



ISSN 0975-413X  
CODEN (USA): PCHHAX

Der Pharma Chemica, 2024, 16(2): 243-248  
(<http://www.derpharmachemica.com/archive.html>)

## A Catalyst Free Simple and Efficient One Pot Synthesis of N-benzyloxazolidinone Derivatives

Mahesh Kumar A<sup>1,2</sup>, Rapolu Venkateshwarlu<sup>1</sup>, Shambhu Nath Singh<sup>1</sup>, Chandra Sekhar VN<sup>1</sup>, Akula Raghunadh<sup>1,2\*</sup>, Venkateswara Rao B<sup>3</sup>, Vidavalur Siddaiah<sup>2</sup>

<sup>1</sup>Department of Process Chemistry, Dr. Reddy's Laboratories, Hyderabad, India

<sup>2</sup>Department of Organic Chemistry and FDW, Andhra University, Visakhapatnam, India

<sup>3</sup>Department of Engineering Chemistry, Andhra University, Visakhapatnam, India

\*Corresponding author: Akula Raghunadh, Department of Process Chemistry, Dr. Reddy's Laboratories, Hyderabad, India, E-mail: [raghunadha@drreddys.com](mailto:raghunadha@drreddys.com)

Received: 01-March-2024, Manuscript no: Dpc-24-128657, Editor assigned: 06-March-2024, PreQC No: Dpc-24-128657 (PQ), Reviewed: 20-March-2024, QC No: Dpc-24-128657, Revised: 22-March-2024, Manuscript No: Dpc-24-128657 (R), Published: 19-April-2024, DOI: 10.4172/0975-413X.16.2. 243-248

### ABSTRACT

An efficient and catalyst free one pot synthesis of N-benzyloxazolidinone derivatives is developed by reaction of N-benzyl-β-amino alcohol derivatives and N, N-Carbonyldiimidazole (CDI) in DMSO. A range of novel N-benzyloxazolidinone derivatives were synthesized by using this one pot methodology with good to excellent yields.

**Keywords:** Oxazolidinones; N-benzyl-β-amino alcohol; N,N-carbonyldiimidazole; Heterocycles

### INTRODUCTION

The effectiveness of latest generation of antibiotics is gradually decreasing towards the treatment of numerous infectious diseases due to the newly emerging resistance mechanism developed inside the microbial. This led to the extensive research and there by discovery of new antibiotics for the treatment of various diseases. N-Aryloxazolidinones and the corresponding derivatives are known to be effective against Vancomycin-Resistant Enterococci (VRE) and Methicillin-Resistant *Staphylococcus Aureus* (MRSA) [1]. The oxazolidinone derivatives, linezolid and posizolid (Figure 1) are found to be active against bacterial infection. Interestingly oxazolidinones also have shown pharmacological activity as antidepressant and antischizophrenia [2]. Toloxatone and befloxatone (Figure 2) are used for the treatment of depression as a reverse inhibitor of MAO-O [3]. Some of the oxazolidinone derivatives are also employed as key structural fragments in biologically active materials for pharmaceutical use [4] and also as auxiliaries in useful synthetic conversations [5].

