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Research Article

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Bio-Waste Curd Water as a Greener Protocol for the Synthesis of Biginelli Products at Ambient Temperature

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Abstract

A highly efficient, greener and reusable protocol has been developed for the Biginelli reaction. The biowaste curd water employed as a green solvent as well as catalyst for the synthesis of dihydropyrimidinones derivatives. The soluble organic acid (i.e. lactic acid) responsible for the acidity to curd water which adequately fulfills the purpose of acid catalyzed reaction, where three component coupling of aldehyde, urea and ethyl acetoacetate reacted together in the presence of curd water at a low temperature and yields classical dihydropyrimidinones derivatives. During the reaction, continuous product formation and isolation was observed. The product precipitate was separated by the successive method of filtration. This bio-waste water catalyzed method is highly retrievable and advantageous over the trend of high-temperature Bronsted acid/metal acid catalyzed reactions offering the product. Compared with the classical Biginelli reaction conditions, this new method has the advantage of good yields (76-82%) and short reaction time (2-3 hours).

Keywords: Catalysis, Curd Water, Bio-Waste, Biginelli, Green Method, Three Components Coupling

Introduction

Biginelli reaction is one-pot three component coupling reaction which have great significance in organic synthesis [1]. Three components namely aldehyde, urea and ethyl acetoacetate (EAA) couples to the formation of dihydropyrimidinones in presence of acid catalyst [2]. Dihydropyrimidinones (DHPMs) have extensive pharmacological activities and are regarded as one of the most essential groups of druglike scaffolds [3]. These compounds and their analogues have recently attracted considerable interest because of their wide range of biological activities such as antiviral, antibacterial, antitumor, and anti-inflammatory properties [4]. The 1,4-dihydropyrimidine moiety is a versatile pharmacophoric characteristics, such as compounds with this structural framework exhibit a broad range of biological activity, e.g. calcium channel modulators, α1a-adrenergic receptor antagonists, mitotic kinesin inhibitors, fungicidal, antihypertensive, anticancer agents etc [5, 6]. Consequently, there has been continuous attention from synthetic organic and medicinal chemists in the improvement of novel methodologies for this set of compounds that involve a three-component reaction of an aldehyde, a β-keto ester or β-diketone, and urea [7]. Since last two decade efforts engage the exercise of Brønsted acid or base, metal Lewis acids, organocatalysts, and heterogeneous catalysts and nonconventional techniques, such as microwave, ultrasound, high pressure, and grindstone chemistry [8-14]. Though, all of these protocols suffer from disadvantages like the use of expensive and highly acidic catalysts and also need more reaction times. Moreover, the yields of the subsequent DHPMs are not reasonable.

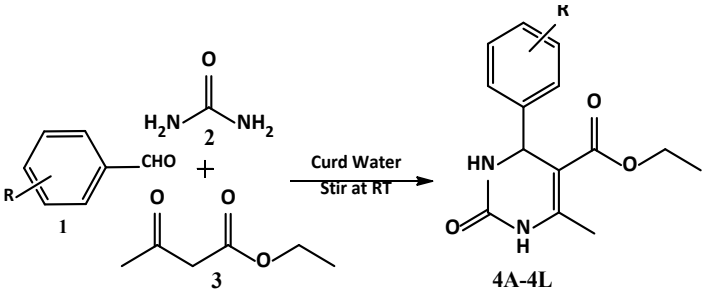
Recently, green chemistry has become a major driving force for organic chemists to develop environmentally benign routes to a numerous of materials [15, 16]. Green chemistry strongly influences chemical research, and there is an insistence on the use of 'greener' reaction conditions [17]. The possibility of performing multi-component reactions under soft conditions with bio waste water as a greener solvent as well as catalysts could enhance their efficiency from an economical point of view. So greener solvent and bio waste catalyst have received much attention in chemical reactions. These reactions offer frequent benefits in preparative procedures, such as environmental compatibility, simplifying work-up, formation of cleaner products, enhanced selectivity, reduction of by products, a reduction in the waste produced, and much improved reaction rates [18].

Curd water is pale yellow colour homogeneous low molecular weight proteinaceous liquid material [19]. We have previously demonstrated the synthesis of 3,3-bisindolylmethanes at room temperature in bio waste curd water [20]. Thus, a number of pro-

cedures for the preparation of DHPMs derivatives have been reported in the literature, using the action of urea, aldehyde and EAA in the presence of either a Lewis acid or Bronsted acid [21]. In continuation, our group has established a simple and economic protocol for the synthesis of the label DHPMs compounds. This homogeneous curd water solution plays dual role being catalyst as well as solvent offering decent reaction productivity. Bio waste curd water is natural feedstock extract, abundantly available, Cheaper. The underutilized greener solvent and biocatalyst further encourages investigation of efficient green method which overcome some inherent disadvantages cited.

