazol-4-ol, 2 (100g, 0.546 mole) is added over 10 min followed by drop wise addition of 150mL DMSO over 30 min at 15°C. After 10 min, to this solution is added epichlorohydrin (75.7g, 0.818 mole) at 15°C over 1 hr. The

TABLE 1 : Impact of temperature to prepare (5) from (6a)

S. No	Temperature	Reaction time (hrs)	Yield (%)
1	80 °C	52*	20
2	100 °C	52*	30
3	120 °C	24	35
4	120 °C	06**	55

*** = no completion, ** With DMAP**

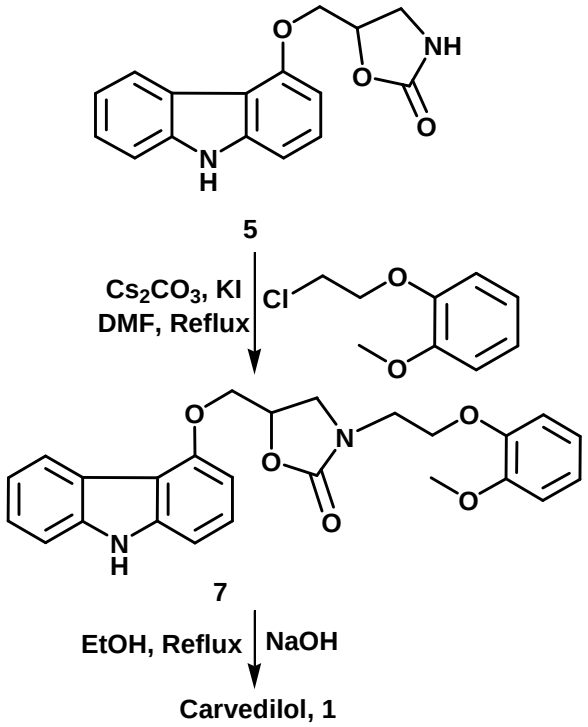
suspension is placed in a constant temperature bath at 50°C and the mixture is stirred for 8 hr. After completion of the reaction, added 400mL water, filtered and washed with water. The crude product was recrystallised in isopraponal gave glycidyl aryl ether, **(3)** as a pale brown solid; yield 76.6%; mp 121-126°C; ^{1}H NMR ($CDCl_3$): δ 11.3 (s, -NH, carbazole), 8.16 (d, -CH, carbazole), 7.3 (m, -CH, carbazole), 7.3 (m, -CH, carbazole), 7.46 (d, -CH, carbazole), 7.18 (t, -CH, carbazole), 7.1 (d, -CH, carbazole), 6.9 (d, -CH, carbazole),4.6 (m,-CH2) 4.1 (m,1H, -CH2),3.6 (m, -CH_2), 3.0 (m, -CH), 2.9 (m, -CH_2). MS: m/z (M^++1) 240.

Preparation of 1-(9H-carbazol-5-yloxy)-3-chloropropan-2-ol (6a)

A mixture 4-(oxiran-2-ylmethoxy)-9H-carbazole **(3)** (50.0g) in 5N 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 produce **(6)** as off white solid; 51.0g, yield 88.5%; mp 102-106°C; ^{1}H NMR (DMSO): δ 11.3 (s, -NH), 8.2 (d, -CH, carbazole), 7.5 (d, -CH, carbazole), 7.2-7.4 (m, -CH, carbazole), 7.15 (m, -CH, carbazole), 7.1 (d, -CH, carbazole), 6.7 (d, -CH, carbazole), 5.8 (s, -CH), 4.2 (dd,-CH_2), 3.8-4.0 (dd, -CH2-); IR (Neat, cm^{-1}): 3401, 2933, 1585,1499; MS: m/z (M^++1) 276.

