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Animal bone meal as a new efficient heterogeneous catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones

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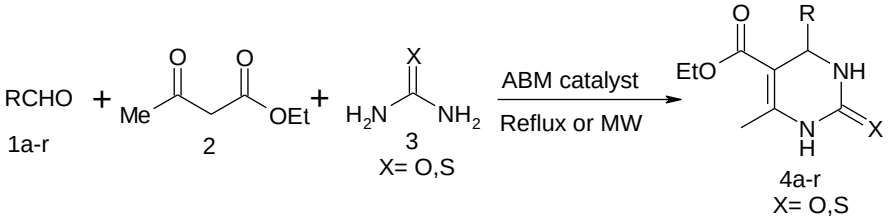
Abstract

Animal bone meal has been used as an efficient catalyst for an improved and rapid one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones and their derivatives through three-component condensation reactions of aldehyde, *β*-ketoester, and urea or thiourea in excellent yields. This catalyst was found to be highly active and selective, affording a high yield of 3,4-dihydropyrimidin-2(1H)-ones/thiones. These reactions were performed via conventional heating in water or under microwave irradiation. Compared to the classical Biginelli reaction conditions, this new approach consistently has the advantage of excellent yields, short reaction times, simple and convenient procedure, inexpensive reagents and eco-friendly preparation.

Keywords: Animal Bone Meal, 3,4-dihydropyrimidin-2(1H)-ones/thiones, Biginelli reaction, *β*-ketoester, urea, microwave (MW).

1.Introduction

Dihydropyrimidinones/thiones and their derivatives are an important class of compounds, because of their therapeutic and pharmacological properties such as antiviral, antibacterial, antitumor, and antihypertensive activities [1–5]. The simple and direct synthesis, originally reported by Pietro Biginelli in 1893 [6, 7], involves the condensation between *β*-ketoesters, aldehydes, and ureas or thioureas in the presence of either Lewis or mineral acids. For Biginelli condensations, more than 100 different experimental conditions are now known [8]. Over the past decades, several new methods for synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones have been reported in the literature including microwave irradiation, ionic liquids, and by using Lewis acids as well as protic acids [9] are found to be effective. In spite of their potential utility, many of these methods involve expensive reagents, strongly acidic conditions, long reaction times, high temperatures, stoichiometric amounts of catalysts, and unsatisfactory yields. Therefore, the discovery of new and an inexpensive catalyst for the preparation of 3,4-dihydropyrimidin-2(1H)-ones/thiones under neutral and mild conditions is of prime importance. Recently, the use of solid supported reagents [10] has received considerable importance in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, simple workup, and recoverability of catalysts. Particularly, Animal Bone Meal (ABM) impregnated with zinc chloride has advantages of low cost, ease of preparation, and catalyst recycling. Since the reaction is heterogeneous in nature, the catalyst can conveniently be separated by simple filtration. In continuation of an attempts to explore the catalytic activity of Animal Bone Meal and its analogs modified for useful organic synthesis, our group has recently developed the preparation and use of Animal Bone Meal as a natural catalyst for C-S bond formation by thia-Michael addition [11], crossed-aldol condensation [12], synthesis of benzimidazoles, benzoxazoles, and benzothiazoles [13], synthesis of various chalcones by Claisen-Schmidt condensation and Aza-Michael addition [14], synthesis of 3-cyanopyridine derivatives [15], Biginelli reaction under microwave irradiation [16], and synthesis of oximes in solvent-free conditions [17, 18]. We report here the utilization of ABM alone and its analog doped with $ZnCl_2$ ($ZnCl_2$/ABM) as new heterogeneous catalysts for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones, via conventional heating in water or under microwave irradiation (Scheme 1).



Scheme 1. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones.

2.Methodology

2.1.Chemicals reagents material

All chemical products and solvents were analytical grade purchased from Sigma–Aldrich and used without further purification. Animal bones were collected from nearby butcher shops. Structures of all the compounds were identified by their spectral data. Silica gel 60 F254 (Pre-coated aluminum plates) from Merck were used to monitor reaction progress. Melting points were determined on a melting point apparatus and are uncorrected. IR (KBr) spectra were recorded on buck scientific IR M-500 spectrophotometer and the values are expressed as ν_{max} cm^{-1}. The 1H NMR spectra were scanned on a Bruker (300 MHz) spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Mass spectral data were recorded on a Waters micromass Spectrometer running under Mass Lynex version 4.0 software and equipped with an ESI source. The chemical shift values are recorded on δ scale and the coupling constants (J) are in Hz.

