# Preparation of amide derivative of proline and its use in condensation reactions

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**Abstract-** Chiral chemistry with the desired isomer is the need of time and very useful in drug synthesis. Proline has been used in chiral synthesis and organocatalysis. The prolinamide derivatives give more selectivity in chiral synthesis. The present study is synthesizing new ligand using proline as starting material. The new prolinamide derivatives prepared are further studied for the condensation reactions like aldol in-order to see the effect of chirality introduced from prochiral center. The organocatalyst synthesized is novel and will surely help in chiral synthesis. The ligand prepared is also very cost effective.

**Keywords:** Chiral Chemistry, Proline, Prolinamide derivative, aldol condensation

## Introduction

The term ‘organocatalyst’ was given in the early 20th century as a portmanteau of the words “organic” and “chemistry”. The definition equates to a low molecular weight organic molecule which in sub stoichiometric amounts catalyzes a chemical reaction. These kinds of catalyst are predominantly composed of Carbon, Hydrogen, Nitrogen, Sulphur, and Phospherous. The study in organocatalysis has been used recently due to environment friendly methodology [1]. Organocatalysis has various advantages. The product can be selectively synthesized from cheap prochiral starting materials without unwanted products being formed. The absence of metal based catalysts in organocatalyst, readily contributes to ‘Green chemistry’. Absence of metal based catalyst, organocatalysis is more useful in green chemistry[1].

DISCOVERY AND HISTORY OF ORGANOCATALYSIS

Literature survey reveals that, Justus von Liebig’s synthesized of oxamide from dicyan and water symbolizes the first organocatalystic reaction ( Figure 1).

Knoevenagel is a condensation type reaction between carboxylic acid and aldehyde active methylene groups, the amine catalysts can be replaced by amino acids [2] [3]. Moreover, small molecules catalysts like L-isovaline and L-Analine able of catalyzing various C-C bond formation reactions [4]. Yamada and Otani worked upon the utility of stoichiometric proline-derived enamines for stimulating asymmetry in a range of transformation [5]. Hojos, Parrish, Eder, Sauer and Wiechert described some staggering, selective reactions such as proline-catalyzed synthesis of optically active steroid overtone structures in 1971 (Figure 2)[6].

L-Proline

Proline is an α-amino acid readily utilized in the biosynthesis of protein. This amino acid comprises both protonated secondary amino groups as well as deprotonated carboxylic acid group and a side chain pyrrolidine. [7]

Moreover, then α- amino acid is directly attached to the pyrrolidine, attaining the α carbon a direct substitution of the side chain. L-Proline is a versatile catalyst for a variety of C–C bond forming reactions and is frequently considered as a mimic for aldolase enzymes. Inwater, L-proline is neither an effective nor a selective catalyst. Hydrophobic fragment is the first proline derivatives that displayed good activity and selectivity in water. These hydrophobic parts cluster, creating hydrophobic pockets in which catalysis occur in water. This realization resulted in many different proline based catalysts that show high activity and selectivity in water [8].

ALDOL REACTION

Aldol reaction is one of the most important tool of organic synthesis. These reactions are extremely used to generate carbon-carbon bonds permitting to link building blocks to generate large and complex molecules. Hence, aldol reaction considered as the most important organocatalytic C-C bond- forming reaction. These reactions can be effectively carried out through various organocatalysts. L-proline outlined as an effective organocatalyst in asymmetric aldol reaction. However, Prolinamide-derived organocatalysts mostly show beneficial catalytic performance [9]. In 1974 Hajos-Parish-Eder-Sauer-Wiechertreaction:Hajos et al. treated triketone as substrate with 30 mol% (S)-(-)-Proline, resulting in 93% ee, which was regarded as entioselective aldol reaction of organocatalyst. List and Barbas aldol reaction discovered by list and barbas et al. in 2000. They took direct Aldol reaction between acetone and p-nitrobenzaldehyde in the presence of (S)-proline as catalyst, and got 68% yield and 76% ee.(Figure/Scheme 3), which is considered as starting of organocatalyst.

**Experimental**

**Material and Methods:**

L-proline and Boc-L-proline were purchased from sigma-Aldrich chemicals. AR Grade used were purchased from sigma-Aldrich chemicals Ltd and Calibochem Ltd.

**General procedure:**

## 1. PREPARATION OF ORGANOCATALYST

### 1.1 SYNTHESIS OF N-(TERT-BUTOXYCARBONYL)-L-PROLINE

To 2 ml of water stirred in 2ml ethanol, 0.5 gram L-proline(1b),1.214 ml (2 Moleq) triethylamine(1b) and 1.497 ml (1.5 Moleq) BocAnhydride(1c)are successively added in the reaction medium. Stirred for 5 hours at room temperature. The reaction was analyzed by thin-layer chromatography (TLC) on glass plates (on which silica gel is act as adsorbent) using 10% methanol/DCM as solvent. After 5 hours at room temperature, the reaction mass was diluted with 40 ml of ethyl acetate and 10 ml water. The layer was separated; the organic layer was washed with 0.5N HCl and finally dried over NaSO4. After filtration and evaporation (using Rota vapour), 0.81 g of brownish-yellow viscous colured compound was formed. To make it as solid, diluted with Ethyl acetate (5ml) in a RBF. The resulting mixture was warm on water bath for 1 hour at 40-45 temperature. The solution was almost clear and white precipitates was observed over there. Finally, filtered on suction pump, dried by the use of hot oven .0.71gram of white coloured solid (1d) product was produced.

