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Exploring the Utility of Fruit Juices as Green Medium for Biginelli Reaction.

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ABSTRACT

A series of Dihydropyrimidinone (DHPM) derivatives were synthesized by Biginelli reaction employing urea, ethyl acetoacetate with a series of different derivatives of benzaldehydes. A green, cost-effective, eco-friendly, simple and efficient method has been developed for performing this Biginelli reaction at room temperature using some common fruit juices as reaction medium. The fruit juices have played the role of solvent cum catalyst for this Biginelli reaction. Our recent approach of doing Biginelli reaction in fruit juice medium has given a new direction in green chemistry.

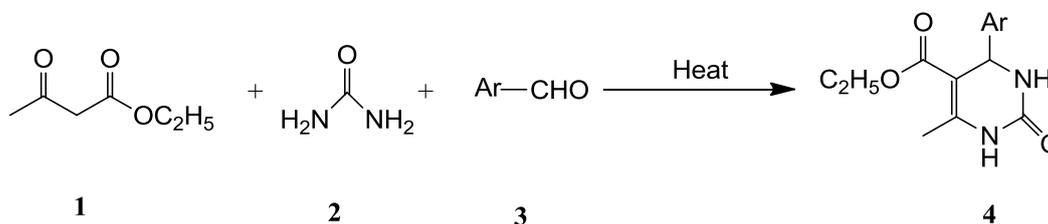
Keywords: Benzaldehyde, Ethyl Acetoacetate, Urea, Biginelli reaction, Fruit Juice, Green Synthesis.

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INTRODUCTION

Dihydropyrimidinone (DHPM) which is an N- contained heterocycle has attracted much attention from the researchers for last few decades. Thanks to a wide range of promising biological activities of this Dihydropyrimidinone derivatives as anticancer, anti-inflammatory, antibacterial, antifungal, anthelmintic, and antitopoisomerase agent [1-4]. Thus, synthesis of this heterocyclic nucleus is of much importance and the most convenient and popular reaction which gives easy access to this N- contained heterocycles is the multi component condensation employing urea, ethyl acetoacetate and aromatic aldehydes via Biginelli reaction [5] [Scheme 1]. Investigation on this reaction was mainly focused on the exploration of catalyst and solvents [6-7]. In literature, a large numbers of Lewis acids such as BF_3 [8], FeCl_3 [9], InCl_3 [10], BiCl_3 [11], LaCl_3 [12], LiClO_4 [13], $\text{Mn}(\text{OAc})_3$ [14], CAN [15] have been successfully employed as catalysts for Biginelli reaction. Mainly EtOH , CH_3CN , CH_2Cl_2 and THF were used as solvent for this reaction. However these catalysts are not completely safe for the environment. It cannot be ignored that the toxicity and volatile nature of many organic solvents posed a serious threat to the environment too [16]. So considering our growing concern for the environment, the researchers got the urge to develop a green and eco-friendly procedure for carrying out Biginelli reaction.

Scheme 1: Conventional route for the Synthesis of DHPM via Biginelli reaction.



As a green and eco-friendly procedure, a solvent-free and catalyst-free condition has been reported in literature [17] for carrying out the Biginelli reaction. But in the solvent-free and catalyst-free condition, the mixture of the reactants need to be stirred at $100\text{-}105^\circ\text{C}$ for approximately one hour [17a] to get the desired DHPMs. As the use of high temperature is also against the basic principle of green chemistry, the need to develop a procedure to perform the Biginelli reaction at room temperature is still there. To fulfill the urge of developing a green methodology for Biginelli reaction, a large number of literatures have reported the synthesis DHPMs via Biginelli reaction using microwave irradiation [17b-17e] and ultrasonic irradiation [17f-17g], however different types of toxic Lewis acids have been used as catalysts to carry out the Biginelli reaction in presence of microwave and ultrasonic irradiation and the usage of such toxic catalysts is not desirable from the green chemistry point of view. So still there is a large scope to develop a green protocol to perform this Biginelli reaction at room temperature without using any non eco-friendly, artificial catalyst and without using any toxic organic solvent.

The feasibility of this Biginelli reaction in weak acid medium have made us think to use some common fruit juices which are weak acidic in nature, as a green medium for this reaction. The bio-degradability, easily availability, non-toxicity, eco-friendly nature of the fruit juice and the natural acids present in the fruit juices have opened the door of opportunity to use it as a green medium for Biginelli reaction. Although many fruit juices have excellent potentiality to be used as a green solvent for this reaction, they have not been well explored yet by the researchers for this purpose. Our extensive literature search has revealed that only Patil *et al.* have reported the synthesis of some dihydropyrimidinone derivatives in pine-apple juice and lemon juice [18-19]. So the need to explore more of the common fruit juices as solvent for Biginelli reaction still remains. To the best of our knowledge orange, lime and amla juice has never been used as green medium for such kind of one-pot multi components condensation reaction.

