

A green method for the synthesis of 4 – Hydroxy – 4 – (2 – hydroxyphenyl) 2 – butanone using L – proline in aqueous micellar medium.

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Abstract

Now a day the green method for organic molecule synthesis is attracting more and more attention. To achieve such a green method it is desirable to replace the organic solvent by water, a green solvent. The L – proline catalyzed intermolecular aldol condensation reactions between salicylaldehyde and acetone in aqueous micellar medium was investigated. Reaction yields and purity of the product were observed to be greater than that of the corresponding reactions in any other organic solvents. Herein I wish to present my results regarding environmentally benign intermolecular aldol condensation reactions catalyzed by amino acid L – Proline in aqueous micellar medium. The use of biogenic L – proline as the catalyst and the aqueous conditions make this method very attractive. The reaction takes place in the emulsion media, which assemble both hydrophobic aldehydes. L – Proline was shown to be a powerful catalyst in asymmetric aldol reactions. From the mass spectra and especially from NMR data. I can get the desired organic product with high purity without any long purification which is very much difficult when the same reaction is carried out in organic medium. In aqueous micellar media the reaction was run even at room temperature without any additional additives.

Keywords:

Green Synthesis;
Micellar Medium;
L - Proline;
water;
Aldol Condensation Reaction.

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1. Introduction

For organic chemists, aldol condensation reactions have become usefully procedure in modern synthetic organic chemistry. Near the end of the twentieth century metal free organic biomolecules attracted attention as organocatalysts. In general organocatalytic reactions are carried out in a single pot process by stirring a carbonyl compound, an additives and a nucleophile in conventional organic solvents such as Dimethyl sulphoxide, chloroform, dichloromethane or dimethyl formamide, which are toxic, flammable and volatile[1]. Two separate technique has been reported in 2006 for aqueous organocatalytic direct cross aldol reactions of aldehyde and ketone as donor and acceptors, trans – L – Siloxyproline was a key catalyst in the aldol reaction of 5 equivalent of cyclohexanone with 18 equivalent of 4 – nitrobenzaldehyde in the presence of water, the reaction is very slow as this is a two phase reaction medium. In the absence of organic solvent such as Dimethyl sulphoxide, chloroform, dichloromethane or dimethyl formamide the yield is very low[2]. This is mainly due to the low solubility of the organic substrates that is aldehyde and ketones in aqueous solvent. Interestingly amino acid can catalyze these reactions in water which is a mild and environmentally compatible media. Kinetics of amino acids catalyzed aldol condensation reaction is titled

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now limited. To achieve green process for industrial application it is desirable (1) to use green solvent such as water and to avoid hazardous organic solvents (2) to use biocatalyst such as amino acids, oligopeptides (3) reaction to be conducted at room temperature to avoid heating (4) work up procedure must involve simple and avoid organic solvent. In organic synthesis aldol condensation is an important synthetic method. I herein report very general and an environmentally benign method for aldol condensation. The use of biogenic L – proline as the catalyst and replace organic solvent by aqueous solvent make this method very much attractive. Although water is easily available, safe, environmentally friendly, benign and also cheap compared with any other organic solvents most of the chemical organic reactions conducted in laboratory as well as in industry need organic solvent as media. For mainly two reasons organic solvent still used instead of water on both industrial as well as laboratory level. First most of the organic compounds used as substrate are insoluble in water and therefore water does not act as a reaction medium. Second water deactivated the reagents, catalyst and reactive substrates. My goal is to develop a system which enables the use of water as a solvent for a wide range of reaction of organic material. In the course of my investigation the solubility problem in water is overcome by using surfactants [3], which solubilize organic substrates in aqueous medium. The surfactant solution used above critical micellar constant, micelles help to solubilize the organic substrate in water. From the practical view point the surfactant aided organic synthesis is still now at primary stage. To overcome second drawback I use water compatible substrate and biogenic amino acids as catalyst [4]. Herein I describe how combined proline surfactant organocatalyst promotes the asymmetric direct aldol condensation reaction of one aldehyde having no alpha hydrogen and one ketone having a alpha hydrogen in the presence of water. Surfactants as amphiphilic molecules tend to mediate between the two phase water and immiscible organic species. If water is present in a large amount the hydrophobic effect drives the formation of spontaneous micellar aggregates in solution when the surfactant is present above the concentration called critical micellar concentration. In the recent years some classes of bio – surfactants have emerged where the amphiphilic molecule presents biological functionalities [5]. While conducting the reaction in aqueous medium it was pointed out that we often forget how to get the organic products out of water. Thus not only the reaction step but also the economics and environmental impact of product workup and reagent preparation should be taken into account in the selection of the reaction medium. Aqueous asymmetric aldol reaction is one such field where water quickly becomes an important alternative to organic solvents.

