Synthesis of Benzimidazole Derivatives in An Aqueous Media and Reflux Conditions Catalysed by L-Proline at pH-4.2

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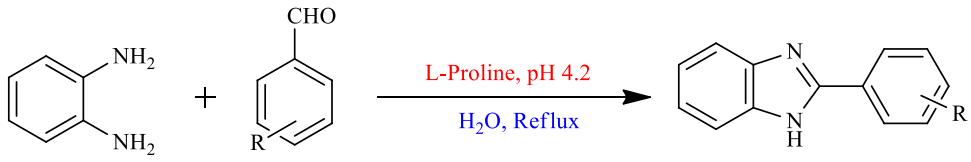
Abstract: An efficient synthesis of Benzimidazole derivatives were prepared by wide range of aldehydes and substituted o-phenylenediamines by using versatile organocatalyst L-Proline in an aqueous media at reflux conditions and pH 4.2. This method gave the desired products in good to excellent yields under reflux conditions. L-Proline catalyzed reaction provides a green and inexpensive method for the synthesis of benzimidazole derivatives.

***Index Terms*: Aldehydes, o-phenylenediamines, L-Proline, Aqueous Media, Reflux.**

I. INTRODUCTION

Heterocyclic compounds, especially N-containing heterocycles possess great applicability in industry as well as in our life in various ways. Among N-containing heterocycles, benzimidazole derivatives are widely used in medical chemistry and specially in the field of drugs and pharmaceutical [1,2] because of their pharmacological properties such as, Gram-positive antibacterial agents[3], antibiotics [4], antiphrastic[3], anti-inflammatory [5], antiproliferative activity [6], anti-stress ulcer [7], and anticancer agents [8],. Also, some benzimidazole derivatives have some optical applications such as photoluminescents [9], whitening agents [10], and dye laser [11]. In addition to this, benzimidazole plays an important role as an intermediate for various organic synthesis [12]. Due to this wide range of applicability of these benzimidazole derivatives, a wide range of methods are available for their synthesis, such as including condensation of o-phenylenediamine, with aldehydes, acid chloride, esters, carboxylic acids, and orthoesters in the presence of various acid catalysts [13-19]. Also, syntheses of these compounds have been reported using ILs [20-22].

Although many of these methods suffer from disadvantages such as the use of organic solvents or toxic reagents, harsh reaction conditions, long reaction times, need to excess amounts of the reagents and catalysts, and non-reusability of the catalyst. Therefore, the introduction of simple, green and efficient procedures with easily separable and reusable catalysts to overcome these problems is still in demand. Taking in view of the feasibility of heterocyclic compounds, the present work was carried out to synthesize heterocycles like benzimidazole derivatives by using the L-proline as a organocatalyst in an aqueous media as a green solvent at reflux condition and pH 4.2 (**Scheme 01**).



Scheme:01, Synthesis of Benzimidazole derivatives by using L-Proline in an aqueous media at reflux condition at pH 4.2

II. EXPERIMENTAL

2.1. Materials and Methods

Melting points were taken in open glass capillaries on a melting-point apparatus and were uncorrected. ^{1}H NMR was noted at room temperature on a Bruker Avance II 400MHz Spectrometer (SAIF, Punjab University, Chandigarh) in $CDCl_3$ using TMS as internal standard. IR spectra (using KBr pellets) were measured with a Perkin Elmer Spectrum RX FTIR (SAIF, Punjab University, Chandigarh) instrument. The progress of reactions were checked on TLC using pre-coated plates (silica gel on aluminum, Merck). All reagents were taken from available sources and used without further purification. Distilled solvents were used for column chromatography before use. The synthesized derivatives were also characterized by comparison of their melting point with literature values. Yields refers to isolated products and all synthesized products were characterized by spectral data (IR, ^{1}NMR and ^{13}C NMR) and melting points were compare with their authentic samples.

2.2. General procedure for synthesis of benzimidazole derivatives:

In a 50 ml round bottom flask, a mixture of o-phenylenediamine (1 mmol) and aldehydes (1 mmol) in water (5 ml) were mixed and refluxed on water bath in the presence of L-proline (10 mol %) and buffer tablet of pH 4.2 (0.1 g) for appropriate time given in a **Table 03**. The progress of the reaction was monitored by using TLC (Pet ether : ethyl acetate, 8:2). After completion of the reaction mixture was cooled and filtered. Wash the residue with distilled water (5 X 5ml) to recover the catalyst and dried it over vacuum. Recrystallize the crude product in ethanol to obtain the pure product. If essential crude product were purified by silica gel column chromatography using ethyl acetate: pet-ether (2:8) as an eluent.

