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A Catalyst Free Simple and Efficient One Pot Syntheis of N-Benzyloxazolidinoe Derivatives

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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 synthesised 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 enterococii (VRE) and methicillin-resistant Staphylococcus aureus (MRSA) [1-3]. The oxazolidinone derivatives, Linezolid and Posizolid (Fig.1) are found to be active against bacterial infection. Interestingly oxazolidinones also have shown pharmacological activity as antidepressant and antisychosis [4-6]. Toloxatone and Befloxatone (Fig.2) are used for the treatment of depression as a reverse inhibitor of MAO-O [7-12]. Some of the oxazolidinone derivatives are also employed as key structural fragments in biologically active materials for pharmaceutical use [13-14] and also as auxiliaries in useful synthetic conversations [15-16].

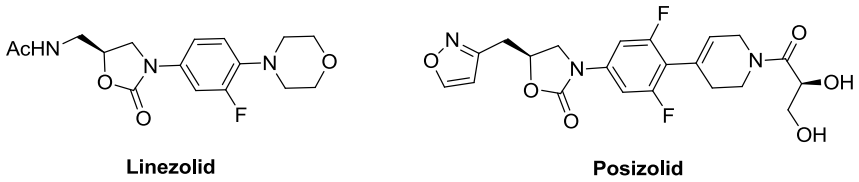


Figure 1: Known oxazolidinones having antibacterial activity.

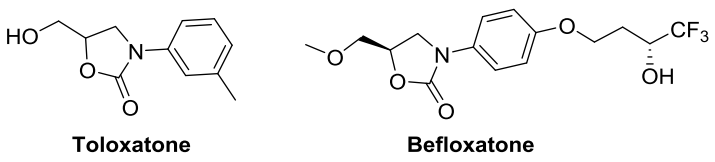


Figure 2: Known oxazolidinones having anti-depressant activity.

Recently, Anacetrapib which contains an oxazolidine core has been identified as ETP inhibitor (Figure 3) and is currently being studied in clinical trials [17]. Locostatin, an oxazolidinone derivative is found to be useful in controlling inflammation, sepsis, and autoimmune diseases [18].

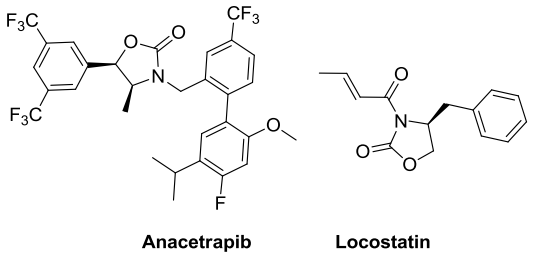
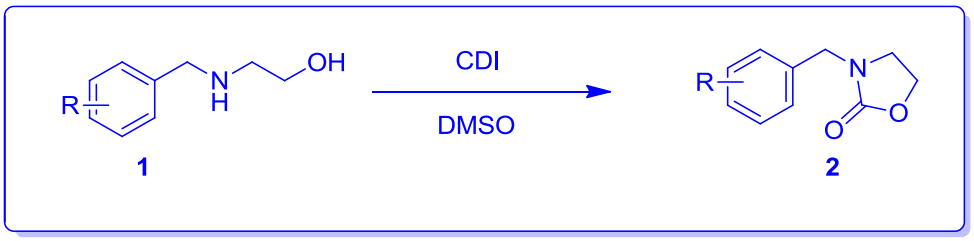


Figure 3: Examples of bioactive oxazolidinones

The most common synthetic routes reported so far for the synthesis of N-benzyloxazolidinones includes N-benzylayion of oxazolidinones [19], carboxylation of N-benzyl-β-amino alcohols [20-24]. 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 [25-26] 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 (Scheme 1).



Scheme 1: One pot synthesis of N-benzyloxazolidinones**.**

MATERIALS AND METHODS

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reactions were stirred using Teflon-coated magnetic stirring bars. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent {(NH4)6MoO4, Ce(SO4)2, H2SO4, H2O}. Chromatographic purification of products was carried out by flash column chromatography on silica gel (60- 120mesh). Melting points were determined using an electro thermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier transform spectrometer. NMR spectra were measured in CDCl3, acetone, DMSO-d6 (all with TMS as internal standard) on a Varian Gemini 400 MHz FT NMR spectrometer magnetic resonance spectrometer. Chemical shifts (δ) are reported in ppm, and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Mass spectra were recorded on an HP-5989A quadrapole mass spectrometer.

