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An Efficient and Green Synthesis of 3, 4-Dihydropyrimidin-2(1*H*)-ones and Thiones in Water

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Abstract: Synthesis of 3,4-dihydropyrimidinones in the absence of catalyst has been efficiently carried out in excellent yields (85-94%) at room temperature in the presence of water by conventional heating, microwave irradiation and shaking procedure in our Laboratory.

Keywords: Biginelli, Water, Green Method, Eco-friendly, Shaking.

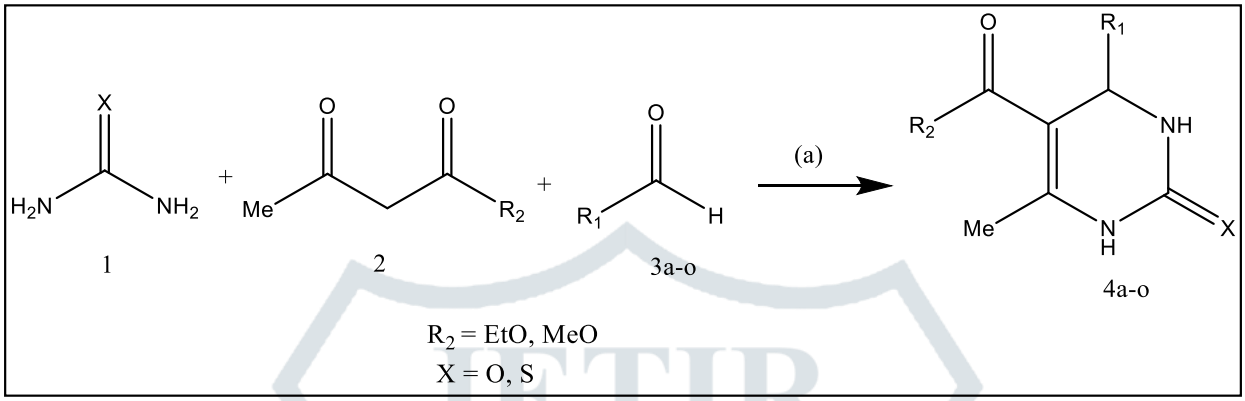
1. Introduction:

Pietro Biginelli in 1893 reported synthesis of dihydropyrimidinones (DHPMs) from an aldehyde, β-keto ester and urea under acidic conditions.[1] Discovery of dihydropyrimidinones led to the development in techniques under acid, solvent and catalyst free conditions.[2-4] Developing green synthetic protocols for synthesizing useful target compounds is a matter of great interest to safeguard the life of living organisms. The replacement of toxic and nonvolatile solvents with environmentally friendly alternatives including water, alcohols, ionic liquids and supercritical fluids have been significantly made in the past decades.[5-6] The solvents like dimethylformamide, tetrahydrofuran, ethylene glycol and methanol were also been extensively used in organic synthesis for their unique properties, costs and greater availability. Of them, water has high demand in chemical transformations for the reasons of cost, availability, toxicity, properties and environmental concerns.[7] Moreover, the use of agitation techniques such as stirring, grinding, shaking and sonication is a step forward in the same direction, which offers many advantages including high yields, easy isolation, low temperature and shorter reaction times over conventional methods. Many heterocyclic compounds consisting pyrimidine scaffold in their structure have exhibited diversified biological activities.[8] Synthesis of 3,4-dihydropyrimidinones has drawn considerable attention of researchers for their wide range of therapeutic and pharmacological properties including antiviral, antitumor, antibacterial, and anti-inflammatory activities.[9-10] Furthermore, dihydropyrimidines constitute important core units of marine polycyclic batzelladine alkaloids which have been found to be active against SARS-CoV-2 and HIV gp-120-CD4 inhibitors.[11-12] Since Pietro Biginelli's synthesis of dihydropyrimidinone involves one-pot a three component condensation namely benzaldehyde, ethylacetoactate and urea under strongly acidic conditions, it has been suffered through certain drawbacks like harsh reaction conditions, long reaction time, low yields and difficulty in product isolation, particularly in case of substituted aromatic and aliphatic aldehydes are employ ed. After this groundbreaking invention, the global researchers have been constantly making their efforts to overcome these drawbacks associating with the Biginelli condensation reaction. The most common methods including microwave irradiation, ultrasound irradiation, conventional heating with our without solvent and catalyst were employed for the synthesis of DHPMs.[13-25] Despite of potential success, most of these methods suffer from notable drawbacks like use of costly reagents and catalysts, toxic solvents and catalysts, long reaction times and high temperature. In order to overcome these drawbacks,

there is an urgent demand to introduce some novel methods which are to be inexpensive, mild, environmental friendly, and more efficient for producing high yields.

