Barium Hydroxyapatite $Ba_{10}(PO_4)_6(OH)_2$ and Barium Nitrate: New Recyclable Catalysts for the Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones

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Summary: In this paper, we report an efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones (DHPMs) from the Biginelli condensation reaction of ethyl acetoacetate, aromatic aldehydes and urea or thiourea catalysed by barium (II) nitrate and barium hydroxyapatite $Ba_{10}(PO_4)_6(OH)_2$ (BaHAp). These new catalysts exhibited an important reactivity and proved reusable

Keywords: Dihydropyrimidinones, Multi-component reactions (MCRs), Biginelli reaction, Barium hydroxyapatite (BaHAp), Recyclable catalyst.

Introduction

Many heterocyclic compounds exhibit diverse pharmacological activities. For example, some dihydropyrimidinones (DHPMs) and their derivatives were reported to be used in calcium channel blockers, alpha-1a-adrenoceptor-selective antagonists, antihypertensive agents, neurpeptide Y(NPY) antagonists[1,2] and inhibitors of the Kinesin motor protein and the HIV gp-120-CD4[3,4]. These pyrimidines display a wide range of biological activities namely antibacterial, antitumor, antiviral and anti-inflamatory actions [5-7]. Consequently, the synthesis of these compounds is gaining more and more importance.

Multi-component reactions (MCRs) have generated great scientific interest as chemical reactions in which three or more substances react in a single, simple and efficient synthetic step to synthesize products in high yields with high atomic efficiency. [8-14]

The Biginelli reaction [15],which uses a three-component reaction one-pot condensation of an aromatic aldehyde, acetoacetate and urea under strongly acidic conditions to afford 3,4-dihydropyrimidin-2-(1*H*)-ones (DHPMs). However, this original procedure suffers low yields and long times especially in the case of some substituted aromatic and aliphatic aldehydes. To overcome those drawbacks, a wide range of novel protocols for the synthesis of dihydropyrimidinones (DHPMs) has been developed in the last two decades, notably featuring the usage of different types catalysts : Cp_2TiCl_2 [16], ($H_3PW_{12}O_{40}$, PTA) supported on ZIF-9(NH_2) [17], zirconium (IV)-salophen perfluorooctanesulfonate [18], ionic liquids [19], ZnO@SBA-15 [20], Polyethylene Glycol Based Dicationic Acidic Ionic Liquid [PEG-DAIL][Cl] [21], Boehmite nanoparticle [22], SiO_2-$CuCl_2$ [23], trysin [24], nanosilica-supported Tin(II) chloride [25], nanomagnetic-supported sulfonic acid [26], microwave irradiation [27], and many others. Nevertheless, in spite of their potential utility, many of these methods suffer drawbacks such as the use of expensive reagents, stoichiometric amounts of catalysts, volatile strong acidic conditions, and prolonged reaction times. Therefore, there is scope for further modifications towards mild reaction conditions, improved yields, and an increased variation of the substituents.

To carry on our studies on the development of methodology for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones **4** via the condensation reaction of ethyl acetoacetate **1**, various aromatic aldehydes **2** and urea or thiourea **3**, we have utilized barium hydroxyapatite $Ba_{10}(PO_4)_6(OH)_2$ (BaHAp) [28, 29] and barium(II) nitrate $Ba(NO_3)_2$ as an efficient catalyst for the first time (Fig 1).

Experimental

The crystalline structure of the catalyst was determined by powder X-ray diffraction (XRD) using an X'Pert Pro Panalytical X-Pert diffractometer using Cu-K□ radiation (λ=1.5418 Å). The 2□ range was between 20° to 70° with a □2□ step size of 0.0167°. The obtained experimental models were compared to compiled standards (JCPDS cards) using the X'Pert High-Score Plus software.