2.3. Spectral data of some important benzimidazole derivatives:

1] 2-(2,4-dichlorophenyl)-1H-benzo[d]imidazole (Entry 8) : ^{1}H NMR (400 MHz, $CDCl_3$): δ7.63-7.61(m, 2H), 8.31-8.28 (m, 2H),7.44-7.43 (d, 1H),7.34-7.30 (d, 1H),7.28-7.19 (d, 1H),5.28 (br s, 1H) **^{13}C NMR (300 MHz, $CDCl_3$)**: δ 152.90, 139.33, 136.43, 135.05, 134.51, 130.95, 130.09, 123.57, 115.69 **Mass (GC/MS)**: *m/z* 265.07 (M+).

2] 2-(4-nitrophenyl)-1H-benzo[d]imidazole (Entry 3) : ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.22 (br s, 1H),8.31-8.29 (m, 2H), 7.63-7.61 (m, 2H),7.46-7.34 (m, 2H),7.24-7.32 (m, 2H). **^{13}C NMR (300 MHz, $CDCl_3$)**: δ 152.49, 147.98, 138.44, 136.39, 126.07,126.84, 123.50,115.04 **Mass (GC/MS)**: *m/z* 240.01 (M+).

III. RESULT AND DISCUSSION

Recently, organometallic catalyst have increased significance in several organic synthesis and reactions due to their remarkable reactivity as well as for cheap availability and environmental reasons. The use of L-proline was reported in the synthesis of benzimidazole derivatives by L-Proline in Chloroform as a Solvent [23] and L-Proline at solvent free condition under microwave irradiation [24]. In continuation focus of our work to develop greener alternatives for organic synthesis, organic reactions in an aqueous media have attracted vast interest as green alternative and environmentally benign conditions. Thus, here we report the formation of 2-arylbenzimidazole by a direct condensation reaction of aryl aldehyde with o-phenylenediamine in the presence of *L*-proline with pH 4.2 under reflux condition in an aqueous media as a greener protocol.

In order to find the optimum reaction conditions for the condensation reaction, preliminary efforts were mainly focused on the evaluation of different reaction conditions and solvents. The model reaction has been carried out between *o*-phenylenediamine and benzaldehyde in the presence of L-proline catalyst under different reaction conditions and solvents and results are summarized in **Table 01 and 02**.

Table 01: Optimization of reaction conditions for preparation of 2-arylbenzimidazole derivatives.

Entry	Reaction conditions	Time in hr	Yield in %
1	Room temperature	10hr	88
2	Microwave	10 min	82
3	Reflux	3 hr	98

Table 02: Preparation of 2-arylbenzimidazole derivatives using various solvents.

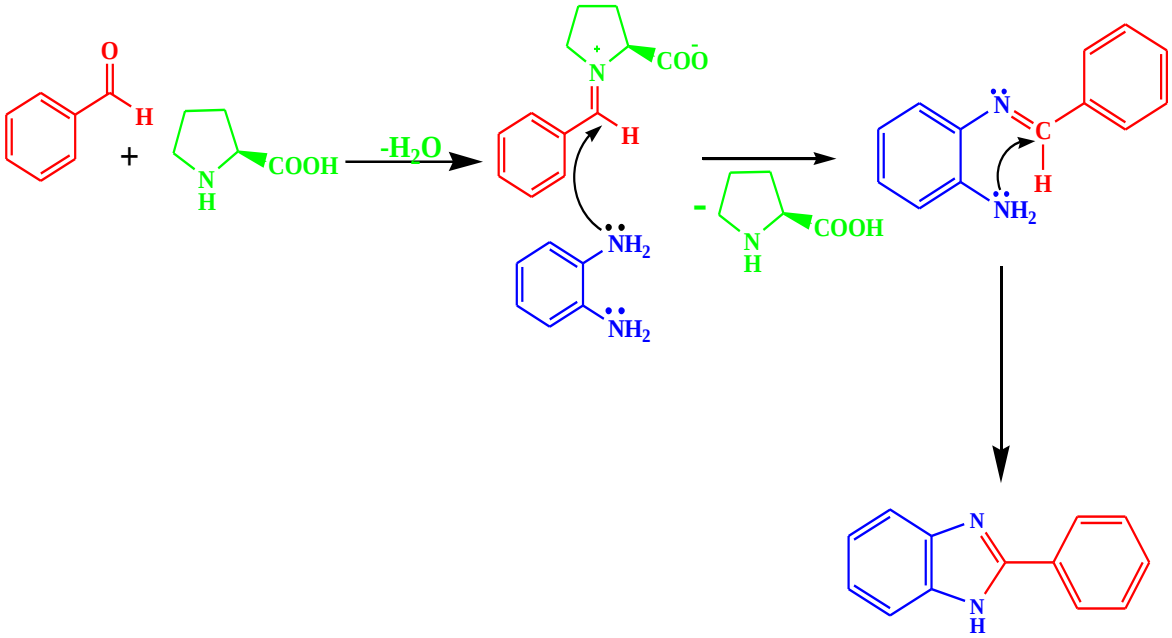
Entry	Solvent used	Time in hr	Yield in %
1	Benzene	8hr	78
2	Toluene	8hr	72
3	1,4-dioxane	10hr	78
4	DMF	8hr	72
5	THF	10hr	81
6	Ethanol	5hr	88
7	Solvent free[24]	5hr	82
8	Chloroform[23]	5hr	95
9	Water	3hr	98

