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

Sana Ben Moussa [a], Jalel Lachheb [a], Michel Gruselle [b, c, *], Birgit Maaten [d], Kadri Kriis [e], Tõnis Kanger [e], Kaia Tõnsuaadu [f], 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
[c] Sorbonne Universités, UPMC Univ. Paris 06, UMR 8232, Institut Parisien de Chimie Moléculaire, F-75005 Paris, France
[d] Department of Energy Technology, Tallinn University of Technology, Ehitajate tee 5, Tallinn 19086, Estonia
[e] Department of Chemistry and Biotechnology, Tallinn University of Technology, Akadeemia tee 15, 12618 Tallinn, Estonia
[f] