International Journal of Pharmacy and Biological Sciences-IJPBS™ (2019) 9 (2): 811-818
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Pharmaceutical Sciences | Open Access | MCI Approved
UGC Approved Journal

A Novel, Efficient, Cost-Effective, and Green Methodology for Biginelli-Reaction: Soy Lecithin-Catalyzed Synthesis Of 4 -Aryl-1, 2, 3, 4 -Tetrahydropyrimidine-2(1h)-Ones / Thiones In Water

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Received: 15 Jan 2019 / Accepted: 20 Mar 2019 / Published online: 1 Apr 2019
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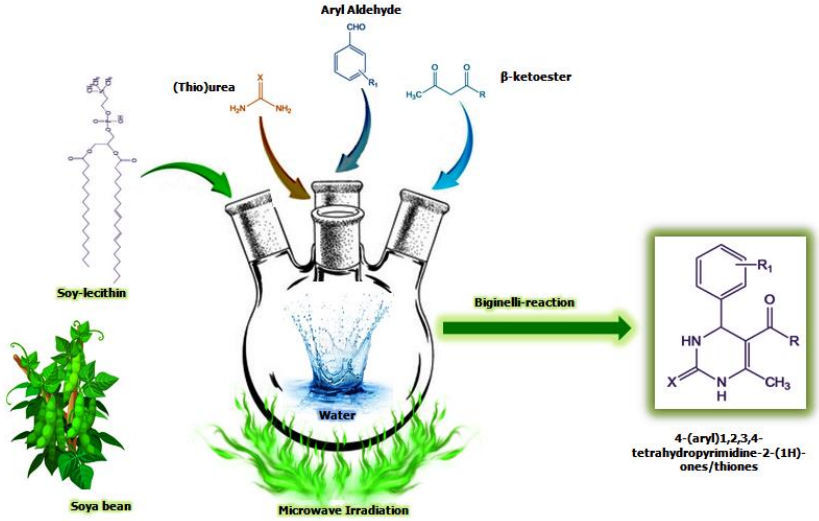
Abstract

Aim: The current research work was designed to develop a simple, green and efficient method for the synthesis of Biginelli-type 4-aryl-1,2,3,4-tetrahydropyrimidine-2(1*H*)-ones/thione scaffold using Soy-lecithin as the catalyst in water. **Materials and Methods:** The reaction mixture [β-ketoester, aldehyde, and (thio)urea] in water or 10%w/v Soy-lecithin aqueous solution was heated by both microwave irradiation and conventional refluxing methods separately. The compounds synthesized were purified using column chromatography; monitored by TLC; characterized by FTIR, 1H NMR, and mass spectral data; and compared for yield and reaction time. **Results:** The Biginelli-reaction in water proceeded with higher rates and resulted in greater yields of 4-aryl-1,2,3,4-tetrahydropyrimidine-2(1*H*)-ones/thiones scaffold (4a-4l) in presence of Soy-lecithin compared to water alone. **Conclusion:** A novel, eco-friendly, and cost-effective method was successfully developed for the high-yield green, one-pot, synthesis of Biginelli-type 4-aryl-1,2,3,4-tetrahydropyrimidine-2(1*H*)-ones/thiones using an environmentally benign solvent, water; and catalyst, Soy-lecithin.

Keywords
Biginelli-reaction, Aldehyde, β-keto ester, Water, Soy-lecithin, and Green chemistry

GRAPHICAL ABSTRACT



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1. INTRODUCTION

The Biginelli-reaction is an acid-catalyzed, one-pot, multi(three)-component condensation reaction between an aldehyde, a β-ketoester and (thio)urea results in dihydropyrimidines (DHPMs) (1,2). Since its disclosure, it has been greatly deployed in the synthesis of many compounds (including DHPMs and their derivatives) and emerged as a key reaction in heterocyclic synthesis (3). The Biginelli-scaffolds (DHPMs and their derivatives) have shown promising value in drug development as they exhibit wide spectrum of pharmacological activities like calcium channel blockers, antihypertensive mitotic kinesine inhibitors, adrenergic receptor antagonists, antimycobacterial and antiviral agents and anti-inflammatory agents (4–8). During the past years, copious research has been done on Biginelli-scaffolds and several reaction conditions were reported to ease the classical Biginelli-reaction (9).

