J. Mater. Environ. Sci. 7 (12) (2016) 4692-4696
ISSN : 2028-2508
CODEN: JMESCN

A novel green synthesis of pyrimidinone derivatives via Biginelli reaction using Animal Bone Meal as catalyst

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Received 10 Mar2016, Revised 19 May 2016, Accepted 01 Jun 2016
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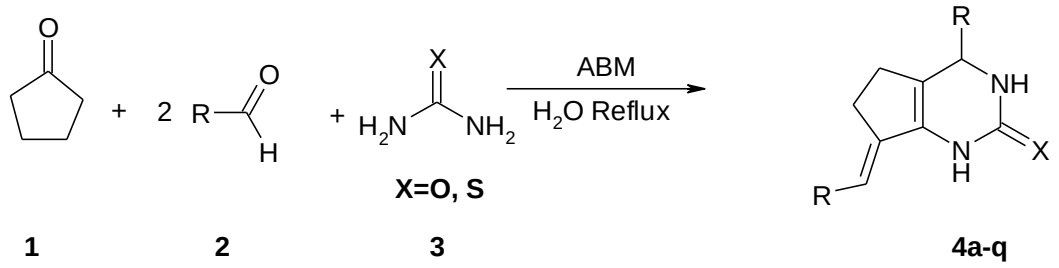
Abstract
A simple, efficient and eco-friendly protocol has been developed for the condensation of various aromatic aldehydes, cyclopentanone and urea of thiourea using animal bone meal as a heterogeneous catalyst. The remarkable catalytic activity and reusability of animal bone meal widens its applicability in Biginelli reaction with good to excellent yields for synthesis of pyrimidinone derivatives. Green organic synthesis is needed to face current environmental pollution. Many synthetic approaches have been developed to produce substituted pyrimidinone. This original method generated good yields and therefore presents the opportunity for the development of clean and environmentally-friendly catalytic processes. The remarkable features of this new protocol are high conversion, short reaction times, cleaner reaction profiles, straightforward procedure, and a reduction in catalyst toxicity. This method has several advantages such as high yields of 66–94 %, short reaction times of 15–60 min, easy purification processes, and methodological simplicity. This method provides new opportunities for the rapid screening of a wide range of compounds, either for the development of new drugs or total synthesis of natural products.

Keywords: Heterocyclic compounds, Animal Bone Meal, Biginelli reaction, Heterogeneous catalysis.

Introduction
Heterocyclic compounds 3,4-dihydropyrimidin-2-(1*H*)-one/-thione derivatives also named Bigenilli adducts, have attracted much attention as important structural motifs in medicinal chemistry because of their significant therapeutic and biological activities, such as antihypertensive, potassium channel antagonist, antiepileptic, antimalarial, antimicrobial, antitumor, antibacterial, anticancer and anti-inflammatory properties [1-3].
During the last years numerous catalytics have been developed to improve the reaction yield, lower the reaction time and/or broaden the scope of the Biginelli reaction. Although numerous methods for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/-thiones are known, a few bronsted-lowry or lewis acids are used as catalyst for the Biginelli reaction [4-10], the use of ionic liquide [11,12], microwave irradiation [13], solid phase reagent [14], baker's yeast [15], polymer supported catalyst [16], zeolite [17], surfactant [18], polyethylene glycol [19,20], organocatalyst [21-24], hydrochloric acid *β*-cyclodextrin [25], sulfonated *β*-cyclodextrin [26], and *β*-cyclodextrin [27].
However, some of these procedures require expensive reagents, strongly acidic conditions, long reaction times, high temperatures, or stoichiometric amounts of catalysts, or they result in environmental pollution and give unsatisfactory yields. Therefore, there is a need for a new catalyst that is readily available or easy to prepare, inexpensive, and recoverable hence reusable and environmentally friendly. Moreover, the workup procedure should be simple. In this regard, animal bone meal and other natural supports have many applications [28-34].
In continuation of our studies, we would like to report for the first time a simple, facile, highly efficient and eco-friendly methodology for the synthesis of 3,4-dihydropyrimidinones for excellent yields by the reaction of

cyclopentanone **1**, aromatic aldehyde **2** and urea or thiourea **3** compounds using Animal Bone Meal (ABM) as a solid heterogeneous catalyst (Scheme 1).



