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ISSN: 2278-1862

Journal of Applicable Chemistry

2019, 8 (6): 2328-2335

(International Peer Reviewed Journal)

Improved synthesis of an adrenergic antagonist drug-Carvedilol

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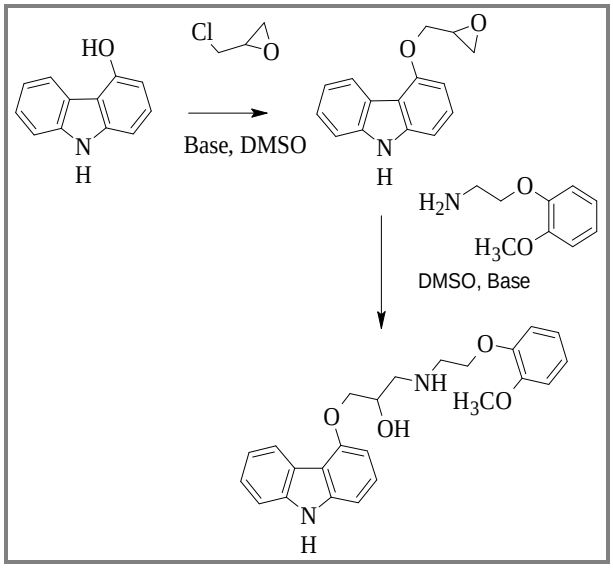
Accepted on 16th October, 2019

ABSTRACT

The present communication reports the preparation of carvedilol an adrenergic antagonist drug by a novel design of synthesis which has improved the yield. An optimized synthesis by screening different solvents and bases was proposed using R software. Finally, better conditions for preparation of carvedilol in high yields were established.

Graphical Abstract



Synthesis of Carvedilol

Keywords: 4-hydroxy carbazole, epichlorohydrin, 4-(2,3-epoxyprpoxy) carbazole, R software, 2-(2-methoxyphenoxy) ethanamine.

INTRODUCTION

Carvedilol (Figure 1) is an adrenergic antagonist with both non-selective β1, β2 and α_1 receptor blocking agent and also a vasodilatation drug with antioxidant activity. Carvedilol has demonstrated significant clinical benefits in the management of patients with heart failure and in the post-myocardial infarction setting. It also possesses unique ancillary properties that may account for positive results in a number of clinical trials. It appears to offer particular advantages in the treatment of co morbid conditions, including coronary artery disease, stroke hypertension, renal failure, diabetes and arterial fibrillation that can independently contribute to the progression of heart failure [**1-10**].

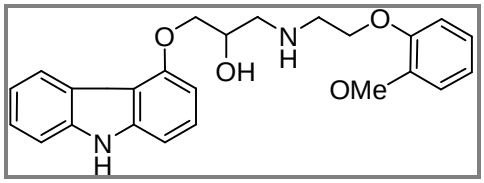


Figure 1. Structure of Carvedilol.

Carvedilol, also known as 1-(9*H*-carbazol-4-yloxy)-3-[[2-(2- methoxy phenoxy)ethyl]amino]-2-propanol. It has a chiral center and can exist either as individual stereoisomers or in racemic form. There are many synthetic methods known in the literature for the synthesis of Carvedilol. Among them Innovator route for the preparation of Carvedilol is described [**11-12**].

F. Wiedemann *et al*., reported the synthetic route to prepare Carvedilol [**13-16**] by treating the compound, 4-hydroxy carbazole **(2)** with epichlorohydrin **(3)** in presence of sodium hydroxide gave 4-(2,3-epoxyprpoxy) carbazole**(4),** which on treated with 2-(2-methoxyphenoxy)ethanamine **(5)** in neat reaction conditions afforded the desired compound Carvedilol **(1)**. The figure 2 shows the preparation of carvedilol [**17-20**].

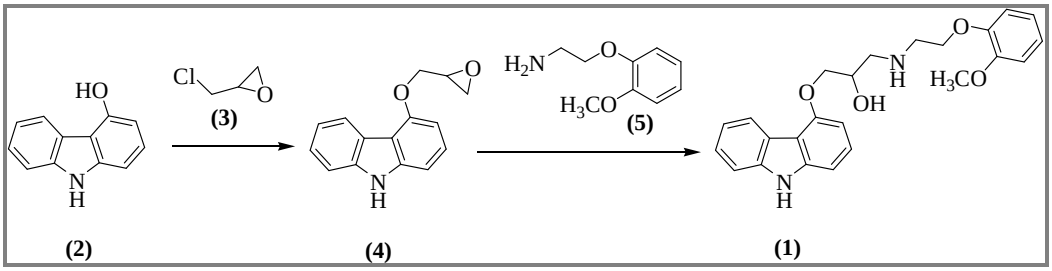


Figure 2. Preparation of Carvedilol.