To address these limitations, we wish to report herein a mild, simple, cost effective, and highly improved one-pot procedure for the synthesis of 3,4-dihydropyrimidinones and thiones from aromatic aldehydes, β-keto ester and urea or thiourea in water using shaking technique at room temperature.

Scheme 1: Synthesis of 3,4-Dihydropyrimidinones in water



Reaction conditions: a) Conventional heating: 80-90 ^{o}C temperature, stirring for 40min to 1.20min; Microwave irradiation: (750 W, 2 min); Shaking method: 1 to1.5 hr.

2. Results and Discussion

In the beginning, we carried out Biginelli condensation of aromatic and heterocyclic aldehydes with ethylacetoacatate and urea or thiourea in water (3 to 4 mL) into a 100 ml round bottom flask under stirring conditions at 80-90 ^{o}C temperature. The reaction mixture becomes solidified at the end of the reaction. It was cooled and added into crushed ice. The solid separated out after stirring was filtered off, washed three to four times by cold water and dried. The crude products were purified *via* recrystallization using ethanol. All the substrates were efficiently converted into corresponding 3,4-dihydropyrimidinones and thiones in excellent yields. The results of experiments are presented in Table 1. To examine the effect of water at room temperature under shaking conditions, we further studied the Biginelli condensation of different aldehydes, ethylacetoacetate and urea or thiourea using water and results are entered in Table 1. The feasibility of condensation under microwave irradiation was tested for a model reaction between benzaldehyde, ethylacetoacatate and urea in the presence of water. Notably, the reaction underwent completion under microwave irradiation within 2 min, it was found to be rapid in comparison to conventional heating and shaking techniques. To evaluate the effect of water, the reaction was carried out between 4-hydroxy benzaldehyde, ethylacetoacetate and urea in the absence of water using conventional heating and microwave irradiation techniques. When reaction was carried by conventional heating, no product formation was observed after 3h, gave black mass only, Similarly, under microwave irradiation the reaction did not afford product after prolonged heating. It is believed that the condensation of an aldehyde with urea to generate iminium intermediate is facilitated due to the presence of water. This generated intermediate further acts as an electrophile for the nucleophilic addition of ketoester enol to give 3,4-DHPMs on cyclization. Therefore, the success of Biginelli condensation depends upon the generation of iminium intermediate, which is considered as key step. To demonstrate the effect of hydrogen bonding in promoting the reaction, we carried out the Biginelli condensation between 4-hydroxybenzaldehyde, ethylacetoacetate, and urea in presence of other protic solvents like ethanol, methanol, and ethylene glycol. In these protic solvents under conventional heating and shaking conditions, reaction proceeded very slow and not afforded satisfactory product yields within same reaction times (Table 2). It is also worth mentioning that under microwave irradiation, the reaction did not proceed to give product formation on long heating. This fact established the key role of water as a promoter for this reaction under convention heating, shaking and microwave irradiation. Furthermore, the reaction of benzaldehyde, ethylacetoacetate, and urea in the presence of a mixture of water and ethanol or methanol or ethylene glycol (1:1) under conventional heating, shaking and microwave irradiation was found to be very slow and afforded poor product yield in longer reaction time. This may be due to more coordination of water with solvents rather than aldehyde. In present methods, the role of water

is promoter which facilitates the condensation of an aldehyde and urea without catalyst and additional solvent. Therefore, the present methods including conventional heating, shaking and microwave irradiation are proved to be efficient for the conversion of three components into corresponding 3,4-DHPMs in excellent yields. Among these three techniques, microwave irradiation was found to more useful as product formation takes place in short reaction time with improved yield. However, microwave irradiations have little synthetic applications for the bulk of reaction mixture. No doubt that microwave radiations (2.45GHz) are very well absorbed by solvents and reacting chemicals, but this phenomenon does not allow sufficiently deep penetration of the microwave radiation into the bulk of reaction mixture. As a result, the pure product formation on large scale is impossible and the chances of isomeric product formations are increased. On the other hand, conventional heating is very useful as it forms 3,4-dihydropyrimidinones in excellent yields, but takes longer time for completion and requires high temperature conditions. To the best of our knowledge, the reaction proceeded under shaking conditions are very advantages on the point of view of yield, time, ease of handling, uniform collision of reactants and low temperature conditions.

