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Hydroxy-apatites-catalysed Biginelli reaction under solvent-free conditions

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Abstract : The Biginelli reaction catalysed by non-modified hydroxy-apatites (HAp) and Zn(II)-, Pd(II)- and Cu(II) modified HAp in different conditions is described. HAp and Cu-HAp appear to be the best catalysts even under solvent free conditions. This efficient solvent-free environmentally benign method for three-component coupling of a 1,3-dicarbonyl compound, urea and benzaldehyde (Biginelli reaction) catalysed by hydroxy-apatites was developed. The catalyst was easily recovered and repeatedly used without significant loss of activity.

Keywords : Zinc; Copper; Palladium modified hydroxy-apatite; Biginelli reaction; Catalysis; Solvent free reaction.

INTRODUCTION

Efficiency has become a major problem in synthetic chemistry nowadays. Continuous efforts have been made to increase efficiency and catalysis plays a crucial role in this context[1]. It is also one of the main principles of green chemistry[2]. Heterogeneous catalysts have the advantage of easy isolation and they can potentially be reused repeatedly. Another important task of green chemistry is the decrease in waste[3]. It is known that solvents are the main source of waste in organic processes. Therefore reactions under neat conditions are of crucial importance.

Hydroxy-apatite ($Ca_{10}(PO_4)_6(OH)_2$, HAp) is a mineral and its surface has acidic (PO_2H) and basic (OH) sites[4]. It is possible to use it as a heterogeneous catalyst for various reactions, such as Knoevenagel condensation[5], Diels-Alder reaction[6], Friedel-Crafts reaction[7], oxidation of propargylic alcohols[8], aldol reaction[9]. We have previously shown its application in Michael addition[10] and Glaser coupling reactions[11]. 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+}[12-17]. Increased reactivity of metal-modified apatite is often reached but the recovery of the catalyst is less convenient because of leaching of the cations.

The Biginelli reaction is a three-component coupling process between an aldehyde, a 1,3-dicarbonyl compound and an urea, affording 3,4-dihydropyrimidinones. These compounds, also called Biginelli compounds, have attracted a great deal of attention as important structural motifs in medicinal chemistry because of their significant biological activities, such as antiviral, antimicrobial, antitumour, antibacterial, and anti-inflammatory properties[18,19]. Many of them are pharmacologically important as potent calcium channel blockers, antihypertensive agents, and neuropeptide antagonists[20]. Originally, the Biginelli reaction was carried out by refluxing a mixture of the benzaldehyde, ethyl acetoacetate and urea in ethanol in the presence of a catalytic amount of HCl. The main disadvantage of the original procedure was the low yield. The process has been improved significantly and several examples of Biginelli reaction with high product yields due to the use of different catalysts and ligands have been described[21-23]. Also, the influence of the solvent has been investigated by running the reaction in polar and apolar solvents[24]. As it is important to produce less wastes, 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]. For example, modifying apatites with Lewis acids ($ZnCl_2$, $CuCl_2$, $CoCl_2$ and $NiCl_2$) increases their catalytic activity and results in products with isolated yields of up to 90%[29]. However, the leaching of the metal is often a resulting problem.

Other efficient heterogeneous catalysts have been reported for the Biginelli reaction[30], all have in common to be acidic, in comparison apatites represent a very cheap and tunable mineral possessing acido-basic properties.

EXPERIMENTAL SECTION

All chemicals were purchased from Aldrich Chemical Co and were used without further purification. The reaction products were characterized by NMR spectra (Bruker AMX-400) and the data was compared to data found in the literature[31].

General procedure for solvent-free synthesis of 3,4-dihydropyrimidin-2(1H)-one 4

A vial equipped with urea (30 mg, 0.5 mmol, 1 equiv.) and the catalyst (50 mg, 10 mol %), *β*-ketoester (329 mg, 2.5 mmol, 5 equiv.) and benzaldehyde (52 mg, 0.5 mmol, 1 equiv.) were added. The reaction was typically carried out at 80 °C for 24 hours. The progress of the reaction was monitored by TLC (heptane/ethyl acetate 1:2). After completion of the reaction, the mixture was cooled to room temperature and filtered with cold heptane and hot methanol. The resulting product did not need any further purification and was analysed by NMR.

Spectral data of the product 4

^1H NMR (400 MHz, MeOD) δ 7.31 – 7.21 (m, 5H), 5.31 (s, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 1.14 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz MeOD) δ 167.5, 155.0, 148.9, 145.8, 129.6, 128.8, 127.7, 102.1, 61.1, 56.4, 18.2, 14.5.

