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One pot synthesis of 3, 4-dihydropyrimidine-2(1H)-thiones using orange peel powder under ultrasonic irradiation

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ABSTRACT

Biginelli, an important multicomponent reaction provides an avenue for the synthesis of different biologically active heterocyclic compounds. During the past decade, one pot multicomponent reactions have attracted the attention of organic and medicinal chemists due to high atom economy, time and enery saving convergent nature. The present manuscript reports a simple one pot three component synthesis of 3, 4-dihydroprimidin-2(1H)-thiones from various diversely substituted aldehydes, ethyl acetoacetate and thiourea using a orange peel powder as a natural catalyst on ultrasonic irradiation in aqueous medium as the solvent. The advantages of this reaction are less reaction time, high yield, easy availability of the catalyst and green nature.

Keywords: *One pot synthesis; Catalyst; Ultrasonication; Water.*

1. INTRODUCTION

Development of green chemical processes using less hazardous catalysts has become a primary goal in synthetic organic chemistry [1]. Multi-component reactions are of increasing importance in organic and medicinal chemistry [2]. They are for the synthesis of various heterocyclic compounds in drug discovery processes [3]. One-pot MCRs are of considerable importance due to short reaction time, high yield, reduced work-up steps and waste as well as energy consumption; hence leading to more effective and sustainable processes [4].

Biginelli condensation; a multicomponent reaction is useful for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones [5]. The first Biginelli reaction was reported by Pietro Biginelli in1893 by the condensation of an aldehyde, β-keto ester and urea or thiourea in ethanol using a catalytic amount of HCl [6]. 3,4-dihydropyrimidin-2(1H)-thiones exhibit a wide range of anti-inflammatory [7], anti-cancer [8], antiviral [9], antibacterial [10], and calcium channel blockers activities [11].

Owing to the importance of 3,4-dihydropyrimin-2(1H)-thiones, scientists have reported various methods for their synthesis using different catalysts such as Tamarind Juice[12], Amberlyst® resin [13], Ammonium carbonate in water [14], Silica-chloride [15], Nickel Nanoparticles [16], L-ascorbic acid [17], Zinc chloride[18], and SiO_2.TTC [19].

Ultrasound irradiation enhances reactivity of molecules towards many chemicals reactions. Ultrasound assisted organic synthesis has become a popular tool for green chemistry. A large number of organic reactions can be carried out at ambient temperatures using ultrasound irradiation which afford high yields within a less reaction time and thus constitute effective protocols in synthetic organic chemistry.

Oranges are popular source of vitamins, especially vitamin C [20]. Orange peel powder contains soluble sugars and pectin as the main components [21]. Citrus fruits are a rich source of flavonoids but the peels contain a high concentration of phenolic compounds and nutrients (used as drug or food supplements) [22]. In continuation of our efforts for the eco-friendly approach for the synthesis of heterocyclic compounds, herein we wish to report one pot synthesis of 3,4-dihydropyrimidine-2(1H)-thiones derivatives by the reaction of an aldehyde, ethyl acetoacetate and thiourea using orange peel powder under ultrasonic irradiation conditions in aqueous medium within a short reaction time.

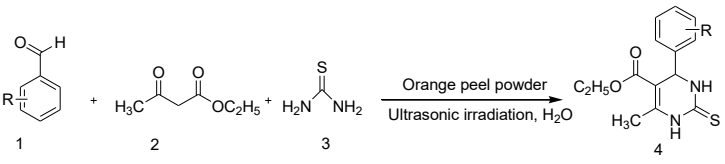
2. MATERIALS AND METHODS

All the melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ solvent on a 400 MHz Bruker spectrometer using tetramethylsilane as the internal standard.

2.1. General procedure for the synthesis of substituted 3, 4-dihydropyrimidine-2(1H)-thiones.

A mixture of benzaldehyde (1 mmol), ethylacetoacetate (1 mmol), thiourea (1.5 mmol) and orange peel powder (10 wt%) in water (2 mL) was irradiated under ultrasonication bath for appropriate time as indicated in **Table 1**. The progress of reaction was monitored by TLC (n-hexane: ethyl acetate, 7:3). After completion of the reaction, the contents were concentrated to evaporate water, diluted with hot ethanol (5 mL) and filtered off to separate recovered catalyst as the residue which was subsequently washed with hot ethanol (3 x 5 mL). The combined filtrates were concentrated and recrystallized from hot ethanol to get pure

dihydropyrimidine-2(1H)-thiones. All the products were confirmed on the basis of melting points, IR, and ^{1}H NMR and Mass analysis.