2.2.General procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via conventional heating

In a 50 mL round-bottom-flask, 1 mmol of arylaldehyde **1**, 1 mmol of *β*-ketoester **2** and 1.5 mmol of urea or thiourea **3** were mixed with 150 mg of catalyst and the mixture was heated classically at reflux of water (5ml). The progress of the reaction was monitored by TLC (Eluent: n-hexane: ethyl acetate, 3:1). After completion of the reaction, the mixture was concentrated and diluted with $CHCl_3$ (10 ml). The mixture was filtered and the solid material was washed with $CHCl_3$ (10 ml). The filtrate was evaporated and the residue was purified by recrystallization or by column chromatography to afford the pure product (**Table** 3).

2.3.A typical procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones with ABM or $ZnCl_2$/ABM under microwave irradiation

To a 50 ml flame-dried round-bottom flask were added 1 mmol of arylaldehyde **1**, 1 mmol of *β*-ketoester 2 and 1.5 mmol of urea or thiourea **3** and were mixed with 150 mg of catalyst. The resulting mixture was placed into the microwave reactor. After the reaction was completed, distilled water was added into the flask and stirred for several minutes and then filtrated through a sintered funnel to afford the crude product, which was further purified by recrystallization (EtOH).

2.4.Preparation of catalysts ABM and $ZnCl_2$/ABM

Animal bones were collected from nearby butcher shops. All of the attached meat and fat were removed and cleaned from the bones. The bones were then washed several times with tap water at room temperature and left in the open air for several days to get rid of odors. Later, they were transferred to the oven at 80°C for drying. The dried bones were crushed and milled into different particle sizes in the range 45–200 µm then calcined for 2h at 800°C. The residue was washed with water and used after drying for 24h at 80°C. The residue was washed with water and dried overnight at 100°C in a conventional drying oven, and then calcined at a heating rate of 2°C/min to 400°C, and kept at this temperature for 4h. The modified bones $ZnCl_2$/ABM was prepared by impregnating the bones with an aqueous solution of zinc chloride. The weight ratio used was $ZnCl_2$/ABM =1/8. The mixture was stirred vigorously at room temperature, evaporated, dried, and calcined at 800ºC for 2 h. The catalysts obtained were characterized by Differential Scanning Calorimetric (DSC) coupled with Thermogravimetric Analysis (TGA) (**Figure** 1), X-ray diffraction (**Figure** 2 and **Figure** 3), Scanning electron microscopy with energy dispersive (SEM/EDS) (**Figure** 4).

2.5.Characterization of ABM and $ZnCl_2$/ABM

2.5.1.Thermal analysis (TGA and DSC)

The thermal gravimetric analysis was carried out on a TGA SHIMADZU DTG-60 Thermogravimetric in an alumina crucible at a heating rate of 10°C/min under air atmosphere. The mass of the sample was 12 mg. The sample pan was placed in the balance system equipment and the temperature was raised from 16 to 900°C.

2.5.2.XRD analysis

It provides information on the purity, crystallinity and crystallographic parameters. The analysis by X-ray diffraction was performed on the powder in ambient conditions of temperature and pressure. The X-ray diffractometer used was a Panalytical diffractometer, equipped with a copper X-ray (wavelength $\lambda = 1.54 \times 10^{-10}$ m; tension V = 45 kV, intensity I=35 mA), and with a monochromator eliminating K_β radiation. The analyses were carried out using the classical θ–2θ configuration, with 2θ angle steps of 0.02° and counting times of 20 s per step.

2.5.3.SEM-EDX analysis

The scanning electron microscope (SEM) is used to obtain images of the surface of substantially solid materials at scales ranging from that of the lens (x 10) of the transmission electron microscope to (x 500000), its principle of operation is the interaction between the material and electron beam. The instrument used is Supra 40 VP COLUMN GEMINI ZEISS coupled to an analyzer (Oxford Instruments X-Max 20 mm^2) with EDXS detector (Energy Dispersive X-rays Spectroscopy) to determine the local quantitative of elemental composition sample with a maximum resolution of 1 micron at voltages ranging from 10 to 25 kV.

