Calcium, Barium and Strontium apatites: A new generation of catalysts in the Biginelli reaction

Sana Ben Moussa, Jalel Lachheb, Michel Gruselle, Birgit Maaten, Kadri Kriis, Tõnis Kanger, Kaia Tõnsuaadu, Béchir Badraoui

Calcium, Barium and Strontium Apatites: A New Generation of Catalysts in the Biginelli Reaction

Sana Ben Moussa[a], Jalel Lachheb[a], , Michel Gruselle*[b], Birgit Maaten[c], Kadri Kriis[d], Tõnis Kanger[d], Kaia Tõnsuaadu[e] and Béchir Badraoui[a]

[a]*U.R. Matériaux et synthèse organique UR 17ES31, Institut Préparatoire aux Etudes d'Ingénieurs de Monastir, Université de Monastir, 5019 Monastir, Tunisia*

[b]*CNRS, UMR 8232, Institut Parisien de Chimie Moléculaire, F-75005 Paris, France; Sorbonne Universités, UPMC Univ. Paris 06, UMR 8232, Institut Parisien de Chimie Moléculaire, F-75005 Paris, France*

[c]*Department of Energy Technology, Tallinn University of Technology Ehitajate tee 5, Tallinn 19086, Estonia*

[d]*Department of Chemistry and Biotechnology, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia;*

[e]*Laboratory of Inorganic Materials, Tallinn University of Technology, Ehitajate tee 5, 19086 Tallinn, Estonia*

Keywords: Biginelli reaction, Hydroxyapatite, Modified hydroxyapatite, Catalysis

*corresponding author Tel. + 33 1 44 27 30 90

e-mail: michel.gruselle@upmc.fr

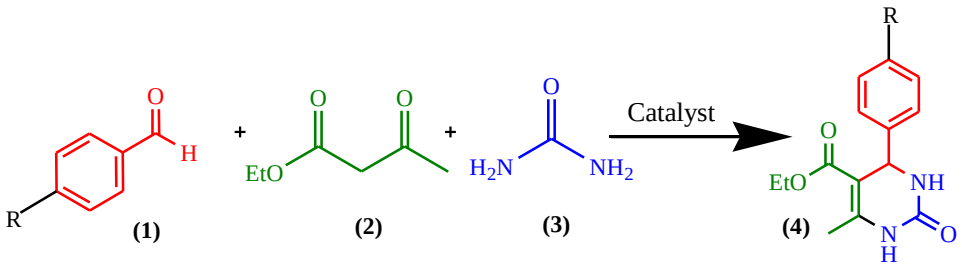
Abstract

We describe herein the use of Calcium, Barium and Strontium hydroxyapatites (CaHAp, BaHAp and SrHAp) as well as CaHAp containing Magnesium, Copper, Zinc and Palladium (MgHAp, CuHAp, ZnHAp and PdHAp) as catalysts in the Biginelli reaction. The efficiency of CaHAp and SrHAp is very low, leading to the expected 3,4-dihydropyrimidin-2(1H)-one in poor yields. Mixed Ba_5Sr_5HAp and Ba_{10}HAp show interesting catalytic properties, especially Ba_{10}HAp leading to pure isolated reaction products in good yields. The use of modified CaHAp seems to be of interest in regard to the yield obtained. Nevertheless the release of Mg, Cu, Zn and Pd ions in the solution during the catalytic process makes the use of such modified apatites less effective.

1. Introduction

Apatites, mostly hydroxyl- and fluorapatites are materials of considerable interest in a large research area [1, 2], including for catalytic applications. Some reviews are devoted to describe their efficiency as catalysts [3-6]. Among these catalytic properties, the C-C bond formation is of first importance in organic synthesis [7]. Pursuing our research in this area we report the use and efficiency of calcium, barium, and strontium hydroxyapatites as catalysts in the Biginelli reaction.

The Biginelli reaction is an one pot three components coupling reaction between an aldehyde (1), a 1,3-dicarbonyl compound (2) and urea (3), affording 3,4-dihydropyrimidin-2(1H)-one (Scheme 1). This reaction was discovered by Pietro Biginelli in 1891 [8, 9].



4a) R= H

4b) R= OCH_3

4c) R= $N(CH_3)_2$

4d) R=NO_2

4f) R= F

Scheme 1. The Biginelli reaction: One pot synthesis of 3,4-dihydropyrimidinones

Originally, the Biginelli reaction was carried out by refluxing a mixture of the benzaldehyde, ethyl acetoacetate and urea in ethanol in the presence of HCl as catalyst. The process has been improved significantly over the years and several examples of this reaction were reported with high product yields using different catalysts and ligands [10-12]. The influence of polar and non-polar solvent has also been studied [13].

These compounds, also called "Biginelli compounds", have attracted attention as important structural motifs in medicinal chemistry because of their significant biological activities, such as antiviral, antimicrobial, antitumor, antibacterial, and anti-inflammatory properties [14,15]. Many of them are pharmacologically used as potent calcium channel blockers, antihypertensive agents, and neuropeptide antagonists [16].

Other efficient heterogeneous catalysts have been reported for the Biginelli reaction [17-19], they have all in common an acidic nature. Contrary to acidic catalysts there are only a few papers describing basic catalysts [20].

The mechanism of the Biginelli reaction, using acidic Brönsted or Lewis catalysts, was discussed by several authors [13, 21, 22]. Kappe [23, 24], re-examining this question concluded that the first step in this mechanism:" *involves the acid-catalysed formation of an N-acyliminium ion precursor from and aldehyde and urea component*".

Conditions that support the formation and reaction of *N*-acyliminium ion provide one route to improving the Biginelli reaction.

Since it is important to produce less chemical waste and to strive towards greener chemistry, there are several examples of solvent-free reaction conditions using different types of catalysts [25-27]. They all have in common a slight excess of urea and a catalyst loading of less than 10 % mol. Some examples of modified and non-modified apatite-catalysed Biginelli reactions can be found in the literature. The use of a Bi- and Na-modified HAp in neat conditions results in high isolated yields of the product (70%) in half an hour [28]. It has also been shown that non-modified hydroxy- and fluorapatites are less active than modified apatites for the Biginelli reaction in refluxing toluene [29, 30]. For example, modified apatites with Lewis acids ($ZnCl_2$, $CuCl_2$, $CoCl_2$ and $NiCl_2$) have a better catalytic activity and lead to isolated yields up to 90%. However, the leaching of the metal is often a resulting problem.

Hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (HAp) is a mineral and its surface of which has acidic (Ca^{2+}, PO_2H) and basic (OH^-, PO_4^{3-}) sites [31]. Due to its diverse properties, it can be used as a heterogeneous catalyst for various reactions, such as Knoevenagel condensation [32], Diels-Alder reaction [33], Friedel-Crafts reaction [34], oxidation of propargylic alcohols [34], aldol reaction [36]. We have previously shown its application in Michael addition [37] and Glaser coupling reactions [38]. The catalytic activity of apatite can be modified by partial replacement of Ca^{2+} ions with other cations, including Zn^{2+}, Cu^{2+}, Co^{2+}, Ru^{3+}, Pd^{2+}, and La^{3+} [39-44]. Increased reactivity of metal-modified apatite is often reached but the recovery of the catalyst is less convenient because of the potential leaching of metallic cations in the solution.

2. Results and discussion

First, we examined the catalytic effect of various apatites on the Biginelli reaction. A mixture of aldehyde **(1)**, ethyl acetoacetate **(2)**, urea **(3)** and catalyst (Scheme 1) was stirred over a period of time mentioned in Table 1. The experiment was performed at reflux conditions in the presence of different solvents. The reaction conditions and the results obtained can be seen in Table 1.

We studied the influence of solvents on the HAp-catalysed Biginelli reaction (Table 1). The reaction between benzaldehyde (**1)**, ethyl acetoacetate (**2)** and urea (**3)** afforded dihydropyrimidinone (**4)** in the presence of 10 mol% of catalyst. The apatites HAp1, HAp2 and HAp3, HAp4 used for the reaction differ from each other in terms of their specific surface area (SSA), which depends on the synthetic method used for their preparation (see experimental 4.2.1).

Table 1. HAp-catalysed Biginelli reaction in different solvents

Entry	Ratio of **1:2:3**	Solvent	Catalyst	Temp (^oC)	Time (d)	Yield[a] (%)
1	1:1.2:1.5	MeOH	HAp1[b]	65	4	4
2	1:1.2:1.5	THF	HAp1[b]	66	3	10
3	1:1.2:1.5	Water	HAp1[b]	100	2	-
4	1:1:3	Toluene	HAp1[b]	80	3	10
5	1:1:3	Toluene	CuHAp3[c]	80	3	40
6	1:1:3	Toluene	ZnHAp2[d]	80	3	20
7	1:1:3	Toluene	PdHAp2[d]	80	3	65
8	1:1:1	Toluene	MgHAp[e]	80	3	35
9	1:1:1	Ethanol	MgHAp[e]	80	2	20

[a] Isolated yield of **4**. [b] SSA of the catalyst 82.3 m^2/g. [c] SSA of the catalyst 77.7 m^2/g. [d] SSA of the catalyst 109 m^2/g, [e] SSA of the catalyst 20 m^2/g.

Using HAp as catalyst, the reaction was extremely slow when refluxing methanol. The isolated yield of dihydropyrimidinone **4** after four days was only 4% (Table 1, entry 1). In THF the yield was only slightly higher (Table 1, entry 2) and no reaction occurred in water (Table 1, entry 3). Upon changing the ratio of the starting material to 1:1:3 and using toluene as solvent, an isolated yield of 10% was obtained after three days (entry 4). These results revealed that non-modified HAp1 is not a suitable catalyst for the Biginelli reaction in protic and aprotic, as well as in polar and nonpolar solvents.

According to the Brönsted acid or Lewis catalytic pathway mechanisms [13] the inefficiency of calcium apatite is not very surprising. As it is well known, apatite surfaces possess basic sites, namely OH^- and PO_4^{3-} and acidic ones, Ca^{2+} and POH acting as Lewis and Brönsted acidic centres respectively [31, 32]. If their specific activity is low, it increases during acid-base catalysis as it is the case in the Michael reaction [37].

Sebti *et al.* have shown that the use of metal halide modified hydroxyapatites or fluoroapatites [29, 30] as catalysts for the Biginelli reaction in toluene increases the yield of the product up to 90%. In this case, the catalyst is the Lewis acid metallic salt supported by the apatite and not the apatite itself.

Buvaneswari *et al* [28] have replaced Ca^{2+} by the couple Na^+-Bi^{3+} and observed that the catalytic activity is better by introducing a highly charged ion Bi^{3+} into the apatitic lattice, which then in turn enhances the acidic character of the material.

According to these results, hydroxyapatites with different Cu^{2+}, Zn^{2+}, Pd^{2+} and Mg^{2+} cationic substitutions were tested in the Biginelli reaction (Table 1, entries 5-7). These cations were chosen since they are better Lewis acids than Ca^{2+} due to a smaller ionic radius (IR) as it is shown in Table 2.

Table 2. Ionic radii for the Ca^{2+}, Cu^{2+}, Zn^{2+}, Pd^{2+} and Mg^{2+}cations [45]

Cations	Ca^{2+}	Cu^{2+}	Zn^{2+}	Pd^{2+}	Mg^{2+}
Ionic radius (IR) In (Å)	1.0	0.73	0.74	0.86	0.72

The best results were obtained when using Pd-modified HAp2 (an isolated yield of 65%, entry 7). Unfortunately leaching of the Pd-ions was observed. The molar ratio of Pd/Ca in the catalyst before and after the reaction was 0.24 and 0.14 respectively (detected by energy-dispersive X-ray spectroscopy). The next best result was obtained with CuHAp3 (40%, Table 1, entry 5) and the use of ZnHAp2 did not lead to high yields (20%, Table1, entry 6).

The yields obtained in this paper were lower than those described by Sebti *et al* [29]. However, there was a substantial difference in the process of modifying the apatite catalyst. Sebti *et al* mixed a water solution of a metal salt with apatite and water was evaporated. This approach does not exclude catalysis by Lewis acids that were not incorporated into the apatite structure. In our case non-incorporated metal salts were washed out with water and the only metal ions present were those in the apatite structure [46, 47]. Although metal-modified apatites had higher catalytic activity than non-modified hydroxyapatite the reaction rate remained slow. Next, a solvent-free apatite-catalysed Biginelli reaction was studied (Table 3).

Table 3. Solvent-free Biginelli reaction[a]

Entry	Catalyst	Time(h)	Yield (%)[b]
1	HAp3	5	50
2	CuHAp3	5	70
3	HAp3	24	85
4	CuHAp3	24	85

[a] Reaction conditions: benzaldehyde **1** (1 equiv.), ethyl acetoacetate **2** (5 equiv.), urea **3** (1 equiv.), catalyst (10 mol%), 80 °C . [b] Isolated yield of **4**.