1 2 3 4

Scheme 1. Synthesis of 3, 4-dihydropyrimidine-2(1H)-thiones using orange peel powder.

2.2. Spectral data of the synthesized compounds.

[1]**5-Ethoxycarbonyl-6-methyl-4-(2-chlorophenyl)-3, 4-dihydropyrimidin-2(1H)-thione:** IR (KBr, cm^{-1}): 3240 and 3300 (N-H), 1740 (C=O, ester), 1485 (C=C), 1205 (C=S); ^{1}H NMR ($CDCl_3$): 7.30 (d, 2H, Ar-H), 7.28 (d, 2H, Ar-H), 7.08 (s, 1H, NH), 5.49 (d, 1H, CH), 5.34 (s, 1H, NH), 5.04 (s, 1H, CH), 4.00 (q, 2H, OCH_2-CH_3), 2.30 (s, 3H, CH_3), 1.20 (t, 3H, -OCH_2-CH_3); ESI-MS: 311 $(M+1)^+$.

[2]**5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3, 4-dihydropyrimidin-2(1H)-thione:** IR (KBr, cm^{-1}): 3325 and 3212 (N-H), 1738 (C=O, ester), 1545 (C=C), 1202 (C=S); ^{1}H NMR ($CDCl_3$): 8.12 (s, 1H, NH), 7.25 (d, 2H, Ar-H), 7.18 (s, 1H, NH), 7.14 (d, 2H, Ar-H), 5.32 (s, 1H, CH), 4.07 (q, 2H, -OCH_2-CH_3), 2.34 (s, 3H, CH_3), 1.17 (t, 3H, -OCH_2-CH_3); ESI-MS: 311$(M+1)^+$.

[3]**5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3, 4-dihydropyrimidine-2(1H)-thione:** IR (KBr, cm^{-1}): 3328 and 3209 (N-H), 1748 (C=O, ester), 1575 (C=C), 1128 (C=S); ^{1}H NMR ($CDCl_3$): 8.21 (s, 1H, NH), 7.52 (s, 1H, NH), 7.14 (d, 2H, Ar-H), 6.90 (d, 2H, Ar-H), 5.10 (s, 1H, CH), 4.10 (q, 2H, -OCH_2-CH_3), 3.75 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.15 (t, 3H, OCH_2-CH_3); ESI-MS: 307 $(M+1)^+$.

[4]**5-(Ethoxycarbonyl)-4-(4-methylphenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-thione:** IR (KBr, cm^{-1}): 3300 and 3245 (N-H), 1740 (C=O, ester), 1560 (C=C), 1140 (C=S); ^{1}H NMR ($CDCl_3$): 8.82 (s, 1H, NH), 7.75 (s, 1H, NH), 7.25 (d, 2H, Ar-H), 7.10 (d, 2H, Ar-H), 5.62 (s, 1H, CH), 4.34 (q, 2H, OCH_2-CH_3), 2.54 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 1.11 (t, 3H, OCH_2-CH_3); ESI-MS: 291$(M+1)^+$.

[5]**5-(Ethoxycarbonyl)-6-methyl-4-(4-hydroxyphenyl)-3, 4-dihydropyrimidin-2(1H)-thione:** IR (KBr, cm^{-1}): 3540 (-OH), 3300 and 3240 (N-H), 1738 (C=O, ester), 1510 (C=C), 1206 (C=S); ^{1}H NMR ($CDCl_3$) 8.20 (s, 1H, NH), 7.83 (s, 1H, NH), 7.30 (d, 2H, Ar-H), 7.14 (d, 2H, Ar-H), 5.37 (s, 1H, CH), 4.09 (q, 2H, OCH_2-CH_3), 2.36 (s, 3H, CH_3), 1.17 (t, 3H, OCH_2-CH_3); ESI-MS: 293 $(M+1)^+$.

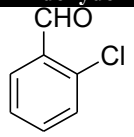
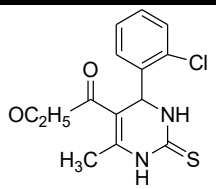
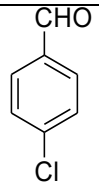
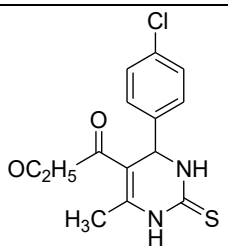
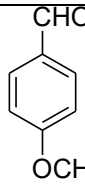
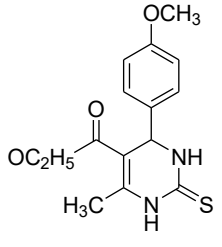
[6]**5-(Ethoxycarbonyl)-6-methyl-4-(2-hydroxyphenyl)-3, 4-dihdropyrimidin-2(1H)-thione:** IR (KBr, cm^{-1}): 3510 (-OH), 3300 and 3209 (N-H), 1715 (C=O, ester), 1520 (C=C), 1202 (C=S), ^{1}H NMR ($CDCl_3$): 7.44 (s, 1H, NH),7.10 (d, 1H, Ar-H), 6.92 (s, 1H, -NH), 6.92 (t, 2H, Ar-H), 6.85 (d, 1H, Ar-H), 4.68 (s, 1H, CH), 4.22 (q, 2H, OCH_2-CH_3), 3.11 (s, 1H, OH), 1.89 (s, 3H, CH_3),1.28 (t, 3H, OCH_2-CH_3); ESI-MS: 293 $(M+1)^+$.