Synthesis and characterization of the catalyst

The apatites were synthesised according to known wet precipitation methods[32]. For HAp1 synthesis, the starting materials were CaO and H_3PO_4. CaO was mixed with deionised 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 and HAp3 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 hydroxy-apatite). 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 deionised water. HAp-s were dried at 110 °C under vacuum, and ground in agate mortar.

Chemical composition and SSA of the hydroxy-apatites

	Ca/P mole ratio	SSA (m^2/g)
HAp1	1.67	82.3
HAp2	1.64	109.0
HAp3	1.57	77.7

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.

A Pd-modified apatite 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 deionised water, and dried overnight at 110 °C.

FTIR ATR analysis of the products revealed slightly carbonated (~1 % CO_2) hydroxy-apatites with different crystallinities. The sorption of Cu, Zn or Pd ions did not change the structure of apatite (Figure 1).

The content of Ca and P of the apatites was detected by standard chemical analyses methods after dissolution of the sample in HCl (1:1).

The content of Cu^{2+} and Zn^{2+} ions in HAp before and after reaction was determined by AAS after dissolution of the apatite in HNO_3 solution.

The content of Pd in HAp2 before and after reaction was detected by energy-dispersive X-ray spectroscopy (EDX) carried out on Oxford Instruments INCA- Energy system using PentaFET x3 analyser. Quantitative analysis was carried out using factory defined standards.

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.

RESULTS AND DISCUSSION

Herein we describe our results in the study of

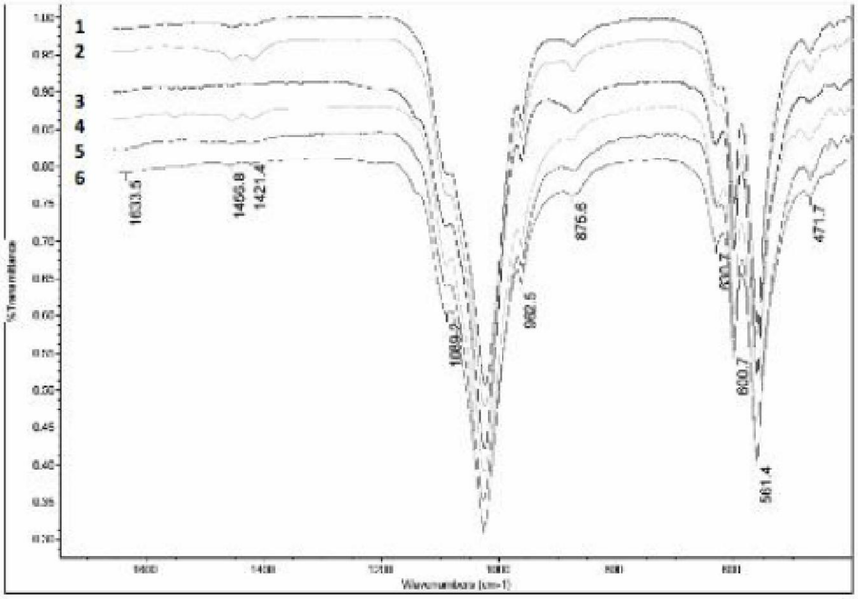

Figure 1 : IR spectra of HAp1 (1), HAp2 (2), HAp3 (3); Cu-HAp3 (4), Zn-HAp2 (5) and Pd-HAp2 (6)

TABLE 1 : HAp-catalysed Biginelli reaction in different solvents

Entry	Ratio of 1:2:3	Solvent	Catalyst	Temp (°C)	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	Cu-HAp3[c]	80	3	40
6	1:1:3	toluene	Zn-HAp2[d]	80	3	20
7	1:1:3	toluene	Pd-HAp2[d]	80	3	65

[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

TABLE 2 : Solvent-free Biginelli reaction[a]

Entry	Catalyst	Time (h)	Yield (%)[b]
1	HAp3	5	50
2	Cu-HAp3	5	70
3	HAp3	24	85
4	Cu-HAp3	24	85
5	-	24	32

[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.

the HAp-catalysed Biginelli reaction. We started our investigations of non-modified and metal-modified HAp-catalysed Biginelli reactions with the screening of solvents (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, 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 2.3).

The reaction was extremely slow in 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, 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, or in polar and nonpolar solvents.