Preparation of 1-(9H-carbazol-5-yloxy)-3-bromopropan-2-ol (6b)

A mixture 4-(oxiran-2-ylmethoxy)-9H-carbazole **(3)** (25.0g) in 48% aq. hydrobromic acid (125ml) was stirred for 8 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 produce **(6b)** as light brown white solid; 30.0g, yield 89.8%. ^{1}H NMR (



Scheme 4

DMSO): δ 11.3 (s, -NH), 8.2 (d, -CH, carbazole), 7.5 (d, -CH, carbazole), 7.2-7.4 (m, -CH, carbazole), 7.15 (m, -CH, carbazole), 7.1 (d, -CH, carbazole), 6.7 (d, -CH, carbazole), 5.8 (b, -CH-), 4.2 (m, -CH_2-), 3.6-3.8 (dd, -CH_2-), IR (Neat, cm^{-1}): 3405,1584; MS: m/z (M^++1) 319.

Preparation of 5-((9H-carbazol-4-yloxy)methyl)-oxazolidin-2-one (5)

A solution of 1-(carbazloe)-3-chloropropan-2-ol **(4)** (10g, 0.036 mole), potassium cyanate (5.89g, 0.072 mole) and 4-dimethylaminopyridine (0.44g, 0.003 mole) in N,N-dimethylformamide (30mL) was heated to 120°C for 6.0 h. After complete conversion reaction mixture was filtered to remove excess potassium cyanate. Solvent is removed from the filtrate under vacuum at 65-70°C. The resulted residue is partitioned between ethyl acetate and water. The reaction mixture is stirred for 10 min. and both the layers are separated. The aqueous layer is extracted with ethyl acetate. Combined organic layers are dried over sodium sulfate, filtered and washed with ethyl acetate. Solvent is removed from the organic layer by distilling at 40-45°C under vacuum to obtain title compound, 5-(carbazloe)methyl)oxazolidin-2-one **(5)** as a solid.; yield 55% m.p. 247-249°C; ^{1}H NMR ($CDCl_3$): δ 11.3 (s, -NH, carbazole), 8.16 (d, -

CH, carbazole), 7.7 (s, -NH, oxazole), 7.4 (d, -CH, carbazole), 7.3 (m, -CH, -CH carbazole), 7.18 (t, -CH, carbazole), 7.1 (d, -CH, -CH carbazole), 6.7 (d, -CH, carbazole), 5.1 (s, -CH), 4.42 (d, -CH), 4.3 (d, -CH), 3.7 (t, -CH), 3.56 (t, -CH). MS: m/z (M^++1) 283.

Preparation of 5-((9H-carbazol-4-yloxy)methyl)-3-(2-(2-methoxyphenoxy)ethyl)oxazolidin-2-one (7)

To a stirred solution of compound **(5)** (10.0g, 0.035 mole) and 50mL N,N-dimethylformamide, cesium carbonate (28.67 g, 0.088 mmol), 1-(2-chloroethoxy)-2-methoxybenzene (9.91g, 0.0531 mole) and potassium iodide (0.2g) are added at 25°C. Reaction mass is heated to 120°C. After completion of the reaction, cooled the reaction mass to 25°C and water was added to the reaction mixture. The reaction mass was filtered and the obtained product was purified using n-hexane to give compound **(6)** as a pale yellow solid; 70% yield; ^{1}H NMR ($CDCl_3$): δ 11.3 (s, -NH, carbazole), 8.1 (d, -CH, carbazole), 7.5 (d, -CH, Carbazole), 7.3 (q, -CH, carbazole), 7.3 (q, -CH carbazole), 7.1 (t, -CH, carbazole), 7.1 (t, -CH, -CH carbazole), 7.0 (m, -CH carbazole), 6.9 (d, -CH), 6.9 (d, -CH), 6.85 (m, -CH), 6.7 (d, -CH), 5.1 (d, -CH oxazole), 4.4 (m, -CH); 4.3 (t, -CH_2), 4.0 (t, -CH), 3.8 (m, -CH_2); 3.7 (s, -CH_3), 3.6 (m, -CH) 3.6 (m, -CH); MS: m/z (M^++1) 431.