### 1.1 SYNTHESIS OF BOC-L-PROLINAMIDE

Charged 0.6033 g (1 moleq) N,N –Diethyl-P-Phenylenediamine sulphate salt (2a)and 0.321 ml (1 moleq) triethylamine(2b) in 50 ml RBF, stirred for 5 minutes. Placed 10 ml dichloromethane (2c)and 0.5 g (1mol eq) (1d)in the reaction mixture and stirred for 5 minutes. Prepared a solution (A) of 0.57g (1.2 mol) N,N-Dicyclohexylcarbidimide(2c) in 2ml DCM, charge (A) in the reaction medium drop wise. Stirred, reaction for 2 hours at room temperature. The reaction was analyzed by Thin Layer Chromatography using Hexane/Ethylacetate (7:3) as solvent. During workup, The reaction mass was filtered by using watt man filter paper and funnel, filter part that was urea(2d) as by product discarded and kept filtrate part aside. The filtrate part washed with 10% NaHCO3 solution. The layer was separated; the organic layer (DCM) was washed with 1% HCL and then water .Finally, the DCM layer was dried over anhydrous sodium sulphate and evaporated on Rota vapour. A solid (2e) compound of 0.75 g was observed.

### 1.3 N-DEPROTECTION FROM BOC –L PROLINAMIDE

Place 0.5g (2d) and 2ml ethanol in 50ml RBF. Prepare a standard solution of 5 % HCL. Charge 2ml HCl in the reaction medium. Then it was stirred for 2 days at room temperature. The reaction is monitored by the use of TLC using DCM/Methanol (7:3) as eluent. The reaction mass was first washed with 10 % NaHCO3 and

diluted with 10 ml ethyl acetate. The layer was separated; the ethyl acetate layer separated out in a beaker then dried over NaSO4. After evaporation using Rota vapor at 40-45 temperature, a brownish viscous 0.15 g product was formed. To convert it into a solid, stirred with 2ml Hexane for 1 hour. After evaporation using Rota vapor, a brown 0.11s g solid (3a) produced.

Aldol Reaction using Benzaldehyde, Acetone and L-prolinamide

Charge 200 mg Benzaldehyde (4a), 2ml Acetone (4b) and 2ml water in 50 ml RBF. After stirring for 20 minutes, 0.2 eq L-prolineamide (3a) was charged into the reaction mixture. Then it was stirred for 1 day. The reaction was monitored by TLC using Hexane/Ethylacetate (9:1) as solvent. The reaction mass was diluted with 10ml ethyl acetate and 10 ml water. It was stirred for 2 minutes. The layers were separated; The organic layer separated in RBF and evaporated on Rota vapor. A very fine, viscous brownish color 0.25g was formed. To make it as solid, it was stirred with Hexane for 1 hour. After that evaporated on Rota vapor and scratched it with a spatula, A brown solid (5a) of 0.15g was observed. In further step, It was observed that +65 specific optical rotation is obtained by the use of polorimeter with 1% solution.

Detection Method: IR, SOR

**Results and Discussion**

**3.1 IR OF BOC-L-PROLINE (1d)**

The ν(C=O) peaks of Boc anhydride appear in the range 1639.55cm-1. The ν(C=O) peak of carboxylic acid appeared in the range 1741.78cm-1 and the peak of ν(OH) of carboxylic acid . Presence of all these three bands in product ensured that Boc Protection take place during the reaction and Boc- L- proline is act as Protected amine as shown in (figure 3.1 ).

**3.2 IR OF BOC –L-PROLINAMIDE (2e)**

The ν(C=O)peak of L-Prolinamide shifted from 1741cm-1 to 1705cm-1and the ν(N-H) amide group appears at 3331.18 cm-1. Presence of these two bands ensured that there is formation of BOC-L-Prolinamide as shown in figure 2.

**3.3 IR ANALYSIS OF L-PROLINAMIDE**

The ν(C=O) peak of BOC anhydride disappeared and The ν(C=O) peak of amide [blue] appeared in the range 1653.05cm-1.The ν(N-H) peak of amide group appeared at 3331.16cm-1.Presence of these two characteristic bands indicates that deprotection taken place during the formation of L-Prolinamide as shown in figure 3.

## 4. IR ANALYSIS OF ALDOL REACTIONS

IR analysis of aldol reaction using L-proline , benzaldehyde and acetone

The ν(OH) peak alcohol of benzaldehyde appeared at 3429.55 cm-1 and the ν(C=O) ketone group of acetone peak observed at 1651 cm-1. Appearance of these peaks assured that aldol reaction taken place as shown in figure 4.

### 4.1 IRanalysis of L-prolinamide, Benzaldehyde and acetone

The ν(OH) peak of alcohol of benzaldehyde appeared at 3444.98 cm-1and ν(C=O) peak of ketone group of acetone appeared in the range 1645 cm-1. Presence of these two bonds ensured that aldol reaction taken place as shown in figure 4.2.

### 4.2 IR analysis of L-Prolinamide, P-Nitrobenzaldehyde and Acetone

IR ν(OH) peak of alcohol group appeared in the range 3371.68 cm-1 and the ν(C=O) of ketone group of acetone appeared at 1703.20cm-1. The ν(N=O) peak of nitro group of p-nitrobenzaldehyde appeared in the range 1529 cm-1. Presence of these three bands ensured that aldol reaction taken place as shown in figure 4.3.

### 4.3 IR analysis of aldol reaction using L-prolinamide , meta-chloro-benzaldehyde and acetone

The ν(OH) peak of alcohol group appeared at 3419.19 cm-1. The ν(C=O) peak of ketone group appeared at 1643.41cm-1 and the ν(C-Cl) of m-chloro-benzaldehyde appeared at 549.73cm-1.Preasence of these three bands indicated that aldol reaction taken place as shown in figure. 4.4.

Firstly, The polorimeter celebrated by the use of methanol solvent. Prepared a 1% solution and taken an optical rotation of Aldol reactions by the use of polorimeter. To the determination of specific optical rotation we used the following formula :

$[\alpha] = \alpha / l.c$

Table 1: Denotes the SOR of reactions Optical rotaion of methanol by the use of methanol : +8

**Conclusions :** The prolinamide derivative was successfully synthesized and characterized.

The derivative was further studied with number of aldol reactions for introducing chiral hydroxyl group from the prochiral keto group. The changes in IR denoted the compound formation. The chirality was further confirmed by SOR.

The SOR values clearly denotes that the new prolinamide derivative synthesized is a very good chiral ligand and it can be used in varied condensation reactions. The slower the reaction, more the chirality. If more time is given to the reactions than surely the prolinamide derivative synthesized will give better chirality in condensation reactions.

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Figure/Scheme 1: Amide synthesis

Figure/Scheme 2: Use of Proline in chiral synthesis

Figure/Scheme 3: Use of Proline in chiral synthesis

Reaction 1.1- Synthesis of Boc- L –Proline

Reaction 1.2- Synthesis of Boc –L-Prolinamide

Reaction 1.3- N-Deprotection from Boc-L-Prolinamide

Reaction 2.1- Aldol reaction using Benzaldehyde, L-Prolinamide and Acetone

Figure 3.1 IR of BOC-L-Proline

Figure 3.2 IR of BOC-L-Prolinamide

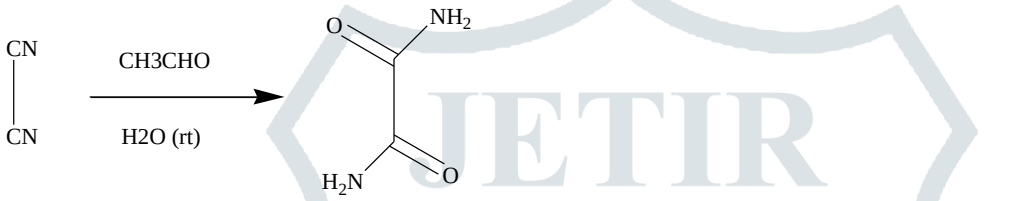
Figure 3.3. IR OF L-PROLINAMIDE

Figure 4: IR of Aldol product using Lproline, Benzaldehyde and Acetone

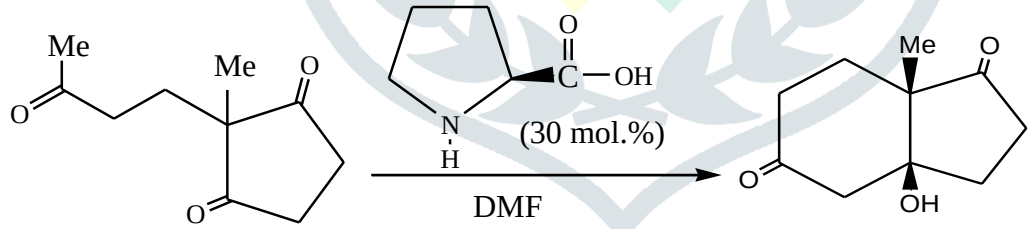
Figure 4.2- IR spectra of aldol reaction using L-prolinamide, benzaldehyde and Acetone

Figure.4.3- IR spectra of aldol reaction using L-prolinamide, P- Nitrobenzaldehyde and Acetone

Figure 4.4- IR spectra of aldol reaction using L-Prolinamide, Meta-chloro- benzaldehyde and Acetone

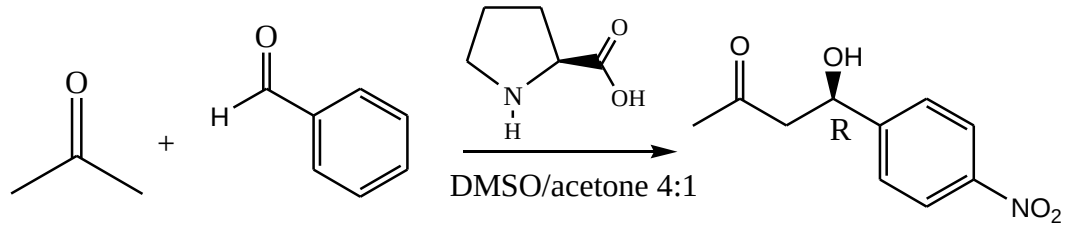



**Scheme 1**

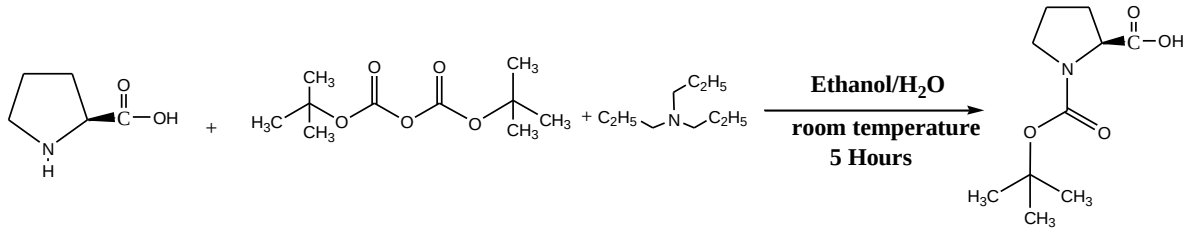



( ee 93% )

