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Der Pharmacia Lettre, 2016, 8 (11):74-78
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Visible light induced Biginelli reaction in fruit juice medium: A green strategy for synthesis of pharmaceutically active dihydropyrimidinones

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ABSTRACT

A series of Dihydropyrimidinones (DHPM) containing both electron rich as well as electron deficient aromatic rings were synthesized with an excellent percentage of yields via visible light induced green Biginelli reactions in fruit juice medium. The series of Biginelli reactions were performed by employing an equimolar mixture of urea, ethyl acetoacetate and aromatic aldehyde as reactants whereas apple, pomegranate and grape juices were used as eco-friendly, bio-degradable and green reaction medium for the same. All the reactions were carried out by applying visible light irradiation as an eco-friendly source of energy. After completion of reactions, the crude DHPMs were purified through re-crystallization to obtain pure DHPMs which were further characterized by FTIR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Keywords: Dihydropyrimidinones, Biginelli reactions, green synthesis, fruit juices, visible light.

INTRODUCTION

Dihydropyrimidinones (DHPM) is an N-contained heterocyclic compound which is of immense importance in various fields of medicinal and pharmaceutical chemistry. Thanks to its wide range of promising applications as anti-bacterials, anti-fungal, anti-inflammatory, anti-cancer and anti-topoisomerase agents [1-4]. The most easy, traditional, conventional and effective method to synthesize DHPM is Biginelli reaction which is an acid-catalyst multi component cyclo condensation reaction employing urea, ethyl acetoacetate and aromatic aldehyde as reactants [5]. Various toxic, non-eco friendly catalyst and hazardous solvents were found to be used by many researchers to carry out these Biginelli reactions [6-13]. Our growing concern for the environment has encouraged the scientists to develop a green and eco friendly protocol for this Biginelli reaction.

Recently our group has focused to develop some green methodologies for synthesizing DHPMs via green Biginelli reactions. Toxic catalysts and hazardous solvents were either completely avoided by doing “Biginelli reaction in catalysts free and solvent free condition” [14] or those toxic acids and solvents were successfully replaced by fresh fruit juices [15-17]. The feasibility of Biginelli reactions in weak acid medium and the mild acidic nature of the bio degradable fruit juices had made us think to employ various natural fruit juices as effective and green reaction medium for our Biginelli reaction [15].

Instead of commercially available toxic lewis acids, the naturally occurring bio-degradable acids present in the fruit juice have been successfully used as green and biodegradable catalyst for our acid catalyst Biginelli reactions. Instead of conventional, hazardous and toxic solvents the aqueous phase present in the fruit juice has been employed as green solvent for our reaction. So the natural fruit juices as a whole, has served the purpose of green reaction medium (solvent cum catalyst) for our reaction.

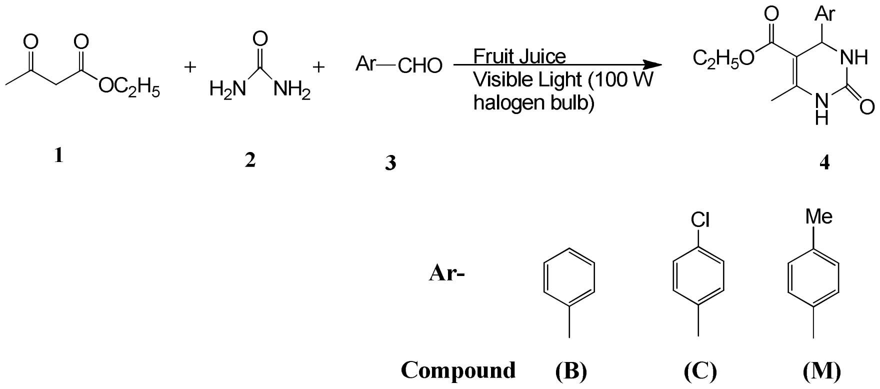
In continuation of our previous series of research work which includes- Microwave assisted green Biginelli reaction in a wide varieties of fruit juices medium like orange, lime, amla, apple, pomegranate and grape [17, 18], hereby we are reporting the green synthesis of DHPM by visible light induced green Biginelli reaction in fruit juice medium for the very first time. Usage of visible light for the purpose of green synthesis is well known in literature [19]. Although visible light induced Knoevenagel condensation is reported by researchers [20], to the best of our knowledge visible light irradiated green Biginelli reaction in fruit juice medium has never been reported in literature till date. Apple, pomegranate and grape juices have been successfully applied as green reaction medium for the very first time by our group [18]. Although the scope of employing apple, pomegranate and grape juice as green reaction medium is still there, these fruit juices were not well explored in literature so far. Our extensive literature search has revealed that our last published report [18] is the sole report in literature so far to show the usage of apple, pomegranate and grape juice as green reaction medium.

So the main objective of this work is to explore the possibilities of green synthesis of DHPM via visible light induced green Biginelli reaction using apple, pomegranate and grape juice as green reaction medium.

MATERIALS AND METHODS

All the commercially available reactants and chemicals were used straightway as they were obtained from the suppliers, without doing further purification. After extracting the fruit juices directly from the corresponding fresh fruits, they were filtered through normal filter paper. After filtering, the fruit juices were used directly for the reaction without adding any foreign chemicals into it.

Scheme-1: Synthesis of DHPM under visible light irradiation in fruit juice medium



General Method for synthesis of DHPM:

As shown in scheme-1, 0.03 mole of urea, 0.03 mole of ethylacetoacetate and 0.03 mole of the desired aldehydes were mixed together into a round bottle flask attached with a reflux condenser. After adding 10 ml of desired fruit juice into this reaction mixture, the mixture was irradiated with halogen bulb (100 W) with continuous stirring. The progress of the reaction was continuously monitored by checking TLC and after completion of reaction (as indicated by TLC) the reaction mixture was allowed to cool down to room temperature. Solid crude product was precipitated out of the reaction mixture upon cooling. The crude products were further purified by doing re-crystallization from ethanol to get pure DHPMs.

The pure DHPMs were characterized by recording their melting point, FTIR, ^{1}H-NMR and ^{13}C-NMR spectral data which all were identical with that of literature reported ones.

Characterization:

Ethyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Compound 4B)
Melting point: 210 ^{0}C (Reported [21]: 209-210 ^{0}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-d^{6}):** 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.

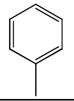
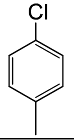
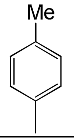
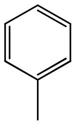
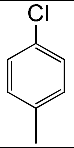
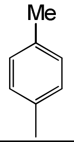
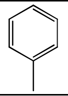
Ethyl-4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (Compound 4C)
Melting point: 215 ^{0}C (Reported [22]: 212-214 ^{0}C) ; **IR (neat):** 3242, 3113, 2929, 1724, 1703, 1649, 1487, 1460 cm$^{-1;}$ **^{1}H-NMR (400 MHz, DMSO–d^{6}):** δ 1.12 (t, 3H), 2.50 (s, 3H), 4.00 (q, 2H), 5.18 (d, 1H), 7.22–7.34 (m, 5H), 9.15 (s, 1H).; **^{13}C NMR (500 MHz, DMSO-d^{6}):** 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.

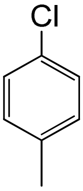
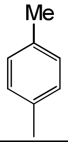
Ethyl-6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate(Compound 4M)
Melting point: 216 ^{0}C (Reported [23]: 215-216 ^{0}C) ; **IR (neat):** 3244, 3117, 2980, 1724, 1703, 1458, 1286, 1198 cm$^{-1;}$ **^{1}H-NMR (400 MHz, DMSO–d^{6}):** δ 1.13 (t, 3H), 2.26 (s, 6H), 4.00 (q, 2H), 5.12 (d, 1H), 7.06–7.60 (m, 5H), 9.07 (s, 1H).; **^{13}C NMR (500 MHz, DMSO-d^{6}):** 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.

RESULTS AND DISCUSSION

Biginelli reactions were performed by applying urea, ethyl acetoacetate and various electron rich as well as electro deficient aromatic aldehydes as reactants. All the reactions were carried out by irradiating the reaction mixture with the visible light from 100 W halogen bulb and by employing individually apple, pomegranate and grape juice as green reaction medium.

Table 1: Visible Light assisted Biginelli reaction with different aldehydes in different fruit juices

Reaction Medium (Fruit Juice)	Ar Group	DHPM	Time	Yield (%)	Melting point (^{0}C) observed	Melting point (^{0}C) reported
Apple Juice (pH 3.3-3.9)		4B	2 hour 15 min	83	208	209-210
		4C	1 hour 55 min	76	213	212-214
		4M	3 hour 15 min	80	214	215-216
Pomegranate Juice (pH 2.93-3.2)		4B	1 hour 25 min	85	210	209-210
		4C	1 hour 10 min	67	212	212-214
		4M	2 hours	78	216	215-216
Grape Juice (pH 3-3.75)		4B	1 hour 35 min	79	210	209-210

		4C	1 hour 10 min	64	212	212-214
		4M	2 hour 20 min	63	214	215-216

The reactions used to take 1 h to 3.5 hours duration (depending on the aldehyde and fruit juice used) to go for completions. The obtained results are summarized in **Table-1**.

The reactions have exhibited serious dependence on the acidity of fruit juice and the electronic nature of the aromatic aldehyde.

It was worth to note that for any particular aldehyde, the reaction was fastest in pomegranate juice that has minimum pH and slowest in apple juice which has maximum pH.

In any particular fruit juice, the reaction was very rapid with electron deficient chloro benzaldehyde whereas the reaction was sluggish with electron rich methyl benzaldehyde.

So it was evident that the rate of reaction increases with increase in acidity of the fruit juice and with increase in electrophilicity of the carbonyl carbon of the aromatic aldehyde. The same trend was also observed and clarified in our previous report [18].

All the products were obtained with excellent percentage of yield and with high purity.

CONCLUSION

Herein a cost-effective, efficient, eco-friendly and easy method for synthesis DHPM has been evolved by our group. Our present study has successfully demonstrated the green synthesis of pharmaceutically important DHPMs in apple, pomegranate and grape juice medium using visible light as ecofriendly energy resource. This is the first of its kind study where visible light has been applied for the very first time to execute green Biginelli reactions in the fruit juice medium.

So our current effort may motivate the scientists to carry out more of visible light induced green multi component condensation reactions in fruit juice medium, in near future.

Acknowledgement

Immense financial and technical support from Department of Chemistry, Lovely Professional University is gratefully acknowledged.

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