Preparation of 1-(9H-carbazol-4-yloxy)-3-(2-(2-methoxyphenoxy)ethylamino)propan-2-ol (1) (Carvedilol)

The stirred solution of compound 6 (10.0g, 0.023 mole) is refluxed in 100mL 96% ethanol containing sodium hydroxide (4.0 g, 0.10 mole) under a nitrogen atmosphere. After completion of the reaction, reaction mixture is cooled to RT and a 50mL 1:1 mixture of toluene and THF followed by 100mL water 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 is recrystallized from ethyl acetate to give Carvedilol **(1)** as a white solid; yield 70%; m.p. 114-116°C; ^{1}H NMR ($CDCl_3$): δ 11.2 (s, -NH), 8.2 (s, -CH), 7.4 (d, -CH), 7.2-7.3 (m, -CH), 7.1 (m, -CH), 6.9 (m, -CH), 6.7 (d, -CH), 5.2 (s, -OH), 4.2 (d, -OCH_2), 4.1 (m, -CH_2), 4.0 (s, -CH), 3.75 (s, -OCH_3), 2.97 (m, -CH_2), 2.8 (m, -CH_2), 2.0 (s, -NH); MS: *m/z* (M^++1) 407.

Preparation of 3-(9H-carbazol-4-yloxy) propane-1, 2-diol (8)

To a stirred solution of compound **(3)** (10.0g, 0.041 mole) and 1,4-dioxane (10mL) was added 5% sulphuric acid. The reaction mass was heated to 95°C for 1.0 h. After completion of reaction, the solvent was distilled off to dryness under reduced pressure. The obtained residue was triturated with water and filtered to give **(8)** as a solid. 6.5 g, yield 60.7%. ^{1}H NMR (DMSO): δ 11.2 (s, -NH, carbazole), 8.2 (d, -CH, carbazole), 7.5 (d, -CH, Carbazole), 7.3 (m, -CH, carbazole), 7.1 (t, -CH, carbazole), 7.05 (d, -CH, carbazole), 6.7 (d, -CH, carbazole), 4.2 (m, -CH_2), 4.0 (m, -CH-), 3.6 (m, -CH_2), 3.2 (s, -OH) MS: *m/z* (M^++1) 256.13.

Preparation of 4-((9H-carbazol-4-yloxy)methyl)-1,3-dioxolan-2-one (9)

To a stirred solution of 1,1'-cabonyl diimidazole (8.2g, 0.050 mole) and dry dichloromethane (50mL) was added a solution of compound **(8)** (10.0g, 0.038 mole) in dry dichloromethane (100mL) at 25°C under nitrogen atmosphere. The reaction mass was maintained 18 hr at 25°C. The obtained solid was filtered and purified with n-hexane to give compound **(9)** as a solid. 8.6g, yield 74.7%. m.p.: 195-98°C; ^{1}H NMR (DMSO): δ 11.3 (s, -NH, carbazole), 8.1 (d, -CH, carbazole), 7.5 (d, -CH, Carbazole), 7.3 (m, -CH, carbazole), 7.1 (m, -CH, carbazole), 6.7 (d, -CH, carbazole), 5.3 (m, -CH-), 4.8 (dd, -CH_2), 4.4-4.7 (dd, -CH_2), MS: m/z (M^++1) 282.

ACKNOWLEDGEMENT

The authors thank Inogent Laboratories Private Limited (A GVK BIO Company) for the financial support and encouragement.

REFERENCES

[1] B.G.Main, H.Tucker; In: 'Medicinal Chemistry', The Role of Organic Chemistry in Drug Research of β-Blockers: S.M.Roberts, B.J.Price; Eds., Academic Press, London, **(1985)**.