Table 1: Synthesis of 3, 4-Dihydropyrimidinones in Water Using Conventional, Microwave and Shaking Methods[a]

Entry	Conventional[b]		Microwave[c]		Shaking[d]	
	t (min)	% Yield[e]	t (min)	% Yield[e]	t (min)	% Yield[e]
4a	50	82	2 min	92	60	84
4b	45	80	2 min	94	70	82
4c	45	84	2min	95	75	82
4d	40	90	2min	90	80	87
4e	60	80	2min	92	70	84
4f	45	85	2min	96	90	85
4g	50	85	2min	95	90	85
4h	60	84	2min	96	80	82
4i	70	78	2min	90	80	82
4j	100	85	2min	90	70	87
4k	80	90	2min	94	70	90
4l	120	80	2min	89	80	84
4m	48	87	2min	89	90	87
4n	60	88	2min	87	90	86
4o	60	85	2min	90	80	87

[b]Heating at 80-90 °C, [c]Microwave irradiation (750 W, reaction time 2 min), [d]Shaking Room Temp., [e]Isolated yields.

Table 2: Synthesis of 3,4-dihydropyrimidinones by shaking method in water[d]

Entry	R_1	R_2	X	Mp (°C) Found[f]	Mp (°C) Reported (Lit.)
4a	C_6H_5	EtO	O	202-204	206
4b	4-CH_3O-C_6H_4	EtO	O	203-205	205-207
4c	4-HO-C_6H_4	EtO	O	224-227	227-228
4d	2-HO-C_6H_4	EtO	O	200-202	199-201
4e	3-NO_2-C_6H_4	EtO	O	225-227	227-228
4f	4-Cl-C_6H_4	EtO	O	207-210	209-212
4g	4-HO-3-CH_3O-C_6H_3	EtO	O	232-233	232-233
4h	3-Br-4-HO-5-CH_3O-C_6H_2	EtO	O	188-190	---------
4i	C_6H_5-CH=CH	EtO	O	228-230	230-232
4j	4-F-C_6H_4	EtO	O	180-183	182-184
4k	2-Furyl	EtO	O	205-206	202-204
4l	4-HO-C_6H_4	EtO	S	200-202	202-203
4m	C_6H_5	EtO	S	205-206	207-208
4n	3-NO_2-C_6H_4	MeO	O	272-275	273-275
4o	C_6H_5	MeO	O	211-213	212-213
4p	3-Br-4-HO-5-CH_3O-C_6H_2	MeO	O	175-178	----------

[d]Reaction conditions: Aldehyde (3 mmoL), β-ketoester (3 mmoL), urea or thiourea (4.5 mmoL), with 5mL water; [f]Melting points are uncorrected.

3. Experimental Section

New compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS spectra. The ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Inova-400 spectrometer using DMSO-D_6, and TMS as an internal standard. LC-MS analyses were performed on a HP-1100 LC-MS. Melting points were determined using a Büchi B-540 instrument. All melting points are uncorrected.

3.1 General experimental procedure: Place an aldehyde (3 mmoL), urea or thiourea (4.5 mmoL), β-ketoester (3 mmoL), and 1mL of water. The resulting suspension was stirred at 80-90 ^{0}C under conventional heating or microwave irradiation (750 W, 2 min). The mixture became solid at the end of the reaction, which was crushed and added into the water. The crude product was isolated by filtration that further purified by recrystallization with ethanol to afford pure 3,4-DHMPs and thiones. In case of shaking method, a small flask containing aldehyde (3 mmoL), urea/thiourea (4.5 mmoL), β-ketoester (2 mmol), and water (5mL) was shaken for the time indicated in Table 2. The crude solid was subjected to usual workup to obtain pure product. All the products were isolated and their isolated yields are given in Table 1. Identity of the products was established by comparing their physical and spectral data with those of reported compounds.

(4h) Ethyl4-(3-bromo-4-hydroxy-5-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

^{1}HNMR (400 MHz, DMSO-d_6, TMS): δ 1.14(t, 3H), 2.25(s, 3H), 3.84(s, 3H), 4.02(quartet, 2H), 5.10(s, 1H), 6.53(s, 1H), 6.92(s, 1H), 7.58(s, 1H), 9.10(s, 1H), 9.67(s, 1H); ^{13}C NMR (400MHz, DMSO-d_6): δ 14.52, 17.31, 52.71, 56.13, 62.04, 105.82, 112.01, 126.12, 140.12, 140.57, 147,32, 150.10, 153.51, 167.31; ESI-MS: m/z = 184.03 [M+].

4. Conclusions

In summary, we have developed a green and environmentally benign water assisted protocol for the synthesis of 3,4-DHMPs in excellent yields without catalyst and additional solvents. All condensation reactions were carried out very successfully under shaking conditions at room temperature for 1.0 to 1.5 hr. The role of water was found to be significant and the reactions were found to be highly efficient under shaking in water in comparison to conventional heating and afforded products in high yields.

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