

Pineapple Juice as a Natural Catalyst: An Excellent Catalyst for Biginelli Reaction

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Abstract

An efficient and greener synthesis of a series of dihydropyrimidinone (DHPMs) derivatives were accomplished via three-component one-pot cyclocondensation between substituted aryl aldehydes, diketone/ketoester and urea. This solvent free approach is totally nonpolluting having several advantages such as shorter reaction time, mild reaction conditions, simple workup and reduced environmental impact.

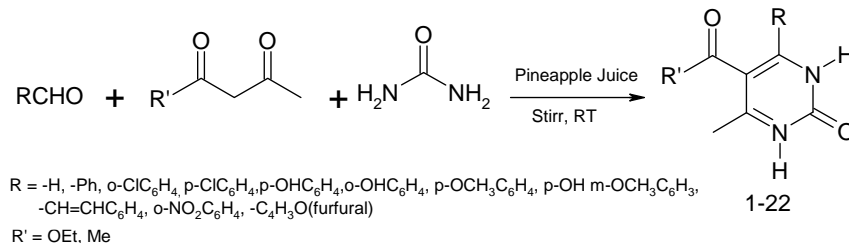
Keywords: Biginelli, Natural Catalyst, Pineapple Juice, Dihydropyrimidinone.

1. Introduction

Among the challenges for chemists include discovery and development of non-hazardous and simple environmentally safe chemical processes for selective synthesis by identifying alternative reaction conditions and solvents for much improved selectivity, energy conservation and even less hazardous waste generation are not desirable and inherently safer chemical products. Therefore, to address depletion of natural resources and preservation of ecosystem it is just urgent to adopt so called "greener technologies" to make chemical agents for well being of human health. Due to acidic nature (pH = 3.7) pineapple juice as a natural catalyst has been found to be a suitable replacement for various homogeneous acid catalysts.

In literature number organic reactions are reported in which natural catalyst like clay [1-3], phosphates [4,5], gold [5], animal bone [6] etc. are employed. In continuation of our research work in application of natural acids as catalyst, here, we report a solvent free one pot cyclocondensation reaction of substituted aryl aldehydes, diketone/ketoester and urea (**Scheme 1**) with good yields.

Pineapple (*Ananas comosus*) is sometimes called the *King of Fruit* [7]. Pineapple is grown extensively in Hawaii, Philippines, Caribbean area, Malaysia, Taiwan, Thailand, Australia, Mexico, Kenya and South Africa. Pineapple has long been one of the most popular of the non-citrus tropical and subtropical fruits, largely because of its attractive flavour and refreshing sugar-acid balance [8]. For the present work, we have used extract of *pineapple* as natural catalyst for synthesis of dihydropyrimidinone (DHPMs). The main ingredients of 100 g pineapple contain 47 - 52 calories, water (85.3 - 87.0 g), protein (0.4 - 0.7 g), fat (0.2 - 0.3 g), total carbohydrate (11.6 - 13.7 g), fiber (0.4 - 0.5 g), ash (0.3 - 0.4 g), calcium (17 - 18 mg), phosphorus (8 - 12 mg), iron (0.5 mg), sodium (1 - 2 mg) and potassium (125 - 146 mg) [9]. It also contains 12% - 15% sugars of which two-third is in the form of sucrose and the rest are glucose and fructose and 0.6% - 1.2% acid of which 87% is citric acid and 13% is malic acid [10,11]. The composition of the juice varies with geographical, cultural and seasonal harvesting and processing.



Scheme 1. Synthesis of dihydropyrimidinones.

The extract of pineapple is acidic having pH 3.7 and the acidity percentage is 53.5% and hence it will be worked as acid catalyst for cyclocondensation. Therefore, we have used this extract as natural catalyst for synthesis of DHPMs.