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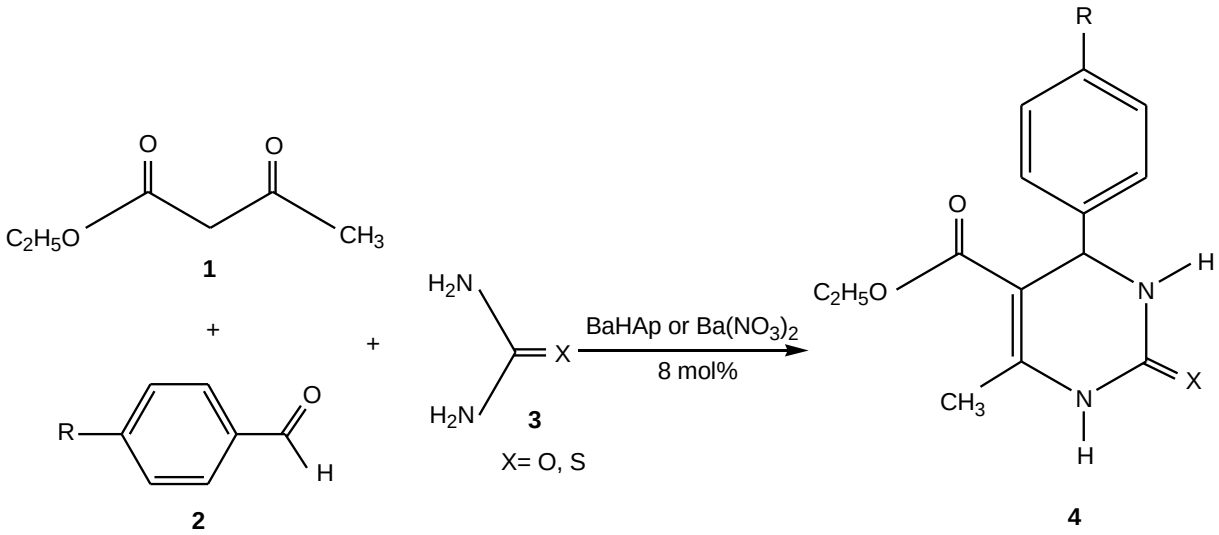

Fig. 1: Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones **4** via Biginelli reaction.

The IR-ATR spectrum was obtained using a Spectrum Two 104462 type IR spectrophotometer in the 4000-400 cm^{-1} range at room temperature. This spectrophotometer is equipped with a diamond attenuated total reflectance (ATR) configuration.

Synthesis of BaHAp

Under a nitrogen atmosphere, we have added a solution of Ba $(NO_3)_2$ (52.26 g, 0.2 M, 150 mL) dropwise to a solution of $(NH4)_2HPO_4$ (26.4 g, 0. 2 M, 250 mL); we have kept boiling, while stirring. To adjust the pH of the mixture to 10, we have added regular NH_4OH. The precipitate obtained was left for 1 h in contact with the reaction mixture. Finally, this precipitate was filtered and washed with hot distilled water several times. The final product was dried overnight at 120°C.

Recycling Protocol of BaHAp

BaHAp has been recycled in two steps: in the first step we have washed and filtered the apatitic powder with hot ethanol then we have dried at 120°C overnight. In the second step, the dried BaHAp has been was grounded in agate mortar then washed several times with hot distilled water, filtrated and dried again at 120°C for 12 h.

General Procedure for the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones

A flask maintained at 90° C and with stirring, (7.5 g , 30 mmol) of ethyl acetoacetate, 10 mmol of aromatic aldehyde, 15 mmol of urea or thiourea and the catalyst (verifying 8% mol) was introduced. Once the reaction was complete (monitored by thin layer chromatography), the catalyst was recovered by filtration. Then the liquid was poured over crushed ice and stirred for 10 min. The solid obtained was filtered under vacuum and then washed with cold water followed by purification by recrystallization from hot ethanol.

Results and Discussion

Identification of BaHAp

X-ray data

The XRD diffractograms of BaHAp shows the presence of only phase indicating a good crystallinity (Fig **2**).

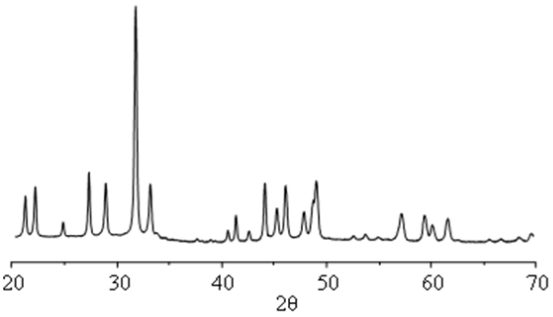

Fig. 2: X-ray spectra of BaHAp.