Initially the aldol reaction of 2 – Hydroxy benzaldehyde with acetone in water in the absence of surfactant is studied by mixing of 40 mmol of acetone, 8 mmol of 2 – Hydroxy benzaldehyde and 30 mol% of proline in water. After seven days at 35° C, the anticipated aldol product, 4 – Hydroxy – 4 – (2 – hydroxyphenyl) 2 – butanone was obtained in very low amount. When a surfactant CTAB (20 mol %) is added to the reaction medium. Above 90% yield of aldol product was obtained in only 4 hr [14]. The above result proves that anionic surfactant Cetyl Trimethyl Ammonium Bromide (CTAB) plays important roles in the reaction [6].

2. Research Method

L – Proline was purchased from Aldrich chemical Co. and before use dried by heating at 100°C for 5 – 6 hours in vacuo. 2 – Hydroxy benzaldehyde and acetone were obtained by E – Merck and were purified by vacuum distillation and stored in refrigerator. Deionised water was used for the reaction and all solvents were of reagent grade and were purified by vacuum distillation. Routine monitoring of the reaction progress was performed by TLC using 0.25 mm E – Merck silica gel 60f254 precoated plates which were visualized with UV light [7]. Samples were taken in open capillaries and melting points were determined on a digital melting point apparatus. The IR spectra were recorded on a JASCO Spectrum 3500 FT-IR unit spectrometer using KBR disc. Proton nuclear magnetic resonance (¹H-NMR) spectra were recorded on a 400 MHz Bruker DPX 400 FT – NMR spectrometer using deuterated solvents, CDCl₃ instrument using TMS standard. The purity of product was confirmed by NMR analysis [15].

The reaction was carried out in the 250 ml three neck glass reactors. 1.35 ml 10 mmol of 2 – hydroxy benzaldehyde and then 3.5 ml, 30 mmol of acetone was added to a mixture of 10 ml 10% of L – proline and 5 ml 0.2 (M) Cetyl Trimethyl Ammonium Bromide (CTAB) solution at 25°C and the resulting emulsion was stirred using magnetic stirrer for 2 hour under a nitrogen atmosphere [8]. The reaction progress was monitored by TLC after 10 min interval of time. After completion of reaction as indicated by TLC, the resulting liquid mixture was neutralized by an aqueous solution of dilute HCl to pH about 6.5. The reaction mixture was extracted with ethyl acetate (2 X 20 ml). The combined organic layer was washed with distilled water and finally washed with brine solution. Finally the separated organic layer was dried under magnesium sulphate and concentrated under reduced pressure. The crude product was recrystallized from water.

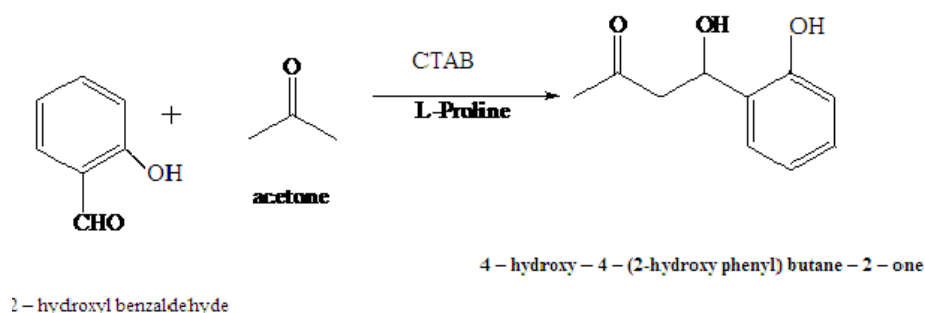


Figure 1. Aldol Condensation Reaction by using 2 – hydroxyl benzaldehyde and acetone

3. Results and Analysis

To examine the role of amino acid L-Proline and surfactant Cetyl Trimethyl Ammonium Bromide (CTAB) during the entire process of asymmetric aldol condensation reaction of 2 – hydroxyl benzaldehyde condensed with acetone in aqueous micellar media I resolved to assess the changes in functional groups that is in my case study the formation of new C-C bond at 1257 cm^{-1} by FT – IR spectroscopy [16].

