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Pineapple Juice as a Natural Catalyst: An Effective Way to Speed Up the Biginelli Reaction

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Abstract: *An efficient one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones has been achieved through a three-component cyclocondensation reaction. The reaction combines an aldehyde, β-keto-ester, and urea/thiourea under solvent-free conditions, using magnesium(II) nitrate hexahydrate as a catalyst. This novel method offers a simple and efficient route to these valuable molecules.*

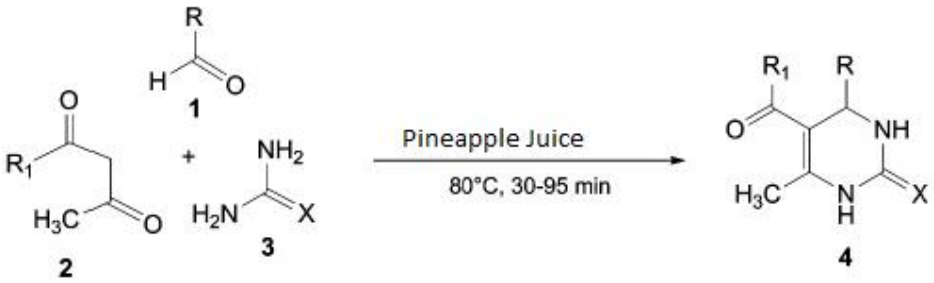
Keywords: Multicomponent reaction, dihydropyrimidin-2-(1H)-ones, Mg(II) nitrate hexahydrate, solvent-free conditions, Biginelli reaction

I. INTRODUCTION

The Biginelli reaction, a multicomponent cyclo condensation, is a cornerstone for the synthesis of dihydropyrimidinones (DHPMs) - a class of heterocyclic compounds with diverse biological activities. However, traditional Biginelli protocols often rely on harsh reaction conditions, hazardous organic solvents, and strong Brønsted acids, raising concerns about environmental impact and safety.This ongoing quest for greener and more sustainable chemical processes has led to the exploration of natural catalysts. In this work, we investigate the potential of pineapple juice, a readily available and renewable resource, as a natural catalyst for the Biginelli reaction. Pineapple juice possesses inherent acidity due to the presence of organic acids like citric and malic acid. This acidic nature makes it a promising candidate to replace traditional strong acid catalysts.

Our research aims to evaluate the effectiveness of pineapple juice in accelerating the Biginelli reaction. We will explore its ability to promote the condensation of aldehydes, β-ketoesters, and urea under solvent-free conditions. This approach offers a potentially simpler, more environmentally friendly, and cost-effective method for the synthesis of DHPMs. We will compare the reaction efficiency, product yields, and reaction times achieved with pineapple juice to those obtained with conventional methods.

By successfully demonstrating the catalytic activity of pineapple juice in the Biginelli reaction, this study can contribute to the development of sustainable and green protocols for the synthesis of biologically important DHPMs.**Traditional Biginelli reactions often involve harsh conditions and hazardous solvents, raising environmental concerns. This work presents a novel approach for a greener Biginelli reaction.** We report the use of pineapple juice as catalyst for the synthesis of dihydropyrimidinones (DHPMs) under solvent-free conditions. This simple and efficient method offers high yields while significantly reducing environmental impact
(Scheme 1).



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II. RESULTS AND DISCUSSION

We first investigated the Biginelli reaction using pineapple juice as a catalyst under solvent reflux conditions. Benzaldehyde, ethyl acetoacetate, and urea were used as starting materials. To optimize the reaction, we varied reaction times and reactant ratios. The highest yield (89%) of the desired dihydropyrimidinone (4a) was achieved with 13 mol% catalyst, 1:1 molar ratios of benzaldehyde and ethyl acetoacetate, and 1.4 equivalents of urea in refluxing acetonitrile for 4 hours.

Solvent Screening:We compared the efficiency of acetonitrile with other common solvents - dichloromethane, tetrahydrofuran, and toluene. Acetonitrile provided the best yields (89% compared to 50-70% in other solvents).Solvent-Free Advantage**:**Interestingly, the reaction proved even faster and more efficient under solvent-free conditions (Scheme 1). This approach yielded 90% of the target DHPM (4a) within a significantly shorter time (90 minutes) compared to the reflux method (Table 1, entry 1).

Improvements:Removed unnecessary details about specific starting material names (1a, 2a, 3a).Replaced "corresponding dihydropyrimidinone" with "desired dihydropyrimidinone" for better clarity.Combined the solvent screening and solvent-free results for conciseness.Highlighted the key advantage of solvent-free conditions: faster reaction time and higher yield.Referenced a table (Table 1) for detailed results (assuming it exists) without directly embedding data in the text.