EXPERIMENTAL

General method for the preparation of β-Aminoalcohol (2a-h): Ethanolamine (1.0mmmol) was added to a stirring solution of Aromatic aldehyde (1mmol) dissolved in methanol (5mL) and stirred at 25-30°C for 1h. After 1h, sodium borohydride (0.5mmol) was added, and stirred at 25-30°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 β-Aminoalcohol.

General method for the preparation of Substituted oxazolidinones derivatives (2i-l): β-Aminoalcohol (1.0mmol) was dissolved in DMSO (2 mL) and added carbonyldiimidazole (1.5mmol) under nitrogen atmosphere and stirred at 23-30°C for 2-3 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.

3-benzyloxazolidin-2-one (2a): 1H NMR (400 MHz, CDCl3): δ7.37- 7.26 (m, 5H), 4.42 (s, 2H), 4.31- 4.27(m, 2H), 3.43- 3.39(m, 2H); 13CNMR (100MHz, CDCl3): δ158.53, 135.76, 128.83(2C), 128.16(2C), 127.98, 61.76, 48.42, 43.95; HRMS: m/z [M + H] calculated for C10H12NO2: 178.0868; found: 178.0865.

3-(4-fluorobenzyl)oxazolidin-2-one (2b): 1H NMR (400 MHz, CDCl3): 7.26-7.22 (m 2H), 7.04-6.99 (m, 2H), 4.37 (s, 2H), 4.30-4.26 (m , 2H), 3.42-3.38 (m, 2H); 13CNMR (100MHz, CDCl3): δ163.68, 161.22, 158.47, 131.60(2C), 129.92(2C), 115.81(2C),61.77, 47.66, 43.88: HRMS: m/z [M + H] calculated for C10H11NO2F:196.0774; found: 196.0773.

3-(4-nitrobenzyl)oxazolidin-2-one (2c): 1H NMR (400 MHz, CDCl3): δ 8.23-8.21 (m, 2H), 7.48- 7.25 (m, 2H), 4.53 (s, 2H), 4.38-4.34 (m, 2H), 3.49-3.45 (m, 2H) ; 13CNMR (100MHz, CDCl3): δ 158.49, 147.69, 143.23, 128.75, 124.12, 61.85,47.88, 44.24; HRMS: m/z [M + NH3] calculated for C10H14N3O4: 240.0984; found: 240.0983.

3-(2-chlorobenzyl)oxazolidin-2-one (2d): 1H NMR (400 MHz, CDCl3): δ 7.37-7.33 (m , 2H), 7.26-7.22 (m, 2H), 4.55 (s, 2H), 4.31-4.27 (m, 2H), 3.49-3.45 (m, 2H); 13CNMR (100MHz, CDCl3): δ 158.49, 133.77(2C), 130.33(3C), 127.34, 41.88, 61.88, 45.65, 44.37; HRMS: m/z [M + H] calculated for C10H11NO2Cl: 212.0478; found: 212.0477.

3-(4-bromo-2, 6-difluorobenzyl)oxazolidin-2-one) (2e): 1H NMR (400 MHz, CDCl3): δ 7.12-7.09 (m, 2H), 4.49 (s, 2H), 4.29-4.25 (m , 2H), 3.48-3.44 (m, 2H); 13CNMR (100MHz, CDCl3): 162.80(2C), 160.27(2C), 122.22(3C), 115.76(6C), 61.69, 44.11, 35.69(3C); HRMS: m/z [M + NH3] calculated for C10H12N2O2F2Br:309.0050; found: 309.0033.

3-(4-bromobenzyl)oxazolidin-2-one (2f): 1H NMR (400 MHz, CDCl3): δ 7.49-7.47 (m, 2H), 7.18-7.16 (d, J = 8.3 Hz, 2H), 4.38 (s, 2H), 4.33-4.29 (m, 2H), 3.43-3.39 (m, 2H); 13C NMR (100 MHz, CDCl3): 158.46, 134.815, 131.985, 121.998, 61.783, 47.835, 43.949: HRMS: m/z [M + NH3] calculated for C10H14N2O2Br: 273.0239; found: 273.0248.

3-(4-methoxybenzyl)oxazolidin-2-one (2g): 1H NMR (400 MHz, CDCl3): δ 7.20-7.18 (m, 2H), 6.87-6.85 (m, 2H), 4.34 (s, 2H), 4.28-4.24 (m, 2H), 3.78 (s, 3H), 3.40-3.36(m 2H); 13C NMR(100 MHz, CDCl3): 159.36, 158.46, 129.54, 127.78, 61.75, 55.28, 47.78, 43.81; HRMS: m/z [M + H] calculated for C11H14NO3: 208.0974; found: 208.1970.