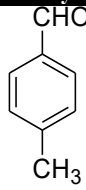
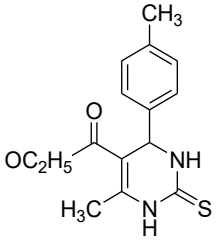
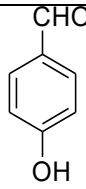
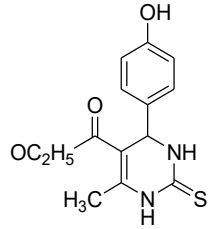
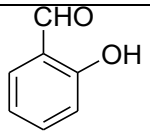
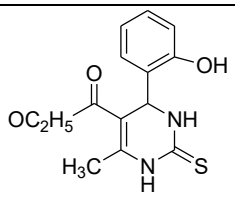
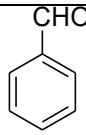
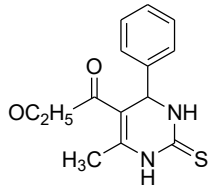
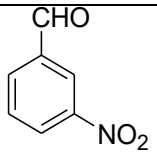
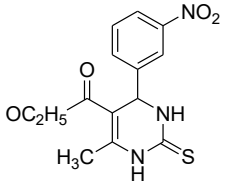
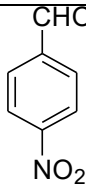
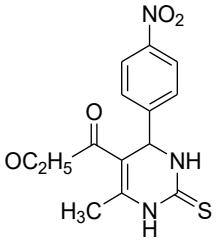
[7]**5-(Ethoxycarbonyl)-4-(phenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-thione:** IR (KBr, cm^{-1}): 3240 and 3210 (N-H), 1725 (C=O, ester), 1490 (C=C), 1196 (C=S) ^{1}H NMR ($CDCl_3$): 9.01 (s, 1H, NH), 8.25 (s, 1H, -NH), 7.16 (dd, 1H, Ar-H), 7.08 (t, 1H, Ar-H), 7.16 (dd, 1H, Ar-H), 7.05 (d, 2H, Ar-H), 4.55 (s, 1H, CH), 4.23 (q, 2H, OCH_2-CH_3), 1.72 (s, 3H, CH_3),1.20 (t, 3H, OCH_2-CH_3): ESI-MS: 277 $(M+1)^+$.

[8]**5-(Ethoxycarbonyl)-4-(3-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-thione:** IR (KBr, cm^{-1}): 3310 and 3236 (N-H), 1745 (C=O, ester), 1590 (C=C), 1545 (C=S); ^{1}H NMR ($CDCl_3$): 8.01 (d, 1H, Ar-H), 7.90 (s, 1H, Ar-H), 7.43 (dd, 1H, Ar-H), 7.39 (d, 1H, Ar-H), 7.07 (s, 1H, -NH), 5.35 (s, 1H, -NH), 5.20 (s, 1H, CH), 4.24 (q, 2H, OCH_2-CH_3), 1.69 (s, 3H, CH_3), 1.21 (t, 3H, OCH_2-CH_3); ESI-MS: 322 $(M+1)^+$.

[9]**5-(Ethoxycarbonyl)-4-(4-nitrophenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-thione:** IR (KBr, cm^{-1}): 3240 and 3200 (N-H), 1745 (C=O, ester), 1575 (C=C). 1571 (C=S); ^{1}H NMR ($CDCl_3$): 8.07 (s, 1H, -NH), 7.15 (s, 1H, NH), 7.24 (d, 2H, Ar-H), 8.05 (d, 2H, Ar-H), 5.27 (s, 1H, CH), 4.07 (q, 2H, OCH_2-CH_3), 1.70 (s, 3H, CH_3), 1.17 (t, 3H, OCH_2-CH_3); ESI-MS: 322 $(M+1)^+$.