In the past, continuing into the present, the solvents used in chemical synthesis are normally hydrocarbons, ethers, and alcohols. Owing to their intrinsic properties like high flammability, volatility, hazardness, and toxicity, they pose destructive insult to the environment. However, since the last decade, the paradigm has been shifted to “Green Chemistry” to meet the challenges of sustainable development. It has become the quest and challenge for chemists to develop green reaction process without affecting their efficiency to reduce the environmental impact(10,11). (12). In spite of other greener solvents, the features like abundance, availability in pure form, cost-efficiency, environmental compatibility, nontoxicity, and nonflammability, solvophobicity makes water to be considered as safest and the most eco-friendly solvent (10,13). Due to unique features of water like polarity, viscosity, and immiscibility, the hydrophobic products can be easily separated and purified from the aqueous medium (water and water-soluble homogeneous catalyst) through a simple extractive workup. After the pioneering works of Breslow and Grieco water has been employed as solvent for carrying out many organic reactions such as Claisen condensation, Aldol condensation, Diels-alder, Benzoin condensation, Mannich and Micheal addition reactions, Kabachnik-fields reaction, Strecker reaction, Hantzsch reaction Kinugasa reaction (10,14). However, most of the non-polor organic reactants are insoluble or have low solubility in water and the “on water” approach, involving surfactants which enhance the solubility of non-polor organic reactants by forming micelles is proposed to overcome the same (14). Many research groups have explored the possibility of a Biginelli-reaction in water medium various catalysts including Lewis acids, protonic acids, and surfactants based catalysts (5,9,14–17). However, they have limitations and to be improved in terms of rate of reaction, cost, yield, stability, toxicity and *environmentally friendly nature.*

Soy-lecithin is an eco-friendly bio-surfactant obtained from soyabean oil with good safety profile. The principal components of soy-lecithin are phospholipids (65-75%), triglycerides (34%). By virtue of its structural and compositional properties, soy-lecithin has got various applications in several industries. It is extensively employed as a wetting agent, surfactant, emulsifying agent, lubricant and nutritional supplement (18,19).

Thus, keeping the perpetual demand for Biginelli-scaffolds and green chemistry in view, there is an immense need to develop a simple, economic and green method to synthesize these scaffolds with improved yields and reaction rates. Hence, the present research was undertaken to develop a green method for one-pot synthesis of Biginelli-scaffolds by both microwave and conventional methods using Soy-lecithin as a potential catalyst and water as the solvent.

2. MATERIALS AND METHODS

All the chemicals used were of analytical grade and purchased from Merck, Mumbai. The completeness of the reactions was monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 ((Merck, Mumbai) and the spots were visualized under UV-light at 254 nm. Melting points of synthesized compounds were determined using Bachi melting point apparatus. The spectral (IR, ^{1}H NMR and Mass) and elemental analysis were done by using Perkin Elmer RX1-FTIR, JEOL 400 spectrometer (using TMS and JEOL DX 300 as internal standards in E1 ionization method at 70ev) and Perkin Elmer series 2400 analyzer respectively.

Chemistry

General Procedure for the synthesis of 4-(aryl)1,2,3,4-tetrahydropyrimidine-2-(1H)-ones/thiones (4a-4l)

The equimolar (each 0.01 mol) mixture of β-ketoester, aldehyde, and (thio)urea in water or 10% W/V Soy-lecithin aqueous medium was subjected to reflux heating for 4-5 hrs with magnetic stirring in the conventional method and microwave irradiation at 220 Wolt for 5-6 min in microwave irradiation method. The completion of the reaction was monitored by TLC using ethylacetate: hexane (6:4) as the mobile phase. The products formed were cooled to room temperature and then poured into 100 ml of cold water and stirred for 5 min. The solid compounds separated in the mixture were filtered, washed, and recrystallized using ethanol to recover the pure product. The reaction for synthesis of 4-(aryl)1,2,3,4-tetrahydropyrimidine-2-(1H)-ones/thiones and substituent groups (R, R1 and X) on reactants is shown in Figure 1.