3-(2-chloro-6-methylbenzyl)oxazolidin-2-one (2h): 1H NMR (400 MHz, CDCl3): δ 7.258-7.23 (d, J = 8.4 Hz, 1H), 7.18-7.11 (m, 2H), 4.67 (s, 2H), 4.27-4.23 (m, 2H), 3.43-3.39 (m, 2H), 2.41 (s, 3H); 13CNMR (100MHz, CDCl3): 158.036, 140.583, 135.475, 131.013, 129.526 (2C), 127.356, 61.881, 43.851, 42.682, 20.053; HRMS: m/z [M + H] calculated for C11H13NO2Cl:226.0635; found: 226.0651

3-benzyl-5-(chloromethyl)oxazolidin-2-one (4a): 1H NMR (400 MHz, CDCl3): δ 7.38-7.32 (m, 3H), δ 7.29-7.26 (m, 2H), 4.72-4.66 (m, 1H), 4.48-4.38 (m, 2H), 3.68-3.60 (m, 2H), 3.59-3.51 (m, 1H), 3.33-3.293 (m, 1H); 13C NMR (100MHz, CDCl3): 157.13, 135.30, 128.90(3C), 71.40, 48.29, 46.90, 44.67; HRMS: m/z [M + H] calculated for C11H13NO2Cl: 226.0635; found: 226.0649.

5-(chloromethyl)-3-((S)-1-phenylethyl)oxazolidin-2-one) (4b): 1H NMR (400 MHz, CDCl3): δ 7.39- 7.29 (m, 5H), 5.25-5.19 (m, 1H), 4.71-4.65 (m, 1H), 3.63-3.57 (m, 2H), 3.50-3.45(m, 1H), 3.05-3.01 (m, 1 H), 1.60-1.59 (d, J = 7 Hz, 3H); 13C NMR (100 MHz, CDCl3): 158.96, 139.89, 129.16(2C), 72.66, 51.96, 44.34, 44.16, 16.13; HRMS: m/z [M + H] calculated for C12H15NO2Cl: 240.0791; found: 240.0779.

4-methyl-3-(naphthalen-1-ylmethyl)oxazolidin-2-one (4c): 1H NMR (400 MHz, CDCl3): δ 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); 13C NMR (100MHz, CDCl3): 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 C15H15NO2: 242.118; found: 242.1188.

4-methyl-3-(naphthalen-2-ylmethyl)oxazolidin-2-one (4d): 1H NMR (400 MHz, CDCl3): δ 7.93-7.89 (m, 3H), 7.78 (s, 1H), 7.53-7.48 (m, 2H), 7.41-7.38 (m, 1H), 4.66-4.62 (m, 1H), 4.49-4.48 (d, J = 3.9Hz, 2H), 3.58-3.53 (t, 1H), 3.01-2.98 (m, 1H), 1.28-1.27 (d, J = 6.2 Hz, 3H); 13C NMR (100 MHz, CDCl3): 157.99, 134.56, 133.36, 132.84, 128.89, 128.13, 128.04, 126.82, 126.76, 126.49, 126.25, 70.34, 50.75, 47.79, 20.81; HRMS: m/z [M + H] calculated for C15H15NO2: 242.118; found: 242.1172.

RESULTS AND DISCUSSION

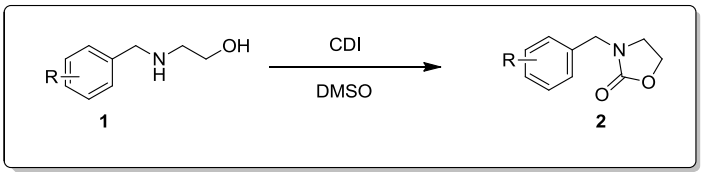
The N-benzyl-β-amino alcohol derivatives required for the synthesis were prepared from benzaldehyde derivatives and ethanolamine following the same procedure reported by Xiong-Jie and his team [11]. Initially, the reaction was performed by stirring beta amino alcohol 1a and CDI in DCM at room temperature 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 (entry1, Table-1). Attempts were made to increase the product yield by extending the reaction time or temperature (entry 2 & 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 & 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. Reactions were carried out using 1a (1.0 mmol) and CDI (1.5 mmol) in a solvent at room temperature under nitrogen bisolated yield.

