

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491

Vol 8, Issue 3, 2016

Short Communication

MICROWAVE IRRADIATED "GREEN BIGINELLI REACTION" EMPLOYING APPLE, POMEGRANATE AND GRAPE JUICE AS ECO-FRIENDLY REACTION MEDIUM

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Received: 01 Jan 2016 Revised and Accepted: 03 Feb 2016

ABSTRACT

Objective: The main objective of this work is to explore the utility of apple, pomegranate and grape juice as an eco-friendly reaction medium for microwave assisted green Biginelli reaction.

Methods: A series of Biginelli reactions were carried out in various fruit juice medium by employing an equimolar mixture of urea, ethyl acetoacetate and aromatic aldehyde as reactants. All the reactions were performed with the help of microwave irradiation. After successful completion of the reactions, the crude products were isolated, and the pure products were obtained after recrystallization of the crude product from hot ethanol.

Results: It was worth to note that all the reactions were completed successfully within few minutes of duration. Pure apple, pomegranate and grape juices were proved to be fruitful as eco-friendly reaction medium for performing microwave-assisted green Biginelli reaction.

Conclusion: A green, eco-friendly and cost-effective method was developed for microwave assisted "*green Biginelli reaction*" in apple, pomegranate and grape juice medium. This new method will further motivate the researchers to use more of common fruit juices instead of toxic solvents as reaction medium for multi-component condensation reactions.

Keywords: Green synthesis, Fruit Juice, Biginelli reaction, Microwave

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Dihydropyrimidinone (DHPM) is an N-contained heterocyclic compound that contains the same pyrimidine unit which is the common moiety present in the main bases like cytosine, thymine, and uracil found in DNA and RNA. This fact makes this dihydropyrimidinone (DHPM) to be a heterocyclic compound of immense importance in various fields of medicinal chemistry and pharmacology [1-4].

The easiest way of synthesizing DHPM is an acid catalyzed multicomponent cyclo condensation reaction namely Biginelli reaction [5] that employs an equimolar mixture urea, ethyl acetoacetate, and aromatic aldehydes as reactants [Scheme-1].



Scheme 1: Synthesis of DHPM via Biginelli reaction

Various toxic catalysts like BF₃ [6], FeCl₃ [7], InCl₃ [8], BiCl₃ [9], LaCl₃ [10], LiClO₄ [11], Mn-(OAc)₃ [12], CAN [13] and toxic solvents like EtOH, CH₃CN, CH₂Cl₂, THF have been employed by the researchers for performing this Biginelli reactions.

To avoid the toxicity of the solvents and catalysts, various ecofriendly reaction methodologies like-"Biginelli reaction in catalysts free and solvent free condition" [14], "Biginelli reaction in fruit juice medium at room temperature" [15, 16] and "Biginelli reaction in fruit juice medium under microwave irradiation" [17] have been successfully developed and reported by our group for performing "green Biginelli reaction".

It's the energy efficiency of microwave (MW) irradiation that made us think to use MW irradiation as a potential tool for carrying out *"green Biginelli reaction"* [18]. Although it was found that the *microwave assisted Biginelli reactions in fruit juice medium* was the greenest and most eco-friendly method reported so far for synthesis of DHPM [17], our extensive literature search has revealed that this methodology is yet to be well explored by the researchers and only limited number of fruit juices [17] have been employed as green reaction medium for microwave assisted Biginelli reactions so far.

Although apple, pomegranate, and grape juice are easily available, completely eco-friendly, bio-degradable, non-toxic and safe for the environment as well as for the human health, to the best our knowledge they have never been employed as an eco-friendly reaction medium for performing any types of chemical reaction till date. So the scope to explore the utility of apple, pomegranate and grape juice as a green reaction medium for MW assisted Biginelli reactions is still there.

In continuation of our search for more of common fruit juices which can be used as a green reaction medium for microwave assisted Biginelli reaction-apple, pomegranate, and grape juice has been selected for the above said purpose.

So the main aim of this work is to explore the utility of apple, pomegranate and grape juice as a green reaction medium for microwave irradiated *"green Biginelli reaction"*.

All the required fruit juices were first directly extracted from their corresponding fresh fruits followed by which the fruit juices were filtered using normal filter paper. The filtered fruit juices were used straightaway for the reaction without adding any foreign chemicals or additives into it and without doing any types of dilution by any solvents.

100 ml borosilicate conical flask was charged with 0.03 mole of urea, 0.03 mole of ethyl acetoacetate and 0.03 mole of the desired aldehyde. After addition of 10 ml of the desired fruit juice into this reaction mixture, the mixture was irradiated with microwave irradiation (frequency=180W) for specified time. While carrying out the reactions, successive cooling and stirring of the reaction mixture at room temperature was done after every 1 min of MW irradiation. The progress of the reaction was monitored by checking TLC of the reaction mixture at a regular interval.

After completion of reaction, the reaction mixture was allowed to cool down to room temperature. The crude solid product was observed to be slowly precipitated out of the reaction mixture upon cooling of the reaction mixture at room temperature. The crude product was re-crystallized from ethanol to get pure DHPM as white/yellowish solid powder. 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.

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

Melting point: 210 °C (Reported [19]: 209-210 °C)

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

¹**H-NMR (400 MHz, DMSO-d**⁶): δ 1.12 (t, 3H), 2.25 (s, 3H), 4.00 (q, 2H), 5.17 (d, 1H), 7.18–7.29 (m, 5H), 7.66 (m, 1H), 9.12 (s, 1H).