The Italian chemist Pietro Biginelli (1893, University of Florence) for the first time reported on the acid-catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde, and urea [12]. The three components reaction mixture in ethanol was simply heated with a catalytic amount of HCl at reflux temperature and the product that precipitated on cooling the reaction mixture was identified as 3,4-dihydropyrimidin-2(1H)-one. This reaction is nowadays referred to as the Biginelli reaction, Biginelli condensation or as the Biginelli dihydropyrimidine synthesis. However, this method is suffered from drawbacks of the longer reaction time and lower yields, hence reaction remained unfocused in the last century. But due to important biological properties of DHPMs, the interest in their synthesis has been increased in the last two decades. Much effort has been made recently to improve and modify this reaction. This gave inspiration to organic chemists to find out more suitable protocol and simpler methods for the synthesis of DHPMs.

DHPM and its derivatives are found in a large family of natural products with broad biological activities, due to which they become important classes of organic compounds. They generally possess intriguing therapeutic and pharmacological properties [13-15]. Several of their functionalized derivatives are used as calcium channel modulators [13-16], Ca-antagonists [16-18] and vasodilative, antihypertensive [19].

For Biginelli reaction, large number of methods have been reported to synthesize DHPMs by altering catalyst. Of them various homogeneous catalysts such as $Mg(NO_3)_2$ [20], $Pb(NO_3)_2$ [21], $LaCl_3 \cdot 7H_2O$ [22], P_2O_5 [23]. Recently Lewis acids like DDQ [24], $InBr_3$ [25], $CaCl_2$ [26], $Y(OAc)_3$ [27], $ZnCl_2$ [28], $RuCl_3$ [29], Metal triflimides $Ni(NTf_2)_2$ [30] etc. have been extensively reported in the literature Biginelli reactions. Apart from these, the Bronsted acids such as *p*-TSA [31], almost neutral catalyst $Zn(BF_4)_2$ [32] also reported. Heterogeneous catalysts such as E4a [33], SiO_2-Cl [34], AMA [35], KSF(montmorillonite) [36], zeolites like HZSM-5, HY, MCM-41 [37] have also been employed. Synthesis of DHPMs can also be catalyzed by ionic liquids [38].

The limitations in using the above mentioned catalysts were such as long reaction time, elevated reaction temperature, harsh reaction conditions, use of expensive reagents, moderate yields of the products, use of harmful organic solvents and toxic and hazardous transition metals (Table 1).

2. Results and Discussion

Herein, we, report a single step synthesis of DHPMs using a pineapple juice as natural catalyst under solvent-free conditions. As per literature survey, there are no earlier reports of pineapple juice as catalyst for Biginelli reaction. In addition to its clean and simplicity, this catalyst resulted in higher yields for different aromatic aldehydes (Table 2).

3. Conclusions

We have developed an eco-friendly and economic process for the synthesis of DHPMs by pineapple juice as a catalyst with good yields. This solvent free approach is totally nonpolluting and there no any use of toxic materials, quantifying it as a green approach to this cyclocondensation reaction. In addition to this, it involved mild.

4. Experimental Section



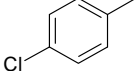
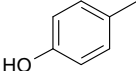

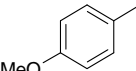
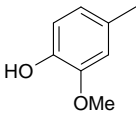
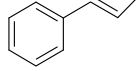




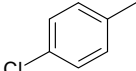
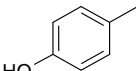

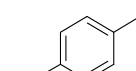
4.1 General Process for Preparation of Pineapple Juice

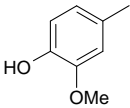
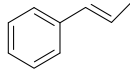
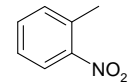
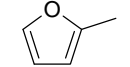
Fresh pineapple (*Ananas comosus*) was procured locally. The crown and stem portions were removed and the skin reaction conditions and simple workup was peeled using

Table 1. Comparison for different catalysts used for synthesis of DHPMs (R = *p*-OCH₃C₆H₄).