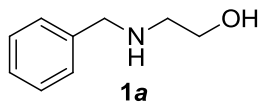
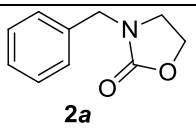
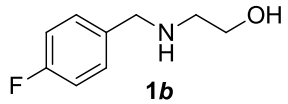
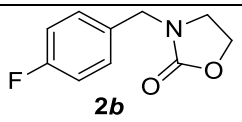
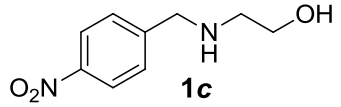
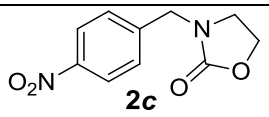
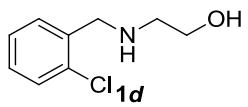
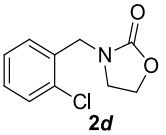
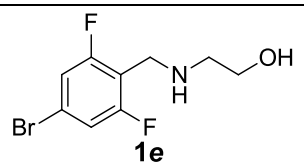
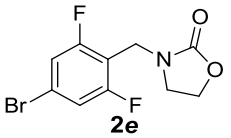
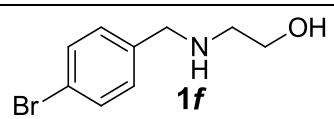
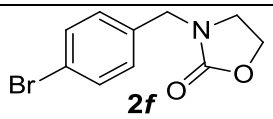
Table 1: Effect of reaction conditions on the conversion of the beta amino alcohol (1) to oxazolidinone derivative (2a)a.

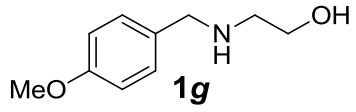
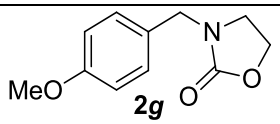
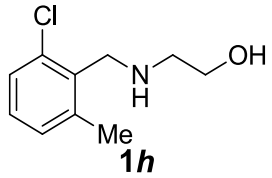
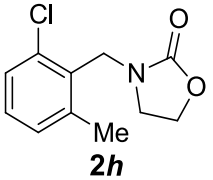
Entry	**Solvent**	**Temp (°C)**	**Time (h)**	**% Yieldb**
1	DCM	30	15	30
2	DCM	30	24	32
3	DCM	40	15	28
4	THF	30	15	25
5	**DMSO**	**30**	**12**	**94**
6	DMF	30	15	70
7	DMSO	45	15	40

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, NO2 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-benzyloxazolidinone derivatives (2a-h) synthesized were characterised by their 1H and 13C NMR and HRMS data and further confirmed by comparing with the data reported for these compounds in literature.

Table 2: Synthesis of N-benzyloxazolidinone derivatives 2 via one pot reaction of 1 and CDIa.



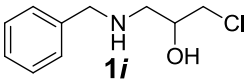
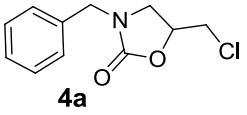
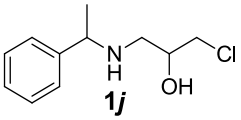
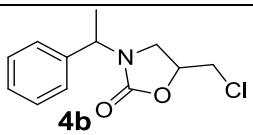
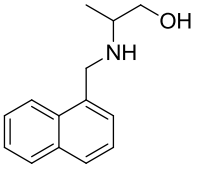
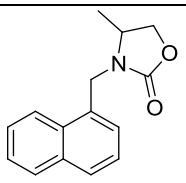
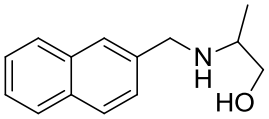
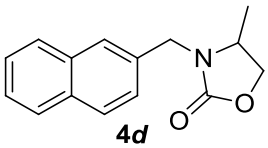
S.NO	**N-benzyl-β-amino alcohol**	**Product**	**Time (h)**	**Yield (%)**
1	 **1a**	 **2a**	1.5	94
2	 **1b**	 **2b**	2.0	92
3	 **1c**	 **2c**	2.0	94
4	 **1d**	 **2d**	2.0	90
5	 **1e**	 **2e**	2.5	92
6	 **1f**	 **2f**	2.0	90

S.NO	N-benzyl-β-amino alcohol	Product	Time (h)	Yield (%)
7	 1g	 2g	3.0	88
8	 1h	 2h	2.5	90

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. bIsolated yield.

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

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

S. NO	N-benzyl-β-amino alcohol derivatives	Product	Time (h)	Yield (%)
1	 1i	 4a	2.0	96
2	 1j	 4b	2.0	94
3	 3C	 4C	3.0	89
4	 3C	 4d	3.0	90

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. bIsolated yield.

CONCLUSION

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

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