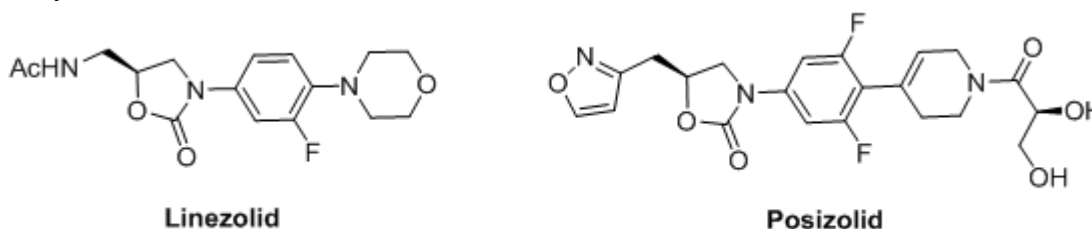
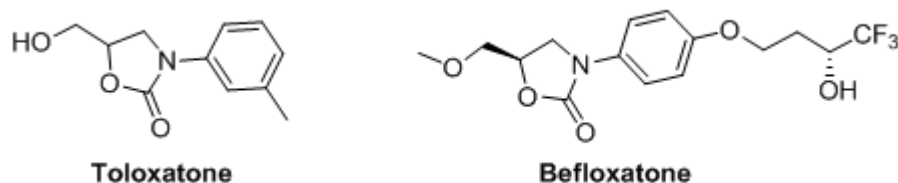
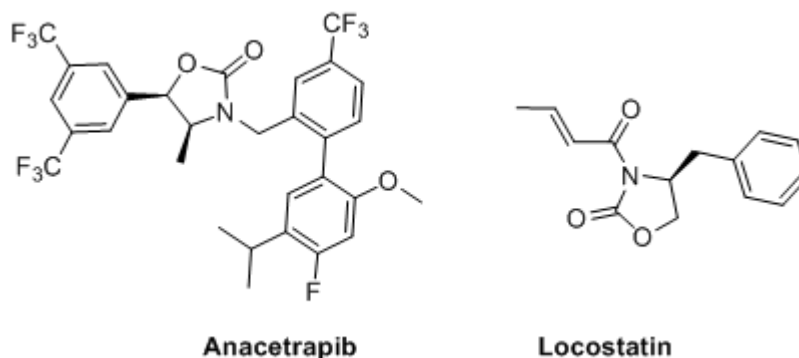


Figure 1: Known oxazolidinones having antibacterial activity.



**Figure 2:** Known oxazolidinones having anti-depressant activity.

Recently, Anacetrapib which contains an oxazolidine core has been identified as ETP inhibitor (Figure 3) and is currently being studied in clinical trials [6]. Locostatin, an oxazolidinone derivative is found to be useful in controlling inflammation, sepsis and autoimmune diseases [7].

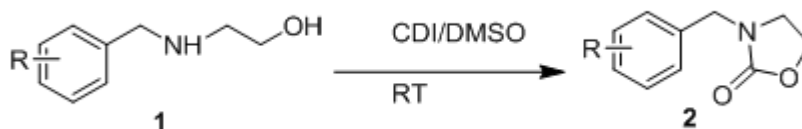


**Figure 3:** Examples of bioactive oxazolidinones.

#### MATERIALS AND METHODS

The most common synthetic routes reported so far for the synthesis of N-benzyloxazolidinones includes N-benzylayion of oxazolidinones [8], carboxylation of N-benzyl-β-amino alcohols [9]. The methods reported so far either involves use of metal catalyst or use of carbon dioxide in the presence of catalyst.

N,N-Carbonyldiimidazole (CDI) is a widely used reagent in organic synthesis. It is frequently used as a replacement for the highly toxic phosgene in reactions with alcohols and amines [10,11] and the by-product imidazole formed after the reaction can be easily removed by dilute acid wash. Based on this, we tried to use CDI as a reagent in our synthesis of N-benzyloxazolidinones and successfully developed a catalyst free approach for the synthesis of N-benzyloxazolidinones (2) from N-benzyl-β-amino alcohol derivatives (1) using N,N-Carbonyldiimidazole (CDI) in DMSO (Figure 4).



**Figure 4:** One pot synthesis of N-benzyloxazolidinones.

#### RESULTS AND DISCUSSION

The N-benzyl-β-amino alcohol derivatives required for the synthesis were prepared from benzaldehyde derivatives and ethanolamine following the same procedure reported by Xiong-Jie and his team. Initially, the reaction was performed by stirring beta amino alcohol 1a and CDI in DCM at room temperature for 15 hrs. To our delight N-benzyloxazolidinone 2a was obtained in 30% yield along with the recovery of the unreacted intermediate N-benzyl-β-amino alcohol (entry 1, Table 1). Attempts were made to increase the product yield by extending the reaction time or temperature (entry 2 and 3, Table 1). But these attempts did not show any significant increase in the product yield. Other solvents like THF, DMSO and DMF (entry 4, 5 and 6, Table 1) were also screened for the reaction. Among the solvents, DMSO was found to be optimum for the reaction and the yield remarkably improved to 94%. Only 25% of the product formation was observed in THF however considerable amount of product (70%) was obtained by using the DMF solvent. Further attempts were made to improve the yield in DMSO by increasing the reaction temperature (entry 7, Table 1) however did not get any positive result. Overall, the reaction conditions presented for the entry 5 in Table 1 found to be superior to other screening experiments.