A considerable increase in the reaction rate was observed in solvent-free conditions. When carrying the reaction out neat, after half an hour, the reaction mixture thickened which indicated that the product was forming rapidly. Therefore, an excess of ethyl acetoacetate **2** was used to keep the mixture in a liquid phase. As these results were promising, as a next step, non-modified and Cu-modified apatites were investigated as catalysts. The isolated yield of product **4** in the presence of HAp3 was 50% after 5 h (Table 3, entry 1). When using CuHAp3, the isolated yield was higher (70%,

Table 3, entry 2). It shows that higher isolated yields of the product can be obtained by modifying the hydroxyapatite with Cu. However, under these harsh conditions leaching of the metal was detected. According to the atom absorption spectroscopy measurement results, the concentration of copper ions in apatite was reduced (before the reaction 4.1% and after the reaction 3.2% of Cu). When the reaction time was increased to 24h, the isolated yields of the product in the presence of unmodified HAp3 and Cu-modified HAp3 increased only by 35% and 15% respectively, resulting in an isolated yield of 85% in both cases (Table 3, entry 3 and 4). Thus, there is no need to use Cu-modified apatite for the Biginelli reaction in solvent-free conditions. Isolation of product **4** is troublesome due to its low solubility in organic solvents. There are several examples of re-crystallization, which mostly use water and ethanol [25]. Therefore, we used a method of double-filtration. The reaction mixture was cooled to room temperature and filtrated first with cold heptane to remove the unreacted starting materials. As a second step, hot methanol was used to isolate the product from the catalyst.

Comparing the obtained isolated yields with the specific surface area (SSA) of the catalyst, the specific surface area seemed to play no significant role in the outcome of the reaction. For example, the PdHAp2 and ZnHAp2 had the same SSA (109 m^2/g), but the isolated yields of the products differed greatly (Table 1, entries 6 and 7). This means that the cation used to modify the apatite is more important than the SSA value and influences the formation of the product to a greater extent. Nevertheless, the use of modified Cu-, Zn-, Pd- and MgHAp is made impossible by a more or less important release of such cations from the structureof the apatite into the solution during the reaction.

We explore an another way to enhance the efficiency of apatites as catalysts in the Biginelli reaction by tunning the basic properties of the apatite surfaces. The idea was to increase the surface hydroxyl group activity. Such an increase in the surface hydroxyl activity in the apatitic structure can be achieved by the presence of cations like Sr^{2+} (IR 1.18 Å) or Ba^{2+} (IR 1.35 Å) which are bigger than Ca^{2+} (IR 1.0 Å) and consequently less acidic, exalting the basicity of the surface hydroxyl ions located near them [32].

Then, the abilities of SrHAp, BaHAp and mixed SrBaHAp to catalyze the Biginelli reaction were tested. The reaction was conducted in refluxing methanol and the yields are calculated for isolated pure crystallized final products. The results obtained are presented in Table 4.

Table 4. Calcium, Strontium and Barium Apatites catalyzed synthesis of different dihydropyrimidinones under reflux condition using methanol and toluene as solvent

Entry	R	Solvent	Samples	Yield (%)	Melting point (Mp) (°C)	
					Found	Reported
4a	H	Methanol	HAp4	8	200-202	198-200 [48]
			SrHAp	5		
			CaSrHAp	12		
			BaHAp	65		
			BaSrHAp	35		
4b	OCH_3	Methanol	BaHAp	54	201-202	201-202 [49]
			BaSrHAp	30		
4c	$N(CH_3)_2$	Methanol	BaHAp	65	256-258	256-257 [49]
			BaSrHAp	40		
4d	NO_2	Methanol	BaHAp	0	205-208	207-209 [50]
			BaSrHAp	37		
			SrHAp	0		
		Toluene	BaHAp	0		
4f	F	Methanol	SrHAp	0		
			BaHAp	0		
			BaSrHAp	0		
		Toluene	BaHAp	0		

SrHAp (5% yield for **4a**) or mixed SrCaHAp (12% yield for **4a**) are not better catalysts than CaHAp (8% yield for **4a**). The better results are obtained for BaHAp when starting from benzaldehyde (65% Yield), 4-methoxybenzaldehyde (54% yield) and 4-dimethylaminobenzaldehyde (65% yield). No reaction occurred using 4-fluorobenzaldehyde or 4-nitrobenzaldehyde as starting material. These results highlight that neutral or donor 4-substituant groups favor the reaction whereas attractive one disfavor the reaction. These results remain the same when changing the solvent from methanol to toluene. The results obtained using a mixed BaSrHAp are generaly not better than for pure BaHAp. The only exception is the nitro compounds, **4c** obtained with a 37% yield.

3. Conclusion

In conclusion, we have developed and shown the use of apatites as catalysts in the Biginelli reaction. Actually, stoichiometric calcium apatites are not efficient catalysts for this reaction since they afford products in low yield and with a low reaction rate. However, under solvent-free conditions non-modified HAp-s were efficient enough to catalyse the Biginelli reaction. In addition, the use of non-modified catalysts avoids the release of cations in the solution. The catalyst could be repeatedly used

in several consecutive runs. It could be activated simply by heating and used again without loss of activity. The simplicity of the procedure makes the protocol potentially useful for other HAp-catalysed reactions.

Using modified apatites obtained by substituting calcium ions with more acidic ones (Mg, Cu, Zn and Pd) enhance significantly the final yield in "Biginelli product". Nevertheless, leaching of such cations in the solution during the reaction process is often a resulting problem. The better results in yields, but not in reaction rate are obtained by using a stoichiometric barium apatite. We assume than the increase in activity of this apatite can be correlated with the enhancement of the OH activity at the surface of the material.

4. Experimental section

4.1. General

All chemicals were purchased from Aldrich Chemical Co and were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were obtained from solution $CDCl_3$ and DMSO-*d6* with TMS as internal standard using BRUKER AVANCE III (400 MHz) spectrometer. Melting points were determined using a Stuart.SMP11 instrument. The infrared (IR) adsorption analysis were obtained using a Spectrum Two 104462 IR spectrophotometer equipped with a diamond Attenuated Total reflectance (ATR) setup in the range 4000-400 cm^{-1}. The content of Cu^{2+} and Zn^{2+} ions in HAp before and after reaction was determined by Atomic Absorption Spectroscopy (AAS) after dissolution of the apatite in HNO_3 solution. The content of Pd^{2+} in HAp2 before and after reaction was detected by energy-dispersive X-ray spectroscopy (EDX) carried out on Oxford Instruments INCA- Energy system using Penta FET x3 analyzer. Quantitative analysis was carried out using factory-defined standards. The phosphorus, magnesium and calcium contents were obtained by ICP-OES on a Horiba Jobin Yvon modele active. X-ray diffraction (XRD) analysis of catalysts were carried out by means of a X'Pert Pro Panalytical X-pert diffractometer using Cu-Kα radiation (λ=1.5418 Å, with θ-θ geometry, equipped with an X'Celerator solid detector and a Ni filter). The 2θ range was from 20 to 70° with a step size Δ2θ=0.0167°. The experimental patterns were compared to standards compiled by the Joint Committee on Powder Diffraction and Standards (JCPDS cards) using the X'Pert High- Score Plus software [51]. Specific surface area (SSA) was determined by the BET-method (adsorptive gas N_2, carrier gas He, heating temperature 150 °C) with Costech instruments Sorbtometer KELVIN 1042.

