Research Article

Citrus Maxima Juice Catalyzed an Efficient Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones

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Abstract

3,4-dihydropyrimidone (DHPM) is very important chemical moiety as it is a core nucleus in synthesis and medicinal chemistry. *Citrus maxima* juice is a clean catalyst for the synthesis of 3,4-dihydropyrimidones derivatives in the excellent yield form the one-pot three component condensation of ethyl acetoacetate, aromatic aldehyde and urea in ethanol is described. The major advantages offered by this method are simple experimental workup procedure, mild reaction condition, excellent yield of the product and utilization of inexpensive green catalyst.

Keywords: 3, 4-dihydropyrimidones, *Citrus maxima* juice

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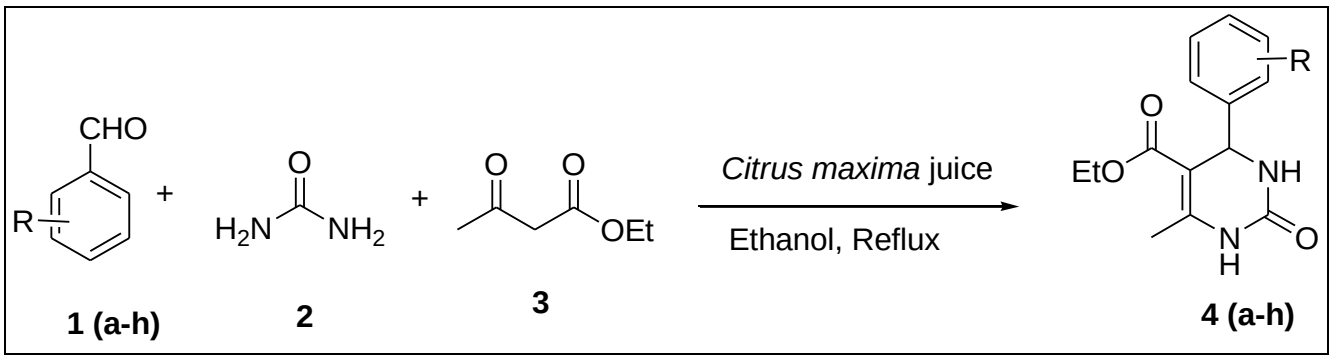
Introduction

Citrus maxima are perennial shrub commonly known as papanus, distributed throughout India. *Citrus maxima* fruit juice contains malonic acid, fumaric acid and citric acid in large amount [1]. It also contains high amount of phenolic compounds like caffeic acid, p-coumeric acid, vanillic acid and like other citrus plant it is rich in vitamin-C.

The 3, 4-dihydropyrimidones (DHPMs) are associated with diverse pharmacological activities and significant medicinal properties [2] such as antiviral, antibacterial, anti-inflammatory and antitumor [3, 4]. 3, 4-dihydropyrimidones (DHPMs) derivatives form a component in number of useful drugs. Several marine alkaloids having core unit of 3, 4-dihydropyrimidones (DHPMs) are showing many interesting biological activities such as antihypertensive agents [5] and calcium channel blockers [6]. 3, 4-dihydropyrimidones (DHPMs) system is one of the most important structures found in pharmacologically active compounds such as calcium channel modulators and α-adrenergic antagonist [7].

Biginelli in 1893 reported the first time one-pot synthesis of 3,4-dihydropyrimidones (DHPMs) by condensation of aldehyde, β-keto ester and urea or thiourea in ethanol using catalytic amount of HCl. Due to its great importance many synthetic strategies has been employed for the synthesis of 3,4-dihydropyrimidones using different both acidic and basic catalytic systems such as nanocomposite ferrite catalyst [8], aluminium sulphate [9], [Hmim] [Tfa] [10], [p-TSA] [11], molecular (I_2) [12], sulphanic acid [13], 1,3,5-triazine-2,4,6-triyltrisulphanic acid [14], mesoporous $NH_4H_2PO_4$/MCM-41 [15], ferrous sulphate [16], 12-molybdophosphoric acid [17] and using zeolite [18]. These reported methods suffer from unsatisfactory yields, cumbersome product isolation procedure, use of harsh solvents and exotic reaction condition which concern for environmental pollution. Therefore, it is necessary to develop an improved route for the synthesis of 3,4-dihydropyrimidones under mild reaction conditions.