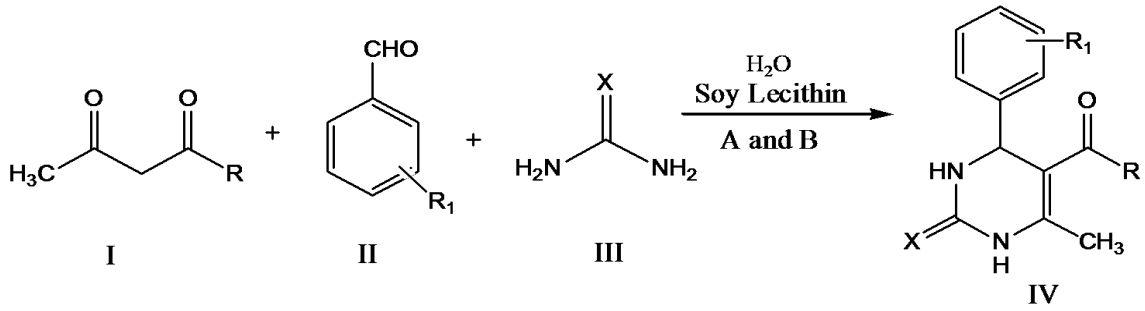

Figure1: The Biginelli-reaction for synthesis of 4-(aryl)1,2,3,4-tetrahydropyrimidine-2-(1H)-ones/thiones. Equimolar concentrations of β-ketoester (I), aromatic aldehyde (II), (thio)urea (III) in water (in presence or absence of Soy-lecithin) reacts to form tetrahydropyrimidin(-thi)ones (IV). A, conventional refluxing method; B, microwave irradiation method; X= O, S; R = -CH_3, –OC_2H_5; R1 = -H, 4-OCH_3, 4-OH, 2-OH, 4-Cl, 4-NO_2.

3. RESULTS AND DISCUSSION

To test our hypothesis, we carried out the Biginelli-reaction for the synthesis of 4-(substituted phenyl-)-1,2,3,4-tetrahydropyrimidine-2-(1*H*)-ones/thiones (4a-4l) using both conventional and microwave irradiation methods in water and in 10%W/V Soy-lecithin aqueous solution separately. Then, the reaction rates and yields were compared to explore the catalytic effect of Soy-lecithin in both the methods. The structural details and melting points of the synthesized compounds (4a-4l) were shown in Table 1.

Table 1. The structural details and melting points of the synthesized compounds

S. No.	Compound Code	R	R_1	X	M.P (°C)	
					Found	Reported
1	4a	C_6H_5	CH_3	O	229-232	233-235
2	4b	C_6H_5	OC_2H_5	O	203-205	201-202
3	4c	4-OCH_3 C_6H_4	OC_2H_5	O	199-201	200-201
4	4d	4-OHC_6H_4	OC_2H_5	O	226-229	222-229
5	4e	2-OH-C_6H_4	OC_2H_5	O	199-201	201-202
6	4f	4-ClC_6H_4	OC_2H_5	O	209-211	212-214
7	4g	4-$NO_2C_6H_4$	OC_2H_5	O	206-208	207-209
8	4h	C_6H_5	OC_2H_5	S	208-210	204-206
9	4i	C_6H_5	CH_3	S	216-218	219-220
10	4j	4-(OCH_3)-C_6H_4	CH_3	O	165-168	167-169
11	4k	4-ClC_6H_4	OC_2H_5	S	190-192	192-194
12	4l	4-OH C_6H_4	OC_2H_5	S	217-219	216-218

In comparison to the conventional reflex heating method, the yields were high in microwave irradiation methods in both the conditions. In line with several reports on expediency and exemplary nature of microwave-assisted synthesis (20, 21), results of our study are clearly indicating microwave irradiation method as rapid, high yielding, environment-friendly and cleaner method. It was observed that the reaction in water alone was found to be very slow and resulted in poor yields and this may be due to the low solubility of reactants in water. Further, interestingly we found that the Biginelli-reaction in presence of soy-lecithin proceeded speedily and resulted in high product yields in both the methods (Table 2).

Table 2. The % yield of synthesized compounds (4a-4l)

S. No.	Compound Code	% Yield			
		In absence of Soy-lecithin		In presence of Soy-lecithin	
		Conventional Method	Microwave Method	Conventional Method	Microwave Method
1	4a	22	32	86	95
2	4b	23	42	90	96
3	4c	29	35	83	89
4	4d	18	33	83	92
5	4e	28	38	89	94
6	4f	25	40	92	96
7	4g	19	29	90	93
8	4h	30	41	82	86
9	4i	28	36	87	95
10	4j	24	40	85	96
11	4k	19	33	90	95
12	4l	29	38	86	89

We speculate that Soy-lecithin hastens Biginelli-reaction and improves yield and reaction time possibly through the surfactant and catalytic activity. As surfactant, it forms aggregates (micelles, vesicles) thereby increases the solubility of three substrates and creates a favorable environment for Biginelli-reaction reaction (14,22). Further, owing to the presence of a catalytically active group (hydrogen phosphate) we assume that Soy-lecithin releases proton required for the classical Biginelli-reaction. Therefore, we propose that Soy-lecithin improves yield and reaction time possibly through micellar catalysis. The proposed mechanism for Biginelli-reaction in this study is represented in Figure 2.