Even the recent review reports entitled "Fruit Juice: A Natural, Green and Biocatalyst System in Organic Synthesis" [20] by Pal *et al* and "Biginelli Reaction: A Green Perspective" [21] by Panda *et al* did not mention about any such usage of orange, lime and amla juice as medium for Biginelli reaction.

So based on the research gap stated above, our main aim of this work was to perform a series of Biginelli reaction at room temperature employing urea, ethyl acetoacetate with a series of different derivatives of benzaldehydes using individually orange, lime and amla juice as green reaction medium.

MATERIALS AND METHODS

All the fruit juices were directly extracted from naturally obtained fruits. No foreign chemicals have been added as additives to any of these fruit juices. So all these fruit juices used are considered to be 100% natural.

General Procedure for Synthesis of DHPM

The equimolar quantities of ethyl acetoacetate (0.02 mole, 2.6 gm), urea (0.02 mole, 1.2 gm) and the corresponding aromatic aldehydes (a-c) (0.02 mole) were stirred together in 3 ml of desired fruit juice at room temperature with continuously monitoring by TLC. After completion of reaction, the solid product was precipitated out of the reaction medium. Upon filtration of the reaction mixture, the crude solid product was collected and crude product was recrystallized from hot ethanol to get the pure compound as yellowish to white solid.

The obtained DHPMs were characterized by melting point, IR and NMR spectroscopy. The melting point, IR and NMR spectra of the synthesized compounds were identical to those of reported ones.

EXPERIMENTAL

Characterizations

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Compound a)

Melting point: 210 °C (Reported [22]: 209-210 °C)

IR (neat): 3242, 3113, 1724, 2958, 1703, 1487, 1321 cm⁻¹;

¹H-NMR (400 MHz, DMSO-d⁶): δ 1.17 (t, 3H), 2.27 (s, 3H), 4.02 (q, 2H), 5.20 (d, 1H), 7.19–7.31 (m, 5H), 7.63 (m, 1H), 9.09 (s, 1H)

Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Compound b)

Melting point: 215 °C (Reported [23]: 212-214 °C)

IR (neat): 3242, 3113, 2929, 1724, 1703, 1649, 1487, 1460 cm⁻¹

¹H-NMR (400 MHz, DMSO-d⁶): δ 1.14 (t, 3H), 2.26 (s, 3H), 4.02 (q, 2H), 5.18 (d, 1H), 7.25–7.31 (m, 5H), 9.10 (s, 1H)

Ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Compound c)

Melting point: 212 °C

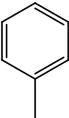
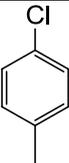
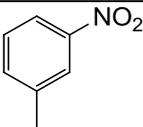
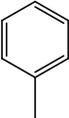
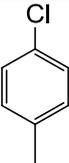
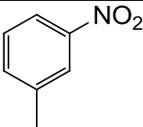
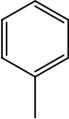
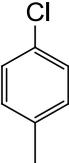
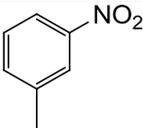
IR (neat) 3244, 3117, 2983, 1720, 1649, 1539, 1489, 1375 cm⁻¹

¹H-NMR (400 MHz, DMSO-d⁶): δ 1.07 (t, 3H), 2.27 (s, 3H), 4.02 (q, 2H), 5.18 (d, 1H), 7.46–8.17 (m, 5H), 9.18 (s, 1H)

RESULTS AND DISCUSSION

The Benzaldehyde, 4-Chloro Benzaldehyde and 3-Nitro Benzaldehyde were employed individually for one-pot multi component condensation reaction with urea and ethyl acetoacetate at room temperature [Scheme-2]. The three common fruit juices namely orange juice, lime juice and amla juice were individually used as the reaction medium for performing these multi component condensation reactions (Biginelli reaction). It was observed that all the reactions were successfully completed at room temperature. After completion of the reactions which was monitored by TLC, the solid products (Dihydropyrimidinone derivatives) were precipitated out of the reaction mixture. The crude solid products were collected by filtering the reaction mixture and the crude products were recrystallized from ethanol to get the pure compounds as yellowish to white solid with reasonable yield.