Entry	Catalyst	Time	Temperature	Yield (%)
1	<i>p</i> -TSA [31]	1 hr	Refluxed in EtOH	90
2	$RuCl_3$ [29]	4.5 hr	Reflux in N_2 atm	82
3	$Zn(BF_4)_2$ [32]	4 hr	Stirring at RT	71
4	$Y(OAc)_3$ [27]	4.5 hr	115°C	89
5	$Mg(NO_3)_2$ [20]	45 min	Refluxed	90
6	$CaCl_2$ [26]	2 hr	Refluxed in EtOH	98
7	$InBr_3$ [25]	7 hr	Refluxed in EtOH	97
8	$Pb(NO_3)_2$ [21]	180 min	Refluxed in CH_3CN	89
9	P_2O_5 [23]	1.5 hr	Refluxed at 100°C	94
10	SA & SSA [39]	10 min	Reflux 120°C	86
11	E4a [33]	8 hr	Heated at 80°C	91
12	AMA [35]	35 min	Heated at 60°C in EtOH	96
13	Yatria-Zirconia Lewis acid [40]	6 hr	Aq. CH_3CN 60°C	92
14	Silica chloride [34]	3 hr	Heated at 80°C	90
15	Pineapple	3.5 hr	Stirring at RT	82

Table 2. Pineapple Juice catalyzed synthesis of DHPMs.

Entry	R	R ¹	Time (hours)	Yield (%)	M.P.	
					Found	Reported
1	H	OEt	3.5	60	232	-
2		OEt	2.5	82	207	202 [32]
3		OEt	3.5	81	216	218 [27]
4		OEt	4.5	85	213	215 [32]
5		OEt	2	86	222	226 [32]
6		OEt	3.5	79	202	201 [32]
7		OEt	3.5	82	203	203 [32]
8		OEt	2.5	85	215	215 [41]
9		OEt	2	89	230	232 [32]
10		OEt	3.5	87	209	208 [32]
11		OEt	5	88	204	203 - 205 [21]
12	H	Me	3.5	61	230	--
13		Me	3.5	90	232	233 [32]
14		Me	3	92	240	-
15		Me	5.5	93	277	-
16		Me	3	90	256	-
17		Me	4	88	220	-
18		Me	3	93	172	166 [32]

19		Me	2	92	232	-
20		Me	5	89	243	-
21		Me	2.5	91	230	234 - 236 [21]
22		Me	4.5	90	197	-

knife. Then the fruit was sliced and the fruit slices pressed in a fruit juicer for one to two minutes to get the semisolid mass which was then filtered through cotton to get liquid pineapple juice.

4.2 General Procedure for Synthesis of 5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one

The synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one is described as a representative example: The equimolar quantities of p-methoxybenzaldehyde (1.36 g, 10 mmol), ethyl acetoacetate, (1.30 g, 10 mmol) and urea (0.6 g, 10 mmol) in 1 ml pineapple juice were stirred for 3.5 hours at room temperature with monitoring by TLC. Then the reaction mixture was filtered, washed with little water. The yellow solid obtained was then recrystallized with ethanol

to get fine yellow crystals of 5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one. The formation of the compound was confirmed by IR, NMR and its melting point.

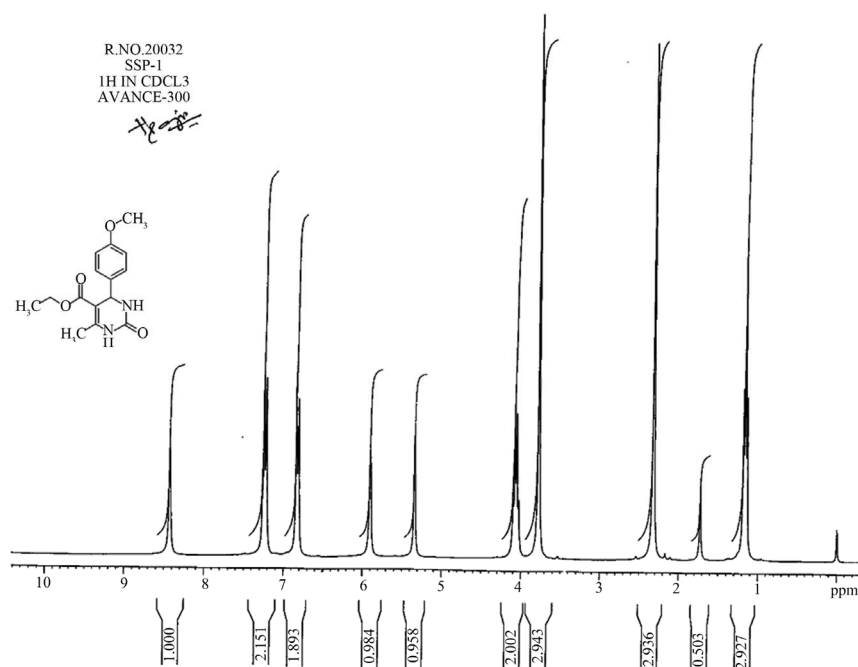
This procedure is followed for the synthesis of all the DHPMs listed in Table 2.