The effect of solvent, reaction conditions, and time on the reaction was systematically investigated, and the results were summarized in **Table 01 and 02.** The optimized reaction conditions for the reaction were found to be L-proline under reflux condition in an aqueous media to generate the respective benzimidazole derivatives in good to excellent yields **(Table 03)**. In order to elucidate the role of L-proline as catalyst, a controlled reaction was conducted using *o*-phenylenediamine and benzaldehyde under reflux condition in an aqueous media in the absence of catalyst. This resulted in the formation of only 45% of the fused product after 10 hr at reflux condition. However, reaction with same substrate using different mole % of catalyst with pH conditions studied for the ease of the product formation. The results shows that at 10 mo l% of L-proline with pH of 4.2 at reflux conditions for 3 hr afforded the product in quantitative yield. Low temperatures reaction conditions required more time to completed the reaction and gives low yields compared to the optimized reaction condition.

In order to study the generality of this procedure, the applicability of the L-proline with pH 4.2 system in an aqueous media at reflux condition was then examined for the reactions of a series of aromatic aldehydes with o-phenylenediamine under the optimized reaction conditions. As shown, a variety of substituted aromatic aldehydes, bearing either electron-donating **(Table 03, entry 2,3,5,10,16,17,21)** or electron-withdrawing **(Table 03, entry 4,7,14,15)** substituent's, afforded the products in excellent yields and high purities. The generality of this reaction also check with substituted aldehydes and 2-animothiophenol are

examined, the reaction also proceeds very smooth with the formation of benzthiazole derivatives with good to excellent yield, the results were summarized in **Table 03**. With this optimized conditions, carboxylic acids also investigated with L-proline at reflux conditions in an aqueous media to give respective benzimidazole and benzthiazole derivatives in good to excellent yield. The product yields of using carboxylic acids with o-phenylenediamine/2-aminothiophenol were generally lower than those of using aldehydes.

General Mechanism for synthesis of Benzimidazole derivatives by L-Proline:



IV. CONCLUSION

In conclusion, we have developed an efficient and green method for the synthesis of benzimidazoles and benzthaizoles derivatives using commercially available, economically cheap L-proline as an organocatalyst in an aqueous media at reflux condition. The present protocol gives us the use of buffer tablet of pH 4.2 as a co-catalyst for L-proline. The present methodology has several advantages such as use of buffer as a co-catalyst, high to excellent yields, operational and experimental simplicity. We believe that this L-proline promoted methodology with buffer of pH 4.2 as a co-catalyst in an aqueous media will be valuable and green method to existing processes in the field of benzimidazole and benzthaizole derivatives.

