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One pot microwave-assisted synthesis of 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one

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Abstract

Oxazolidinone is a five-member heterocyclic ring used as a privileged structure for the synthesis of ligands for different biological targets. Many synthetic approaches have been made available for oxazolidinone, however, they were found to be either time/energy consuming or multistep process. One of the approach is a one-pot method to synthesize 3-benzyl-5-hydroxymethyl-oxazolidin-2-one using reflux overnight (>12 h). The aim of the present work was to develop an improved method by the use of microwave irradiation to make 3-benzyl-5-hydroxymethyl-oxazolidin-2-one. Benzyl amine was reacted with the various carbonate salts and epichlorohydrin, in presence of bases and solvent and the reaction was carried out under open and sealed-vessel conditions. Various factors including the use of carbonate salts, base, solvent, time, temperature and power were optimized. Microwave-assisted synthesis of 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one gave yields of 69.59% and 77.0% in an open vessel and a closed vessel, respectively with reduction in reaction time from overnight (>12 h) to 1 h in the open vessel and to 30 min in closed vessel.

Key words: Green chemistry, 1,3-oxazolidin-2-one, microwave synthesis, optimization

INTRODUCTION

Green chemistry is defined as "the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances". This is based on the 12 principles that can reduce the need for other approaches to environmental protection.[1–3] The concept such as microwave-assisted organic synthesis is gaining widespread acceptance in drug discovery laboratories. Microwave heating helps in performing chemical reactions that were not possible by conventional means, thus helping in exploring the structural diversity in the chemistry world by producing products in shorter time and lesser energy. [4] Microwave-assisted organic synthesis has several advantages over conventional heating methods such as high reaction yields, shorter reaction time, improved product selectivity, and environmentally friendly and low solvent waste. [5] The microwave irradiations are used to perform a wide range of organic reactions including a one-pot reaction, using 'green' reagents like water, recyclable catalyst like osmium tetroxide etc. [6,7] The advantages of this technology have, more been recently exploited in the context of multistep synthesis, medicinal chemistry, drug discovery, and have additionally entered different fields such as polymer synthesis, material sciences, nanotechnology and biochemical processes.[8]

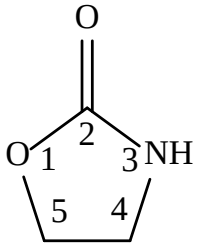


Fig. 1: Structure of 1,3-oxazolidin-2-one

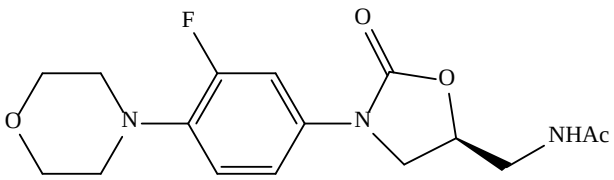
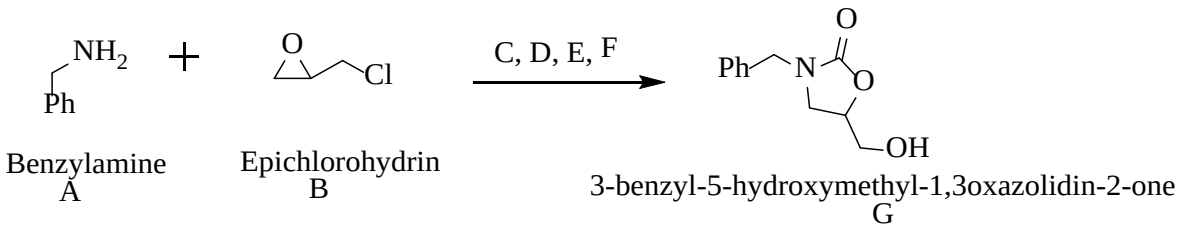