4.3 Spectral Data for Representative Compounds

5-ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (Compound 7 Table 2):

IR (CHCl₃, cm⁻¹): max 3230, 1720, 1690 cm⁻¹.

¹H NMR (CDCl₃): 1.14 (s, 3H, -OCH₂CH₃), 2.32 (s, 3H, -CH₃), 3.78 (s, 3H, -OCH₃), 4.05 (s, 2H, -OCH₂CH₃), 5.34 (s, 1H, -NH), 5.90 (s, 1H, -NH), 6.84 (s, 2H, Ar-H), 7.21 (s, 2H, Ar-H), 8.42 (s, 1H, -CH) (Figure 1).



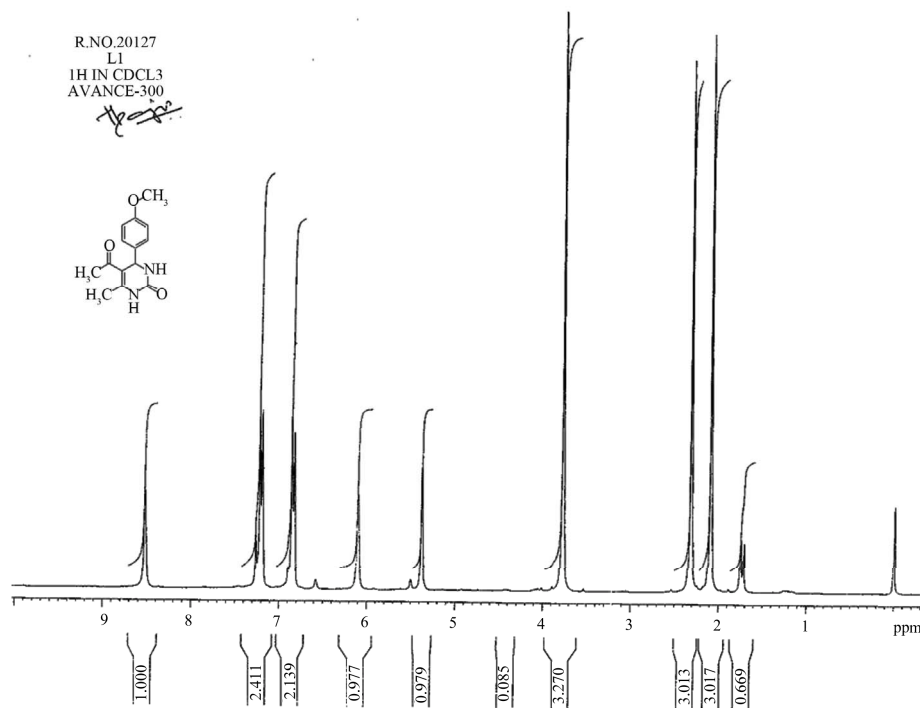


Figure 2. NMR Spectrum (2).

5-acetyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyridin-2(1H)-one (Compound 18 **Table 2**)

IR (CHCl₃, cm⁻¹): max 3235, 1721, 1692 cm⁻¹.

¹H NMR (CDCl₃): 2.09 (s, 3H, -CH₃), 2.32 (s, 3H, -CH₃), 3.77 (s, 3H, -OCH₃), 5.37 (s, 1H, -NH), 6.10 (s, 1H, -NH), 6.85 (s, 2H, Ar-H), 7.21 (s, 2H, Ar-H), 8.52 (s, 1H, -CH) (**Figure 2**).

5. Acknowledgements

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6. References

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