Scheme 2

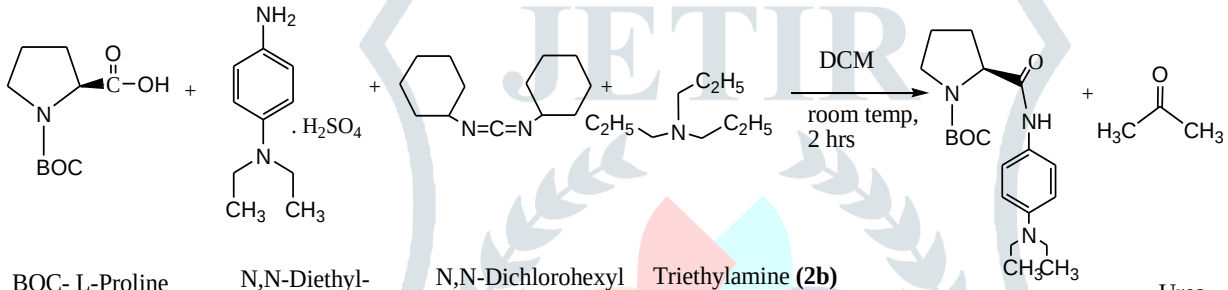



Scheme 3




**L-Proline (1a)** **BOC- Anhydride (1c)** **Triethylamine (1b)** **BOC- L-Proline (1d)**

Reaction 1.1- Synthesis of Boc- L –Proline




BOC- L-Proline **(1d)**

N,N-Diethyl-phenylene diamine-Sulphate **(2a)**

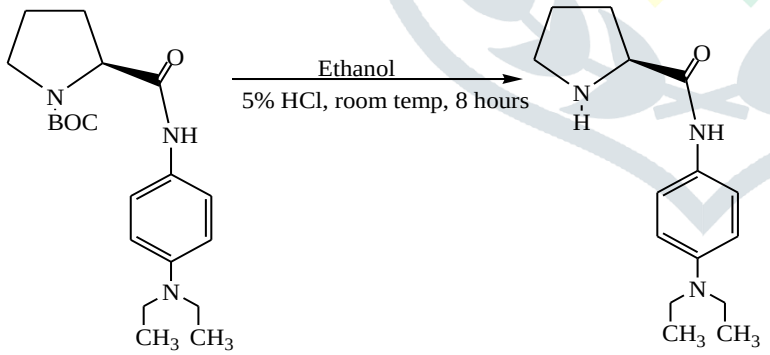
N,N-Dichlorohexyl carbidimide **(2c)**

Triethylamine **(2b)**

BOC-L-Prolinamide **(2e)**

Urea **(2d)**

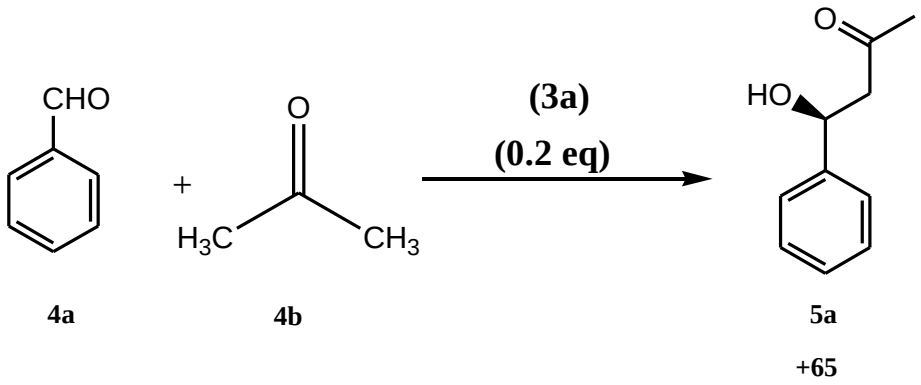
Reaction 1.2- Synthesis of Boc –L-Prolinamide