Fig. 2: Structure of Linezolid

1,3-Oxazolidin-2-one (Figure 1) is a five-member versatile intermediate used as scaffold for the synthesis of various ligands for different targets. [9] This fragment could be seen in antibiotics like linezolid, muscle relaxant like Metalaxone and is utilized as a privileged structure because of its occurrence in ligands for anti-muscarinic, anti-inflammatory, serotonergic targets etc. [10-13] Linezolid (Figure 1) is the first oxazolidinone approved for the treatment of Gram-positive bacterial infections in humans. [9]
3-benzyl-5-hydroxymethyl-1,3-oxazolidon-2-one fragment could be seen in muscarinic, serotonergic and MAO inhibitors. [12-14] This fragment can be made using either two step or one step method [9] Under the present investigation, we chose a one pot reaction from the literature to synthesize 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one as shown in Scheme 1. [5] The method utilized benzylamine, epibromohydrin, carbonate salt and suitable base using overnight reflux conditions (>12 h). Therefore, efforts were made to develop a new method based on microwave irradiation to synthesize 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one to make it available for biological importance. Two types of microwave conditions were chosen (open vessel and close vessel). [16,17] A literature search for 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one and *N*3-substitutedbenzyl-5-hydroxymethyl-1,3-oxazolidin-2-one (markush) did not give any microwave assisted synthesis references which further strengthened the aim of this work.

MATERIAL AND METHODS

All chemicals used in the microwave study were of high purity grade (AR grade). All reactions were conducted under an inert nitrogen atmosphere in CEM-Discover Lab-Mate microwave (CEM Corporation, USA). The FT-IR spectrum if the synthesized compounds were recorded on Perkin-Elmer infrared spectrometer using KBr discs. ^{1}H-NMR was recorded in deuterated chloroform ($CDCl_3$) on a 400 MHz Bruker spectrometer (Bruker Corporation, USA) with tetramethylsilane (TMS) as internal standard. The mass spectra was recorded on Thermo Finnigan LCQ
Advantage MAX LC/MS/MS (Thermo Scientific, USA). Thin layer chromatography (TLC) was performed on pre-coated plates of silica gel 60, F 254, from Merck using dichloromethane and methanol mobile phase.



Benzylamine A | Epichlorohydrin B | 3-benzyl-5-hydroxymethyl-1,3oxazolidin-2-one G

Scheme 1: Reagents and Reaction Conditions: (C) M_2CO_3 [M= K, Na, Pb, Ca, Mg]; (D) base [TEA, DIEA, DBU]; (E) sovent [MeOH, THF, DMF, H_2O]; (F) microwave irradiation

Synthesis of 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one

To an accurately weighed quantity of the selected carbonate salts (Tables 1, 2 and 3) (1 Eq) in 50 mL round bottom flask (RBF) or 10 mL microwave vials, was added a suitable solvent (10 ml or 2 mL), benzylamine (2 Eq), epichlorohydrin (3 Eq) and the selected base (3 Eq). The RBF/vial was heated under varying experimental conditions to optimize the method such as power (100-200 W), temperature (50-100 ^oC) and time (15-120 min). Reactions were carried out under open vessel (nitrogen atmosphere) and close vessels conditions (nitrogen flushed). The reaction was monitored by developing the TLC plate in 10% MeOH in dichloromethane (DCM), visualised under UV 254 nm, and stained in $KMnO_4$ solutions. After completion of the reaction time, the mixture was cooled, filtered and solvent was evaporated under rotary evaporator, followed by the purification with flash chomatography (Combiflash Rf, Teledyne Isco, USA) using DCM and MeOH (0-10 %). The purified compound (white solid) was analysed by FTIR, ^{1}H-NMR and MS. The spectral studies corresponded with the literature[12,14,15]

RESULTS AND DISCUSSION

The present work investigated the synthesis of 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one (Scheme 1) using microwave energy. Our reaction scheme used epichlorohydrin instead of epibromohydrin as the literature method indicated no difference observed in the yield between epibromohydrin (83%) and epichlorohydrin (81%) under reflux condition.[16] The reaction conditions were optimized as indicated in Tables 1, 3 (open vessel) and Table 2 (closed vessel).

Open Vessel Conditions

Table 1 shows open vessel conditions, which has the reaction ratio of carbonate, benzylamine, epiclorohydrin, base as 1:2:3:3. The reaction was studied by changing the each variable such as carbonate salt, solvent, base, power, time and temperature.