[13]C NMR (500 MHz, DMSO-d⁶): δ 14.16, 18.21, 39.71, 54.41, 59.74, 99.80, 126.45, 128.88, 130.06, 145.22, 148.78, 165.85.

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

Melting point: 215 °C (Reported [20]: 212-214 °C)

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

¹H-NMR (400 MHz, DMSO-d⁶): δ 1.12 (t, 3H), 2.50 (s, 3H), 4.00 (q, 2H), 5.18 (d, 1H), 7.22–7.34 (m, 5H), 9.15 (s, 1H).

[13]C NMR (500 MHz, DMSO-d⁶): δ 14.46, 18.23, 39.54, 53.9, 59.79, 99.37, 131.76, 149.13, 152.52, 160.48, 165.70, 167.35.

Ethyl-6-methyl-2-oxo-4-(p-tolyl)-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (Compound 4M)

Melting point: 216 °C (Reported [21]: 215-216 °C)

IR (neat): 3244, 3117, 2980, 1724, 1703, 1458, 1286, 1198 cm⁻¹

¹H-NMR (400 MHz, DMSO-d⁶): δ 1.13 (t, 3H), 2.26 (s, 6H), 4.00 (q, 2H), 5.12 (d, 1H), 7.06–7.60 (m, 5H), 9.07 (s, 1H).

[13]C NMR (500 MHz, DMSO-d⁶): δ 14.50, 18.19, 21.46, 53.88, 61.66, 99.95, 126.80, 130.33, 136.93, 143.53, 148.58, 152.75, 165.87.

A series of green Biginelli reactions were performed under MW irradiation using apple, pomegranate, and grape juice as green reaction medium [Scheme-2].

It was the easy availability, biodegradability, non-toxicity and mild acidic nature of the three fruit juices which made them potentially useful green reaction medium for our acid catalysts "*green Biginelli reactions*". The three fruit juices namely apple, pomegranate and grape juice were used individually as a green reaction medium for our Biginelli reactions.

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Table 1. MW	anistad amagin D	lainelli neestien uuit	h different oldek	udaa in annla	mana a ama maka a ma	amama iniaaa
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Reaction medium (fruit juice)	Ar group	DHPM	Time	Yield(%)	Melting point (°C) observed	Melting point (°C) reported
Apple Juice (pH 3.3-3.9)	\bigcirc	4B	12 min	70	209	209-210
	-CI	4C	9 min	77	212	212-214
	Me	4M	14 min	33	216	215-216
Pomegranate Juice (pH 2.93-3.2)		4B	8 min	70	210	209-210
	CI	4C	5 min	72	213	212-214
	Me	4M	11 min	63	215	215-216
Grape Juice (pH 3-3.75)		4B	8 min	74	209	209-210
	-CI	4C	6 min	73	212	212-214
	- Me	4M	15 min	67	215	215-216

Here in a series of MW irradiated "green Biginelli reactions" were reported in apple, pomegranate, and grape juice medium.



Scheme 2: Synthesis of DHPM under MW irradiation in fruit juice

After charging the equimolar amounts of the three reactants into 10 ml of fruit juice, the reaction mixture was irradiated under MW irradiation. A series of Biginelli reactions were performed by varying the aromatic aldehydes and by using three different fruit juices as the reaction medium. The obtained results are summarized in table-1. All the reactions were completed successfully within 6 min to 15 min time of duration, depending on aldehyde and fruit juice used.

It was interesting to note that the reactions that used to take few hours to go for completion at room temperature [15, 16] were completed successfully within few minutes of duration under MW irradiation.

It was worth to note that the minimum frequency of MW irradiation which was required for the reaction to occur successfully was 180W. No significant progress of the reaction was observed if the reaction mixtures were irradiated with a MW irradiation of less than 180W of frequency.

The rates of the reactions have shown a significant dependence on the acidity (pH value) of the fruit juices used. For a particular aldehyde, the reaction was most facile in pomegranate juice which has the minimum pH value while the reaction was comparatively slower in apple juice which has the maximum pH value (minimum acidity). So the rate of the reaction was found to become faster with an increase in acidic nature of the medium.

The reaction rates were also got influenced by the electronic nature of the aromatic aldehydes. The electron rich 4-methyl benzaldehyde has made the reaction sluggish whereas the electron deficient 4-chloro benzaldehyde has made the reaction much faster. The same trend of the reactivity of the aromatic aldehydes towards Biginelli reaction has also been observed earlier by our group, and it's well documented with proper explanation in our previous report [16, 17].

Being completely eco-friendly, non-toxic and safe-apple, pomegranate and grape juice have been used fruitfully as a green reaction medium for a chemical reaction for the very first time in literature.

In the field of green chemistry, our current work has opened a wide door of opportunities for the researchers to explore the utility of apple, pomegranate and grape juice medium as a green reaction medium for carrying out many more one pot multi-component condensation reactions like Biginelli, in near future.

Exploration of various eco-friendly reaction methodologies for performing *"green Biginelli reactions"* in apple, pomegranate, and grape juice medium is currently under progress in our laboratory.

ACKNOWLEDGEMENT

The authors are thankful to the Department of Chemistry, Lovely Professional University for its financial and technical supports in this research project.

CONFLICT OF INTERESTS

Declared none

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