MATERIALS AND METHODS

In the present work, synthesis of carvedilol was optimized by screening various bases, different solvents and established better conditions to improve yields by proper design of the experiments.

General procedure for preparation of carvedilol involves2 steps.

Preparation of carvedilol Step 1: Base sodium hydroxide was added over to 4-hydroxy carbazole in DMSO solvent at cool temperature 10-15°C. Then added epichlorohydrin, stirred for 5-6 h at ambient temperature. The reaction monitored by Thin layer chromatography. It was then quenched with cold water and filtered the precipitated solid.

Initially the synthesis was carried by taking DMSO as solvent and screened with different bases such as sodium carbonate, sodium bicarbonate, potassium hydroxide and potassium carbonate shown in figure 3.

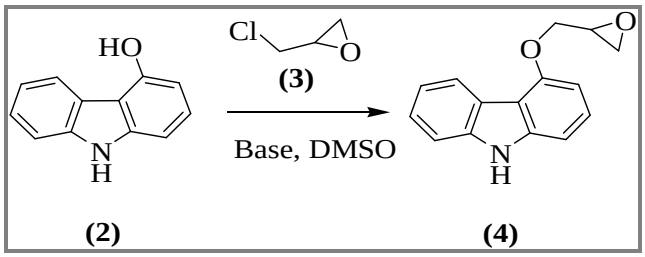


Figure 3. Carvedilol step 1.

After the screening process, the synthesis was carried out by taking Potassium carbonate as a base and screened with different solvents such as N,N-dimethyl formamide, toluene, n-hexane and neat condition shown in figure 4.

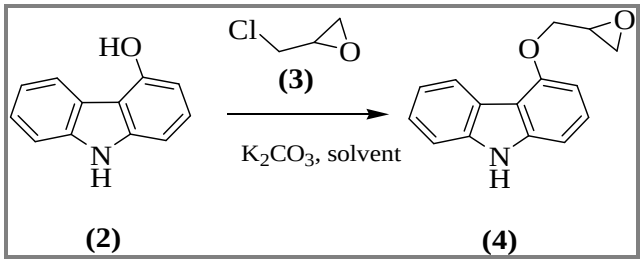


Figure 4. Carvedilol step 1

Optimised synthesis of 4-(2, 3-epoxyprpoxy) carbazole (Neat reaction): To a stirred solution of potassium carbonate (6.0 g, 0.0436 mol) in 5 mL water,4-hydroxy carbazole (2) (2 g, 0.0109 mol) was added over a period of 10-15 min. The reaction mass was cooled to 10-15°C. After stirring for 15 min, epichlorohydrin (2 g, 0.0218 mol) was added over 1 h duration by maintaining the temp at 10-15°C. The reaction mass temperature was slowly raised to 50-55°C and the suspension were maintained for 4 to 6 h under stirring at 50-55°C temperature. Reaction was monitored by TLC, checked absence of starting material, and then the product was diluted with 10 mL water, filtered and washed with water. The obtained crude product was recrystallized in acetone resulted as an off-white crystalline powder with 60.5% yield.

Spectral data analysis of 4-(2, 3-epoxyprpoxy) carbazole: 1H-NMR (400 MHz, DMSO): δ 11.2 (s, 1H, -NH), 8.1 (d, 1H Ar), 7.6 (m, 1H , Ar), 7.4 (m, 2H ,Ar), 7.2 (m, 2H, ArH), 6.7 (d, 1H , Ar), 4.2 (m, 2H, -CH_2-), 4.1 (m, 1H, -CH-), 2.9 (d, 2H, -CH_2- epoxy); MS: *m/z* (M^++1) 240 ; Anal. Calcd for $C_{15}H_{13}NO_2$: C – 75.30, H – 5.48, N – 5.85%; Found: C –75.32, H – 5.50, N – 5.87%.

RESULTS AND DISCUSSION

For the optimization of the synthetic scheme, R software is used as shown below.

Quality by design for step 1: Finally, by DOE (Design of experiments) using R software which is completely aligned with Quality by Design principles, better reaction conditions were established to improve yields.

In stage 1, the following parameters are selected [based on optimized process] for conducting design of experiments to establish the acceptable ranges

- Quantity of epichlorohydrin
- Quantity of potassium carbonate
- Epichlorohydrin addition time

Experiment design is prepared by considering ±10% to standard ranges.

Table 1. Study variable settings

Name	standard	Range/Levels
Epichlorohydrin	2.0 molar equivalence	1.8-2.2 molar equivalence
Potassium carbonate	4.0 molar equivalence	3.6-4.4 molar equivalence
Epichlorohydrin addition time	1.0 h	30-90 mins

Table 2. Factorial Experiments Design

Run No.	Factor:1 Epichlorohydrin (eq.)	Factor:2 Potassium carbonate (eq)	Factor:3 Time(mins)	Yield
1	2.2	3.6	30	71.7
2	1.8	4.4	30	73.7
3	2.2	3.6	30	71.2
4	2.2	4.4	30	77.1
5	2.2	4.4	30	71.6
6	1.8	4.4	30	76.2
7	1.8	3.6	30	73.6
8	2.2	3.6	30	78.9
9	2.2	3.6	90	57.9
10	1.8	4.4	90	78.4
11	1.8	3.6	90	75.7
12	1.8	3.6	90	74.2
13	2.2	3.6	90	74.3
14	2.2	4.4	90	73.6
15	1.8	4.4	90	72.7
16	2.2	4.4	90	73.4

After optimization, 4-(2,3-epoxyprpoxy) carbazole was prepared from 4-hydroxy carbazole with 2.0 mole equivalents epichlorohydrin and 4.0 mole equivalents potassium carbonate as a base in neat condition without using solvent. As per DOE, 16 experiments were conducted with different mole equivalents of epichlorohydrin, different mole equivalents of potassium carbonate and changing addition time of epihalohydrin. The above table 2 discloses the yield of total 16 experiments. Here the 10^{th} experiment with epichlorohydrin 1.8 mole equivalents(less quantity compared to 8^{th} experiment), potassium carbonate 4.4 mole equivalents and addition time 90 min resulted higher yield 78.4%. There is a good improvement in yield from 60.5% to 78.4% was observed. The application of DOE after optimization process, gave better yield of carvedilol step 1which will show decrease on the cost factor in bulk manufacture.

Preparation of carvedilol Step 2: Above compound epoxy propoxy carbazole (4)**,** which on treatment with 2-(2-methoxyphenoxy)ethanamine (5)in solvent maintained for 3-4 h at hot condition, monitored by TLC. Finally, on pH adjustment, followed by filtration provided the desired compound Carvedilol.

Initially the synthesis was carried out by taking DMSO as solvent and screened with different bases such as sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and aqueous ammonia as shown in figure 5.

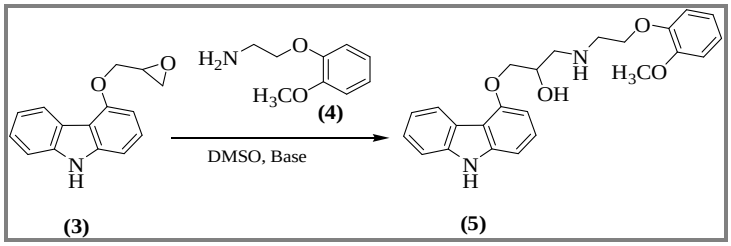


Figure 5. Carvedilol step 2.

After the screening process, the synthesis figure 6 was carried out by taking aqueous ammonia as a base and screened with different solvents such as N,N-dimethyl formamide, toluene, n-hexane and neat condition.

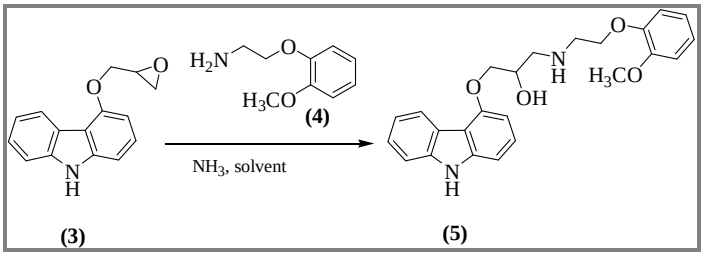


Figure 6. Carvedilol step 2.

