Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 7, Issue 11, 2015

Short Communication

MICROWAVE ASSISTED GREEN SYNTHESIS OF PHARMACEUTICALLY IMPORTANT DIHYDROPYRIMIDINONES IN FRUIT JUICE MEDIUM

TANAY PRAMANIK*[a], POULAMI MAJI[a]

[a]Department of Chemistry, Faculty of Technology and Sciences, Lovely Professional University, Phagwara, P. O. Box 144411, India
Email: tanay.pramanik@gmail.com

Received: 24 Aug 2015 Revised and Accepted: 22 Sep 2015

ABSTRACT

Objective: The objective of this research project was to perform the green synthesis of a series of Dihydropyrimidinone (DHPM) derivatives which are having immense importance in biological and pharmaceutical science, via microwave assisted Biginelli reaction in fruit juice medium.

Methods: Urea and ethyl acetoacetate were made to react with different electron rich as well as electron deficient aromatic aldehydes in various fruit juice medium under microwave irradiation. After successful completion of the reaction the crude product was precipitated out of the reaction medium and after re-crystallization of the crude product the pure desired DHPMs were obtained with quite good percentage of yield.

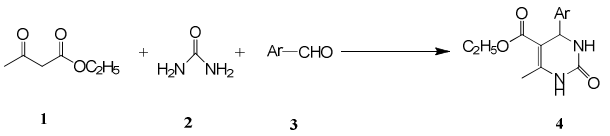
Results: It was observed that our green Biginelli reaction was completed successfully within few minutes duration and the microwave assisted Biginelli reaction in fruit juice medium was much faster, greener and cleaner compared to that of room temperature Biginelli reaction in the same fruit juice medium. The acidity of the fruit juices and the electronic effect of the aromatic aldehydes have shown significant influence on the rate of reaction.

Conclusion: Thus an efficient, green, cost-effective and eco-friendly method has been developed and reported for the very first time for microwave assisted synthesis of dihydropyrimidinone using some common fruit juices as reaction medium. The fruit juices have served as the solvent cum catalyst in these Biginelli reactions. Our current approach of synthesizing DHPM via microwave assisted Biginelli reaction in fruit juice medium has given a new direction in the field of green chemistry.

Keywords: Biginelli reaction, Fruit Juice, Microwave, Dihydropyrimidinone**,** Green synthesis**.**

Due to wide range of promising and multifaceted biological activities of N-contained heterocyclic compound known as dihydro pyrimidinone (DHPM) as anticancer, anti-inflammatory, antibacterial, antifungal, anthelmintic and antitopoisomerase agents [1-4], the synthesis of DHPM derivatives bearing diverse substitution patterns has attracted much attention from the researcher for last few decades [5].

The most convenient and popular reaction that gives easy access to various derivatives of DHPM is the Biginelli reaction [6] which is a multi component condensation employing urea, ethyl acetoacetate and aromatic aldehydes [Scheme-1].



Scheme 1: Synthesis of DHPM via Biginelli reaction

A large number of Lewis acids like BF_3 [7], $FeCl_3$ [8], $InCl_3$ [9], $BiCl_3$ [10], $LaCl_3$ [11], $LiClO_4$ [12], Mn-$(OAc)_3$ [13], CAN [14] have already been explored as catalysts for performing this Biginelli reaction. Verities of solvents like EtOH, CH_3CN, CH_2Cl_2, THF have also been employed by the researchers as the reaction medium for synthesis of DHPM via Biginelli reaction. Unfortunately none of these catalysts and solvents is completely safe for the environment and human health. The toxicity of these solvents and catalysts posed a serious threat to the environment and human health. Our growing concern for the environment has motivated the researchers to develop a green and eco friendly method for synthesis of DHPM.

To avoid the toxic effects of solvents and catalysts, "a solvent free and catalyst free Biginelli reaction" has been reported in literature [15, 16]. But the reactants mixture needs to be stirred at a high temperature (100-105 °C) while performing the reaction in a "solvent-free and catalyst-free" condition. So the scope and need of developing a green methodology for *synthesizing DHPM at room temperature* was still there. So recently a green methodology has been developed by our group [17, 18] to *synthesize DHPM at room temperature employing common fruit juices as reaction medium.*

According to our previous reports [17, 18] the DHPMs were synthesized without employing any toxic artificial solvents or catalyst, rather natural acids present in the common fruit juices were successfully employed as eco friendly, nontoxic and safe biocatalysts in our reaction.