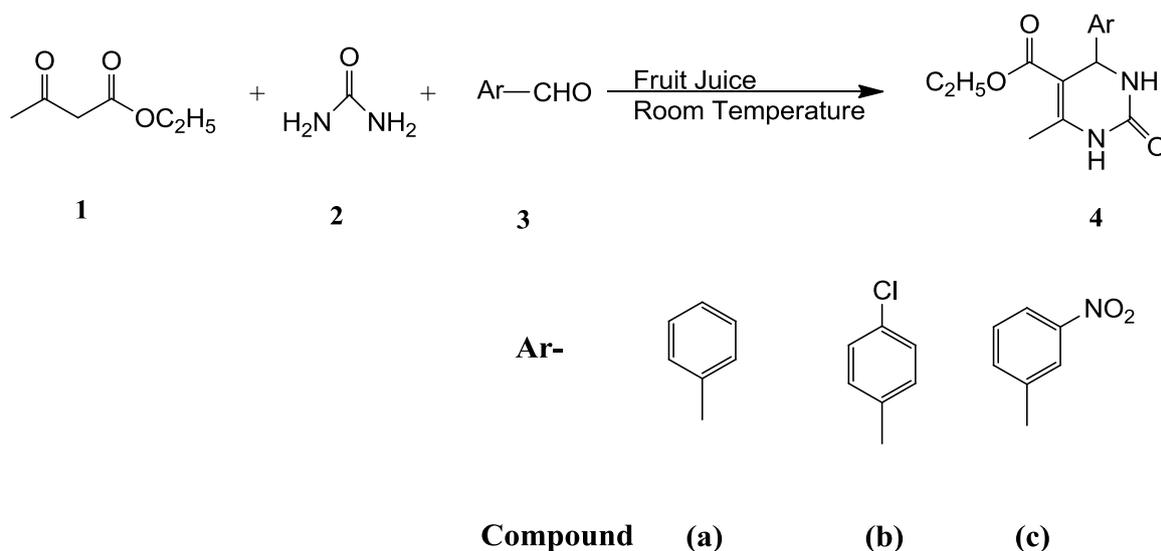
Table 1: Biginelli reaction with different aldehydes in different fruit juice.

Reaction Medium (Fruit Juice)	Ar Group	DHPM	Time	Yield (%)
Orange Juice (pH 3.3-4.1)		4a	4 h	65%
		4b	1.5 h	59%
		4c	1.5 h	70%
Lime Juice (pH 2-2.8)		4a	1 h	67%
		4b	1 h	61%
		4c	1 h	73%
Amla Juice (pH 2.8-3.1)		4a	8 h	58%
		4b	1 h	73%
		4c	1 h	77%

The results obtained are summarized in table-1. It is interesting to note that the reaction was much easier and faster with electron deficient aromatic aldehydes (4-chloro benzaldehyde and 3-nitro benzaldehyde) compared to normal benzaldehyde. It's due to the fact that the electrophilicity of the aldehyde carbon is more if an electron withdrawing group is attached to the aromatic ring, which in turn makes the nucleophilic attack on the aldehyde carbon to be comparatively easier.

It is also noted that the pH of the fruit juice medium has significant effect on the rate of the reaction, usually the duration of the reaction become lesser with increase in acidic nature of the fruit juice (decrease in pH value). Lime juice being the most acidic in nature makes the reaction to be most facile. So the reaction with benzaldehyde was completed in just one hour in lime juice medium, whereas the same reaction with benzaldehyde needs much longer time to complete in orange and amla juice. The reason can easily be understood from the fact that with increase of acidity of the medium, the protonation on the oxygen atom of the aldehyde group become easy which again makes the nucleophilic attack on the aldehyde carbon to be easier.

Scheme 2: Biginelli reaction with different aromatic aldehydes in fruit juice medium.



CONCLUSION

Herein we report the synthesis of DHPM derivatives via one-pot multi component cyclocondensation namely Biginelli reaction in fruit juice medium at room temperature. The orange juice, lime juice and amla juice which all are easily available common fruit juice in all over the world, were used as the green medium for Biginelli reaction. All these fruit juices are totally non-polluting, completely eco-friendly, 100% biodegradable, inexpensive, non toxic and safe, so they posed no threat to the environment. So an eco-friendly, efficient, green and economic method has been successfully developed for synthesis of DHPM at room temperature with good yield. So our current work has given a new direction for the researcher in the field of green chemistry to use common fruit juice as green medium for carrying out Biginelli and other such one-pot multi component condensation reaction at room temperature.

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