2.5.4.FTIR analysis

Fourier transformed infrared (FTIR) spectrum of the sample was recorded by Fourier transform infrared (Nicolet 6700 FT-IR, Thermo Scientific) spectrophotometer. The FTIR spectrum ranged from 4000 to 500 cm^{-1} at a resolution of 4 cm^{-1} by making an ATR mode.

3.Results and discussion

3.1.Thermal analysis

The curves of Thermogravimetric analysis (TGA) and flow profiles of heat from 16.25°C to 900°C C were presented in **Figure** 1. The obtained thermogram generally shows three successive stages of the weight loss. The first stage is below 200°C, the second is between 200°C to 600°C, the third is between 600°C to 800°C and the last stage is above 800°C where the weight change is not significant [19, 20]. The results of DSC showed an endothermic peak at 67.8°C related to loss of surface and structural water. It is then followed by two exothermic peaks with a maximum value around 359.66°C which is related to loss of both collagen and shoulder, while the loss of collagen and organic matter is around 535.31°C [21]. In the end, one single small endothermic peak at 693.2°C occurs due to loss of mineral CO_2 (**Figure** 1).

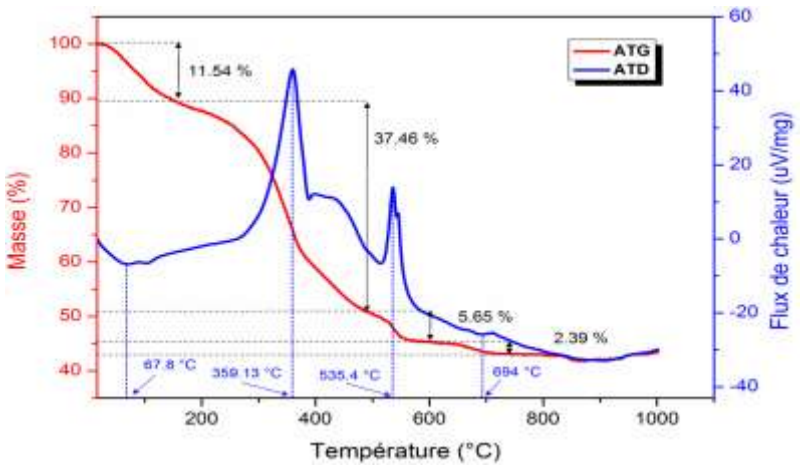


Figure 1. TGA and DSC plots of the control samples (non-calcined bovine bone) in the 16.25–1000°C temperature range.

3.2.XRD analysis

The XRD pattern of the ABM phase thermally calcined at 900°C was reported in **Figure** 2. First, these results confirm that the amorphous organic material was removed after calcination. Second, it should be recalled that the XRD analyses for ABM in the range 2θ = 10-80° clearly showed that the hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ powder was in a major structured form by comparison with the standards JCPDS data (96-901-0052) [22]. This identification allowed

attributing (*hkl*) Miller indices to Bragg peaks, in conformity with the approximate parameters of a compact hexagonal a = b = 9.4148 Å, c = 6.8791 Å, α = β = 90°, γ = 120° [23] which was characterized with P63/m space group (N° 176).

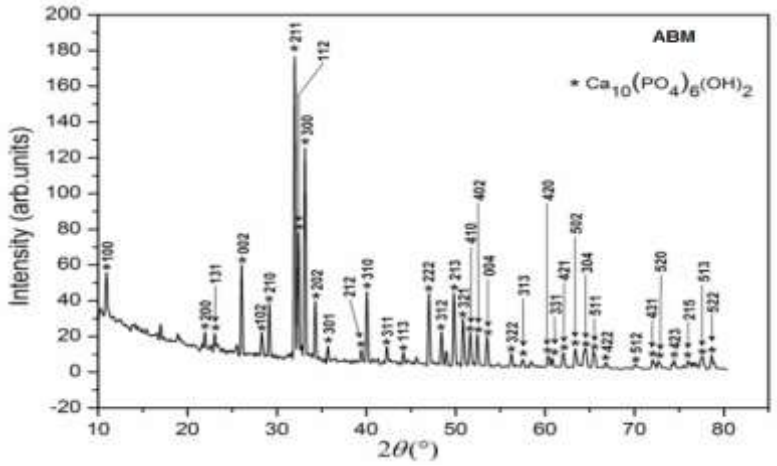


Figure 2. X-Ray diffraction patterns of ABM.