**(2e)**

**L-prolinamide (3a)**

Reaction 1.3- N-Deprotection from Boc-L-Prolinamide




Reaction 2.1- Aldol reaction using Benzaldehyde, L-Prolinamide and Acetone

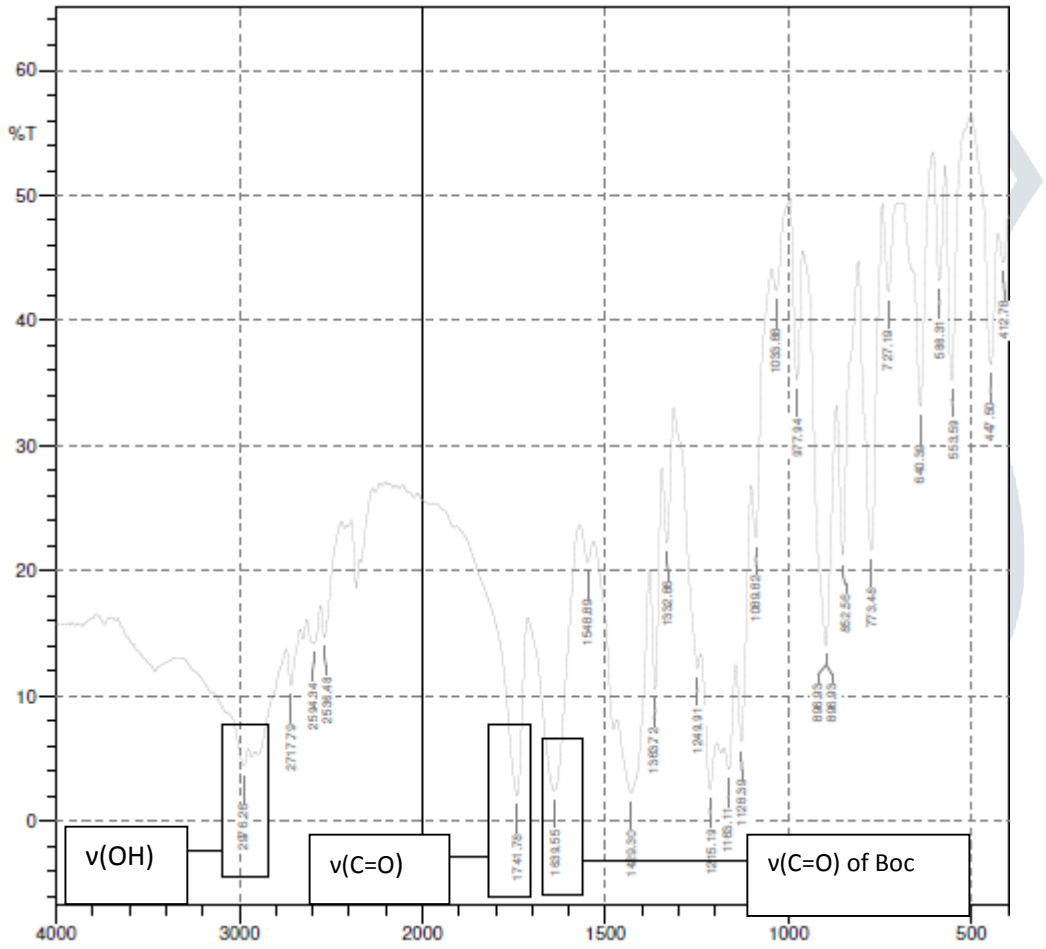