ESI-MS experiments were carried out using a LTQ-Orbitrap XL from Thermo Scientific (Thermo Fisher Scientific, Courtaboeuf, France) and operated in positive ionization mode, with a spray voltage at 3.6 kV. Sheath and auxiliary gas were set at a flow rate of 45 and 15 arbitrary units (a.u.), respectively. Applied voltages were 20 and 70 V for the ion transfer capillary and the tube lens, respectively. The ion transfer capillary was held at 275°C. Detection was achieved in the Orbitrap with

a resolution set to 60,000 (at m/z 400) and a m/z range between 110-1200 in profile mode. Spectrum was analyzed using the acquisition software XCalibur 2.1 (Thermo Fisher Scientific, Courtaboeuf, France). The automatic gain control (AGC) allowed accumulation of up to 2.10^5 ions for FTMS scans. Maximum injection time was set to 300 ms and 1 µscan was acquired. 5µL was injected using a Thermo Finnigan Surveyor HPLC system (Thermo Fisher Scientific, Courtaboeuf, France) with a continuous infusion of methanol at 100 $\mu L.min^{-1}$.

4.2. Synthesis of the catalysts

4.2.1 Synthesis of HAp

The apatites were synthesised according to known wet precipitation methods [52]. For HAp1 synthesis, the starting materials were CaO and H_3PO_4. CaO was mixed with deionized water (1g in 30 mL) under an N_2 atmosphere with magnetic stirring for 1 h and then 0.4 M H_3PO_4 solution was added at a rate of 0.3 mL/min with continuous mixing at room temperature. The mixing was continued for 24 h then the slurry mixture was filtrated and dried at 110 °C.

HAp2, HAp3 and HAp4 were synthesised by adding $Ca(NO_3)_2$ and $(NH_4)_2HPO_4$ solutions (0.5 M and 0.3 M, respectively) simultaneously with a rate of 5 mL/min into water–NH_4OH solution at 23 °C at a Ca/P molar ratio of 1.67 (corresponding to a stoichiometric hydroxyapatite). The pH was maintained between 9 and 11 in the case of HAp2 and between 8 and 9 in the case of HAp3 by the discontinuous addition of concentrated aqueous NH_3. The formed dispersion was continuously stirred for 3 h, aged at 23 °C for 24 h, then filtrated and washed several times with deionized water. HAp were dried at 110 °C under vacuum, and ground in agate mortar.

4.2.2 Synthesis of SrHAp, CaSrHAp, BaHAp and BaSrHAp

The synthesis of BaHAp, SrHAp, CaSrHAp and BaSrHAp were carried out by a double decomposition method [53]. In nitrogen atmosphere, a solution of different metal cations $Ca(NO_3)_2{\cdot}4H_2O$, $Ba(NO_3)_2$, or $Sr(NO_3)_2$ (0.2 M, 150 mL) was added dropwise to a solution of $(NH_4)_2HPO_4$ (0.2 M, 250 mL), maintained at boiling temperature, under stirring. The pH value of the mixture was adjusted to 10 with regular addition of NH_4OH. The resulting precipitate was maintained in contact with the reaction solution for 1 h, then filtered and repeatedly washed with hot distilled water. The final product was dried at 120 °C overnight.

4.2.3 Synthesis of Mg, Cu, Zn and Pd modified HAp

The Mg modified apatite (MgHAp) has been synthesized using the hydrothermal method [54]. A demineralized aqueous solution (14 mL, 0.75 M) of a mixture of the two nitrates $Ca(NO_3)_2.4H_2O$ and $Mg(NO_3)_2.6H_2O$ in the desired proportions is added to a $(NH_4)_2HPO_4$ aqueous solution (25mL, 0.25 M). The final pH of the solution is adjusted to 9 by adding a NH_4OH solution (d = 0.89, 28%). The final mixture is transferred to an autoclave and is maintained there at 120°C for 20h. After filtration and washing using hot demineralized water, the final product is dried at 120°C

The Cu and Zn-modified apatites were obtained by mixing 100 mg of the HAp3 with 50 mL of $Cu(CH_3COO)_2$ solution (0.01 M) and HAp2 with 50 mL of $Zn(NO_3)_2$ solution (0.002 M), respectively. The suspension (pH = 6) was stirred at 25°C for 24 h. The obtained slurry was filtered, washed with deionised water, and dried overnight at 110 °C.

Pd-modified apatite (PdHAp) was obtained by mixing 200 mg of the HAp2 with 250 mL of $Pd(NO_3)_2{\cdot}2H_2O$ solution (0.001M). The suspension (pH = 5.4) was stirred at 25°C for 24 h. The obtained slurry was filtered, washed with deionized water, and dried overnight at 110 °C. The content of Ca and P of the apatites was measured by standard chemical analytical methods after dissolution of the sample in HCl (1:1). Chemical composition and SSA of the synthesized apatites are shown in Table 5.

4.3. Synthesis of 3,4-dihydropyrimidin-2(1H)-one

A mixture of aldehyde (10 mmol), ethyl acetoacetate (10 mmol), urea (10 mmol) and catalyst (2.5 mol%) were mixed by stirring over a period of time shown in Table 1. The experiment was performed at reflux conditions in the presence of solvents such as methanol, ethanol and toluene (12 mL).

After the completion of the reaction (monitored by thin layer chromatography), the catalyst was separated from the reaction mixture by filtration and then the liquid part was poured into water. The obtained solid product was filtered and dried. The crude product was purified by recrystallization in methanol.

4.4. Identification of the catalysts

4.4.1 Chemical composition and SSA of the HAp

Table 5. Chemical composition and SSA of the apatites

Samples	Atom ratio ($Cation^{2+}$/P)	SSA (m^2/g)

HAp1	1.67	82.3
HAp2	1.64	109
HAp3	1.57	77.7
HAp4	1.68	42
SrHAp	1.65	40
BaHAp	1.67	7
BaSrHAp	1.64	18
CaSrHAp	1.66	44
MgHAp	1.65	20

4.4.2. CaHAp Infra-red spectra

FTIR ATR analysis of the products revealed slightly carbonated (~1 % CO_2) hydroxyapatites. The sorption of Mg, Cu, Zn or Pd ions did not change the structure of apatite. IR spectra for these apatites are shown in Figure 1 and 2. All the IR spectra displayed the characteristic absorption bands of calcium apatite [55]. The P–O bands in the range 1089.2-1026.0 cm^{-1} and 600.7-661.4 cm^{-1} are attributed to the asymmetric stretching and bending vibrations of PO_4^{3-} respectively. The peaks ate 962.5 cm^{-1} and 471.7 cm^{-1} correspond to the symmetric stretching and bending vibrations of PO_4^{3-} respectively. The libration hydroxyl band is observed at 630.7 cm^{-1} and the –OH stretching vibration at 3570 cm^{-1} [56, 57].