In recent years, natural acid have gained special attention as catalyst in organic synthesis because of many advantages such as excellent solubility in water, homogenous nature, easy availability, inexpensiveness and eco-friendly nature. Recently several synthetically useful transformations using fruit juices are reported. Rammohan Pal *et.al* synthesized arylidenemalenonitrite using aqueous extract of *keora* fruit [19]. In 2013 Rammohanpal *et.al* reported the condensation of indole and aldehyde in fruit juice of *citrus lemon* for the synthesis of Bis and Tris (indolyl) methane [20]. Knoevengel condensation by employing heena leave extract has been also reported [21]. In this continuous efforts for the search of environment friendly catalyst for 3,4-dihydropyrimidones we found *Citrus maxima* juice quite effective. Here we first time reported *Citrus maxima* juice can be used as synthetic protocol for preparation of 3,4-dihydropyrimidones derivatives. As *Citrus maxima* juice is acidic in nature with pH about 2-3 and percentage of citric acid is quite high than acids present. It worked as acid catalyst for this cyclocondensation reaction (scheme 1).



Scheme 1

Experimental

All chemicals were purchased from SD fine and Merck used without further purification. The melting points were taken in an open capillary in a paraffin bath and were uncorrected. The progress of the reaction was monitored by TLC. IR spectra were recorded on Perkin Elmer FTIR spectrometer in KBR disc. ^{1}H NMR spectra were recorded on 300 MHZ-FT-NMR spectrometer in $CDCl_3$ as a solvent and chemical shift values are recorded in units of ppm relative to tetramethylsilane (Me_4Si) as internal standard.

General Procedure for synthesis of 3,4-dihydropyrimidines 4 (a-h)

A reaction mixture of benzaldehyde (10 mmol), ethylacetoactate (10 mmol) and urea (10 mmol), and catalytic amount of citrus maxima juice (1 mL) was refluxed in ethanol (10 mL) for the time mentioned in Table 2. The progress of the reaction was monitored by thin layer chromatography using (petroleum ether: ethyl acetate = 7:3 as eluent). After completion of reaction, the reaction mixture was poured onto crushed ice and the solid product, separated was filtered and recrystallized from ethanol to afford pure products 4(a-h). As the catalyst is soluble in ice cold water, its separation is easy.

Spectral data of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine 2 (1H)-one 4(a)

^{1}H NMR (300MHz, $CDCl_3$):δ 1.19 (t, 3H, J=7.10 Hz), 2.36 (s, 3H), 4.08 (q, 2H, J=6.90 Hz), 5.45 (d, 1H, J=2.15 Hz), 7.28 (m, 5H), 8.07(s, 1H, NH), 8.40 (s, 1H, NH).FT-IR (KBr, cm^{-1}): 3329, 1722, 1638.

Results and Discussion

The present communication reports the one-pot three-component synthesis of 3,4-dihydropyrimidones using *Citrus maxima* juice in a catalytic amount. To optimize reaction conditions, the reaction of benzaldehyde, ethylacetoactate and urea was considered as a standard model reaction. In our initial efforts to optimize the reaction condition this model reaction was carried out using various solvents such as dichloromethane (DCM), methanol, acetone, acetonitrile, tetrahydrofuran (THF) and ethanol. The results shows that as dichloromethane (DCM), methanol, acetone, acetonitrile and tetrahydrofuran gave moderate yields with catalyst. We found reaction was efficient in ethanol compared to other solvents treated and yield was found relatively better as shown in **Table 1**(entry 6). By using *Citrus maxima* extract the desired product was obtained in satisfactory yield. Considering the reaction time and yields of the product, *C. maxima* extract selected as the optimum catalyst for cyclocondensation reaction.