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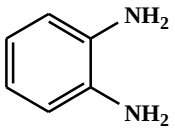
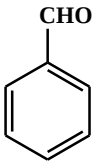
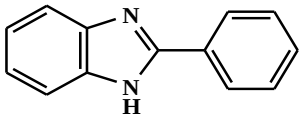
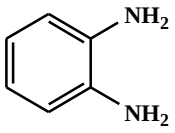
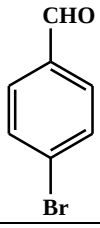
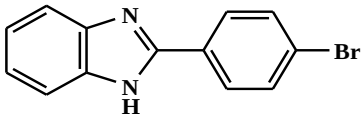
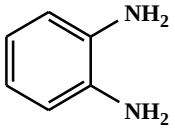
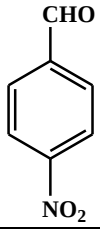
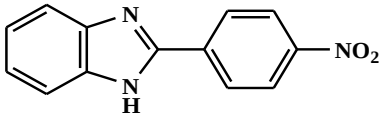
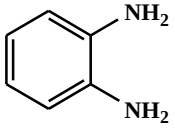
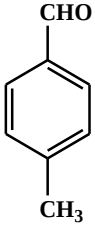
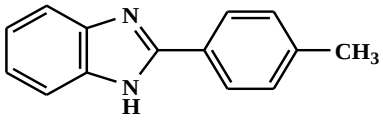
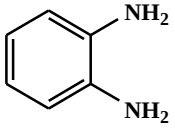
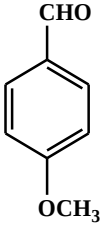
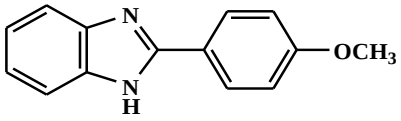
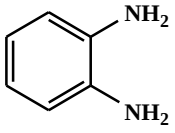
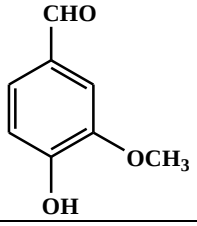
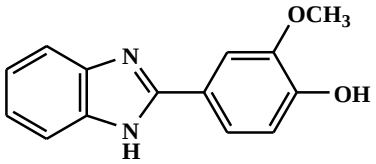
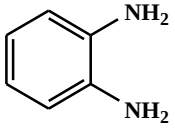
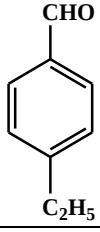
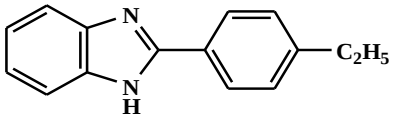
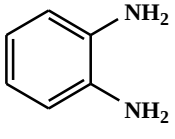
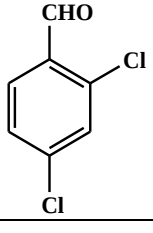
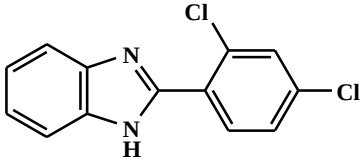
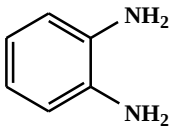
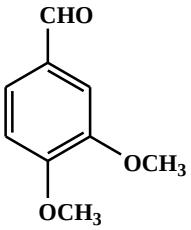
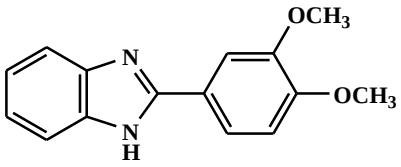
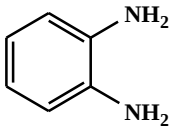
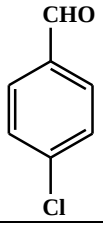
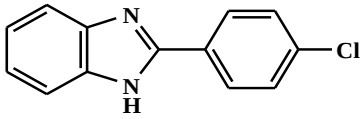
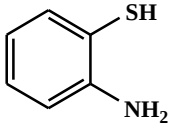
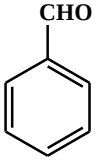
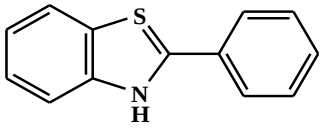
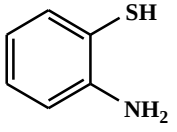
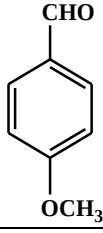
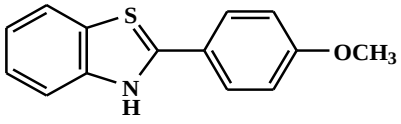
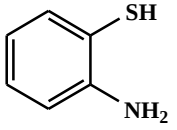
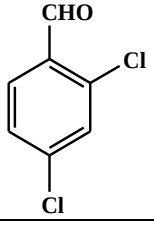
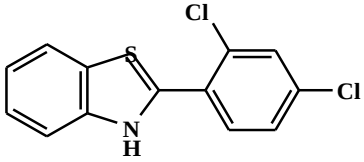