The room temperature Biginelli reactions used to take more than an hour to go for completion in fruit juice medium [17, 18]. So to make this reaction even more eco friendly and green, the reaction time need to be minimized by making the reaction faster and more efficient.

Organic synthesis using microwave assisted heating method is considered to be much cleaner, greener and eco friendly compared to that of conventional heating method [19]. The energy efficiency of microwave (MW) irradiation and the ability of MW irradiation to speed up the chemical reaction [20] have made us think to employ this technique (MW irradiation) as a potential tool for our green synthesis of DHPM. Large verities of "Microwave assisted Biginelli reactions" have already been well explored by researchers and well documented in literature [21-23]. But unfortunately the solvents or catalysts like $FeCl_3$ [21], $CaCl_2$ [22], ZnI_2 [23] those were used so far for those "Microwave assisted Biginelli reactions" are toxic, non eco friendly and unsafe for human health.

The fruit juices are completely eco friendly, biodegradable, non-polluting and non toxic. Moreover they are completely safe for human health and environment. Some common fruit juices like amla, orange and lime juices have already been proven to be effective as green reaction medium for room temperature Biginelli reaction [17, 18]. Microwave assisted synthesis of DHPM in fruit juice medium is expected to be much efficient, faster and cleaner compared to that of room temperature but our extensive literature search has revealed that so far no attempt has been made by the researcher to *synthesize DHPM in fruit juice medium using microwave (MW) irradiation.* So based on the research gap stated above, the main aim of this work is to synthesize a series of DHPM derivates bearing both electron rich

as well as electron deficient aromatic aldehydes via microwave assisted Biginelli reaction in fruit juice medium.

Materials

All the required fruit juices were extracted directly from their corresponding fresh fruits and the freshly obtained 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.

General method for synthesis of DHPM

In a 100 ml borosilicate conical flask 0.03 mole of urea, 0.03 mole of ethyl acetoacetate and 0.03 mole of desired aldehyde were taken. Then 8 ml of desired fruit juice was added to this reaction mixture. The reaction mixture was irradiated at 180W under microwave condition for specified time (with successive cooling and stirring of the reaction mixture at room temperature after every 1 min of MW irradiation). The progress of the reaction was continuously monitored by checking TLC. After completion of reaction (which was indicated by TLC) the reaction mixture was cooled down to room temperature after which the solid crude product was slowly precipitated out of the reaction mixture. The crude product was re-crystallized from hot 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.

Characterizations

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

Melting point: 210 °C (Reported [24]: 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)

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

Melting point: 215 °C (Reported [25]: 212-214 °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).

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

Melting point: 216 °C (Reported [26]: 215-216 °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).

A series of DHPM derivatives were synthesized employing urea, ethyl acetoacetate and aromatic aldehydes (bearing either electron rich or electron deficient functional groups) as reactants [Scheme 2].

Three different fruit juices namely orange juice, lime juice and amla juice were used individually as green and eco friendly reaction medium. Equimolar mixture of the three reactants was taken into the respective fruit juice and the mixture was irradiated at 180W under microwave condition for specified time (with successive cooling and stirring of the reaction mixture at room temperature after every 1 min of MW irradiation). The obtained results are summarized in table 1.

It was interesting to note that in a given fruit juice medium a particular reaction used to take about an hour time to go for completion at room temperature [17, 18] but the same reaction was completed within few minutes duration in the same fruit juice medium under microwave irradiation.

While comparing the reactivity of the three aromatic aldehydes, it was worth to note that reaction was most facile with electron deficient aromatic aldehydes compared to that of electron rich aromatic aldehydes. This observation is consistent with our previous findings [16]. The electrophilicity of carbonyl centre of electron deficient aromatic aldehyde is more compared to that of electron rich aromatic aldehyde. So the nucleophilic attack is much faster on electron deficient aromatic aldehyde which in turn makes the whole reaction to be much facile.