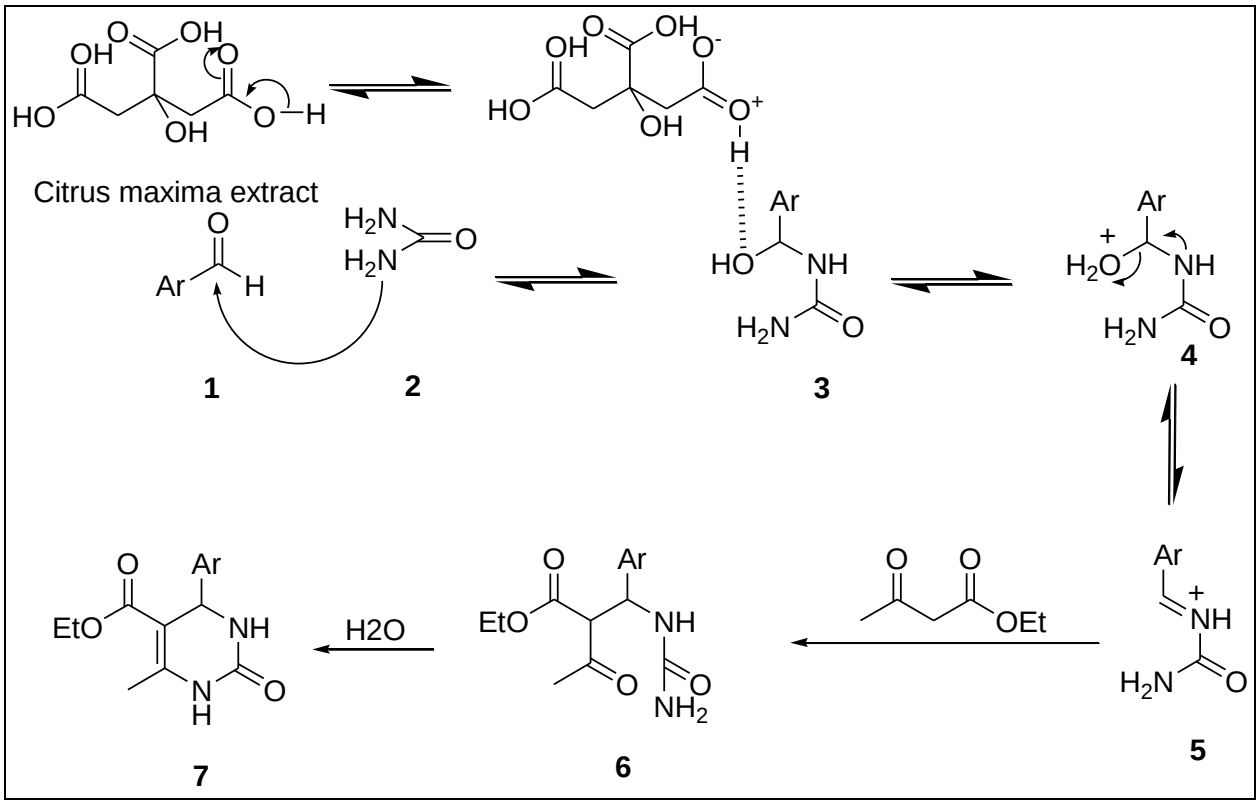
Table 1 Effects of various solvents on synthesis of 3,4-dihydropyrimidin2(1H)-ones

Entry	Solvent	Time/h[a]	Yield (%)[b]
1	Dichloromethane (DCM)	3.5	92
2	Methanol	4	91
3	Acetone	4	92
4	Acetonitrile	4.5	90
5	Tetrahydrofuran (THF)	4.5	91
6	Ethanol	2.5	94

[a]All reactions were carried out using *Citrus Maxima* extract under reflux. [b]Isolated yields

The first step in the mechanism is believed to be condensation between aldehyde and urea. The iminium ion (5) generation is accelerated by acid catalyst. The iminium generated acts as an elctrophile for the nucleophilic addition of the ketoester enol and the ketone carbonyl of the resulting adduct undergoes condensation with urea NH_2 to give cyclized product (7). The plausible mechanism of the reaction is depicted as in **Scheme 2**.

Table 2 shows the generality of the present protocol for variety of aldehydes. Several aldehydes bearing electron donating and electron withdrawing substituents gave good to excellent yields of the desired product.



Scheme 2 Plausible mechanism for the final product

Table 2 Synthesis of 3,4-dihydropyrimidin2(1H)-ones using *Citrus maxima* extract in catalytic amount[a]

Entry	R	Time/h	Yield (%)[b]	M.P. (^{0}C)
4a	C_6H_5	2.5	94	209˚C
4b	$4MeOC_6H_4$	2.6	95	198˚C
4c	$4ClC_6H_4$	2.5	90	212˚C
4d	$4NO_2C_6H_4$	2.6	94	207˚C
4e	$4MeC_6H_4$	2.5	90	216˚C
4f	$3NO_2C_6H_4$	2.5	92	227 ˚C
4g	$4OHC_6H_4$	2.7	91	225˚C
4h	$2ClC_6H_4$	2.7	89	216˚C

[a]Reaction conditions: benzaldehyde (10 mmol), ethylacetoacetate (10 mmol), urea (10 mmol), catalyst 1mL, ethanol 10 mL; [b] Isolated yields

Conclusion

The present work focuses the importance of fruit juices as a natural and biocatalyst in dihydropyrimidones synthesis. The efficient, green, cost effective and eco-friendly method has been developed and reported for the synthesis of dihydropyrimidones using *C.maxima* juice in catalytic amount. Use of environmental benign catalyst, reduced reaction time, easy workup procedure and operational simplicity are the main features of this proposed protocol.

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