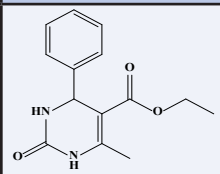
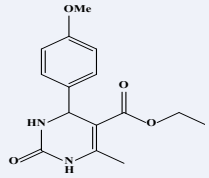
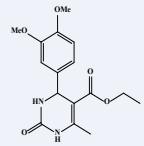
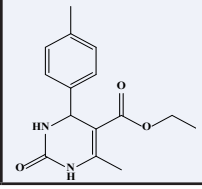
Result and Discussion

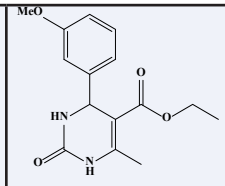
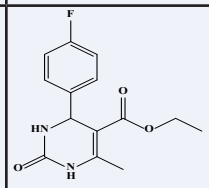
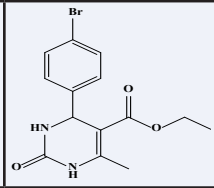
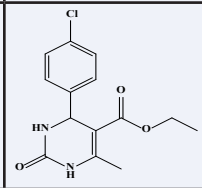
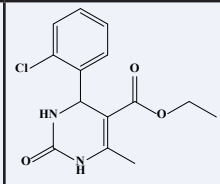
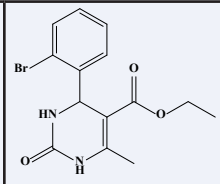
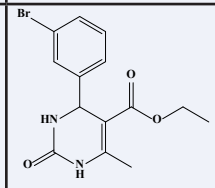
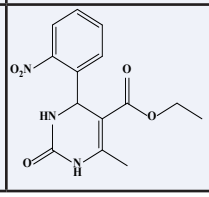
One-pot multicomponent reactions are well known for the production of several organic moieties in pharmaceuticals industries [22]. A variety of protocols have been tried for this one pot synthesis, using various acids and metal salts as a catalyst [23, 24]. Apart from these precious acids and metal salts, some cheaper and environmentally benign acid catalyst like biowaste curd water extract has been already reported for the synthesis of 3,3-bisindolylmethanes [20]. In continuation to that, with best of our knowledge, the reaction of 1 mol of aldehyde (1), 1.2 mol of urea (2) and 1.4 mole of ethyl acetoacetate (3) was never reported under ambient conditions in curd water. This reaction, we considered here as a typical model reaction. Further, the methodology was extended for the synthesis of various DHPMs derivatives. Thus, a high yield of dihydropyridones (80–82%) was obtained (Table 1) in the presence of curd water liquid. Curd water is a homogeneous, stable, non-dispersed solution exists for a long time without segregation overcoming the general problem of precipitation. The lactic acid content in the curd water was confirmed for its presence quantitatively by the standard method of analysis. The lactic acid induced acidity was determined by the digital pH meter as well as by the titration method with 0.1 N NaOH. The lactic acid present in the curd water solution is responsible for the quantitative conversion of final compounds 4A-4L (Table 1). Lactic acid imparts sufficient accessible acidity to the solution which accelerates the conversion into DHPMs. It is worth observing that this work is an input to the green chemistry protocol since the method is environmentally benign. This method was further extended and optimized for scope compounds (4A-4L), which were easily separated. ^{1}H NMR and 13C spectra characterization confirms the formation of the final product. The presence of lactic acid truly influences the formation of the final product as depicted in the scheme 1.



Scheme 1: The Biowaste Curd Water Catalysed Synthesis of Dihydropyrimidinones Derivatives at Ambient Temperature

Table 1: Biowaste Curd Water Catalysed Synthesis of Dihydropyrimidinones

Sr. No.	Product	Yield[a]	Recrystallized in	Time (hrs)	Melting point Present Method
4A		80	water ethanol system (20:80)	2.30	206
4B		78	water ethanol system (20:80)	2.45	210
4C		76	water ethanol system (20:80)	3.00	240
4D		78	water ethanol system (20:80)	2.32	208

4E		80	water ethanol system (20:80)	2.30	226
4F		82	water ethanol system (20:80)	2.15	178
4G		80	water ethanol system (20:80)	2.16	196
4H		79	water ethanol system (20:80)	2.18	212
4I		80	water ethanol system (20:80)	2.20	206
4J		78	water ethanol system (20:80)	2.15	212
4K		80	water ethanol system (20:80)	2.10	182
4L		82	water ethanol system (20:80)	2.00	220

[a]Isolated yield

Physico-Chemical Properties of Curd Water

The physicochemical properties of the curd water like pH, total acidity, total carbohydrate and total protein contents were analyzed by standard methods. The pale colour water was derived from curd and subjected to determine the pH by digital pH meter (HANNA, instruments), while the total acidity (Titrable acidity) was determined by titration of curd water against the 0.1 N NaOH solution with phenolphthalein indicator and the total acidity was expressed in percent (% lactic acid) by using the following formula.

$$\% \text{ Lactic acid} = \frac{\text{Vol. of 0.1 N NaOH required for neutralization x 0.009}}{\text{Weight of sample}} \times 100$$

The total carbohydrate and protein were estimated by Phenol sulphuric acid and Biuret method respectively, and the contents were calculated in gram % by using standard graphs (S1). The physicochemical parameters of curd water were determined as shown in table 2. The total acidity, carbohydrate and protein were found to be 1.20±0.01(%), 0.22±0.03 and 1.22±0.03(g %) respectively. The titrable acidity was higher than the milk due to lactic acid fermentation which plays an important role in the acceleration of organic reactions like condensation, ring transformations and multicomponent reactions. The low percentage of carbohydrates indicates the conversion of milk sugar into lactic acid.