The XRD pattern of BaHAp is presented by Fig **3**. All the peaks are identical to the diffractograms of a hexagonal system (P63/m) corresponding to hydroxyapatite structure (JCPDS-01-084-1998).

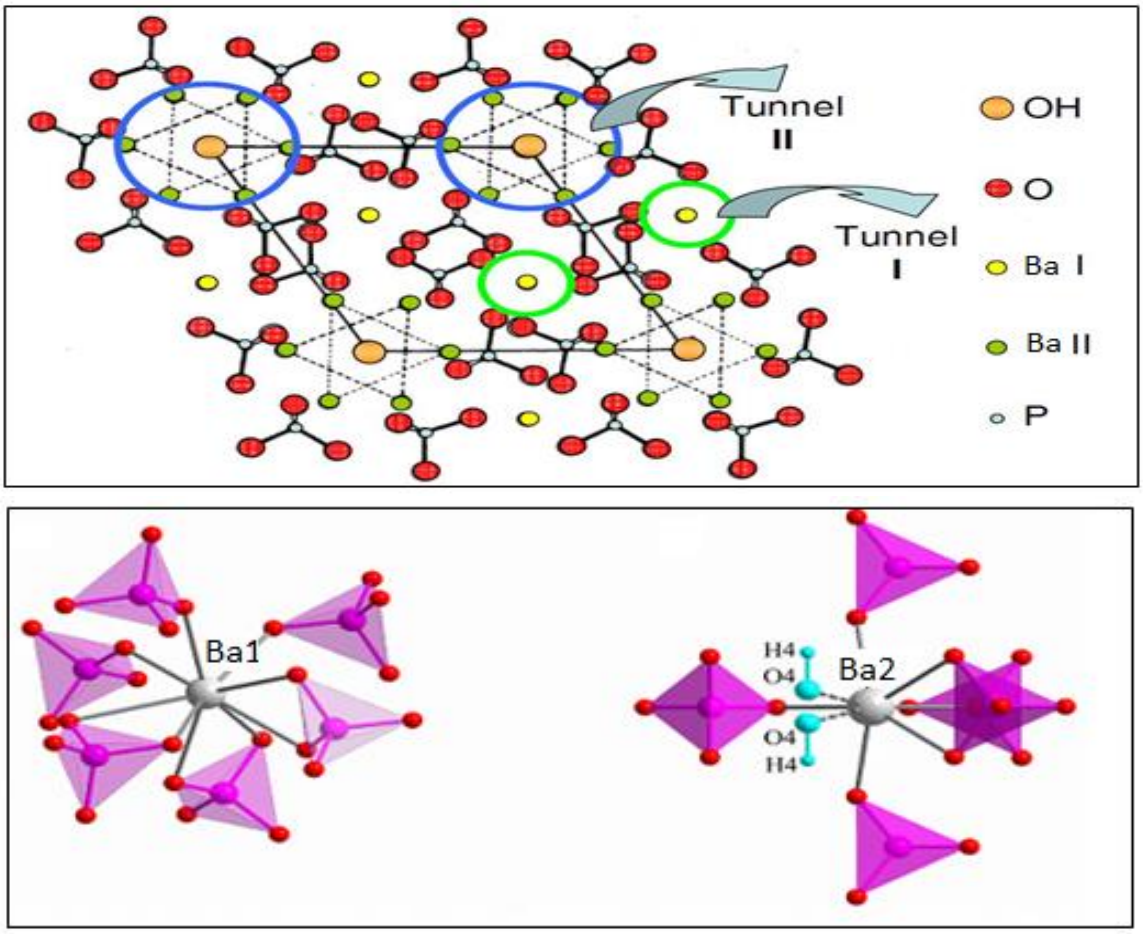

Fig. 3: The XRD pattern of BaHAp.

Infra-Red analysis

The IR-ATR spectrum of BaHAp is given in Fig **4**. The analysis of this spectrum shows the existence of a small quantity of carbonate located on the surface of BaHAp. Adsorption bands attributed to the PO_4^{3-} groups are located at 962.5 cm^{-1}, 471.7 cm^{-1}, 1089.2-1026 cm^{-1} and 661.4-600.7 cm^{-1} indicating the presence of the apatitic structure. The bands located at 630 cm^{-1} and 3570 cm^{-1} are attributed to hydroxyl groups.

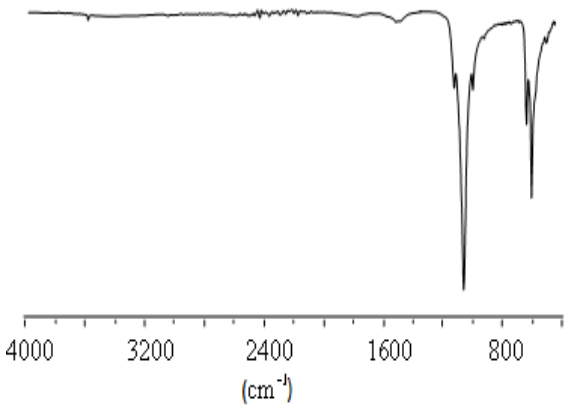

Fig. 4: IR spectra of BaHAp.

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

Initially, we have studied the Biginelli reaction of benzaldehyde with ethyl acetoacetate and urea using barium (II) nitrate under different quantities. The results are presented in Table **1**.

The best yield of the reaction was obtained with 8 mol % barium (II) nitrate (entry 6). We used excess ethyl acetoacetate to keep the mixture still in a liquid phase.

Encouraged by these results, we examined a number of aromatic aldehydes with ethyl acetoacetate and urea to illustrate the condensation under the optimized conditions. The results are summarized in Table **2**.

Table-1: Effect of catalyst $Ba(NO_3)_2$ under different quantities for the condensation of benzaldehyde, ethyl acetoacetate and urea [a].

Entry	Cat. (mol %)	Yield (%) [b]
1	1	65
2	2	72
3	3	78
4	4	82
5	5	86
6	8	95

[a]*Condensation conditions: benzaldehyde (10 mmoL), ethyl acetoacetate (30 mmoL), urea(15 mmoL) and catalyst $Ba(NO_3)_2$ at 90°C for 2h;* [b]*Isolated yield.*

Table-2: $Ba(NO_3)_2$ catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones [a].

Entry	R	Yield [b] (%)	Mp (°C) [c] found	Mp (°C)[c] reported
4a	H	95	202-204	207-208 [13]
4b	OCH_3	96	201-202	203-205 [9]
4c	CH_3	88	214-216	216-217 [13]
4d	NO_2	35	208-209	210-211 [13]
4e	$N(CH_3)_2$	92	256-258	256-257 [13]

[a]*Reaction conditions: aromatic aldehyde (10 mmoL), ethyl acetoacetate (30 mmoL), urea (15 mmoL) and catalyst $Ba(NO_3)_2$ (0,8 mmoL) at 90°C for 2h (X=O);* [b]*Isolated yield;* [c]*Melting points are uncorrected.*

These results highlight that aromatic aldehydes carrying either neutral or electron donating substituents have all very well reacted to give the desired products with high purity and excellent yields using $Ba(NO_3)_2$ as a catalyst.

Under typical experimental conditions, we examined the reactivity of recycled $Ba(NO_3)_2$. The desired products are obtained with yields of 95%, 93% and 89% after 1 to 3 trials, respectively (entry 4a).

On the other hand, when we compared these results to those obtained during the use of barium hydroxyapatite $Ba_{10}(PO_4)_6(OH)_2$ (BaHAp) as a catalyst, we notice that the catalyst $Ba(NO_3)_2$ is more active than the catalyst BaHAp in the synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions (entry 4a-e). (Fig **5**)

The synthesis of the product **4d**, catalyzed by BaHAp has been repeated in many solvents such as ethanol, methanol and toluene but we always find a yield of 0%.

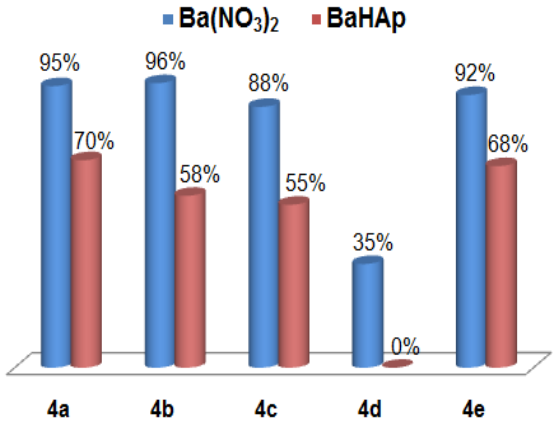

Fig. 5: Comparison of the catalytic activity of $Ba(NO_3)_2$ and BaHAp in the synthesis of products 4a-e under solvent-free conditions at 90°C for 2 h.

The low yield obtained for the product **4d** can be correlated with the attractive electronic effect of NO_2 substituent.

This effect reduces the activity of the 4-nitrobenzaldehyde and therefore disadvantages its condensation reaction with the ethyl acetoacetate and urea.

Under typical experimental conditions, we examined the reactivity of recycled BaHAp. The desired products are obtained with yields of 70%, 60% and 45% after 1 to 3 trials, respectively (entry 4a).

In another section, we have synthesised the 3,4-dihydropyrimidin-2-(1*H*)-thiones **4f-h** by a condensation reaction between the ethyl acetoacetate, thiourea and aromatic aldehydes in the presence of $Ba(NO_3)_2$ and BaHAp as catalysts under solvent-free conditions. The results of these syntheses are presented in the following Table **3**.

Table-3: Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-thiones 4f-h [a].

Entry	R	Yield [b] (%)	Mp (°C) [c]
4f	H	$Ba(NO_3)_2$: 80 BaHAp : 60	Found : 205-207 Reported: 208-209[13]
4g	OCH_3	$Ba(NO_3)_2$: 78 BaHAp : 53	Found : 135-137 Reported: 138-140[15]
4h	CH_3	$Ba(NO_3)_2$: 75 BaHAp : 50	Found : 190-191 Reported: 192-193[13]

[a]*Reaction conditions: aromatic aldehyde (10 mmoL), ethyl acetoacetate (30 mmoL), thiourea (15 mmoL) and catalyst (0,8 mmoL) at 90°C for 3 h (X=S);* [b]*Isolated yield;* [c]*Melting points are uncorrected.*

For our synthesis, we proposed the following reaction mechanism: the acylimine intermediate **5**, obtained by reaction between the aromatic aldehyde **2** and urea (or thiourea) **3**, gave by coordination with barium the intermediate active **6**. Then, the latter is added to the barium enolate **7** derived from ethyl acetoacetate. Finally, intermediate **8** resulting from this addition undergoes cyclization followed by dehydration to produce 3,4-dihydropyrimidin-2-(1H)-ones/thiones **4** (Fig **5**)

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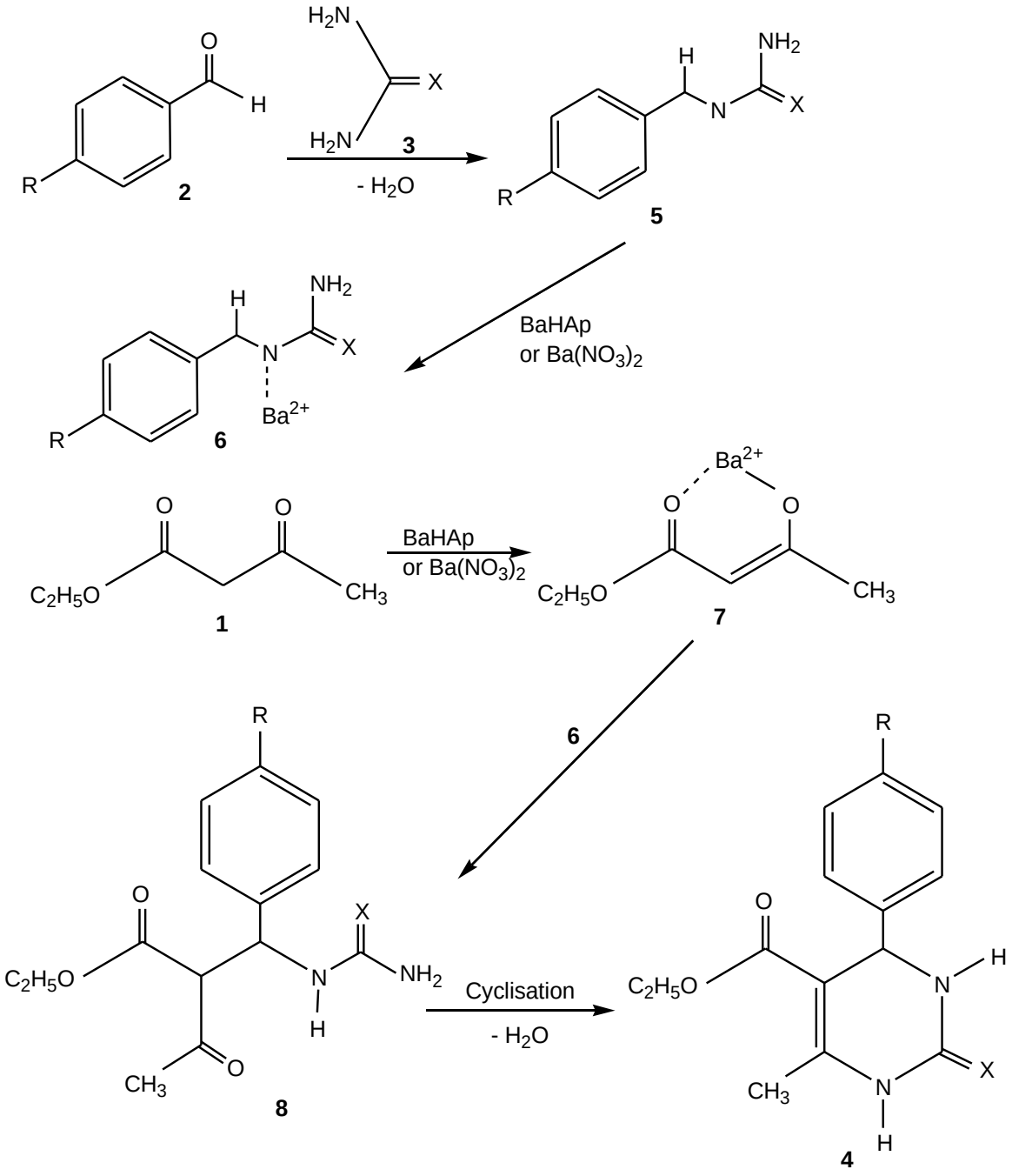