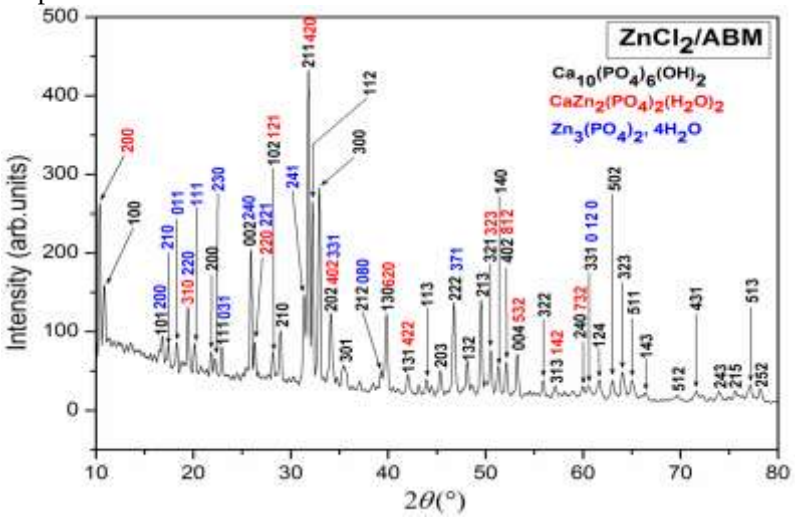


Figure 3. X-Ray diffraction patterns of $ZnCl_2$/ABM.

The XRD pattern of $ZnCl_2$/ABM sample is shown in **Figure** 3. The diffraction rays characteristics of hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ are identified clearly. These rays are consistent with standard JCPDS (01-074-0566). This identification allowed attributing (hkl) Miller indices to Bragg peaks in conformity with the approximate parameters of a compact hexagonal a = b = 9.4240 Å, c = 6.8790 Å, α = β = 90°, γ = 120° [24] which was characterized with P63/m space group (N° 176). In addition, the corresponding rays of calcium zinc phosphate hydrate $CaZn_2(PO_4)_2(H_2O)_2$ (standard JCPDS file 01-071-0889) is comparable with orthorhombic structure a = 17,1490 Å, b = 7,4120 Å, c = 6,6670 Å, α = β = γ = 90° [25], which is characterized by Pbcn space group (N° 60). Furthermore, the corresponding rays of zinc phosphate hydrate $Zn_3(PO_4)_2(H_2O)_4$ (standard JCPDS file 00-037-0465) is comparable with orthorhombic structure a = b = 10,6067 Å, c = 5,0284 Å, α = β = γ = 90° [26], characterized by Pnma space group (N° 62).

3.3.SEM-EDX analysis

The scanning electron analysis (SEM) of ABM (**Figure** 4) shows that its spherical morphology is characterized by small particles whose average size is between 0.2 to 1 µm (image 4a and 4b). The image 4c shows that these particles form agglomerates (size 10 and 50 µm). These shapes showed the presence of a significant percentage of cavities (in all images) which will be interesting for the catalysis.

EDX analysis was performed on a large perspective of ABM sample including small and large grains (4d). The results of this analysis showed that the mean experimental atom fractions (in atomic %) of the Ca and P heavy atoms were about 63% and 35% respectively (ignoring light atoms such as C, H, and O). The ratio of Ca/P is equal to 1.8 higher than that which characterizes the stoichiometric hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (1.67) and other minor phases which contain calcium Ca.

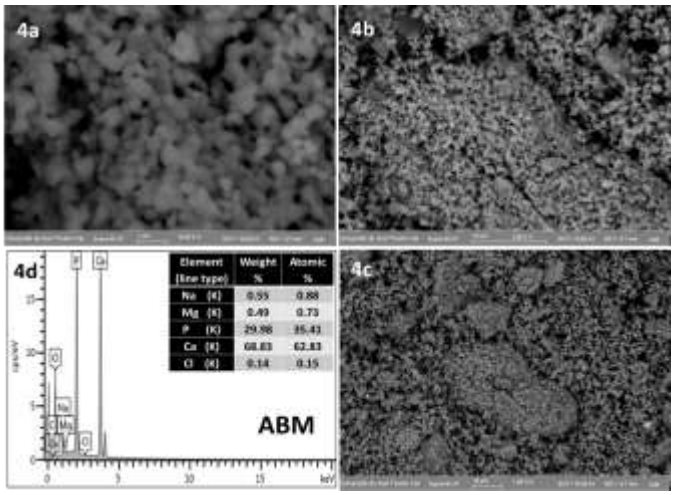


Figure 4. SEM images and EDX of ABM.