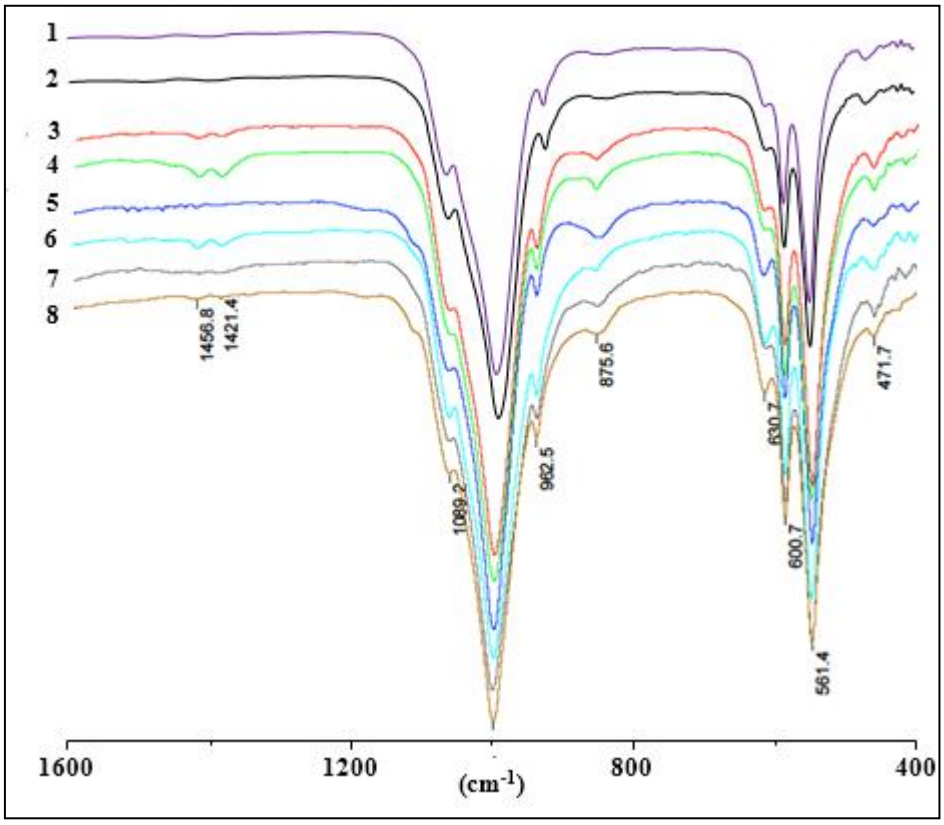


Fig.1. IR spectra of HAp1 (1), HAp2 (2), HAp3 (3), HAp4 (4), CuHAp3 (5), ZnHAp2 (6), MgHAp (7) and PdHAp2 (8)

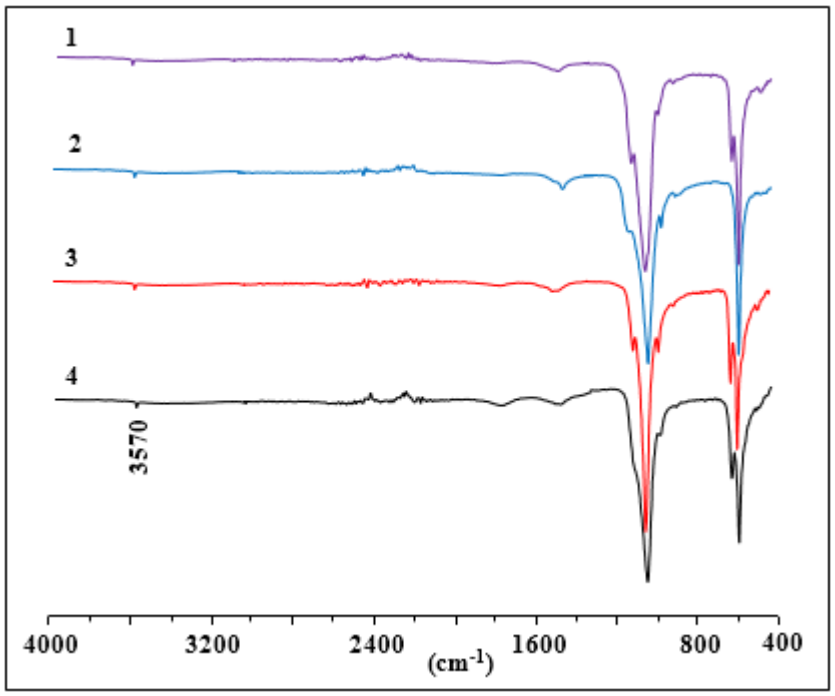


Fig.2. IR spectra of CaSrHAp (1), SrHAp (2), BaHAp (3) and BaSrHAp (4)

4.4.3. X-ray data

Powder X-ray diffraction analysis of the samples HAp4, CaSrHAp, SrHAp, BaHAp and MgHAp indicates single phase and good crystallinity. The X-ray diffraction patterns are shown in Figure 3. All the peaks of every motive were indexed in the hexagonal system ($P6_3/m$ space group) based on the hydroxyapatite model $Ca_{10}(PO_4)_6(OH)_2$ (JCPDS 01-084-1998).