Fig. 5: Mechanism reaction.

Table-4: Comparison of the reactivity of $Ba_{10}(PO_4)_6(OH)_2$ (BaHAp) and $Ba(NO_3)_2$ with some other catalysts used for the synthesis of ethyl-6-methyl-4-(phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

Catalyst	Catalyst amount	Reaction cond.	Yield (%)	Time (h)	Ref.
Cp_2TiCl_2	10 mol%	Ethanol, 70°C	93	9	16
$(H_3PW_{12}O_{40}$,PTA)@ZIF-9(NH_2)	30 mg	S. F., 110°C	86	0.5	17
zirconium(IV)-salophen perfluorooctanesulfonate	5 mol%	S. F., 90°C	96	0.5	18
ZnO@SBA-15	0.02 g	Ethanol, 65°C	96	2.5	20
[PEG-DAIL][Cl]	0.3 mmol	Toluene, 80°C	86	5	21
p-SA/calixarene	0.5 mol%	Reflux in Ethanol	81	8	30
$Ba_{10}(PO_4)_6(OH)_2$	0.8 mmol	S. F., 90°C	70	2	
$Ba(NO_3)_2$	0.8 mmol	S. F., 90°C	95	2	

S. F refers to Solvent free

Comparison of the reactivity of $Ba_{10}(PO_4)_6(OH)_2$ (BaHAp) and $Ba(NO_3)_2$ with some other catalysts

The present work has been compared to some later works (Table 4). Condensation of benzaldehyde, acetoacetate and urea synthesized ethyl-6-methyl-4-(phenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate. We chose this reaction as a model to compare the yield, the reaction time and the mole % of catalyst used. Although some works found slightly higher yields, they still required a higher molar percentage of catalyst and longer reaction times. This protocol used a small amount of recyclable catalyst under solventless conditions and required a relatively short reaction time.

Conclusion

In conclusion, we have described a simple method for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones/thiones via a new and reusable $Ba_{10}(PO_4)_6(OH)_2$ and $Ba(NO_3)_2$ catalysts by using the multicomponent Biginelli reaction. We noticed that $Ba(NO_3)_2$ is more active than $Ba_{10}(PO_4)_6(OH)_2$. Our method offers several benefits including good yields, a short reaction time, an environmentally friendly procedure, and an easy isolation, making it a useful process for the synthesis of DHPMs.

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