After the completion of reaction I analyze the $^1\text{H-NMR}$ data of the isolated product which is fairly dissimilar from the reactant 2 – hydroxy benzaldehyde. From the $^1\text{H-NMR}$ data of the newly formed product there was a clear indication of the formation of new C-C bond which is key feature for aldol condensation reaction.

In this experiment my plan was to use bioorgano catalyst for synthesis of asymmetric aldol condensation product in aqueous micellar media, a green solvent [17]. The intention of my experiment was to illustrate the utility of L – proline as the bio organo catalyst in the synthesis of chiral compounds. L- Proline is non – toxic, commercially available natural basic amino acid. Generally in aldol condensation reaction lewis bases are act as catalyst but it is very much moisture sensitive therefore lewis bases could not act as catalyst where the solvent is water [9], as a result of that I could not use Lewis bases as catalyst when I try to proceed the reaction in aqueous media, but L – proline had been evaluated in asymmetric aldol reaction in water as catalyst instead of lewis bases. The poor solubility of 2 – hydroxy benzaldehyde and acetone in water is also a big trouble for synthesis of aldol condensation product in aqueous media. To overcome the solubility problem I use surfactant cetyl Trimethyl Ammonium Bromide. The aldehydic group of hydrophobic 2 – hydroxy benzaldehyde was found to interact with the reagent acetone and L – proline forming a concentrated organic phase in micellar nano reactor in the surrounding water [10]. The micellar nano reactor also increases the rate of reaction compare to organic solvents which eliminates the formation of those concentrated micellar nano reactor , moreover the reaction completed with the formation of product with high purity when surfactant was used, which supported the role of the surfactant and micellar nano pocket[16-19].

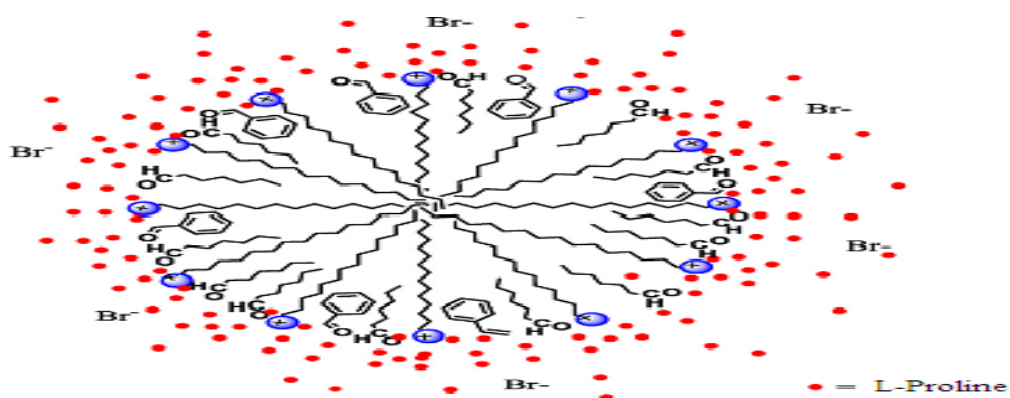


Figure 2. Micellar effect on surfactant catalyzed Aldol Condensation Reaction in aqueous medium

3.1. Characterization of the substrate and product using FT – IR spectroscopy.

To analyze the change of functional group during the reaction, elucidation of the functional group present in the reactant used and product formed was determined by means of FT – IR spectroscopy [11-13].

Analysis of the chemical structure of 2 – hydroxy benzaldehyde was done by means of FT – IR Spectroscopy (Figure 3).

In this spectra displayed characteristic bands in the region of $1620 - 1630 \text{ cm}^{-1}$ which confirmed the presence of the aldehydic group (-CHO). The band appear near $2800 - 2900 \text{ cm}^{-1}$ was due to the hydroxyl group (-OH), while the ones at $1400 - 1600 \text{ cm}^{-1}$ corresponding to the aromatic C=C stretching frequency. The peaks appear near $3000 - 3300 \text{ cm}^{-1}$ was due to the presence of phenolic -OH group.