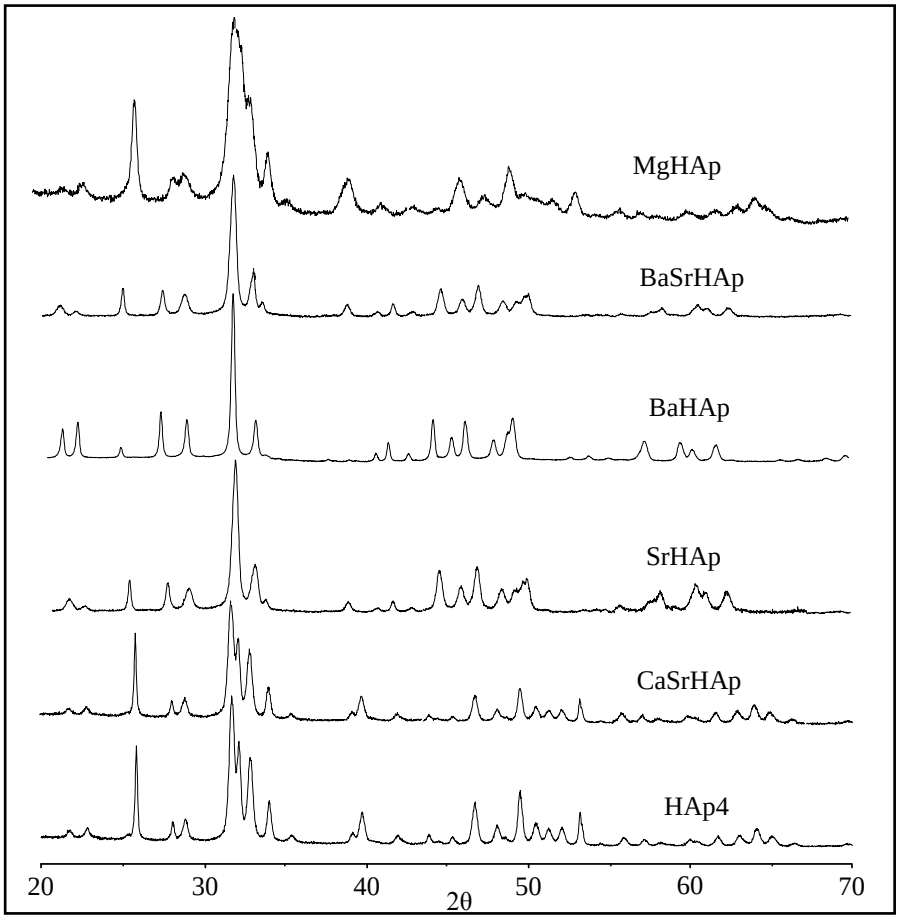


Fig.3. X-ray diffractograms for HAp4, CaSrHAp, SrHAp, BaHAp an MgHAp

4.5. Spectral data of the obtained products R = H (4a), O-CH_3 (4b), $N(CH_3)_2$ (4c), and NO_2 (4d)

Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4a**)

^{1}H NMR ($CDCl_3$): δ = 7.62 (s, 1H, NH), 7.24 (m, 5H, C_6H_5), 5.51 (s, 1H, NH), 5.31 (s, 1H, CH), 4.02 (q, J=7.2Hz, 2H, OCH_2CH_3), 2.26 (s, 3H, CH_3), 1.05 (t, J=7.2Hz, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 165.6, 153.2, 146.2, 143.7, 128.7, 127.9, 126.5, 101.3, 60.0, 55.7, 18.6, 14.1.

IR: cm^{-1} 3230, 3110, 1725, 1700, 1638.

HRMS (ESI, $[M+Na]^+$): $C_{14}H_{16}N_2O_3Na$, Calculated 283.1053, Experimental: 283.1050; 1.1 ppm.

Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4b**)

^{1}H NMR ($CDCl_3$): δ = 8.06 (s, 1H, NH), 7.18–6.72 (m, 4H, C_6H_4), 5.66 (s, 1H, NH), 5.25 (s, 1H, CH), 3.98 (q, J=7.2Hz, 2H, OCH_2CH_3), 3.71 (s, 3H, OCH_3), 2.26 (s, 3H, CH_3), 1.08 (t, J=7.2Hz, 3H, CH_3).
^{13}C NMR ($CDCl_3$): δ = 165.6, 159.2, 153.2, 145.8, 136.1, 127.8, 113.9, 101.6, 59.9, 55.3, 55.2, 18.6, 14.1.
IR: cm^{-1} 3240, 3110, 1725, 1710, 1655.

HRMS (ESI, $[M+Na]^+$): $C_{14}H_{28}N_2O_4Na$, Calculated 313,1159, Experimental: 313.1155; 1.2 ppm.
Ethyl 4-(4-(dimethylamino)phenyl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4c**)
^{1}H NMR ($CDCl_3$): δ = 7.21 (s, 1H, NH), 7.10 (d, J=8.2Hz, 2H, C_6H_4), 6.58(d, J=8.3Hz, 2H, C_6H_4), 5.28 (s, 1H, NH), 5.22 (s, 1H, CH), 4.00 (q, J=7.2Hz, 2H, OCH_2CH_3), 2.85 (s, 6H, $N(CH_3)_2$), 2.25 (s, 3H, CH_3), 1.12 (t, J=7.2Hz, 3H, CH_3).
^{13}C NMR (DMSO-*d6*): δ = 165.9, 152.8, 150.0, 147.7, 133.2, 127.4, 112.4, 100.4, 59.4, 53.9, 43.4, 18.2, 14.5.
IR: cm^{-1} 3340, 3190, 2976, 1706, 1648, 1528.
HRMS (ESI, $[M+H]^+$): $C_{16}H_{22}N_3O_3$, Calculated 304.1656, Experimental: 304.1653; 0.9 ppm.
Ethyl 4-(4-nitrophenyl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**4d**)
^{1}H NMR ($CDCl_3$): δ = 8.12 (d, J=9.6Hz, 2H, C_6H_4), 7.87 (s, 1H, NH), 7.40 (d, J=9.6Hz, 2H, C_6H_4), 5.49 (s, 1H, NH), 5.42 (s, 1H, CH), 4.02 (q, J=7.2Hz, 2H, OCH_2CH_3, 2.30 (s, 3H, CH_3), 1.12 (t, J=7.2Hz, 3H, CH_3).
^{13}C NMR ($CDCl_3$): δ = 165.1, 152.6, 150.3, 147.5, 146.9, 127.5, 124.1, 100.6, 60.4, 55.2, 18.9, 14.1.
IR: cm^{-1} 3320, 3085, 2986, 1730, 1694, 1588.
HRMS (ESI, $[M+Na]^+$): $C_{14}H_{15}N_3O_5Na$, Calculated 328.0899, Experimental: 328.0899; 1.5 ppm.

Acknowledgments

Authors thank the University of Monastir (Tunisia); the University Pierre and Marie Curie (France) and CNRS (France); the Tallinn University of Technology (Estonia). This work was supported by institutional research funding IUT (19-32) of the Estonian Ministry of Education and Research and EU European Regional Development Fund (3.2.0101.08-0017). Parrot program 2013–2014, No. 29519 PK is also acknowledged.

References

[1] J.C. Elliot, Structure and Chemistry of the Apatites and Other Calcium Ortho-phosphates. First Ed., Elsevier, Amsterdam, 1994.

[2] C. Rey, C. Combes, C. Drouet, D. Grossin, In: Comprehensive Biomaterials; P. Ducheyne, K. Healy, D. Hutmacher, D.E. Grainger, J. Kirkpatrick, J. Eds. Elsevier, 1 (2011) 187-221.

[3] J. Gomez-Morales, M. Iafisco, J. M. Delgado-Lopez, S. Sarda, C. Drouet, Progress on the preparation of nanocrystalline apatites and surface characterization: Overview of fundamental and applied aspects. Cryst. Growth Charact. Mater. 59(1) (2013) 1-46.