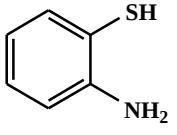
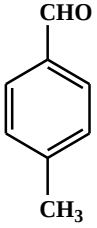
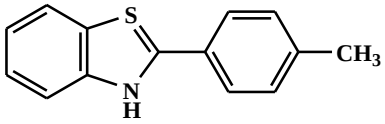
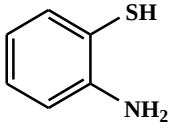
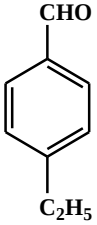
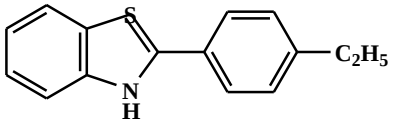
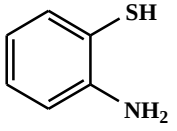
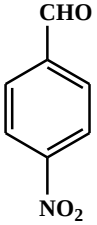
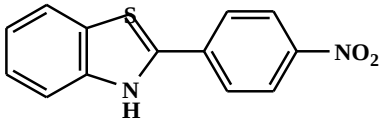
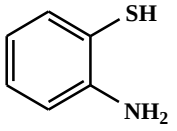
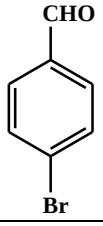
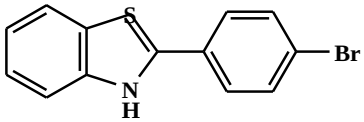
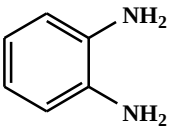
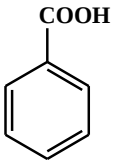
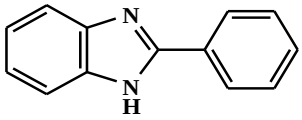
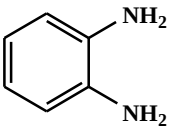
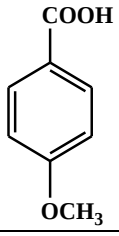
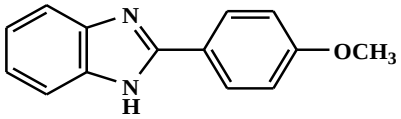
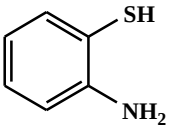
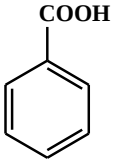
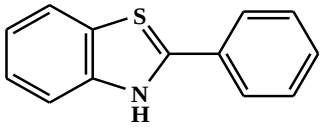
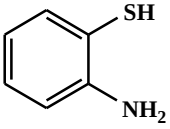
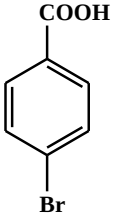
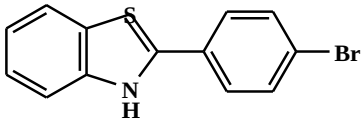
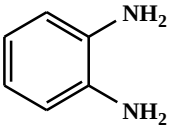
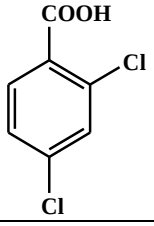
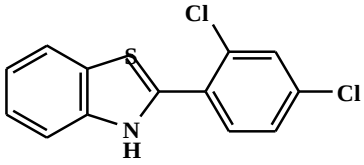
Table 03: Synthesis of benzimidazole and benzthiazole derivatives by using L-proline in an aqueous media.

Sr. No.	Amines	Aldehydes	Product	Time (Hr)	Yield (%)	M.P/ B.P. (°C)
1				3	98	289
2				1.5	98	285
3				1	99	>300
4				4	96	265
5				3.5	97	220
6				6	96	255
7				5	97	235
8				5	95	290

9				4.5	95	>300
10				2	98	174
11				5	97	110
12				5	96	120
13				4	97	288
14				5.5	97	87
15				7	96	263
16				3	96	180
17				3.5	95	131

18				4	88	290
19				5	80	221
20				5.5	84	110
21				4	85	130
22				4.5	80	286