Sebti *et al.* have shown that using metal halide modified hydroxy-apatites or fluoro-apatites[29] as catalysts for the Biginelli reaction in toluene increases the yield of the product up to 90%. Therefore, hydroxy-apatites with different cationic substitutions were tested. As can be seen from TABLE 1 (entries 5-7), 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 the reaction was 0.24 and after the reaction 0.14 (detected by energy-dispersive X-ray spectroscopy). The next best result was obtained with Cu-HAp3 (40%, TABLE 1, entry 5) and the use of Zn-HAp2 did not give high yields (20%, TABLE 1, entry 6). We have previously shown that there is no leaching in the case of Cu-Hap, when used in CH_3CN medium.[11] Therefore, Cu-HAp was selected for the following experiments.

Yields obtained by us were lower than those described by Sebti *et al*[29]. However, there was a substantial difference in 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[33]. Although metal-modified apatites had higher catalytic activity than non-modified hydroxy-apatite the reaction rate remained slow.

Comparing 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 Pd-HAp2 and Zn-HAp2 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

TABLE 3 : Reuse of HAp in Biginelli reaction[a]

Cycle	1	2	3	4	5	6	7
Yield (%)[b]	85	88	80	74	70	91	69

[a] Reaction conditions: benzaldehyde 1 (1 equiv.), ethyl acetoacetate 2 (5 equiv.), urea 3 (1 equiv.), catalyst HAp2 (10 % mol), 80 °C, reaction time 24 h. [b] Isolated yield of 4.

the SSA and influences the formation of the product.

Next, a solvent-free apatite-catalysed Biginelli reaction was studied (TABLE 2).

A considerable increase in the reaction rate was observed. When carrying out the reaction neat, after half an hour, the reaction mixture thickened which indicated that the product was formed rapidly. Therefore, an excess of ethyl acetoacetate **2** was used to keep the mixture in a liquid phase. After that, 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 2, entry 1). When using Cu-HAp3, the isolated yield was higher (70%, TABLE 2, entry 2). This shows that when modifying the hydroxy-apatite with Cu, higher isolated yields of the product can be obtained. However, under these harsh conditions leaching of the metal was detected. According to atom absorption spectroscopy measurement the concentration of copper ions in apatite was reduced (before the reaction 4.1% and after the reaction 3.2% of Cu). Increasing reaction time to 24 h, the isolated yields of the product in the presence of non-modified HAp3 and Cu-modified HAp3 increased to 85% (TABLE 2, entry 3 and 4). Thus, there is no need to use Cu-modified apatite for the Biginelli reaction in solvent-free conditions. Without using a catalyst, an isolated yield of only 32% was obtained in 24 hours (TABLE 2, entry 5). This fact indicates the catalytic role of apatite in the Biginelli reaction.

Isolation of product **4** is troublesome due to its low solubility in organic solvents. There are several examples about re-crystallization, which mostly use water and ethanol[25]. By using HAp as the catalyst it can be reused and therefore it should be regenerated with as large amount as possible. Therefore, we developed 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 followed by hot methanol to isolate the product from the catalyst. The purity of the product was confirmed by TLC and NMR and no traces of starting materials were found. The catalyst could be dried and reused (TABLE 3).

The first experiment with HAp resulted in 85% of isolated yield (TABLE 3, cycle 1), which is in good correlation with the previous results (TABLE 2, entry 3). The product was isolated with the double-filtration method, the catalyst was dried at room temperature and it was used again under the same reaction conditions. The catalyst activity decreased slightly but steadily over the course of reactions. After 5 cycles the isolated yield had decreased by 15% (cycle 1 vs cycle 5). For comparison, the yield with Zn-modified fluoro-apatite dropped with three cycles from 90% to 30%[29b]. In our case it was assumed that moistening of the catalyst was responsible for the decrease of the yield. Therefore, after step 5, the recovered hydroxy-apatite was heated at 100 °C for one hour and reused again affording 91% of isolated yield (cycle 6). After drying it at room temperature and using it once more, an isolated yield of 69% was obtained (cycle 7).

CONCLUSION

In conclusion, we have developed a solvent-free protocol for the Biginelli reaction. Among the non-modified and modified apatites used in this reaction, the most efficient catalyst is the highly stable non-modified HAp, which avoided poisoning the target with metal cations. The catalyst could be repeatedly used in several consecutive runs. It could be activated simply by heating and used again without loss of its activity. The simplicity of the procedure makes the protocol potentially useful for other HAp-catalysed reactions.

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