Effect of carbonate salts and time:

In batches 1.0-1.6, the reactions were carried out using potassium carbonate (K_2CO_3), trimethylamine (TEA), methanol (MeOH) at 100W at 50, 60 and 65 ^oC from 60-120 min. No observable product was seen for batches 1.0-1.3. Increasing the reaction temperature to 60 ^oC for 60 min also did not show any product, however the product was observed at 120 min with 44.5% yield (batch 1.5). The maximum yield obtained was for batch 1.6 at reflux temperature at 60 min with 69.59 % yield.

Changing the reaction ratio from 1:2:3:3 at this point to 1:5:5:5 (batch 9.0) dropped the yield to 47.09 %. Hence, further reactions (batches 2.0-8.1) were carried out at a ratio of 1:2:3:3 (C:D:A:B). We studied other carbonate salts of sodium (Na), lead (Pb), calcium (Ca), magnesium (Mg) and caesium (Cs) (batches 2.1-6.0) keeping the base and solvent as before. With Na_2CO_3, the reaction did not proceed at 50 ^oC at 60 min (batch 2.0) and low yield of 6.9 % was seen when the reaction was extended till 120 min (batch 2.1). Increasing the temperature to 60 ^oC for 60 min failed to produce any observable product at 120 min (batches 2.2, 2.3). At reflux temperature for 60 min, the yield observed was 6.3% (batch 2.4). The remaining carbonate salts were tested at reflux temperature for 60 min (batches 3.0-6.0). Calcium carbonate ($CaCO_3$) gave the lowest yield of 0.96% whereas caesium carbonate ($CsCO_3$) gave 60%. Among all the carbonate salts tried and tested as per literature (batches 1.0-6.0), the highest yield was obtained by using K_2CO_3 (batch 1.6) as supported by literature.(15) Hence, K_2CO_3 was taken as optimum carbonate salt and was used for further reactions (batches 7.0-8.1).

The next variables changed were bases (batches 7.0-7.1), solvent (batches 7.2-7.5), and power (batches 7.6-8.1).

Effect of base:

In literature, it was observed that addition of strong base has shown to increase the yield. [15] Therefore, different bases like TEA (trimethylamine), DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) and DIEA (diisopropylethylamine) were investigated and TEA was found to provide a yield of 70 % followed by DBU and DIEA having 58.78 % and 2.7 % respectively (batches 7.0-7.1). Keeping DIEA and changing the solvent to polar aprotic such as THF did not show any improvement in the yield (6.08%, batch 7.2).

Effect of solvent:

We investigated polar protic (MeOH and H_2O) and polar non-protic like THF, DMF solvents (batches 7.3-7.5). Amongst the different solvent systems, the yield ranged between 1.35-2.02% which was irrespective or the polarity of the solvents. Based on the observations, methanol was the best solvent for the reaction, which is in accordance with the literature study.[15]

Effect of power:

The final variable changed was power from 150W-200W (batches 7.6-8.1) with time varying between 15-60 min with constant temperature of 65 ^oC. At 150W, the maximum yield obtained was 22.29%. On further increasing the power to 200W, for 15 min, the yield obtained was 14.86% and the reaction charred at 30 and 60 min. From the present studies, we infer that for the synthesis of 3-benzyl-5-hydroxymehtyl-oxazolidon-1,2-dione under open vessel microwave system gave a maximum yield of 69.59% requiring the presence of TEA, K_2CO_3, MeOH at 100W, 65°C for 60 min.

Closed Vessel Conditions

The close vessel conditions were carried out using TEA, K_2CO_3, MeOH with varying power (100W-200W), temperature (50 ^oC-100 ^oC) and time (15 min-120 min).

Effect of temperature and time:

At 50 ^oC, the yield increased with the increase in time from 15 min (13.5 %) to 60 min (56 %) and later dropped to 39 % if continued for 120 min (batches 10.0-10.3). Increasing the temperature to 60 ^oC helped in increase in the yield from 35 % to 65 % at 15-60 min (batches 10.4-10.6) with a drop in yield to 7 % at 120 min (batch 10.7). Comparing the reaction carried at 50 ^oC vs 60 ^oC (batches 10.0-10.7), we observed that, with the increase in the time from 15-30 min, there was an modest increase in the yield, 13.5 % vs 35.81 % (batches 10.0 and 10.4) and 24.32 % % vs 64.86 % (batches 10.1 and 10.5). A marginal increase in yield (56 % vs 58.78 %) was observed for batches 10.2 and 10.6. Increasing the temperature to 80 ^oC and 100 ^oC for 15 min (batches 10.8 and 10.9) resulted in bumping of the reaction mixture inside the microwave vessel. Hence, the remaining reactions were carried at temperatures below 80 ^oC.