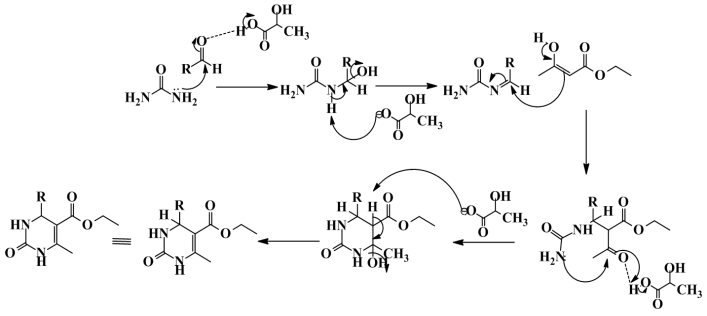
Table 2: Physicochemical Parameters of Curd Water

Parameters	
Color	Pale yellow
pH	3.6
Total Acidity (%)	1.20±0.01
Total Carbohydrate (g %)	0.22±0.03
Total Protein (g %)	1.22±0.03

Results expressed in mean of three individual test with ± standard deviation

Plausible Mechanism

We propose a mechanistic course of the reaction under the catalytic influence of the lactic acid as shown in scheme 2. The three-component reaction of an aldehyde, a *β*-dicarbonyl compound and urea has been proposed to proceed by three distinctive routes: (a) intermediate formation the imine or iminium salt of the aldehyde and the urea which undergoes subsequent nucleophilic attack by the active methylene carbon of the *β*-dicarbonyl compound through its enol form followed by intramolecular cyclocondensation, (b) formation of the Knovenagel adduct of the *β*-dicarbonyl compound and the aldehyde and subsequent aza-Michael reaction with urea followed by intramolecular cyclodehydration, and (c) formation of enaminone through aza-Michael reaction of urea with the enol form of the *β*-dicarbonyl compound and subsequent aldol-type reaction of its enamine moiety with the aldehyde followed by cyclodehydration [25].



Scheme 2: Plausible Reaction Mechanism for The Biginelli Reaction

Experimental

Procedure for The Preparation of Curd Water Solvent

Remove the water from freshly prepared curd using a muslin cloth, collect the turbid liquid into a conical flask. Centrifuged turbid liquor on cooling centrifuges machine at 4000 rpm for 15 min. Finally, filtered off the liquor using ordinary Whatman paper. Use the pale-yellow color liquid for further reaction.

Synthetic Procedures

Initially properly mixed 1 mole of urea, 1.2 mole substituted benzaldehyde and 1.4 mole ethyl acetoacetate in RBF. Add 5 mL of curd water and 5 mL of distilled water stir the reaction mixture at room temperature. The progress of the reaction was checked by TLC during the reaction. Product formation was observed, and the insoluble final product was crystallized itself in the reaction mixture. After end of the reaction in requiring time final product was separated by subsequent filtration and washed with a required amount of hot distilled water. Further product was recrystallised in water ethanol system (20:80).

Reusability study

An extremely efficient catalytic protocol for the synthesis of a series of dihydropyrimidinone derivatives developed in a 3 MCR approach in the presence of catalytic amount of curd water. The reusability of the curd water containing catalyst was studied in the reaction of urea, substituted benzaldehyde and ethyl acetoacetate in curd water at ambient temperature with constant stirring. After each cycle, the catalyst was recovered by simple filtration. Due to the washing of the final product with water, the mother liquor was diluted, the recovered dilute mother liquor was reused three times, result in the loss of its activities (Table 3). After three cycles, the use of such catalyst resulted in a lower yield of the product. It will not be significant enough for continuous use, many washings of distilled water reduces its acidity.

Table 3: Reusability of Curd Water for Biginelli Reaction

Cycle	Time	Yield	Catalyst recovery
1	2.30	80	Up to 80%
2	2.40	75	Up to 60%
3	3.00	72	Up to 40%

Conclusion

In conclusion, the dual role of curd water as a catalyst as well as solvent provides an efficient and much improved amendment of Biginelli reaction. The yields of the one-pot Biginelli reaction increased up to 82% while the reaction time shortened from 18 hours to 2-3 hours. This improved modification of Biginelli reaction is a simple, high-yielding, timesaving, and eco-friendly process.

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