While the SEM of $ZnCl_2$/ABM (**Figure** 5) shows that this sample is characterized by small particles with irregular morphology whose average size is between 0.1 to 1 µm (image 5a and 5b). These particles form agglomerates whose sizes are between 5 and 10 µm (5c). These shapes showed the presence of a significant percentage of cavities (in all images) which will be interesting for the catalysis.

$ZnCl_2$/ABM EDX analysis showed a high rate of Ca (30%), P (35%), and Zn (21%) with the existence of a small amount of the others elements such as Na, Cl, K (5d). These analyses confirm those of XRD (presence of $Ca_{10}(PO_4)_6(OH)_2$, $CaZn_2(PO_4)_2(H2O)_2$, and $Zn_3(PO_4)_2(H_2O)_4$).

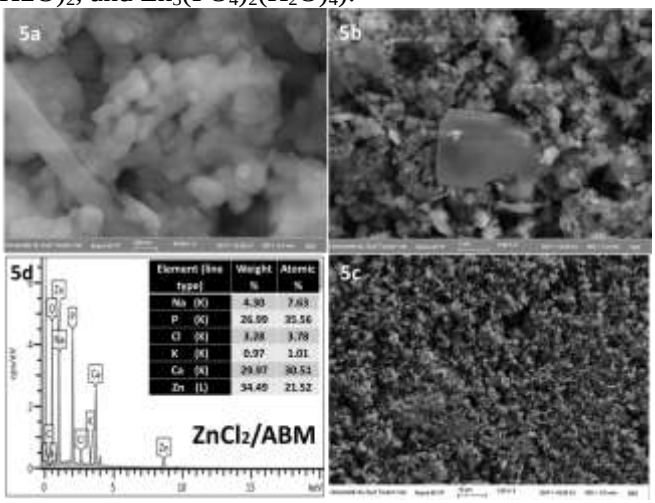


Figure 5. SEM images and EDX of $ZnCl_2$/ABM.

3.4.Application of ABM and $ZnCl_2$/ABM catalysts in the synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones

As expected, the catalytic system is influenced by various reaction parameters, such as the amount of the catalyst employed, the effect of catalyst and solvent system. Therefore, Initial studies were undertaken using benzaldehyde, ethyl acetoacetate and urea as a model reaction.

3.4.1.Effect of catalysts

Various catalysts were employed to evaluate the capability and efficiency of the catalyst (**Table** 1). Initially, the model reaction was performed in the absence of any catalyst and no reaction occurred (entry 1). When the model reaction was examined with $AlCl_3$ or PTS the reaction took a long time period for completion with a lower yield of the product (entries 2 and 3). With $ZnCl_2$ and ZnO again lower yields of the product were obtained after prolonged heating (entries 4 and 5). With other catalysts (such as $NiCl_2$ and L-proline) either reactions were unsuccessful or products were obtained in traces (entries 6 and 7). When we have tested the Animal bone meal (ABM) alone, the reaction was accelerated with moderate yield (entry 8). To enhance the activity of ABM, the later was doped with Lewis acid ($ZnCl_2$) for evaluation of catalytic performance. In effect, the catalyst was found to be highly active in the presence of $ZnCl_2$/ABM (entry 9).

Table 1. Effect of various catalysts for model reactions in water.

Entry	Catalyst	Time	Yield (%)
1	No catalyst	6h	No reaction
2	$AlCl_3$	9h	50
3	PTS	8h	66
4	$ZnCl_2$	6h	39
5	ZnO	6h	50
6	$NiCl_2$	48h	No reaction
7	L-proline	8h	Trace
8	ABM	2h	65
9	$ZnCl_2$/ABM	25 min	92

Reaction of benzaldehyde **1a** with ethylacetoacetate **2** and urea **3** in the presence of 150 mg of catalyst in water

Table 2. Comparison of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihidropyrimidine-2(1H)-one (**4a**) using different catalysts.