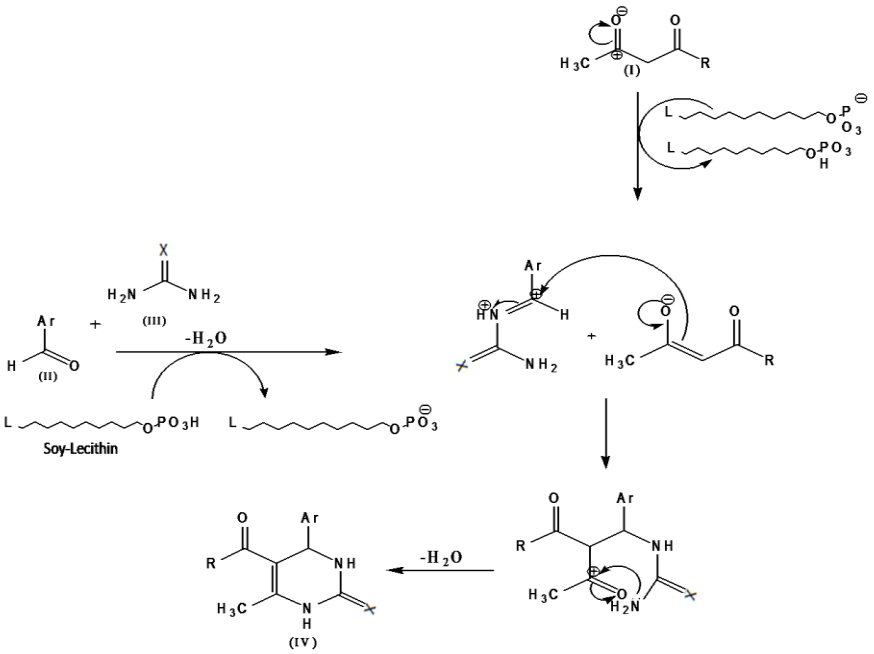

Figure 1. The mechanism involved in the synthesis of 4-(aryl)1,2,3,4-tetrahydropyrimidine-2-(1H)-ones/thiones. The aromatic aldehyde (II) and (thio)urea (III) interacts to form N-acyliminium ion which further interacts with β-ketoester (I) to form ureide that undergoes cyclodehydration to give tetrahydropyrimidin(-thi) ones. X= O, S; R = -CH_3, –OC_2H_5.

Soy-lecithin promotes the interaction between aldehyde and urea to form an intermediate *N*-acyliminium ion. This iminium ion interacts with β-ketoester in enol-tautomeric form to form an open chain ureide, which subsequently undergoes cyclodehydration to tetrahydropyrimidin(-thi) ones.

As a representation, the IR, ^{1}HNMR and Mass spectra of 5-(acetyl)-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one (4a) are shown in Figures 3, 4 and 5 respectively.

The IR spectra of the compound 4a showed the absorption bands at 3306, 3172, and 1702 cm^{-1} due to presence of -NH, Ar-H and C=O groups respectively. The base peak of mass spectra is shown as M+1 peak and also characteristic of all the remaining derivatives. The ^{1}H NMR spectra shows signals at δ2.2 (s, -$COCH_3$), 7.2 (m,Ar-H), 7.8 & 9.1 (br, -NH).