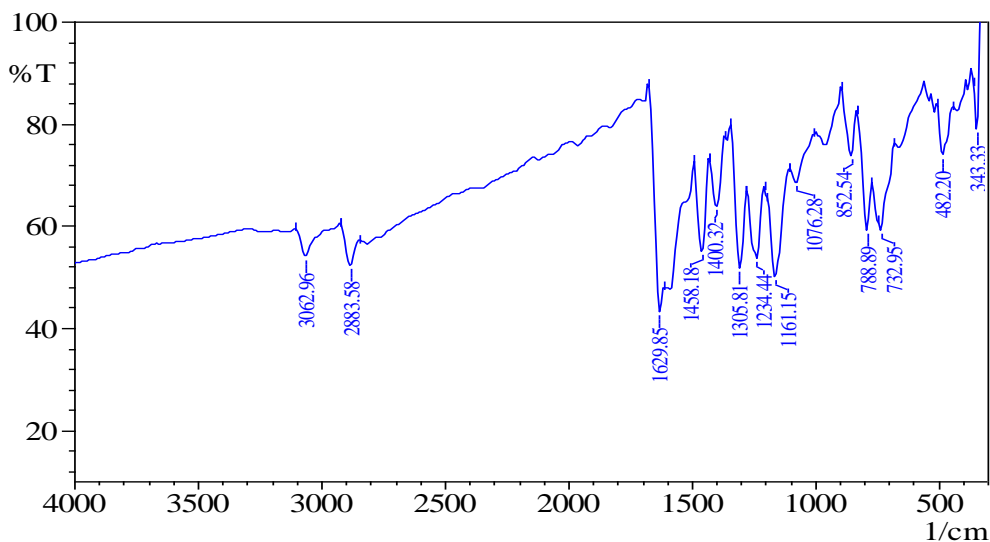


Figure 3. FT – IR spectra of 2-Hydroxy benzaldehyde

3.2. Characterization of the product by using FT – IR spectroscopy (Figure 4)

The product characterized separately by FT – IR spectroscopy. Here for the confirmation of the preparation of aldol product was confirmed by the presence of strong sharp band at 1257 cm^{-1} . This strong sharp band appeared at 1257 cm^{-1} is due to C-C bond formed in the aldol condensation reaction. This is the key factor for aldol condensation reaction. Another strong sharp band peak appeared at around 2918 cm^{-1} that confirmed the newly formed hydroxyl group (-OH). Therefore by comparing the obtained spectroscopy data with the literature data it is evident that 4 – hydroxy – 4 – (2-hydroxy phenyl)2- butanone was produced accompanying with a high conversion and selectivity.

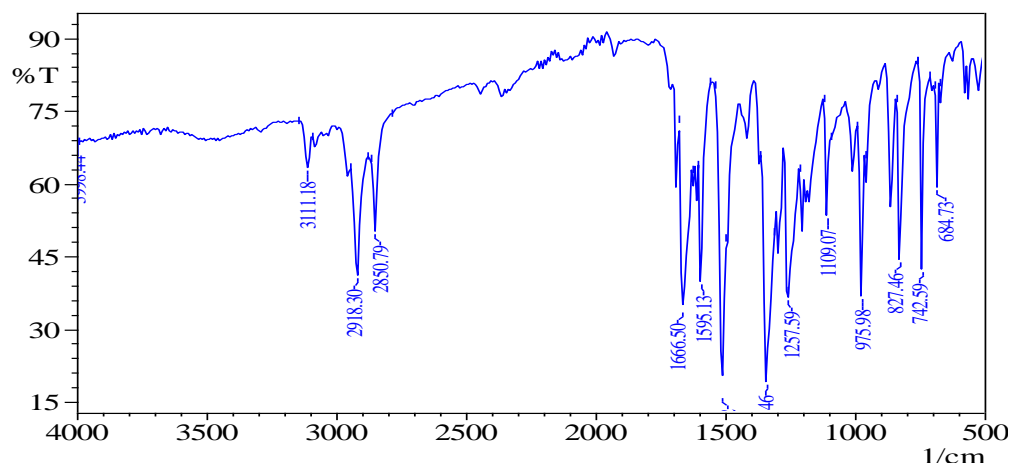


Figure 4. FTIR spectra of product 4 – hydroxy – 4 – (2-hydroxy phenyl) 2- butanone

3.3 $^1\text{H-NMR}$ data analysis (Figure 5)