Entry	Catalyst	Time	Yield (%)
1	AlKIT-5(10)	3h	92 [27]
2	Fluorapatite	72h	90 [28]
3	$Cu(OTf)_2$	6h	95 [29]
4	Bakers' yeast	24h	84 [30]
5	$LaCl_3{\cdot}7H_2O$	5h	95 [31]
6	NH_4Cl	3h	90 [32]
7	ABM	2h	65
8	$ZnCl_2$/ABM	25min	92
9	ABM/microwave	2min	77
10	$ZnCl_2$/ABM/microwave	1min	96

In order to show the merit of the present work in comparison with some reported protocols, we compared the results of the synthesis of 5-ethoxycarbonyl-4-phenyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one (**Table** 5, product **4a**) in the

presence of lanthanum chloride, ammonium chloride, fluorapatite, AlKIT-5(10), $Cu(OTf)_2$, Bakers' yeast and $ZnCl_2$/ABM with respect to the reaction times (**Table** 2). The yield of product in the presence of $ZnCl_2$/ABM is comparable with these catalysts. However, other catalysts in **Table** 2 required longer reaction times than $ZnCl_2$/ABM.

3.4.2.Loading of the catalyst

The influence of ratio weight of $ZnCl_2$/ABM has been studied using 150 mg of catalyst, we tried to determine the best $ZnCl_2$/ABM ratio (r=mo/m1). We carried out the synthesis of **4a** with 0.15g of the catalyst using different $ZnCl_2$/ABM ratios (r=1/6, 1/8, 1/10, 1/15, and ABM alone). The yields obtained successively after 25min of reaction (91, 92, 70, 45, and 18%), show that the weight ratio 1/8 w/w is the optimal composition.

Furthermore, the effect of the catalyst concentration on the synthesis of **4a** was also investigated over different amounts of ABM and $ZnCl_2$/ABM at reflux temperature for 2h and 25min respectively; the results are presented in **Table** 3.

Table 3. Effect of the weight of ABM and $ZnCl_2$/ABM on the synthesis of product **4a**.

Weight of catalyst (mg)	Yield (%)	
	ABM (2h)	$ZnCl_2$/ABM (25 min)
50	25	47
100	52	75
150	65	92
200	64	95

It has been found that the amount of the catalyst significantly alters the outcome of the final product. The yield of the final product increases, from 25 to 65% in the presence of ABM alone and from 47 to 95% in the presence of $ZnCl_2$/ABM, with increasing the weight of the catalyst from 50 to 200 mg, respectively. This could be mainly due to the availability of a huge number of surface acidic sites in the reactant mixture as the weight of the catalyst is increased. This result indicates the positive effect of the catalyst in this transformation. We have chosen 150 mg of the catalyst for further study. In a blank reaction in the presence of 18mg (quantity present in 150 mg of $ZnCl_2$/ABM) of $ZnCl_2$ alone without ABM, the **4a** was obtained with low yield (10%, 1h).

3.4.3.Effect of solvents

Table 4. Effect of solvent on the synthesis of product **4a** catalyzed by $ZnCl_2$/ABM.

Entry	Solvent	Reaction time	Yield (%)
1	Toluene	2h	10
2	THF	2h	25
3	Chloroform	2h	60
4	Acetonitrile	2h	75
5	Methanol	2h	80
6	Ethanol	2h	93
7	Water	25min	92

Thus, this procedure offers easy access to substituted dihydropyrimidinones with a variety of substitution patterns. In the presence of $ZnCl_2$/ABM, various solvents were tested. Thus, after 25min the yields of product **4a** obtained were 92%, 93%, 80%, 75%, and 60% in the presence of water, ethanol, methanol, acetonitrile, and chloroform respectively. In the cases of toluene and tetrahydrofuran only the mixture of raw material and the desert product was recovered. It has been shown that the water gave the highest yield in a short time for the desired product (entry 7).