[4] S. Sebti, M. Zahouily, H. B. Lazrek, J. A. Mayoral, D. J. Macquerie, Phosphates: New generation of liquid-phase heterogeneous catalysts in organic chemistry, Curr. Org. Chem. 12 (2008) 203-232.

[5] K. Kaneda, T. Mizukagi, Development of concerto metal catalysts using apatite compounds for green organic synthesis. Energy Environ. Sci. 2 (2009) 655-673.

[6] M. Gruselle, Apatites A new family of catalysts in organic synthesis. J. Organomet. Chem. 793 (2015) 93-101.

[7] M. Gruselle, K. Tõnsuaadu, Tunable calcium-apatites as solid catalysts for classical organic reactions. Current Org. Chem. 21 (2017) 688-697.

[8] P. Biginelli, Ueber Aldehyduramide des Acetessigäthers, Chem. Ber. 24 (1891) 1317-1319.

[9] P. Biginelli, Ueber Aldehyduramide des Acetessigäthers. II, Chem. Ber. 24 (1891) 2962-2967.

[10] S. Sandhu, J. S. Sandhu, Past, present and future of the Biginelli reaction: a critical perspective, ARKIVOC, 2012, 66-133.

[11] Q. Haijun, L. Xuejian, M. Fan. L. Xufeng, Efficient synthesis of dihydropyrimidinones via a three-component Biginelli-type reaction of urea, alkylaldehyde and arylaldehyde, Beilstein, J. Org. Chem. 9 (2013) 2846-2851.

[12] J. P. Wan, Y. Liu, Synthesis of Dihydropyrimidinones and Thiones by Multicomponent Reactions: Strategies Beyond the Classical Biginelli Reaction, Synthesis, 42 (2010) 3943-3953.

[13] J. H. Clark, D.J. Macquarrie, J. Sherwood, The combined role of catalysis and solvent effects on the biginelli reaction: improving efficiency and sustainability, Chem. Eur. J. 19 (2013) 5174-5182.

[14] N. Gangwar, V.K. Kasana, 3,4-Dihydropyrimidin-2(1H)-one derivatives: Organocatalysed microwave assisted synthesis and evaluation of their antioxidant activity, Med. Chem. Res. 21 (2012) 4506-4511.

[15] C. O. Kappe, O. V. Shishkin, G. Uray, P. Verdino, X-Ray Structure, Conformational Analysis, Enantioseparation, and Determination of Absolute Configuration of the Mitotic Kinesin Eg5 Inhibitor Monastrol, Tetrahedron, 56 (2000) 1859-1862.

[16] F. Ali, K.M. Khan, U. Salar, S. Iqbal, M. Taha, N. Ismail, S. Perveen, A. Wadood, M. Ghufran, B. Ali, Dihydropyrimidones: As novel class of β- glucuronidase inhibitors, Bioorg. Med. Chem. 24 (2016) 3624-3635.

[17] M. Arjun, D. Sridhar, M. Adharvana Chari, M. Sarangapani, You have full text access to this contentAn efficient Biginelli one-pot synthesis of new benzoxazole-substituted dihydropyrimidinones and thiones catalysed by alumina-supported trifluoromethane sulfonic acid under solvent free conditions, J. Heterocyclic Chem. 46 (2009) 119-123.

[18] G. R. Chaudhary, P. Bansal, S.K. Mehta, Recyclable CuS quantum dots as heterogeneous catalyst for Biginelli reaction under solvent free conditions, Chem. Engineering J. 243 (2014) 217-224.

[19] A. K. Mitra, K. Banerjee, Clay catalysed synthesis of dihydropyrimidinones under solvent-free conditions, Synlett. 10 (2003) 1509-1511.

[20] Z. L. Shen, X. P. Xu, S. J. Ji, Brønsted Base-Catalyzed One-Pot Three-Component Biginelli-Type Reaction: An Efficient Synthesis of 4, 5, 6-Triaryl-3,4-dihydropyrimidin-2(1H)-one and Mechanistic Study J. Org. Chem. 75 (2010) 1162-.1167.

[21] P. Rajentral, C. Jagdish, B. Avul, Review biginelli reaction. Reagent support based approaches World, J. Pharm. Pharma. Sci. 5 (2016) 419-432.

[22] M. Puripat, R. Ramozzi, M. Hatanaka, W. Parasuk, V. Parasuk, K. Morokuma, The biginelli reaction is a urea-catalyzed organocatalutic multicomponent reaction, J. Org. Chem. 80 (2015) 6959-6967.

[23] C.O. Kappe, A reexamination of the Mechanism of the Biginelli Dihydropyrimidine Synthesis. Support for an N-Acyliminium Ion Intermediate, J. Org. Chem. 62 (1997) 7201-7204.

[24] C. O. Kappe, Biologically active dihydropyrimidones of the Biginelli type a literature survey, Eur. J. Med. Chem. 35 (2000) 1043-1052.

[25] M. Küçükislamoğlu, S. Beşoluk, M. Zengin, M. Arslan, M. Nebioğlu, An efficient one-pot synthesis of dihydropyrimidinones catalyzed by zirconium hydrogen phosphate under solvent-free conditions, Turk. J. Chem. 2010, 34, 411-416.

[26] M. Kargar, R. Hekmatshoar, A. Mostashari, Z. Hashemi, Efficient and green synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones using imidazol-1-yl-acetic acid as a novel, reusable and water-soluble organocatalyst, Catal. Comm. 15 (2011) 123-126.

[27] N. A. Liberto, S.P. Silva, A. Fátima, S.A. Fernandes, β-Cyclodextrin-assisted synthesis of Biginelli adducts under solvent-free conditions, Tetrahedron, 69 (2013) 8245-8249.

[28] S. Sumathi, G. Buvaneswari, Synthesis of apatite structure based $BiNaCa_3(PO_4)_3OH$ and its application for condensation reaction, Ceram. Int. 38 (2012) 3547-3552.

[29] H. El Badaoui, F. Bazi, S. Sokori, S. Boulaajaj, H.B. Lazrek, S. Sebti, One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using $ZnCl_2$, $CuCl_2$, $NiCl_2$ and $CoCl_2$ doped hydroxyapatite, Lett. Org. Chem. 2 (2005) 561-565.

[30] H. El Badaoui, F. Bazi, R. Tahir, H. B. Lazrek, S. Sebti, Synthesis of 3,4-dihydropyrimidin-2-ones catalysed by fluorapatite doped with metal halides, Catal. Comm. 6 (2005) 455-458.

[31] L. Garcia Rodenas, J.M. Palacios, M.C. Apella, P.J. Morando, M. A. Blesa, Surface properties of various powdered hydroxyapatites, J. Colloid Interface Sci. 290 (2005) 145-154.

[32] A. Venugopal, M. S. Scurrell, Hydroxyapatite as a novel support for gold and ruthenium catalysts: Behaviour in the water gas shift reaction, Appl. Catal. A: Gen. 245 (2003) 137-147.