Scheme 1: Synthesis of pyrimidinone derivatives *via* Biginelli.

2. Materials and methods

Animal Bones were collected from nearby butcher shops. All the attached meat and fat were removed and cleaned from the bones. The bones were then washed several times with tap water and left in 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 a range comprising of 45-200 µm and then calcined for 2 h at 600°C. The residue was washed with water and was used after drying for 24h at 80°C. The residue was washed with water and was 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 4 h. The calcined material was ground to a fine powder in an electrical grinder. This was then passed through a mesh screen to get particles <500 µm size. This was then stored in an air tight container for further use.

Elemental analysis of ABM showed a high yield of Ca (49.62%) and P (42.36%) with a (Ca/P) ratio equal to 1.17. Small amounts of Si (3.88%), Mg (1.32%), Na (0.77%), Al (0.35%), Fe (0.24%), Cl (0.24%), S (0.11%), K (0.07%), Sr (0.03%), Cu (0.03%) and Zn (0.02%) were found. FTIR spectra were carried out by the encapsulation of 0.5 mg of finely powder with 400 mg of KBr to get translucent disc (except 'disk' in computers). Carbonate is the most abundant substitution in bone mineral and according to its crystal position, carbonate apatite is designated as type A (OH^-) or type B (PO_4^{3-}), the latter being the most frequent in bones. It is recognized that hydroxyapatite is derived from a natural bone [35,36]. FTIR spectrum of ABM given in Figure 1 shows the characteristic bands of hydroxyapatite 571, 603, 962 (shoulder), 1047 and 1091 (shoulder) cm^{-1} due to phosphate vibrations and collagen (C=O) stretching vibrations at 1635 cm^{-1}, N-H in plane bending at 1458 cm^{-1}, C-H and N-H stretching modes at 3000-3571 cm^{-1} region) [37-39]. Additionally, the typical bands of carbonate substituting for phosphate site (type B) in the apatite lattice are also observed: band at 874 cm^{-1} and double bands 1385 and 1445 cm^{-1} [40-41].

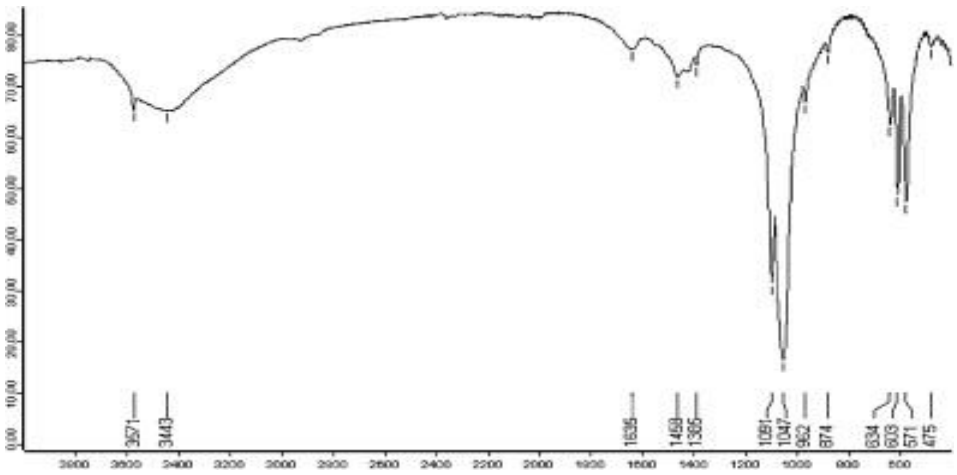


Figure 1: IR spectra of ABM.