The $^1\text{H-NMR}$ spectra of newly synthesized product showed three sets of doublets corresponding to the methylene group and aromatic protons. A typical characteristics doublet pattern was appeared at around 6.772 ppm and 6.732 ppm corresponding to the methylene group $\text{ArCHOH}(\text{CH}_2)\text{COCH}_3$ protons of the product. Two high field symmetrical doublets appeared at around 7.621 ppm and 7.643 ppm was assigned to the aromatic ring protons. A singlet due to three protons appeared at a high field 2.355 ppm is clearly indicating that a keto (COCH_3) group which is also confirmed by FT-IR spectrum. The singlet appeared at low field 1.102 ppm is deshielded proton being attached with oxygen atom (secondary alcoholic hydroxyl group). The $^1\text{H-NMR}$ spectra of the substrate 2 – hydroxyl benzaldehyde showed one peak assigned to the aldehydic proton at around 10.181 ppm, as expected, the same peak was disappeared for the newly synthesized aldol product. This data indicated that C-C bond formation between 2 – hydroxyl benzaldehyde and acetone assisted by organo catalyst L – proline was completed.

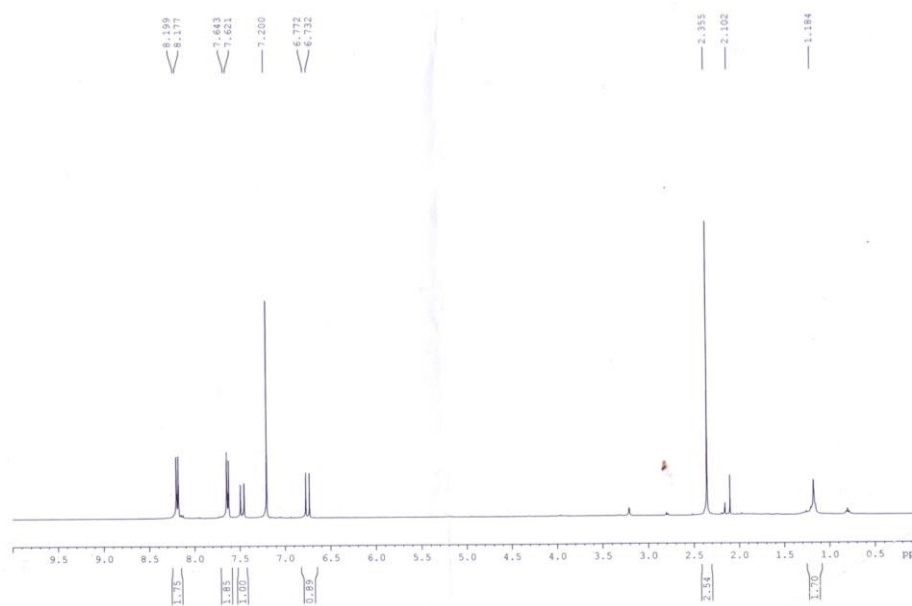


Figure 5. $^1\text{H-NMR}$ spectra of Product 4 – hydroxy – 4 – (2-hydroxy phenyl) 2- butanone

4. Conclusion

Due to hydrophobic nature of organic molecules micelles, formed by aqueous solution of cetyl trimethyl ammonium bromide, act as catalyst. In micellar solution organic molecules are concentrated to the hydrophobic core of micelle nano reactor [20]. This increase the collision rate among the organic reactant molecules and consequently enhance the reaction rate and yield than in the absence of micellar medium . Organocatalytic reaction in aqueous micellar solution has the various important features. : 1) reaction product can be more easily isolated , 2) minimum amount of catalyst loading might be achieved , 3) reaction rate is much faster in aqueous micellar solution than those in organic solvent , and 4) the use of toxic organic solvent can be avoided . From economic and ecological point of view these feature move aqueous micellar based organo catalytic procedure advantageous. The uses of aqueous micellar solution are rapidly advancing and improvements in aldol reaction are continuously being reported. The L – Proline promoted reaction [6] of aldehyde and ketone in aqueous micellar solution has furnished the corresponding condensation products in good yields. This procedure is environmentally friendly applicable to various aldehydes and ketones. From the $^1\text{H-NMR}$, FTIR data it is concluded that under the organocatalytic micellar condition C – C bond formation was completed through aldol condensation reaction [13]. As final points, the synthesis of 4 – hydroxy – 4 – (2-hydroxy phenyl) 2- butanone from 2-Hydroxy benzaldehyde and acetone has been accomplished using inexpensive, available and relatively non toxic CTAB surfactant in water as a catalyst and reaction medium. I anticipated that this environmental friendly protocol will be of wide synthetic and industrial interest.

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