Table 1. Synthesis of 3, 4-dihydropyrimidine-2(1H)-thiones using orange peel powder.

Sr. No.	Aldehyde	Product	Time	Yield (%)	M.P. (^{o}C) Found	Ref
1			45	80	201-202	202-204[12]
2			45	80	181-182	181-183[9]
3			45	90	136-137	136-138[9]

Sr. No.	Aldehyde	Product	Time	Yield (%)	M.P. (^{o}C) Found	Ref
4			45	88	190-192	192-194[24]
5			45	82	201-203	202-204[16]
6			45	80	189-190	188-190[12]
7			45	90	209-211	210-212[9]
8			45	82	205-207	205-208[9]
9			45	84	109-111	108-109[23]

3. RESULTS

A model reaction of 4-methoxybenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), thiourea (1.5 mmol) and orange peel powder (10 wt%) was used to optimize reaction conditions such as solvents and catalyst concentrations.

In the present work, we synthesized 3, 4-dihydropyrimidine-2(1H)-thiones derivatives using various substituted aldehydes. A model reaction was performed on 4-methoxybenzaldehyde, ethyl acetoacetate, and urea using orange peel powder as a catalyst in water solvent or without water or ethanol solvents at room temperature, under reflux and ultrasound irradiation conditions.

Initially, the model reaction was carried in the absence of solvent at room temperature, reflux condition and ultrasonic irradiation. But the corresponding product was obtained in a lower amount (35%-52%). Then we carried out the same reaction in the presence of water, ethanol solvent under room temperature, reflux condition and ultrasonic condition. We observed that the reaction required a less reaction time in water with high yields as compared with ethanol. Excellent yields were obtained in water solvent under ultrasonic irradiation as compared to room temperature and reflux condition. Results obtained are presented in **Table 2.**

Table 2. Effect of various solvents on the model reaction.

Entry	Solvent	Temperature	Time (min)	Yield (%)
1	Water	Ultrasonic irradiation	45	90
2	Solvent free	Ultrasonic irradiation	180	35
3	Ethanol	Ultrasonic irradiation	120	52

Next, we optimized the amount of catalyst concentration on the same reaction by using 5 wt%, 10 wt%, 20 wt% and 30 wt% of the catalyst. We observed 50%, 90%, 90%, and 91% yield of the products respectively.

We also carried out the same reaction under solvent free condition, but the product was obtained in very less amount i.e. 10%. In conclusion, the best result was obtained with 10 wt% of orange peel powder in water solvent under ultrasonic irradiation **(Table 3).** Further increasing the amount of catalyst does not affect the yield of the product.

Table 3. Effect of catalyst on the synthesis of 3, 4-dihydropyrimidine-2(1H)-thiones under ultrasonic irradiation.

Entry	Amount of catalyst (wt%)	Yield (%)
1	No catalyst	10
2	5	50
3	10	90
4	20	90
5	30	91

After completion of reaction (monitored by TLC), the reaction mixture concentrated to remove the water, diluted with hot ethanol (5 mL) and filtered off to recover the catalyst as a residue which was subsequently washed with hot ethanol (3 x 5 mL). The combined filtrates were concentrated and to get crude product which was recrystallized from ethanol to afford pure 3, 4-dihydropyrimidine-2(1H)-thiones.

Antifungal activity of the synthesized compounds was studied against fungal species *Fusarium oxysporum* using Carbendazim as the standard. Agar well diffusion method was used for the screening purpose. Observations were recorded after 72 hr and the zone of inhibition was measured in mm at a concentration of 10 mg mL^{-1} in DMSO solvent. The antifungal activity was measured in terms of zones of inhibition as shown in **Table 4**.

Table 4. Zone of inhibition in mm of synthesized 3, 4-dihydropyrimidine-2(1H)-thiones derivatives.

Compound	Zone of inhibition (mm)
1	20
2	21
3	19
4	18
5	17
6	16
7	15
8	14
9	12
STANDARD	18

4. CONCLUSIONS

In conclusion, we developed a green method for the synthesis of biologically significant 3, 4-dihydropyrimidine-2(1H)-thione heterocyclic compounds using one pot multicomponent reaction. The use of aquous medium, orange peel powder as a natural and biodegradable catalytic material and ultrasound irradiation makes the present protocol attractive for the synthesis of these heterocyclic compounds. Easy recovery of catalyst and short reaction time, use of universal solvent water, natural catalyst are the advantages of present method. It also involves easy handling, atom economic reaction and high conversions resulting in good yields of the products. The synthesized compounds showed good antifungal activity against *Fusarium oxysporum* fungus.

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6. ACKNOWLEDGEMENTS

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