3.4.4.Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones with the others aldehydes

The use of microwave is very helpful to improve the yields and to decrease the reaction time in comparison to classical thermal reflux (**Table** 5). It was noticed that there was no reaction under microwave without a catalyst. This shows a certain synergy between the catalyst and the microwave. It is thus completely reasonable to think that the effect of the temperature is a determining factor to promote this condensation. The optimized reaction conditions were extended to the condensation of other aldehydes with *β*-ketoester and urea or thiourea at reflux of water. Aromatic aldehydes bearing both electron-deficient and electron-rich substituents as well as aliphatic aldehydes afforded the desired 3,4-dihydropyrimidin-2(1H)-ones/thiones (**4a-r**) in excellent yields (**Table** 5).

Table 5. Synthesis of the 3,4-dihydropyrimidin-2(1H)-ones and 2-thiones derivatives using ABM and $ZnCl_2$/ABM in water.

Product[a]	R	X	Yield[b] (%)/Time [Water /Δ]		Yield[b] (%)/Time [Micowave]		Mp[c] (°C) Found (Reported) [Ref]
			ABM	$ZnCl_2$/ABM	ABM	$ZnCl_2$/ABM	
4a	C_6H_5	O	65/2h	92/25min	77/2min	96/1min	200-203 (200-202) [29]
4b	4-$MeOC_6H_4$	O	50/2.5h	80/30min	78/3min	93/1min	199-200 (200-201) [29]
4c	4-$O_2NC_6H_4$	O	45/2.5h	90/30min	78/3min	94/1min	206-208 (207-209) [29]
4d	4-HOC_6H_4	O	51/3h	93/30min	79/3min	95/1min	230-233 (235-236) [30]
4e	4-MeC_6H_4	O	45/3h	87/30min	80/3min	86/1min	202-204 (204-205) [30]
4f	4-ClC_6H_4	O	52/3h	92/30min	82/3min	90/1min	210-212 (212-213) [29]
4g	3-$MeOC_6H_4$	O	50/2.5h	94/30min	76/3min	90/1min	205-207 (205-206) [30]
4h	3-$O_2NC_6H_4$	O	50/2h	90/25min	77/3min	90/1min	227-230 (230-231) [30]
4i	2-Furyl	O	54/3h	80/25min	75/3min	86/1min	204-206 (203-205) [29]
4j	C_6H_5	S	45/3.5h	91/35min	80/5min	92/3min	205-206 (205-207) [33]
4k	4-$MeOC_6H_4$	S	42/3.5h	88/40min	79/5min	88/3min	143-146 (146-148) [33]
4l	4-$O_2NC_6H_4$	S	46/3.5h	83/40min	76/5min	87/3min	208-211 (207-210) [27]
4m	4-HOC_6H_4	S	51/3.5h	88/40min	75/5min	90/3min	195-196 (193-194) [30]
4n	4-MeC_6H_4	S	52/3.5h	86/40min	80/5min	89/3min	189-191 (190-192) [33]
4o	4-ClC_6H_4	S	50/3.5h	94/40min	80/5min	90/3min	193-194 (193-195) [33]
4p	3-$MeOC_6H_4$	S	45/3.5h	86/40min	76/5min	88/3min	148-151 (150-151) [30]
4q	3-$O_2NC_6H_4$	S	46/3.5h	82/40min	77/5min	80/3min	204-207 (206-207) [27]

4r	2-Furyl	S	48/3.5h	80/40min	74/5min	82/3min	182-183 (183-185) [27]

[a] Products were characterized by MS, IR, 1H NMR and 13C NMR spectroscopies. [b] Isolated yield. [c] Melting points are uncorrected.

The structures of the products were determined by IR, 1H NMR and 13C NMR spectroscopy, mass, CHN analysis and also by comparison with authentic samples.

3.4.5. Reusability of the catalyst

We have plotted the recycling efficiency of the catalyst for these six consecutive catalytic cycles for the condensation. It should be noted that even in the sixth round, reuse of the catalyst recovered can produce the corresponding product **4a** in fairly good yield.

4. Conclusion

In conclusion, we have developed a highly efficient method for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones from aromatic aldehydes, ethyl acetoacetate, and urea or thiourea at conventional heating in water or under microwave irradiation. This method has the ability to tolerate a wide variety of substitutions in all three components which is lacking in existing reported procedures.

Short reaction time, high yields, clean process, simple methodology, easy workup, and green sustainable conditions are the key features involved in the present protocol. These features will enable this protocol to find widespread applications in the field of organic synthesis.

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