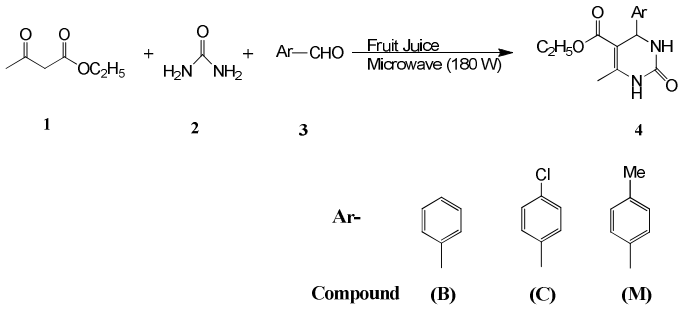
It was worthwhile to note that the pH value of the fruit juice has significant influence on the rate of reaction. The reaction with a particular aldehyde was faster in lime juice medium compared to that of orange or amla juice medium. Being the most acidic in nature (with minimum pH value) the lime juice has been proven to be the best among these three fruit juices which were under consideration as reaction medium. However, all the DHPM products were obtained with quite good percentage of yield in any of these three fruit juice medium under microwave assisted reaction condition.

Herein a green, eco-friendly, inexpensive and efficient method is reported for the very first time for synthesizing DHPM derivatives via one-pot multi component condensation namely Biginelli reaction under microwave irradiation using fruit juices as green reaction medium. This method is applicable to synthesize DHPM derivatives containing both electron rich as well as electron deficient aromatic ring. Three fruit juices namely orange, amla and lime juices which are used in our current work are not only easily available in any part of the world but also they are 100% biodegradable, completely eco-friendly, non-polluting, nontoxic and safe.

It was observed that in fruit juice medium the Biginelli reaction is much faster, cleaner and greener under "MW irradiation" compared to that of "room temperature".

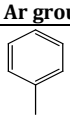
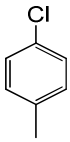
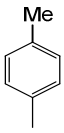
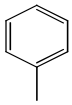
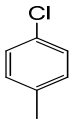
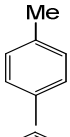
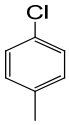
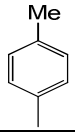
So, for the synthesis of DHPM, the greenest and most eco-friendly method reported so far is the "*Microwave-assisted Biginelli reaction in fruit juice medium*" which is developed and reported for the very first time by our group.

This work has given us an opportunity to explore more of other common fruit juices as green reaction medium for carrying out microwave assisted Biginelli and various other such multi-component condensation reactions. So exploration of various other common fruit juices as green reaction medium for above said purposes is currently under progress in our laboratory.



Scheme 2: Synthesis of DHPM under MW in fruit juice

Table 1: MW assisted green Biginelli reaction with different aldehydes in different fruit juices

Reaction medium (Fruit juice)	Ar group	DHPM	Time	Yield (%)
Orange Juice (pH 3.3-4.1)		4B	12 min	73
		4C	9 min	79
		4M	14 min	64
Lime Juice (pH 2-2.8)		4B	8 min	78
		4C	6 min	83
		4M	10 min	71
Amla Juice (pH 2.8-3.1)		4B	10 min	83
		4C	8 min	77
		4M	13 min	73

ACKNOWLEDGEMENT

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

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Kappe CO. Recent advances in the biginelli dihydropyrimidine synthesis. New tricks from an old dog. Acc Chem Res 2000;33:879–88.
2. Sakata KI, Someya M, Matsumoto Y, Tauchi H, Kai M, Toyota M, *et al*. Gimeracil, an inhibitor of dihydropyrimidine dehydrogenase, inhibits the early step in homologous recombination. Cancer Sci 2011;102:1712–6.
3. Ramesh B, Bhalgat CM. Novel dihydropyrimidines and its pyrazole derivatives: Synthesis and pharmacological screening. Eur J Med Chem 2011;46:1882–91.
4. Zhu L, Cheng P, Lei N, Yao J, Sheng C, Zhuang C, *et al*. Synthesis and biological evaluation of novel homocamptothecins conjugating with Dihydropyrimidine derivatives as potent topoisomerase i inhibitors. Arch Pharm Chem Life Sci 2011;344:726–34.
5. Xuejian QL, Fan M, Xufeng L. Efficient synthesis of dihydropyrimidinones via a three-component Biginelli-type reaction of urea, alkylaldehyde and arylaldehyde. Beilstein J Org Chem 2013;9:2846-51.
6. Biginelli P. The combination of an aldehyde 1, β-keto ester. Gazz Chim Ital 1893;23:360-416.
7. Hu EH, Sidler DR, Dolling UH. Unprecedented catalytic three component one-pot condensation reaction: an efficient synthesis of 5-alkoxycarbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones. J Org Chem 1998;63:3454-7.
8. Lu J, Ma H. Iron(III)-Catalyzed Synthesis of Dihydro pyrimidinones. Improved Conditions for the Biginelli Reaction. Synlett; 2000. p. 63-4.
9. Ranu BC, Hajra A, Jana U. Indium(III) chloride-catalyzed one-pot synthesis of dihydropyrimidinones by a three-component coupling of 1,3-dicarbonyl compounds, aldehydes, and urea: an improved procedure for the biginelli reaction. J Org Chem 2000;65:6270-2.
10. Ramalinga K, Vijayalakshmi P, Kaimal TNB. Bismuth(III)-catalyzed synthesis of dihydropyrimidinones: improved protocol conditions for the biginelli reaction. Synlett 2001;6:863-5.
11. Lu J, Bai Y, Wang Z, Yang B, Ma H. One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using lanthanum chloride as a catalyst. Tetrahedron Lett 2000;41:9075-8.
12. Yadav JS, Reddy BVS, Srinivas R, Venugopal C, Ramalingam T. $LiClO_4$-catalyzed one-pot synthesis of dihydropyrimidinones: an improved protocol for Biginelli reaction. Synthesis 2001;9:1341-5.