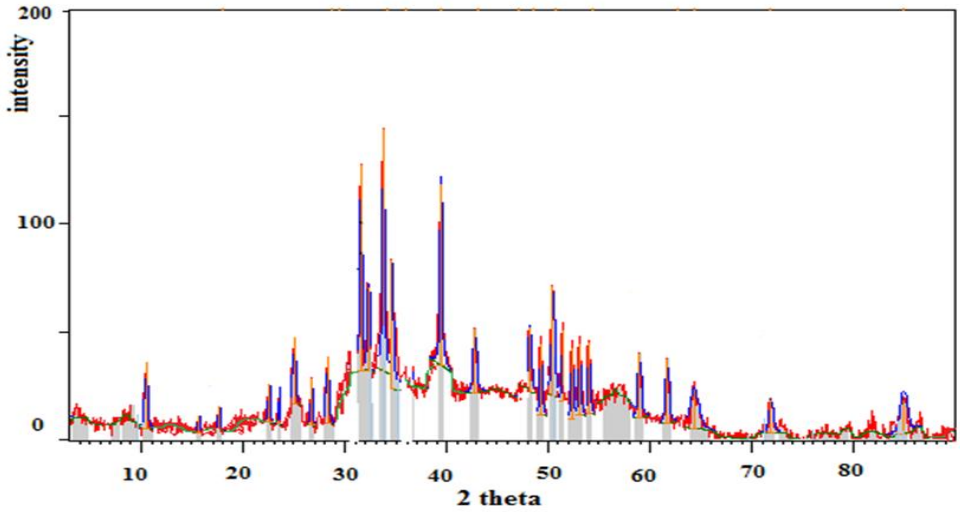


Figure 2: X-ray diffraction of ABM.

Figure 2 depicts the XRD spectrum of catalyst ABM. The diffractogram of ABM shows only the characteristic pattern of hydroxyapatite. These results confirm that the amorphous organic component was removed after calcinations as found in literature. For 2θ between 25° and 45°, the main lattice reflections originate peaks at 25°, 28.1°, 32.8°, 33.7°, 34.5° and 39.7° being respectively assigned to the (0 0 2), (1 0 2), (2 1 0), (2 1 1), (1 1 2) and (3 0 0) Miller plans of hydroxyapatite [42].

Typical procedure for the synthesis of substituted cyanopyridine 5d: A mixture of cyclopentanone **1** (4 mmol) and aldehyde **2** (8 mmol), urea or thiourea **3** (5 mmol) and ABM (0,1 g) was heated in the oil bath at 100°C for an appropriate time under solvent water 10 mL conditions. The progress of the reaction was monitored by TLC. The reaction mixture was cooled to room temperature and 5 mL of ethanol was added and filtered to separate the catalyst then it cooled therefore be recycled by simple filtration. The crude product was recrystallized from the ethanol to give pure compounds **4**.
The analytical data were identical to those reported in the literature [43].

3. Results and discussion

3.1. Procedure for lead determination method

To generalize the reaction we carried out the reactions of various aromatic aldehydes **2** with cyclopentanone **1** and urea or thiourea **3** in presence of catalytic amount of $ZnCl_2$/ABM or $CuCl_2$/ABM under conventional thermal conditions these results are presented in Table 1.
Under similar conditions but in the presence of $ZnCl_2$ or $CuCl_2$ alone, only the starting material was recovered. In each assay, $ZnCl_2$/ABM and $CuCl_2$/ABM gave higher yields than using ABM alone, both results highlighting the role of our doped ABM catalysts.
Under classical heating conditions, full conversions were obtained after 15-60 min and the attempted products were isolated in fairly good yields. As shown in Table 1, all aromatic aldehyde reactions carried out with bearing electron-donating groups and electron-withdrawing groups with cyclopentanone **1** and urea or thiourea **3** in water and in the presence of doped ABM, proceeded smoothly to afford the corresponding substituted 3,4-dihydropyridinones **4a-q** in good yields (Table 1, Entries 1-5).