[33] K. Mori, T. Hara, T. Mizugaki, K. Ebitani, K. Kaneda, Hydroxyapatite-Bound Cationic Ruthenium Complexes as Novel Heterogeneous Lewis Acid Catalysts for Diels−Alder and Aldol Reactions, J. Am. Chem. Soc. 125 (2003) 11460-11461.

[34] S. Sebti, R. Tahir, R. Nazih, S. Boulaajaj, Comparison of different Lewis acid supported on hydroxyapatite as new catalysts of Friedel–Crafts alkylation, Appl. Catal. A: Gen. 218 (2001) 25-30.

[34] Y. Maeda, Y. Washitake, T. Nishimura, K. Iwai, T. Yamauchi, S. Uemura, Calcium phosphate-vanadate apatite (CPVAP)-catalyzed aerobic oxidation of propargylic alcohols with molecular oxygen, Tetrahedron, 60 (2004) 9031-9036.

[36] E. G. Rodrigues, T. C. Keller, S. Mitchell, J. Pérez-Ramirez, Hydroxyapatite, an exceptional catalyst for the gas-phase deoxygenation of bio-oil by aldol condensation, Green Chem. 16 (2014) 4870-4874.

[37] M. Gruselle, T. Kanger, R. Thouvenot, A. Flambard, K. Kriis, V. Mikli, R. Traksmaa, B. Maaten, K. Tõnsuaadu, Calcium Hydroxyapatites as Efficient Catalysts for the Michael CC Bond Formation, ACS Cat. 1 (2011) 1729-1733.

[38] B. Maaten, J. Moussa, C. Desmarets, P. Gredin, P. Beaunier, T. Kanger, K. Tõnsuaadu, D. Villemin, M. Gruselle, Cu-modified hydroxy-apatite as catalyst for Glaser–Hay C-C homo- coupling reaction of terminal alkynes, J. Mol. Cat. A: Chem. 393 (2014) 112-116.

[39] J.W. Jaworski, S. Cho, Y. Kim, J.H. Jung, H.S. Jeon, B.K. Min, K.Y. Kwon, Hydroxyapatite supported cobalt catalysts for hydrogen generation, J. Colloid Interface Sci. 394 (2013) 401-408.

[40] Y. Masuyama, K. Yoshikawa, N. Suzuki, K. Hara, A. Fukuoka, Hydroxyapatite-supported copper (II)-catalyzed azide-alkyne [3+2] cycloaddition with neither reducing agents nor bases in water, Tetrahedron Lett. 52 (2011) 6916-6918.

[41] Z. Opre, J. D. Grundwaldt, M. Maciejewski, D. Ferri, T. Mallat, A. Baiker, Promoted Ru–hydroxyapatite: designed structure for the fast and highly selective oxidation of alcohols with oxygen, J. Catal. 230 (2005) 406-419.

[42] K. Mori, S. Kanai, T. Hara, T. Mizugaki, K. Ebitani, K. Jitsukawa, K. Kaneda, Development of Ruthenium-Hydroxyapatite-Encapsulated Superparamagnetic γ-Fe_2O_3 Nanocrystallites as an Efficient Oxidation Catalyst by Molecular Oxygen, Chem. Mater. 19 (2007) 1249-1256.

[43] Y. Xu, F.W. Schwartz, Sorption of Zn^{2+} and Cd^{2+} on hydroxyapatite surfaces, Environ. Sci. Technol. 28 (1994) 1472-1480.

[44] K. Mori, M. Oshiba, T. Hara, T. Mizugaki, K. Ebitani, K. Kaneda, Creation of monomeric La complexes on apatite surfaces and their application as heterogeneous catalysts for Michael reactions, New J. Chem. 30 (2006) 44-52.

[45] R. D. Shannon, Revised effective ionic radii and systematic studies of interatomic distances in halides and chalcogenides, Acta Cryst. A 32 (1976) 751-767.

[46] K. Viipsi, S. Sjöberg, K. Tõnsuaadu, A. Shchukarev, Hydroxy- and fluorapatite as sorbents in Cd(II)-Zn(II) multi-component solutions in the absence/presence of EDTA, J. Hazardous Mat. 252-253 (2013) 91-98.

[47] M. Sljivic, I. Smiciklas, I. Plecas, M. Mitric, The influence of equilibration conditions and hydroxyapatite physico-chemical properties onto retention of Cu^{2+}, Chem. Eng. 148 (2009) 80-88.

[48] Y. Yu, D. Liu, C. Liu, G. Luo, One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using chloroacetic acid as catalyst, Bioorg. Med. Chem. Lett. 17 (2007) 3508-3510.

[49] K. Folkers, H. Adkins, The catalytic hydrogenation of esters to alcohols, J. Am. Chem. Soc. 154 (1932) 1145–1154.

[50] G. H. Mahdavinia, H. Sepehrian, MCM-41 anchored sulfonic acid (MCM-41-R-SO_3H): A mild, reusable and highly efficient heterogeneous catalyst for the Biginelli reaction, Cin. Chem. Lett. 19 (2008) 1435-1439.

[51] PANalytical X'Pert Higth Score Plus version 2.0.

[52] M. Sadat-Shojai, M. T. Khorasani, E. Dinpanah Khoshdargi, A. Jamshidi, Synthesis methods for nanosized hydroxyapatite with diverse structures, Acta Biomater. 9 (2013) 7591-7621.

[53] E. Boanini, M. Fini, M. Gazzano, A. Bigi, Hydroxyapatite Nanocrystals Modified with Acidic Amino Acids, Eur. J. Inorg. Chem. 23 (2006) 4821-4826

[54] A. Bigi, G. Falini, E. Foresti, M. Gazzano, A. Ripamonti, N. Roveri, Magnesium influence on hydroxyapatite cristallization, J. Inorg. Biochem. 49 (1993) 69-78.

[55] S. Shanmugam, B. Gopal, Copper substituted hydroxyapatite and fluorapatite: synthesis, characterization and antimicrobial properties, Ceram. Int. 40 (2014) 15655-15662.

[56] V. Stanic, D. Janackovic, S. Dimitrijevic, S.B. Tanaskovic, M. Mitric, M.S. Pavlovic, A. Krstic, D. Jovanovic, S. Raicevic, Synthesis of antimicrobial monophase silver-doped hydroxyaaptite nanopowder for bone tissue engineering, Appl. Surf. Sci. 257 (2011) 4510-4518.

[57] A. Hadrich, A. Lautie, T. Mhiri, Vibrational study and fluorescence bands in the FT-Raman spectra of $Ca_{10-x}Pb_x(PO_4)_6(OH)_2$ compounds, Spectrochim. Acta A 57 (2001) 1673-1681.