Figure 3.1 IR of BOC-L-Proline

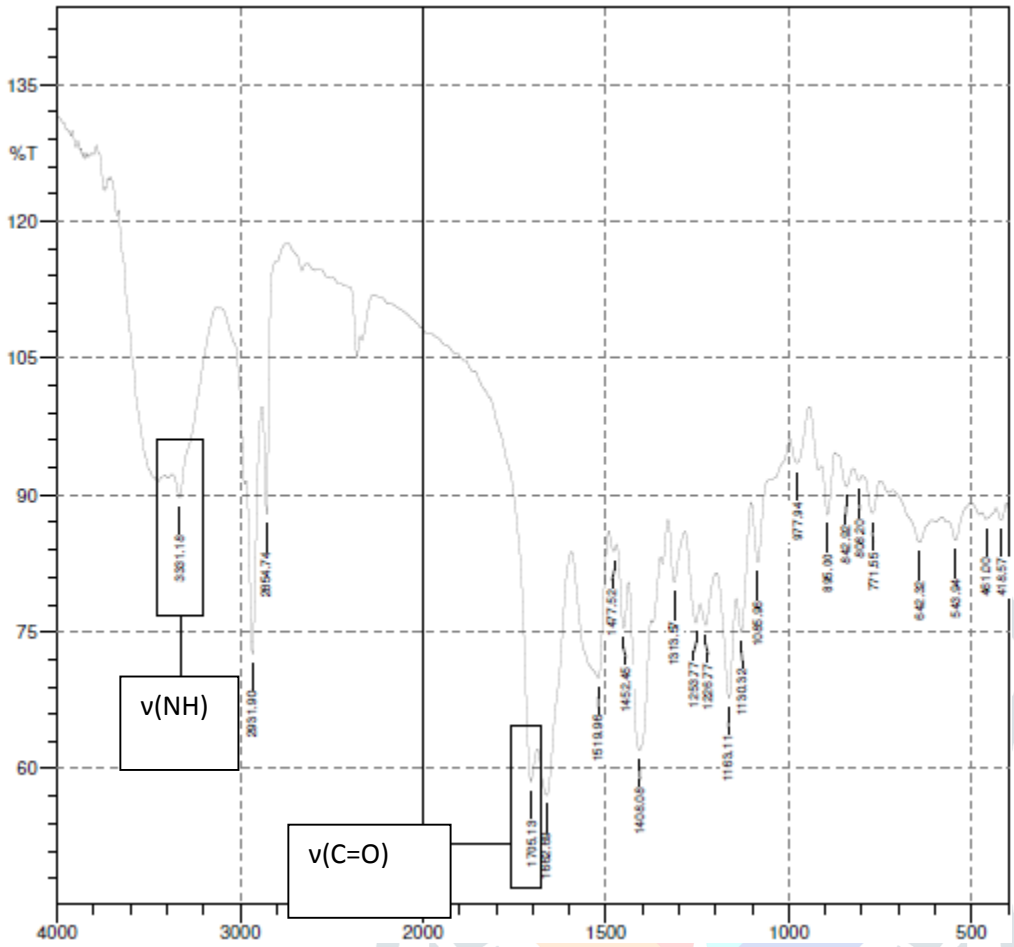



Figure 3.2 IR of BOC-L-Prolinamide

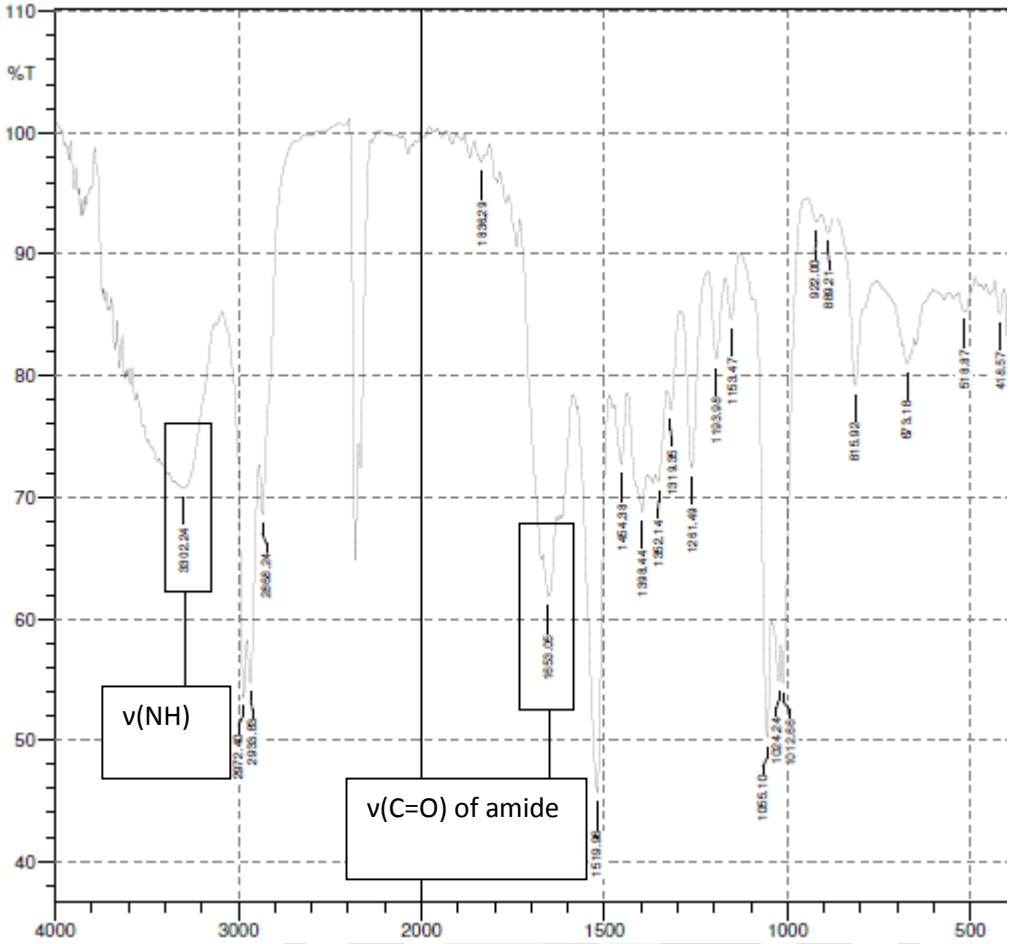



Figure 3.3. IR OF L-PROLINAMIDE

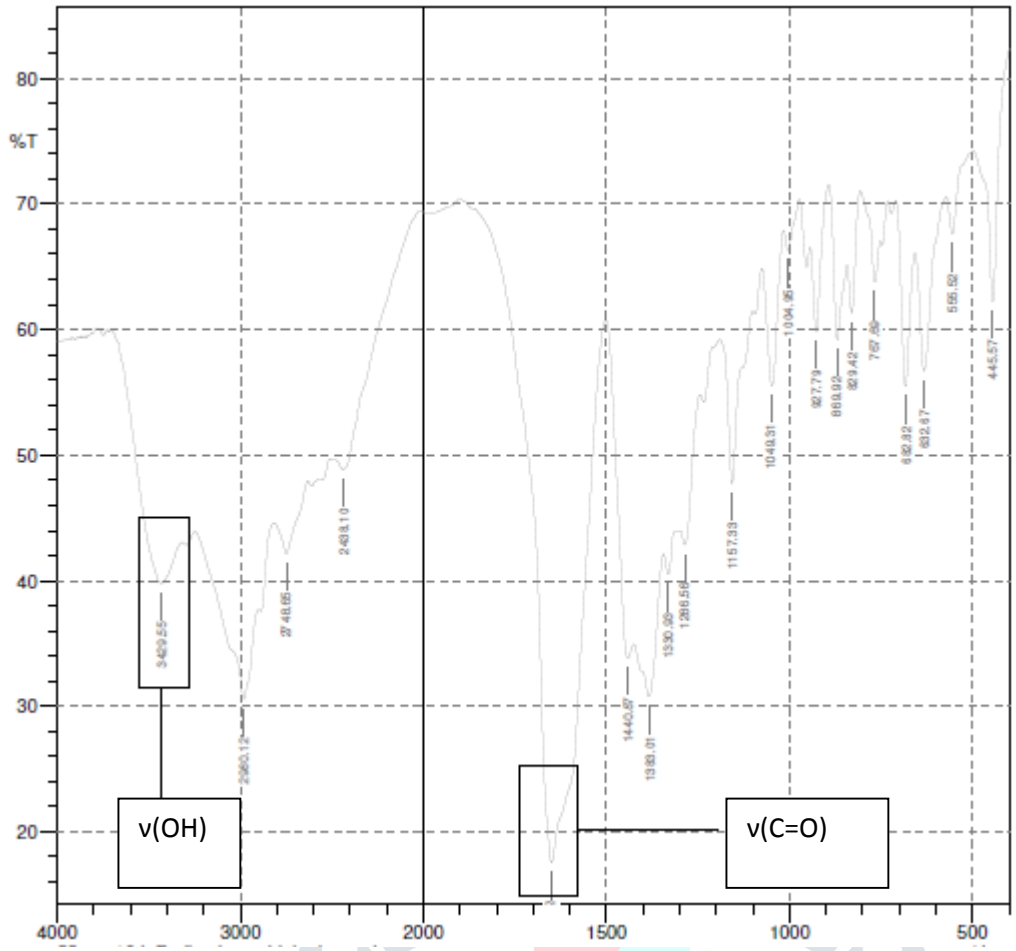