Table 1: Percent isolated yield of 3-benzyl-5-hydroxymethyl-1, 3-oxazolidin-2-one under open vessel condition using starting material ratio (C:A:B:D) of 1:2:3:3

Batch No.	A	B	Carbonate salt (C)	Base (D)	Solvent (E)	Microwave (F)			Percent isolated yield (G)
						Power (W)	Temp. (°C)	Time (min)	
1.0	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	50	30	No rxn
1.1	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	50	60	No rxn
1.2	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	50	90	No rxn
1.3	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	50	120	No rxn
1.4	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	60	60	No rxn
1.5	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	60	120	44.59
1.6	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	65	60	69.59
2.0	Benzylamine	epichlorohydrin	Na_2CO_3	TEA	MeOH	100	50	60	No rxn
2.1	Benzylamine	epichlorohydrin	Na_2CO_3	TEA	MeOH	100	50	120	6.9
2.2	Benzylamine	epichlorohydrin	Na_2CO_3	TEA	MeOH	100	60	60	No rxn
2.3	Benzylamine	epichlorohydrin	Na_2CO_3	TEA	MeOH	100	60	120	7.69
2.4	Benzylamine	epichlorohydrin	Na_2CO_3	TEA	MeOH	100	65	60	6.3
3.0	Benzylamine	epichlorohydrin	$MgCO_3$	TEA	MeOH	100	65	60	16.14
4.0	Benzylamine	epichlorohydrin	$PbCO_3$	TEA	MeOH	100	65	60	27.92
5.0	Benzylamine	epichlorohydrin	$CaCO_3$	TEA	MeOH	100	65	60	0.96
6.0	Benzylamine	epichlorohydrin	Cs_2CO_3	TEA	MeOH	100	65	60	60.13
7.0	Benzylamine	epichlorohydrin	K_2CO_3	DIEA	MeOH	100	65	60	2.70
7.1	Benzylamine	epichlorohydrin	K_2CO_3	DBU	MeOH	100	65	60	58.78
7.2	Benzylamine	epichlorohydrin	K_2CO_3	DIEA	THF	100	65	60	6.08
7.3	Benzylamine	epichlorohydrin	K_2CO_3	TEA	DMF	100	80	60	1.35
7.4	Benzylamine	epichlorohydrin	K_2CO_3	TEA	THF	100	65	60	2.02
7.5	Benzylamine	epichlorohydrin	K_2CO_3	TEA	H_2O	100	100	60	1.35
7.6	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	65	15	2.7
7.7	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	65	30	8.1
7.8	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	65	60	22.29
7.9	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	65	15	14.86
8.0	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	65	30	Charred
8.1	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	65	60	Charred

Table 2: Isolated percent yield of 3-benzyl-5-hydroxymethyl-1, 3-oxazolidin-2-one using close vessel conditions at the starting materials ratio (C:A:B:D) of 1:2:3:3

Batch No.	A	B	Carbonate salt (C)	Base (D)	Solvent (E)	Microwave (F)			Isolated % yield
						Power (W)	Temp. (°C)	Time (min)	
10.0	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	50	15	13.50
10.1	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	50	30	24.32
10.2	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	50	60	56.08
10.3	Benzylamine	Epichlorohydrin	K_2CO_3	TEA	MeOH	100	50	120	39.18
10.4	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	60	15	35.81
10.5	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	60	30	64.86
10.6	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	60	60	58.78
10.7	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	60	120	7.43
10.8	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	80	15	Bumping
10.9	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	100	15	Bumping
11.0	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	50	15	39.86
11.1	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	50	30	49.32
11.2	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	50	60	77.02
11.3	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	50	120	69.59
11.4	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	60	15	75.67
11.5	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	60	30	76.35
11.6	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	60	60	24.32
11.7	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	60	120	23.64
11.8	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	150	70	30	72.29
11.9	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	50	15	23.64
12.0	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	50	30	77.02
12.1	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	50	60	61.48
12.2	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	50	120	38.51
12.3	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	60	15	71.62
12.4	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	60	30	46.62
12.5	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	60	60	24.32
12.6	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	200	60	120	19.59