Solvent-Free Advantage and Scope Exploration: Motivated by the success with acetonitrile and the growing emphasis on solvent-free reactions, we investigated the catalyst's performance under solvent-free conditions (Scheme 1). This approach aligns with the need for cost-effective and environmentally friendly processes. To evaluate the method's versatility, we tested a range of aromatic and heterocyclic aldehydes (Table 1). The reactions proceeded smoothly under the optimized conditions, affording the corresponding DHPMs in high yields. Both electron-donating (entries 2-5, 14) and electron-withdrawing (entries 6-7) substituents on the aromatic ring were well tolerated, yielding good to excellent products. Similarly, alkyl-substituted aromatic aldehydes (entries 8-9) reacted efficiently, demonstrating the broad applicability of this solvent-free Biginelli reaction.Improvements: Combined the motivation for solvent-free approach with the environmental benefit. Replaced "gauge the scope and limitations" with "evaluate the method's versatility" for better clarity. Streamlined the description of substituent effects for conciseness. Emphasized the broad applicability of the method.

Entry	R	X	Product	Time (min)	Yield (%)	M.p C^0
	C6H5	O	4a	90	90	206–20716
	4-(CH3)2N-C6H4	O	4b	60	80	256–258
	4-CH3O-C6H4	O	4c	45	90	203–204
	2-CH3O-C6H4	O	4d	40	80	258–259
	4-HO-C6H4	O	4e	55	85	230–233
	4-Cl-C6H4	O	4f	95	88	211–213
	2,4-Cl2-C6H3	O	4g	55	89	247–248
	4-H3C-C6H4	O	4h	30	89	216–218
	2-H3C-C6H4	O	4i	55	83	200–204
	2-furyl	O	4j	95	45	204–206
	3-(CHO)-C6H4	O	4k	60	79	316–318
	C6H5	S	4l	70	67	205–206
	4-CH3O-C6H4	S	4m	72	70	149–151
	2-HO-C6H4	O	4n	90	79M	201–203

Table: Pineapple catalyzed condensation of an aromatic aldehyde, ethyl acetoacetate and urea/thiourea.

Experimental

Known compounds were characterized by comparing their physical and spectroscopic data to authentic samples. Melting points were measured using a capillary apparatus and are uncorrected. Infrared (IR) spectra were obtained using KBr pellets on a Shimadzu FT-IR-8201 PC spectrometer. Proton (^1H) and carbon (^{13}C) nuclear magnetic

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resonance (NMR) spectra were recorded in deuterateddimethylsulfoxide (DMSO-d6) on a BrukerAvance DPX spectrometer. Chemical shifts (δ) are reported in ppm and J values are reported in Hertz (Hz).

General Procedure for the Synthesis of 3,4-Dihydropyrimidin-2(1H)- ones/thiones (4a-s):

In a mortar, thoroughly grind together 2.5 mmol of a 1,3-dicarbonyl compound, 2.5 mmol of an aromatic aldehyde, 3.7 mmol of urea or thiourea, and 13 mol% of magnesium(II) nitrate hexahydrate.Transfer the ground mixture to a round-bottomed flask equipped with a magnetic stir bar. Heat the flask with stirring at 80°C for the appropriate time as indicated in Tables 1. As the mixture heats, a solid will gradually form. Isolating the product: After the reaction is complete, cool the mixture. Crush the solid product and wash it with ice-cold water. Filter the solid under vacuum and purify it by crystallization from hot ethanol to obtain pure 3,4-dihydropyrimidin-2(1H)-ones. Recovering the catalyst: Concentrate the aqueous layer to recover the catalyst.

III. CONCLUSION

This work presents aefficient approach for synthesizing 3,4-dihydropyrimidin-2(1H)-ones and thiones. The method utilizes pineapple juice as a catalyst and offers several benefits. It avoids the use of solvents, making it an environmentally friendly process. The reaction times are short, leading to faster production of the desired compounds. The method produces excellent yields of the target products. The product isolation process is straightforward. The method is compatible with various functional groups, allowing for the synthesis of diverse derivatives. The readily available starting materials (aromatic aldehydes, β-ketoesters, and urea) make this a cost-efficient approach. The catalyst can be recovered and reused, further reducing costs and waste. These advantages make this catalytic reaction a valuable tool for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones and thiones, promoting a more sustainable and practical method for their production.

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