Figure 4: IR of Aldol product using Lproline, Benzaldehyde and Acetone

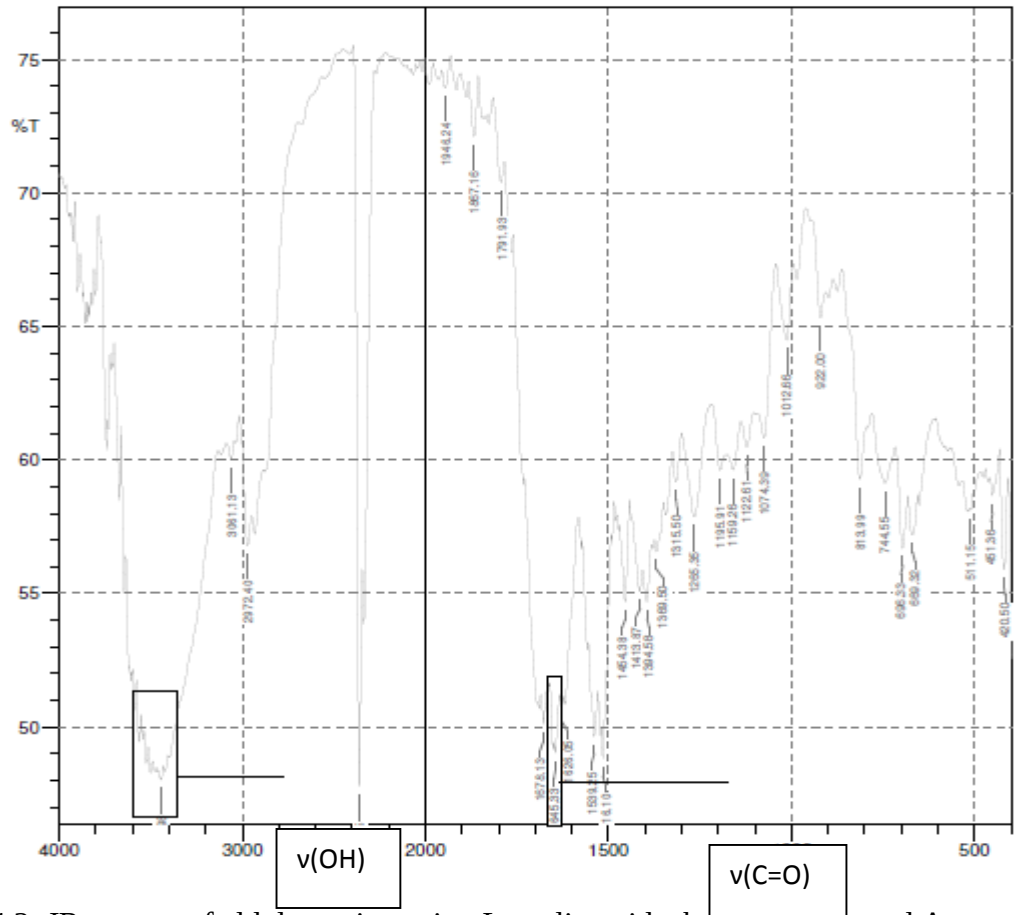



Figure 4.2- IR spectra of aldol reaction using L-prolinamide, benzaldehyde and Acetone