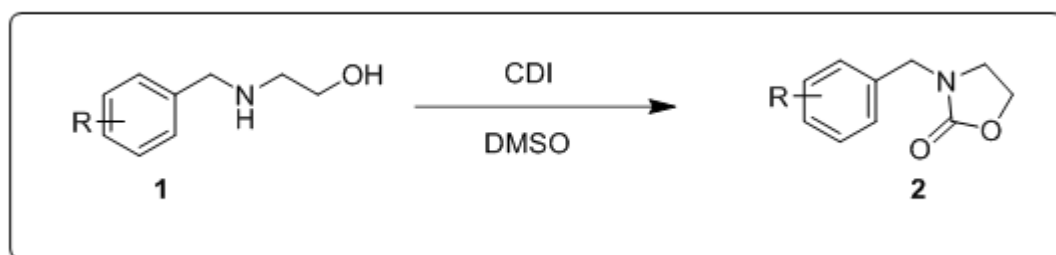
**Table 1:** Effect of reaction conditions on the conversion of the beta amino alcohol to oxazolidinone derivative.

Entry <sup>a</sup>	Solvent	Temp (°C)	Time (h)	% Yield <sup>b</sup>
1	DCM	30	15	30
2	DCM	30	24	32
3	DCM	40	15	28
4	THF	30	15	25

5	DMSO	30	12	94
6	DMF	30	15	70
7	DMSO	45	15	40

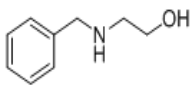
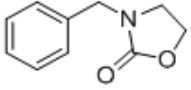
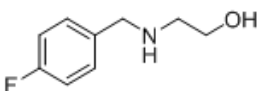
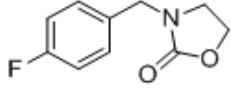
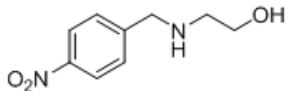
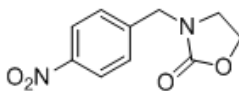
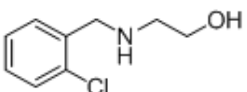
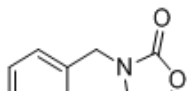
**Note:** <sup>a</sup>Reactions were carried out using 1a (1.0 mmol) and CDI (1.5 mmol) in a solvent at room temperature under nitrogen; <sup>b</sup>Isolated yield.

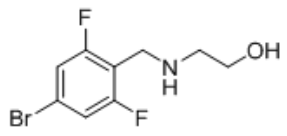
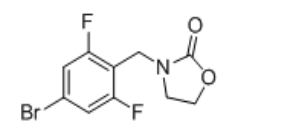
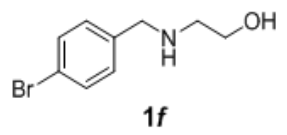
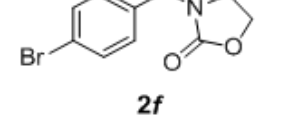
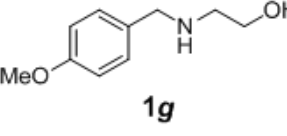
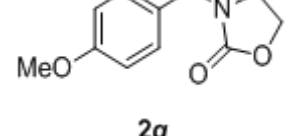
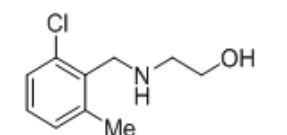
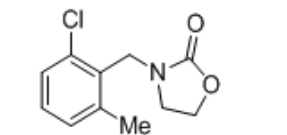
The scope and generality of the reaction was further tested by performing the reactions using variety of N-benzyl-β-amino alcohol derivatives (1). Substituents such as Cl, Br, F, NO<sub>2</sub> on the benzene ring (entries 1-6, Table 2) were well tolerated. The reaction proceeded well in all these cases affording desired N-benzylloxazolidinones 2 in good to excellent yields. All the N-benzylloxazolidinone derivatives (2a-h) synthesized were characterized by their <sup>1</sup>H and <sup>13</sup>C NMR and HRMS data and further confirmed by comparing with the data reported for these compounds in literature (Figure 5 and Table 3).