Table 3: Percent isolated yield of 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one under open vessel conditions at the starting materials ratio of 1:5:5:5 (C:A:B:D)

Batch No.	A	B	Carbonate salt (C)	Base (D)	Solvent (E)	Microwave			Percent isolated yield (G)
						Power (W)	Temp. (°C)	Time (min)	
9.0	Benzylamine	epichlorohydrin	K_2CO_3	TEA	MeOH	100	65	60	47.09

Effect of power, temperature and time:

The next set of reactions were carried out at 150W and the temperature was varied from 50 ^{o}C to 70 ^{o}C from 15-120 min (batches 11.0 to 11.8). At 150W and 50 ^{o}C, as we increased the time from 15 min to 120 min, it was observed that the yield was increased from 39.86 % to 77 % (batches 11.0-11.2) and dropped to 69.59 % (batch 11.3) as we further carried the reaction to 120 min. On increasing the temperature to 60 ^{o}C, we observed that there was an increase in the yield from 39.86 % to 75.67 % at 15 min (batch 11.0 vs batch 11.4) and 49.32 % to 76.32 % at 30 min. (batch11.1 vs 11.5). At 60 and 120 min, a drop in yield from 77 % to 24.32 % and 69.59 % to 23 % was observed on increasing the temperature from 50 ^{o}C to 60 ^{o}C suggesting that lower time (15 min) and temperature (50 ^{o}C) was better for the product yield. Further increasing the temperature to 70 ^{o}C at 30 min showed slight drop in the yield to 72 % when compared with 60 ^{o}C at 30 min (batch 11.5).

The final set of reactions were studied at 200 W with the temperature was varied from 50 ^{o}C to 60 ^{o}C from 15-120 min (batches 11.9 to 12.6). We observed that at 50 ^{o}C, the yield initially increased from 23.64 % to 77 % from 15-30 min (batch 11.9 and 12.0) and later dropped to 61 % and 38 % when time was further increased from 60-120 min. At 60 ^{o}C, the isolated yield started dropping from 71 % to 19 % as the time was increased from 15 to 120 min (batches 12.3-12.6). Comparing the reaction carried at 50 ^{o}C vs 60 ^{o}C (batch 11.9 vs 12.3), we observed that significant increase in yield was observed at 15 min from 23.64 % to 71 %. From 30-120 min, the reaction yield started dropping with the increase in temperature from 50 ^{o}C to 60 ^{o}C (batches 12.0 and 12.4, 12.1 and 12.5 and 12.2 and 12.6). Taking all factors into consideration such as power, temperature and time, we infer that the reaction is best carried out at 200W at 50 ^{o}C and 30 min giving yield of 77 % which comparable to the literature yield of 81 % under conventional heating requiring more than 12 h. Close vessel condition was also found to better than open vessel in terms of temperature, time and yield (batch 1.6 vs 12.0). We can also conclude that microwave-assisted organic synthesis has showed advantages over conventional heating methods such as comparable reaction yields, shorter reaction time with respect to the literature method. [15]

CONCLUSION

At present, the available methods for synthesizing 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one involve either one/two steps using reflux conditions with possible conventional drawbacks. In the present study, the use of novel and simple method has been developed to improve resulting from the use of microwave irradiation as well as occurrence of non-thermal effect. Microwave assisted synthesis, yielded 69.59% and 77.0% of the product in an open vessel and a closed vessel, using TEA, MeOH at reflux temperature for either 60 min-open vessel or 30 min-closed vessel. The yields are comparable to the literature values. The overall reaction time was reduced from overnight (>12 h) to 1h in the open vessel and to 30 min in closed vessel. In conclusion, microwave irradiation for synthesizing 3-benzyl-5-hydroxymethyl-1,3-oxazolidin-2-one was found to be facile and results in almost productive yield, short duration time, mild reaction condition and simple workup procedure. Further work, is in progress, to investigate the microwave conditions for other substituted benzyl amines.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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