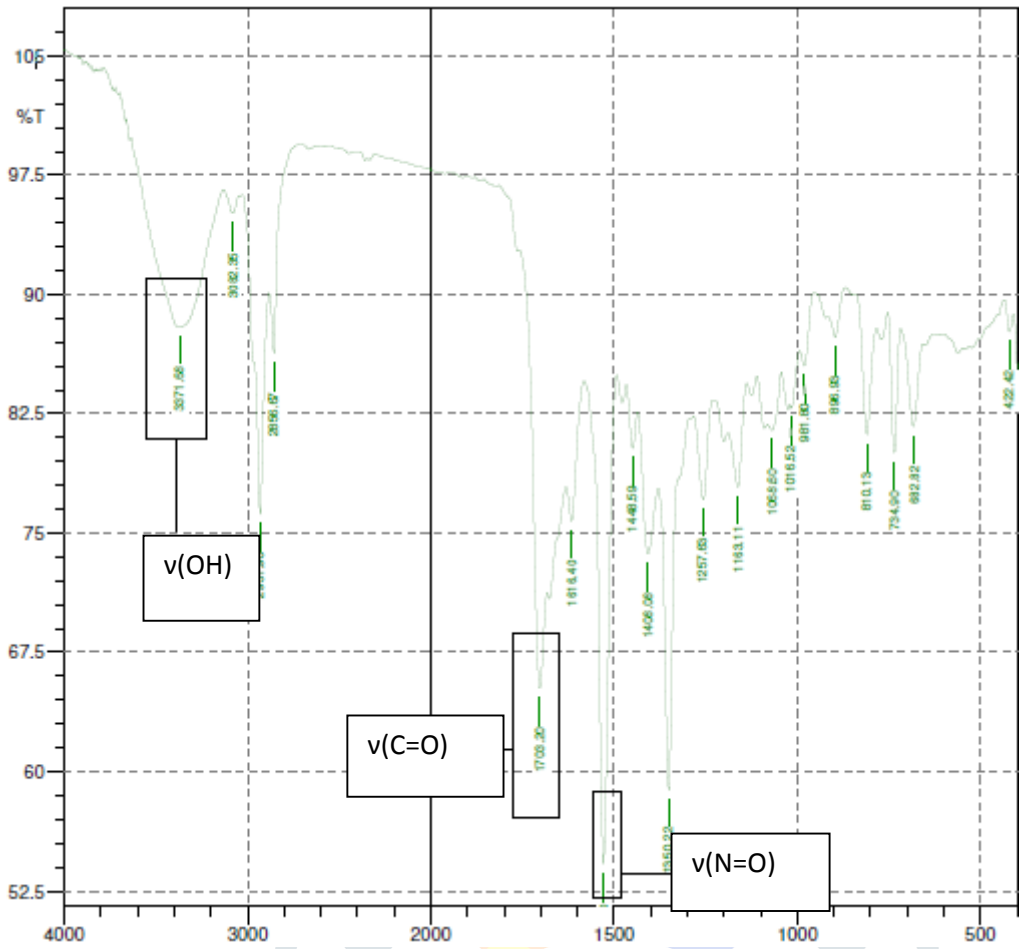



Figure.4.3- IR spectra of aldol reaction using L-prolinamide, P- Nitrobenzaldehyde and Acetone

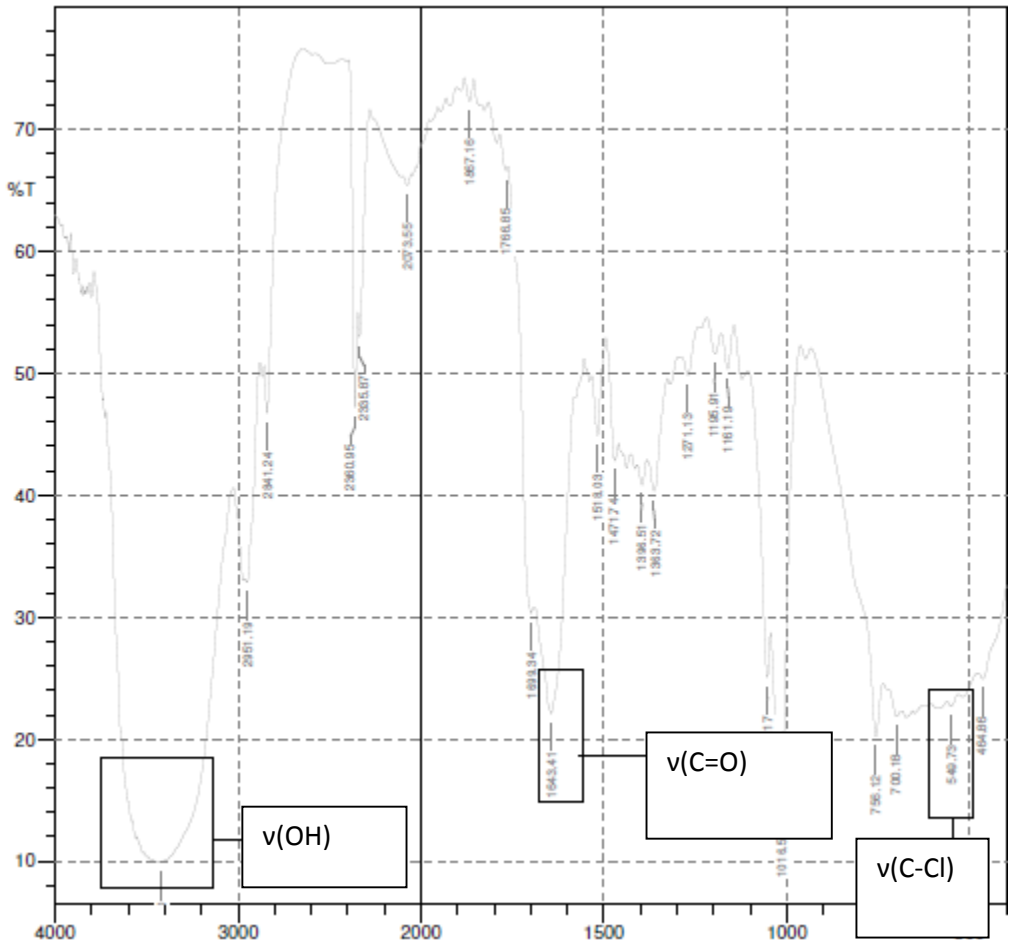



Figure 4.4- IR spectra of aldol reaction using L-Prolinamide, Meta-chloro- benzaldehyde and Acetone

Table 1 : SOR determination of aldol reactions

| Aldol reaction | Optical Rotation (α) with methanol (b) | Exact optical rotation = (b) – error (a) | Concentration (C) | Length of the tube (l) | Specific Optical Rotation [α]= α/C.l |
|---|---|---|---|---|---|
| 4.1 | +79 | +81 | 1 | 1 | +81 |
| 4.2 | +81 | +83 | 1 | 1 | +83 |

| | | | | | |
|---|---|---|---|---|---|
| 4.3 | +72 | +84 | 1 | 1 | +84 |
| 4.4 | +73 | +85 | 1 | 1 | +85 |