**Figure 5:** Synthesis of N-benzylloxazolidinone derivatives.

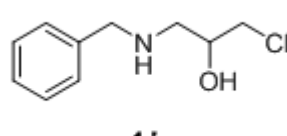
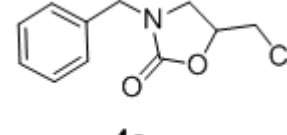
**Table 2:** Synthesis of N-benzylloxazolidinone derivatives 2 via one pot reaction of 1 and CDI<sup>a</sup>.

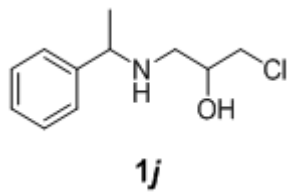
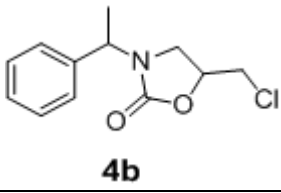
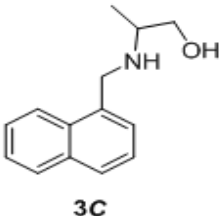
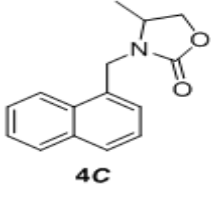
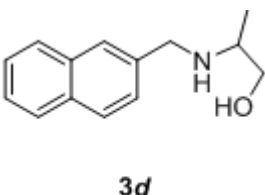
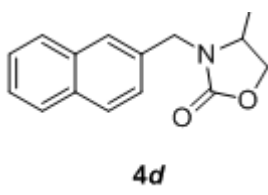
S. NO	N benzyl β amino alcohol derivatives	Product	Time (h)	Yield (%)
1	 <b>1a</b>	 <b>2a</b>	2	96
2	 <b>1b</b>	 <b>2b</b>	2	94
3	 <b>1c</b>	 <b>2c</b>	3	89
4	 <b>1d</b>	 <b>2d</b>	3	90

5	 <b>1e</b>	 <b>2e</b>	2.5	92
6	 <b>1f</b>	 <b>2f</b>	2.0	90
7	 <b>1g</b>	 <b>2g</b>	3.0	88
8	 <b>1h</b>	 <b>2h</b>	2.5	90
<b>Note:</b> <sup>a</sup> Reactions were carried out using N-benzyl beta amino alcohol (1) (1.0 mmol) and CDI (1.5 mmol) in DMSO at room temperature under nitrogen; <sup>b</sup> Isolated yield.				

We have also extended this methodology for the preparation of functionalized oxazolidinone derivatives (4a-d, Table 3). The methodology worked well for the synthesis of these derivatives.

**Table 3:** Synthesis of functionalized oxazolidinone derivatives 4a-d via one pot reaction.

S. No	N-benzyl-β-amino alcohol derivatives	Product	Time (h)	Yield (%)
1	 <b>1i</b>	 <b>4a</b>	2.0	96

2	 <b>1j</b>	 <b>4b</b>	2.0	94
3	 <b>3c</b>	 <b>4c</b>	3.0	89
4	 <b>3d</b>	 <b>4d</b>	3.0	90
<b>Note:</b> <sup>a</sup> Reactions were carried out using <i>N</i> -benzyl beta amino alcohol (1) (1.0 mmol) and CDI (1.5 mmol) in DMSO at room temperature under nitrogen; <sup>b</sup> Isolated yield.				

### Experimental

**General method for the preparation of  $\beta$ -aminoalcohol (1a-h):** Ethanolamine (1.0 mmol) was added to a stirring solution of aromatic aldehyde (1 mmol) dissolved in methanol (5 mL) and stirred at 25°C-30°C for 1 h. After 1h, sodium borohydride (0.5 mmol) was added and stirred at 25°C-30°C for 2 h under nitrogen atmosphere. After the completion of reaction, quenched the reaction mass with water, extracted the product with ethyl acetate and washed with water. Dried the organic layer with sodium sulphate and distilled under vacuum to get the required  $\beta$ -aminoalcohol.