Optimized synthesis of 1-(9*H*-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]-2- propanol: To 4-(2,3-epoxyprpoxy) carbazole **(3)**(1.0g,0.0041 mol)in N,N Di Methyl Formamide added 6.0 mL aqueous ammonia and thenadded2-(2-methoxyphenoxy)ethanamine **(4)** (2.1g, 0.0125 mol) to the mixture. This was heated to 85°c for 5-6 h. Then the reaction mass was cooled to 25-30°C, slowly extracted into DCM at neutral pH and distillation done. The gummy residue was dissolved in 4.0 M lacetone and filtered through hyflow bed and distilled off the organic layer under reduced pressure. The obtained crude material was purified by column chromatography by eluting with 25-30% ethyl acetate in toluene to get required compound as off white solidwith 68.4% yield.

Spectral data analysis of 1-(9*H*-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl amino]-2-propanol: IR (KBr): 3344 cm^{-1} (-OH); ^{1}H NMR ($CDCl_3$; 400 MHz): δ8.5 (m, 2H, -Carbazole), 7.4 (m, 4H, -Aromatic), 7.1 (m, 5H, -Carbazole), 6.4 (d, 1H, J=6.8 -carbazole), 4.1 (m, 5H, $-CH_2-CH-CH_2$), 3.85 (s, 3H, $-OCH_3$), 2.92 (m, 2H, $-CH_2$), 2.9 (m, 2H, $-CH_2$), 2.1 (bs, -NH); ^{13}C NMR (100 MHz, DMSO) δ 48.48, 52.13, 54.95, 68.17, 68.69, 70.21, 100.13,103.63, 109.71, 111.93, 112.21, 114.25, 118.42, 120.76, 121.49, 122.17, 124.26, 126.04, 139.29, 141.53, 148.15, 149.71, 155.11; MS: *m/z* (M+1) 407.

Quality by design for step 2: Finally, by DOE (Design of experiments) using R software which is Completely aligned with Quality by Design principles, better reaction conditions were established to improve yields.

In stage 2, the following parameters are selected [based on optimized process] for conducting design of experiments to establish the acceptable ranges

- Quantity of ksm 2
- Quantity of aqueous ammonia
- Temperature

Experiment design is prepared by considering ±10% to standard ranges.

Table 3. Study variable settings

Name	standard	Range/Levels
Ksm2	3.0 molar equivalence	2.7-3.3 molar equivalence
Aqueous ammonia qty	6.0 v	4.0-8.0 molar equivalence
temperature	85	70-100

Table 4. Factorial Experiments Design

Run No.	Factor:1 ksm2 (eq.)	Factor:2 Aqueous ammonia(v)	Factor:3 Temperature (°C)	Yield
1	3.3	8.0	100	78.9
2	2.7	4.0	70	64.7
3	2.7	4.0	100	64.7
4	3.3	8.0	70	71.4
5	3.3	4.0	100	80.5
6	2.7	4.0	70	64.9
7	2.7	8.0	100	60.8
8	2.7	8.0	70	63.4
9	3.3	4.0	70	71.2
10	3.3	4.0	70	76.3
11	2.7	8.0	70	59.55

After optimization, carvedilol was prepared from 4-(2,3-epoxyprpoxy) carbazole, 3.0 mole equivalents 2-(2-methoxyphenoxy)ethanamine with 6 volumes aqueous ammonia as a base in N,N Di Methyl Formamide as a solvent media at temperature 85°C. As per DOE, 11 experiments were conducted with different mole equivalents of 2-(2-methoxyphenoxy)ethanamine, different volumes of aqueous ammonia and at different reaction temperatures. The above table 4 discloses the yield of total 11 experiments. Here the 5^{th} experiment with 3.3 mole equivalents of 2-(2-methoxyphenoxy) ethanamine, 4.0 volumes of aqueous ammonia, at temperature 100°c resulted higher yield 80.5%.

There is a good improvement in yield from 68.4% to 80.5%. The application of DOE after optimization process, gave better yield which will show decrease on cost factor in bulk manufacture.

APPLICATION

The results reported in this communication have potential application involving efficient synthesis of API carvedilol an adrenergic antagonist drug.

CONCLUSION

The carvedilol is of great interest due to its pharmacological properties. In the present communication a simple and convenient synthetic method which gives good yield of target molecule is reported. The main purpose of the present work is to optimize the best conditions for the synthesis of this molecule It also ensures the use of Quality design in establishing better conditions for synthesis after optimization. This is simple and convenient synthetic method which gives good yield of target molecules.

ACKNOWLEDGEMENTS

The authors are thankful to GITAM (Deemed to be University), Visakhapatnam for providing necessary facilities to carry out this research work and for kind encouragement. Dept of Chemistry, GIS, GITAM is grateful to DST for the DST-FIST programme.

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