[2] R.Howe, A.F.Crowther, J.S.Stephenson, B.S.Rao,

L.H.Smith; J.Med.Chem., **11**, 1000 **(1968)**.
[3] A.F.Crowther, L.H.Smith; J.Med.Chem., **11**, 1009 **(1968)**.
[4] **(a)** R.Howe, B.S.Rao; J.Med.Chem., **11**, 1118 **(1968).**
[5] **(a)** J.R.Powell, I.W.Wainer, D.E.Drayer; Drug Stereochemistry Analytical Methods and Pharmocology, M.Dekker, USA, **(1988)**; **(b)** M.E.Connolly, F.Kersting, C.T.Bollery; Prog.Cardio-vas.Dis., **19**, 203 **(1976)**.
[6] **(a)** R.Rabkin, D.P.Stables, N.W.Levin, M.M.Suzman; Am.J.Cardiol., **18**, 370 **(1966)**; **(b)** E.M.M.Bestermann, D.H.Friedlander; Postgrad. Med.J., **41**, 526 **(1965)**; **(c)** E.J.Ross, B.N.C.Prichard, L.Kaufmann, A.I.G.Robertson, B.J.Harries; Br.Med.J., 191 **(1967)**; **(d)** B.N.C.Prichard, P.M.S.Gillam; Br.Med.J., **725**, **(1964)**; **(e)** C.F.Geroge; Prescriber's Journal, **14**, 93 **(1974)**; **(f)** G.Sandler, A.C.Pistevos; Br.Med.J., 254 **(1971)**.
[7] **(a)** D.Gas, M.Kregar; Ann.Inter.Med., **70**, 985 **(1970)**; **(b)** P.Granville-Grossmann, P.Turner; Lancet, 788 **(1966)**; **(c)** H.J.Grosz, Lancet, 564 **(1972)**; **(d)** D.R.Hadden, D.A.Montogomery, R.G.Shanks, J.A.Weaver; Lancet, 852 **(1968)**; **(e)** H.F.Morelli; Ann.Inter.Med., **78**, 913 **(1973)**; **(f)** D.A.L.Owen, C.D.Marsden; Lancet, 1259 **(1965)**; **(g)** R.B.Weber, O.M.Reinmuth; Neurology, **22**, 366 **(1972)**; **(h)** R.R.Young, J.H.Gowen, B.T.Shahani; N.Engl.J.Med., **293**, 950 **(1975)**.
[8] W.Fritz, K.Wolfgang, T.Max, S.Gisbert, R.Egon, D.D.E.Karl; **2**, 815, 926 A1, Oct 18, **(1979)**, Chem.Abstr., **92**, P128716e **(1979)**.
[9] R.Zoltan, B.Jozsef, S.Gyula, G.Tamas, V.G.Donáth, N.Norbert, N.Kalman, C.Judit, S.Tibor, B.Laszlo, D.Imre, G.Zoltan, N.P.Kotay, S.Peter; EP 0, 918, 055 A1, May 26, **(1999)**, Chem.Abstr., **130**, P352184r **(1999)**.
[10] H.Jean, F.Sergey, A.Judith, B.Z.Dolitzky, B.V.Shoshana, K.Ilan; WO 02/00,216 A1, Jan 3, **(2002)**, Chem.Abstr., **136**, P90914e **(2002)**.
[11] P.Thomas, F.Erik, T.S.Peter; WO 01/87837 A1, Nov 22, **(2001)**, Chem.Abstr., **136**, P5898k **(2002)**.
[12] **(a)** K.Chinnam Naidu, G.Ravi Babu, L.Gangaiah, K.Mukkanti, G.Madhusudhan; Tetrahedron Lett., **51**, 1226 **(2010)**; **(b)** G.Madhusudhan, K.Chinnam Naidu, B.Anand Kumar, R.Satyanarayana, V.Balraju; Indian J.Chem.B, **48**, 741 **(2009)**; **(c)** G.Madhusudhan, G.Om Reddy, T.Rajesh, J.Ramanatham, P.K.Dubey; Tetrahedron Lett., **49**, 3060 **(2008)**.
[13] **(a)** M.E.Dyen, D.Swern; Chem.Rev., **67**, 197 **(1967)**; **(b)** M.E.Dyen, D.Swern; J.Org.Chem., **33**, 379 **(1968)**; **(c)** Y.M.Beasley, V.Petrow, O.Stephemon, A.J.Thomas; J.Pharm.Phormocd., **9**, 10 **(1957)**; **(d)** B.L.Phillips, P.A.Argabright; J.Heterocyclic Chem., **3**, 84 **(1966)**; **(e)** J.R.Piper, L.M.Rose, T.P.Johnston, M.M.Grenan; J.Med.Chem., **22**, 631 **(1979)**.