3-benzylloxazolidin-2-one (2a): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  7.37- 7.26 (m, 5H), 4.42 (s, 2H), 4.31- 4.27(m, 2H), 3.43-3.39(m, 2H); <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  158.53, 135.76, 128.83(2C), 128.16(2C), 127.98, 61.76, 48.42, 43.95; HRMS: m/z [M+H] calculated for C<sub>10</sub>H<sub>12</sub>NO<sub>2</sub>: 178.0868; found: 178.0865.

**General method for the preparation of oxazolidinones derivatives (2a-2h) and (4a-d):**  $\beta$ -Aminoalcohol (1.0 mmol) was dissolved in DMSO (2 mL) and added carbonyldiimidazole (1.5mmol) under nitrogen atmosphere and stirred at 23°C-30°C for 2 h-3 h. After the completion of reaction, reaction mass was diluted with water and extracted the product with ethyl acetate. Washed the ethyl acetate layer with dilute HCl solution followed by with water. Dried the organic layer with sodium sulphate and distilled under vacuum to get the pure product.

4-methyl-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (4c): <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  8.10-8.08 (d, J=7.9Hz, 1H), 7.97-7.95 (m, 1H), 7.91-7.89 (d, J=7 Hz, 1H), 7.59-7.51 (m, 2H), 7.49-7.45 (m, 2H), 4.85-4.82 (d, J=14.9 Hz, 1H), 4.74-4.71 (d, J=14.9Hz, 1H), 4.58-4.53 (m, 1H), 3.45-3.41 (t, 1H), 2.91-2.87 (t, 1H), 1.20-1.19 (d, J=6.1Hz, 3H); <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>): 157.59, 133.94, 131.49, 129.13, 128.94, 127.28, 127.03, 126.51, 125.88, 123.72, 70.31, 50.59, 45.93, 20.81; HRMS: m/z [M+H] calculated for C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub>: 242.118; found: 242.1188.

### CONCLUSION

In conclusion, we have reported a simple and efficient one pot synthesis of *N*-benzyl- $\beta$ - amino alcohols and CDI in DMSO in good to excellent yields. The methodology does not require any use of base, catalyst or hazardous solvents.

### ACKNOWLEDGEMENT

The authors would like thank the management of Dr. Reddy's laboratories limited for providing support to carry out this work. We also thank the analytical department of Dr. Reddy's laboratories for providing timely support.

### REFERENCES

- [1] Crich D. J Org Chem. **2011**; 76(22): p. 9193-9209.
- [2] Christensen HM, Oscarson S, Jensen HH. Carbohydr Res. **2015**; 408: p. 51-95.
- [3] Van Delft FL, Timmers CM, Van der Marel GA, et al. Synthesis. **1997**; 1997(04): p. 450-454.
- [4] Park CS, Kim MS, Sim TB, et al. J Org Chem. **2003**; 68(1): p. 43-49.
- [5] Ella-Menye JR, Wang G. Tetrahedron. **2007**; 63(40): p. 10034-10041.
- [6] Mancuso R, Maner A, Ziccarelli I, et al. Molecules. **2016**; 21(7): p. 897.
- [7] Buur A, Bundgaard H. Int J Pharm. **1988**; 46(1-2): p. 159-167.

- [8] Lindsay KB, Ferrando F, Christensen KL, et al. *J Org Chem.* **2007**; 72(11): p. 4181-4188.
- [9] Sonzini P, Damiano C, Intriери D, et al. *Adv Synth Catal.* **2020**; 362(14): p. 2961-2969.
- [10] Pulla S, Felton CM, Ramidi P, et al. *J CO<sub>2</sub> Util.* **2013**; 2: p. 49-57.
- [11] Peilleron L, Retailleau P, Cariou K. *Adv Synth Catal.* **2019**; 361(22): p. 5160-5169.