

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.

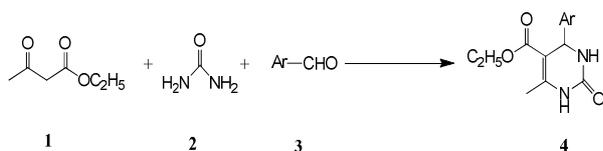
Conclusion: A green, eco-friendly and cost-effective method was developed for microwave assisted "green Biginelli reaction" in apple, pomegranate and grape juice medium. This new method will further motivate the researchers to use more of common fruit juices instead of toxic solvents as reaction medium 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 multi-component 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 BF_3 [6], FeCl_3 [7], InCl_3 [8], BiCl_3 [9], LaCl_3 [10], LiClO_4 [11], $\text{Mn}(\text{OAc})_3$ [12], CAN [13] and toxic solvents like EtOH, CH_3CN , CH_2Cl_2 , THF have been employed by the researchers for performing this Biginelli reactions.

To avoid the toxicity of the solvents and catalysts, various eco-friendly 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 of 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;

¹H-NMR (400 MHz, DMSO-d₆): 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).

[¹³C] 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).

[¹³C] 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).

[¹³C] 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.

Table 1: MW assisted green Biginelli reaction with different aldehydes in apple, pomegranate and grape juices

Reaction medium (fruit juice)	Ar group	DHPM	Time	Yield(%)	Melting point (°C) observed	Melting point (°C) reported
Apple Juice (pH 3.3-3.9)		4B	12 min	70	209	209-210
		4C	9 min	77	212	212-214
		4M	14 min	33	216	215-216
Pomegranate Juice (pH 2.93-3.2)		4B	8 min	70	210	209-210
		4C	5 min	72	213	212-214
		4M	11 min	63	215	215-216
Grape Juice (pH 3-3.75)		4B	8 min	74	209	209-210
		4C	6 min	73	212	212-214
		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.