$ZnCl_2$/ABM could be quantitatively recovered by simple filtration and regenerated by calcinations at 400°C for a few hours and were reused in future reactions. Investigations were performed on synthesis of product **4a** (Table 2). Whatever the assay, completion of the reaction was always achieved in 30 min but a decrease in yield was observed at the fourth round. Catalyst was fully recovered after the first reaction, afterwards a relative stability was observed till the fifth reaction but the amount of the promoter decreased strongly after.

Table 1: Synthesis of dihydropyrimidin-2(1*H*)-ones or thiones in water catalyzed by ABM.

Entry	R	X	Products	Yields[a] (%) (Time, min)		
				ABM	$ZnCl_2$/ABM	$CuCl_2$/ABM
1	C_6H_5	O	**4a**	72% (90)	90% (30)	94% (30)
2	4-$CH_3OC_6H_4$	O	**4b**	62% (90)	78% (20)	82% (20)
3	3-$CH_3OC_6H_4$	O	**4c**	42% (90)	67% (20)	66% (20)
4	2-$CH_3OC_6H_4$	O	**4d**	52% (90)	75% (20)	80% (20)
5	4-$NO_2C_6H_4$	O	**4[e]**	56% (90)	88% (20)	91% (20)
6	4-$CH_3C_6H_4$	O	**4f**	61% (90)	83% (20)	85% (20)
7	4-FC_6H_4	O	**4g**	70% (90)	86% (15)	94% (15)
8	4-ClC_6H_6	O	**4h**	65% (90)	87% (20)	83% (20)
9	3-ClC_6H_6	O	**4i**	38% (90)	56% (20)	66% (20)
10	2-ClC_6H_6	O	**4j**	54% (90)	84% (20)	83% (20)
11	4-CNC_6H_4	O	**4k**	75% (90)	91% (20)	88% (20)
12	C_6H_5	S	**4l**	54% (120)	80% (60)	84% (60)
13	4-$CH_3OC_6H_4$	S	**4m**	48% (120)	68% (70)	66% (70)
14	4-$CH_3C_6H_4$	S	**4n**	34% (120)	63% (60)	69% (60)
15	4-FC_6H_4	S	**4o**	68% (120)	84% (60)	87% (60)
16	4-$NO_2C_6H_4$	S	**4p**	58% (120)	78% (60)	81% (60)
17	4-ClC_6H_6	S	**4q**	71% (120)	82% (60)	81% (60)

[a] Reaction conditions : Aldehyde (8.0 mmol), cyclopentanone (4.0 mmol), and urea or thiourea (5.0 mmol) in water (10 mL) was added to doped ABM (100 mg). [b] Yields are indicated in pure isolated products.

Table 2: Studies on the reuse of $ZnCl_2$/ABM.[a]

Round	Yield in **4a** (%)[b]	$ZnCl_2$/ABM recovered
1	90	98 %
2	90	95 %
3	88	93 %
4	87	92 %
5	85	90 %
6	78	84 %

[a] Each reaction was carried out as described in the references.
[b] Yields are indicated in pure isolated products.

Conclusion

We have developed a very simple and new procedure for the synthetic of dihydropyrimidin-2(1*H*)ones and thiones by three component reaction of cylopentanone, aromatic aldehyde and urea or thiourea under reflux conditions using Animal Bone Meal as catalyst and water as solvent. This method offers several advantages such as inexpensive catalyst, environmental friendly procedure, short reaction time, excellent yield in addition to the work-up and the isolation, which are easy to make this method attractive environmentally as synthetic tool for Biginelli condensation.

Acknowledgements-The authors thank the College of Pharmacy, Sattam Bin Abdulaziz University and Université Hassan II Mohammedia-Casablanca, Mohammedia, Morocco.

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