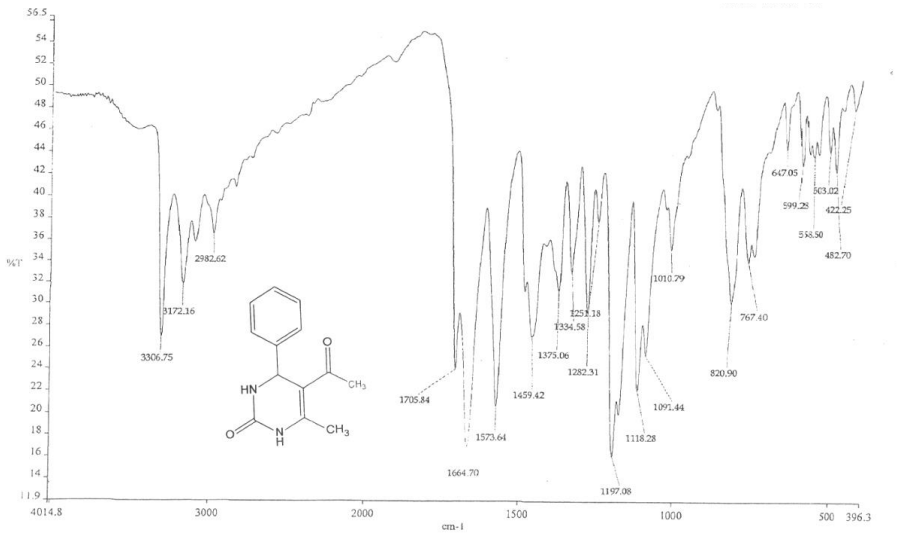

Figure 2. IR Spectra of 5-(acetyl)-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one (4a)

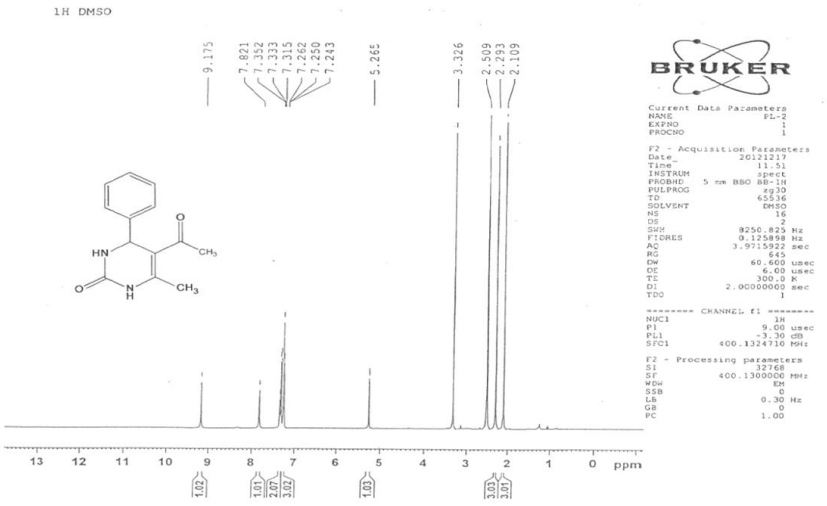

Figure 3. 1HNMR Spectra of 5-(acetyl)-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4a).

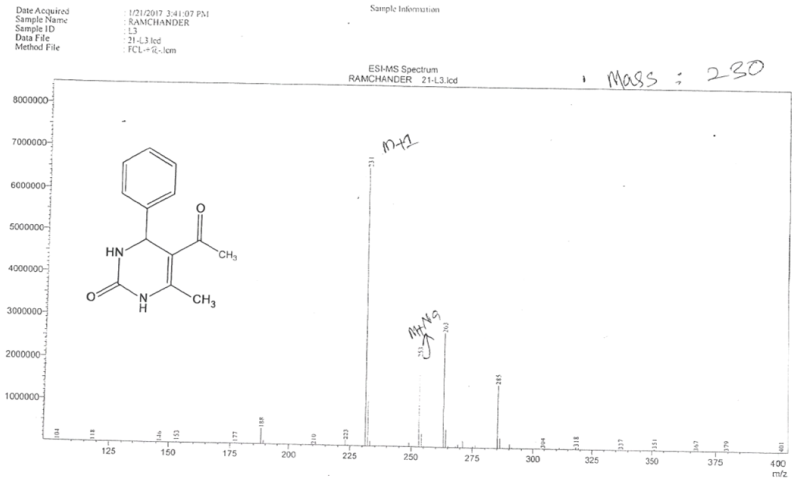

Figure 4. Mass Spectra of 5-(acetyl)-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4a).

Spectral data of synthesized compounds (4a-4l):

5-(acetyl)-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4a): IR(KBr)cm^{-1}: 3306(N-H), 3172 (C-H, Ar), 1702 (C=O); ^{1}H-NMR (DMSO-d_6) ppm: δ 2.1(3H, s,-CH_3), 2.2 (3H, s,-CH_3), 5.2 (1H, s, H of pyrimidine ring),7.2 (5H, m, Ar-H) 7.8 (1H,s,-NH), 9.1 (1H, s, -NH). Mass (ESI-MS): m/z 231 (M+1). Elemental analysis: For $C_{13}H_{14}N_2O_2$ Calculated 67.81% C, 6.12% H, 12.16% N; Found 67.82% C, 6.08% H, 12.17% N.

5-(ethoxycarbonyl)-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4b): IR (KBr) cm^{-1}: 3248(N-H), 3073(C-H, Ar), 1737(C=O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.03(3H,t,-OCH_2CH_3), 2.24(3H,s,-CH_3), 3.94(2H,q,-OCH_2CH_3), 5.18(1H, s, H of pyrimidine ring), 7.15(5H, m, Ar-H), 7.76 (1H, s, NH), 9.84(1H, s,-NH). Mass (ESI-MS): m/z 261 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_3$ Calculated 64.61% C, 6.19% H,10.76% N; Found 64.61% C, 6.15% H, 10.76% N.

5-(carboethoxy)-4-(4-methoxyphenyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4c): IR(KBr) cm^{-1}: 3245 (N-H), 3041(C-H, Ar), 1710(C=O).^{1}H-NMR (DMSO-d_6) ppm: δ1.04(3H, t, -OCH_2CH_3), 2.22 (3H, s, -CH_3), 3.78 (3H, s, -OCH_3), 3.93 (2H, q, -OCH_2CH_3), 5.16(1H, s, H of pyrimidine ring), 6.96(4H, m, Ar-H), 7.74(1H,s,-NH), 9.74(1H,s,-NH). Mass (ESI-MS): m/z 291 (M+1). Elemental analysis: For $C_{15}H_{18}N_2O_4$Calculated 62.06% C, 6.25% H, 9.65% N; Found 62.06% C, 6.20% H, 9.65% N.

5-(carboethoxy)-4-(4-hydroxyphenyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4d): IR (KBr) cm^{-1}: 3291(N-H), 3093 (C-H, Ar), 1691(C=O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.04(3H,t, OCH_2CH_3), 2.21(3H, s,-CH_3), 3.93(2H,q,-OCH_2CH_3), 5.11(1H,s,H of pyrimidine ring), 6.61(4H,m,Ar-H), 7.74(1H,s,-NH), 8.86(1H,s,-NH), 9.75(1H,s,-OH). Mass (ESI-MS): m/z

277 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_4$ Calculated 60.86% C, 5.83% H, 10.04% N; Found 60.86% C, 5.79% H, 10.14% N.

5-(ethoxycarbonyl)-4-(2-hydroxyphenyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4e): IR (KBr) cm^{-1}: 3222(N-H), 3083(C-H,Ar),1747(C=O). ^{1}H-NMR (DMSO-d_6) ppm: δ 1.05(3H,t,-OCH_2CH_3), 2.24(3H,s,-CH_3), 3.94(2H,q,-OCH_2CH_3), 5.14(1H,s,H of pyrimidine ring), 6.73(4H,m,Ar-H), 7.75(1H,s,-NH), 8.26(1H,s,-NH), 9.72(1H,s,-OH). Mass (ESI-MS): m/z 277 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_4$ Calculated 60.86% C, 5.83% H, 10.04% N; Found 60.86% C, 5.79% H, 10.14% N.

5-(carboethoxy)-4-(4-chlorophenyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4f): IR(KBr)cm^{-1}:3241(N-H),3095(C-H,Ar),1722(C=O).^{1}H-NMR(DMSO-d_6)ppm:δ1.03(3H,s,-OCH_2CH_3),2.21(3H,s,-CH_3),3.22(2H,q,-CH_2CH_3),5.22(1H,s,H of pyrimidinering),7.15(4H,m,Ar-H),8.51(1H,s,-NH),9.45(1H, s,-NH). Mass (ESI-MS): m/z 295 (M+1). Elemental analysis: For$C_{14}H_{15}N_2O_3Cl$ Calculated 57.05% C, 5.13% H,9.50% N; Found 57.14% C, 5.10% H, 9.52% N.

5-(ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4g): IR (KBr) cm^{-1}: 3273 (N-H), 3053 (C-H, Ar), 1757(C=O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.07(3H, t, -OCH_2CH_3), 2.25 (3H, s, -CH_3), 3.94 (2H, q, -OCH_2CH_3), 5.22 (1H, s, H of pyrimidine ring), 7.47 (m, 4H, Ar-H), 7.85(1H, s, -NH), 9.34(1H, s, -NH). Mass (ESI-MS): m/z 306 (M+1). Elemental analysis: For $C_{14}H_{15}N_3O_5$ Calculated 55.08% C, 4.95% H, 13.76% N; Found 55.08% C, 4.91% H, 13.77% N.

5-(ethoxycarbonyl)-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-thione(4h): IR (KBr) cm^{-1}: 3264(N-H), 3085(C-H,Ar), 1741 (C=O).^{1}H-NMR (DMSO-d_6) ppm: δ1.13(3H,t,-OCH_2CH_3), 2.32(3H,s,CH_3), 4.02(2H,q,-OCH_2CH_3), 5.21(1H,s,H of pyrimidine ring), 7.28(5H,m,Ar-H), 9.62(1H,s,-NH), 10.26(1H,s,-NH). Mass (ESI-MS): m/z 277 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_2S$Calculated 60.84% C, 5.83% H, 10.14% N; Found 60.86% C, 5.79% H, 10.14% N.

5-(Acetyl)-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-thione(4i): IR (KBr) cm^{-1}: 3284 (N-H), 3099(C-H, Ar), 1713(C=O).^{1}H-NMR (DMSO-d_6) ppm: δ1.91 (3H, s, -CH_3), 2.01(3H, s, -CH_3), 5.06 (1H, s, H of pyrimidine ring), 7.05 (5H, m, Ar-H),9.51(1H, s, -NH), 10.04 (1H, s, -NH). Mass (ESI-MS): m/z 247 (M+1). Elemental analysis: For $C_{13}H_{14}N_2OS$ Calculated 67.81% C, 6.12% H, 12.16% N; Found 67.82% C, 6.08% H, 12.17% N.

5-(acetyl)-4-(4-methoxyphenyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-one(4j): IR (KBr) cm^{-1}: 3214 (N-H), 3057(C-H, Ar), 1714(C=O). ^{1}H-NMR (DMSO-d_6) ppm: δ2.05 (3H, s, CH_3), 2.26 (3H, s, CH_3), 3.72(3H, s, -OCH_3), 5.23(1H, s, H of pyrimidine ring), 6.85(4H, m, Ar-H), 7.70(1H, s,-NH), 9.11(1H, s,- NH). Mass (ESI-MS): m/z 258 (M+1). Elemental analysis: For $C_{13}H_{14}N_2O_2$Calculated 63.38% C, 5.72% H, 11.37% N; Found 63.41% C, 5.69% H, 11.38% N.

5-(ethoxycarbonyl)-4-(4-chlorophenyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-thione(4k): IR (KBr) cm^{-1}: 3203(N-H), 3081(C-H, Ar), 1699(C=O). ^{1}H-NMR (DMSO-d_6) ppm: δ 0.98 (t, 3H, -OCH_2CH_3), 2.22(3H, s, CH_3), 3.81(2H, q, -OCH_2CH_3), 5.42(1H, s, H of pyrimidine ring), 7.30(m,4H,Ar-H), 7.95(1H,s,-NH), 8.82(1H,s, -NH). Mass (ESI-MS): m/z 279 (M+1). Elemental analysis: For $C_{14}H_{15}N_2O_2SCl$ Calculated 60.32% C, 5.42% H, 10.05% N; Found 60.43% C, 5.39% H, 10.07% N.

5-(ethoxycarbonyl)-4-(4-hydroxyphenyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-2(1H)-thione(4l): IR (KBr) cm^{-1}: 3423(O-H), 3218(N-H), 3075(C-H, Ar), 1673 (C=O). ^{1}H-NMR (DMSO-d_6) ppm: δ1.13 (t,3H,-OCH_2CH_3), 2.29 (3H,s,-CH_3), 3.98 (2H, q, -OCH_2CH_3), 5.17 (1H, s, H of pyrimidine ring), 6.83 (4H, m, Ar-H), 7.66 (1H, s, -NH), 9.17 (1H, s, -NH), 9.86 (1H, s, OH). Mass (ESI-MS): m/z 293 (M+1). Elemental analysis: For $C_{14}H_{16}N_2O_3S$ Calculated 57.52% C, 5.51% H, 9.58% N; Found 57.53% C, 5.47% H, 9.58% N.

4. CONCLUSION

In summary, we have developed a novel and eco-friendly Biginelli one-pot three component condensation reaction permitting the ''green synthesis'' of 4-Aryl-1,2,3,4-tetrahydropyrimidine-2(1*h*)-ones/thiones using an environmentally benign reaction medium, water and catalyst, Soy-lecithin. This method is experimentally simple, clean, cost-effective, high yielding, green, and with reduced reaction times. Several merits of method make it a simple powerful tool for the green synthesis of Biginelli adducts.

ACKNOWLEDGEMENTS:

The authors wish to express their sincere thanks to the Management and Principal of Jyothishmathi Institute of Pharmaceutical Sciences, Karimnagar, Telangana, India for providing research facilities and the support.

CONFLICT OF INTEREST

All authors declare that they have no conflict of interest.

REFERENCES

1. Biginelli P., Aldehyde-Urea Derivatives of Aceto- and Oxaloacetic Acids. Gazzetta Chim Ital, 23: 360–413, (1893)
2. Biginelli P., Synthesis of tetrahydropyrimidinones by the acid-catalyzed condensation of an aldehyde, a b-keto ester and urea. Chim Ital, 26: 447–449, (1893)
3. Nagarajaiah H., Biginelli reaction: an overview. Tetrahedron Lett, 47(57): 5135–49, (2016)
4. de Fátima Â., A mini review on Biginelli adducts with notable pharmacological properties. J Adv Res, 6(3): 363–73, (2015)
5. Durga Prasad B., Green Chemistry Protocol for the Synthesis and Antimycobacterial Activity of Multicomponent Biginelli Condensation Catalyzed by Surfactant in Aqueous Media. Pharmacologia, 6(7): 300–306, (2015)
6. Durga Prasad B., Synthesis, Cytotoxic Activity and Molecular Docking Studies of 4-Aryl-6-methyl-3,4-Dihydropyrimidin-2(1H)-ones/thiones with Eg5 Protein. Chem Sci Trans. 4(4):1077–82, (2015)
7. Kappe CO., Biologically active dihydropyrimidones of the Biginelli-type--a literature survey. Eur J Med Chem, 35(12):1043–52, (2000)
8. Panda SS., Biginelli Reaction: A Green Perspective. Curr Org Chem, 16(4): 507–20, (2012)
9. Kamali M., One-pot, solvent-free synthesis via Biginelli reaction: Catalyst-free and new recyclable catalysts. Cogent Chem, 1(1):1081667.
10. Andrade CKZ., Environmentally Benign Solvents in Organic Synthesis: Current Topics. Curr. Org. Chem, 9(2):195–218, (2005)
11. Nieddu M., Green Chemistry, a Paradigm Shift. Nat Sci Sociétés, 22(2):103–13, (2014).
12. Tanaka K., Solvent-Free Organic Synthesis. Chem Rev, 100(3):1025–74, (2000)
13. Hartonen, K., Riekkola, M-L., in: Pena-Pereira, F., Tobiszewski, M., (Eds.),. Chapter 2 - Water as the First Choice Green Solvent. The Application of Green Solvents in Separation Processes, Elsevier; 2017, pp. 19–55.
14. Paprocki D., Multicomponent Reactions Accelerated by Aqueous Micelles. Front Chem, 6:502, (2018).
15. Fng X., New Procedure for One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones by Biginelli Reaction. Synthetic Communications, 38(8):1299–310, (2008)
16. Heravi MM., Current progress in asymmetric Biginelli reaction: an update. Mol Divers, 22(3):751–67, (2018).
17. Kolosov MA., A chemical placebo: NaCl as an effective, cheapest, non-acidic and greener catalyst for Biginelli-type 3,4-dihydropyrimidin-2(1H)-ones (-thiones) synthesis. Mol Divers, 13(1):5–25, (2009)
18. Saikia T., Evaluation of Soy Lecithin as Eco-Friendly Biosurfactant Clathrate Hydrate Antiagglomerant Additive. J Surfactants Deterg, 21(1):101–11, (2018)
19. Xu, Q., Mitsutoshi, Nakajima., Zengshe, Liu., Takeo, Shiina., in: Tzi-Bun Ng, (Eds.) (April 26th 2011). Soybean-based Surfactants and Their Applications, Soybean - Applications and Technology. Intech Open, 2011. DOI: 10.5772/15261.
20. Jacob J., Microwave Assisted Reactions in Organic Chemistry: A Review of Recent Advances. Int J Chem, 4(6):29-43, (2012)
21. Kalyan Kumar R., Microwave Reactors: A Brief Review on Its Fundamental Aspects and Applications. Open Access Libr J, 01:1-20, (2014)
22. Scholfield CR., Composition of soybean lecithin. J Am Oil Chem Soc, 58(10):889–92, (1981)