13. Kumar KA, Kasthuraiah M, Reddy CS, Reddy CD. $Mn(OAc)_3 \cdot 2H_2O$-mediated three-component, one-pot,condensation reaction: an efficient synthesis of 4-aryl-substituted 3,4-dihydropyrimidin-2-ones. Tetrahedron Lett 2001;42:7873-5.
14. Yadav JS, Reddy BVS, Reddy KB, Raj KS, Prasad AR. Ultrasound-accelerated synthesis of 3, 4-dihydropyrimidin-2 (1 H)-ones with ceric ammonium nitrate. J Chem Soc Perkin Trans 2001;1:1939-41.
15. Ranu BC, Hajra A, Dey SS. A practical and green approach towards synthesis of dihydropyrimidinones without any solvent or catalyst. Org Process Res Dev 2002;6:817-8.
16. Pramanik T, Wani TA, Singh A. Influence of electronic factors on "Solvent-Free and catalyst free Biginelli Reaction". Orient J Chem 2013;29:1209-12.
17. Pramanik T, Pathan AH. Exploring the utility of fruit juices as green medium for biginelli reaction. Res J Pharm Biol Chem Sci 2014;5:444-9.
18. Pramanik T, Pathan AH, Gupta R, Singh J, Singh S. Dihydropyrimidinone derivatives: green synthesis and effect of electronic factor on their antimicrobial properties. Res J Pharm Biol Chem Sci 2015;6:1152-7.
19. Ravichandran S, Karthikeyan E. Microwave synthesis-a potential tool for green chemistry. Int J ChemTech Res 2011;3:466-70.
20. Mingoes D. The energy efficiency of microwave (MW) irradiation and the ability of MW irradiation to speed up the chemical reaction. Chem Indian 1994;4:596-9.
21. Choudhary VR, Tillu VH, Narkhede VS, Borate HB, Wakharkar RD. Microwave assisted solvent-free synthesis of dihydropyrimidinones by Biginelli reaction over Si-MCM-41 supported $FeCl_3$ catalyst. Catal Commun 2003;4:449-53.
22. Misra AK, Agnihotri G, Madhusudan SK. Microwave induced eco-friendly solvent-free Biginelli reaction catalyzed by calcium chloride. Indian J Chem 2004;43B:2018-20.
23. Sharma S, Mishra S, Gupta M, Mishra A. Microwave assisted one pot synthesis, Mass spectral analysis and DFT studies of 6-Substituted-3,4-dihydro-4-phenylpyrimidin-2(1H)-one. J Mater Environ Sci 2014;5:1079-84.
24. Bose AK, Pednekar SN, Ganguly S, Chakraborty GM, Manhas S. A simplified green chemistry approach to the Biginelli reaction using 'Grindstone Chemistry'. Tetrahedron Lett 2004;45:8351-3.
25. Baskaran SS, Koenig B. Efficient synthesis of 3,4-dihydropyrimidin-2-ones in low melting tartaric acid–urea mixtures. Green Chem 2011;13:1009-13.
26. Fu NY, Yuan YF, Zhong C, Wang S, Wang, T, Peppe C. Indium (III) bromide-catalyzed preparation of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction. Tetrahedron 2002;58:4801-7.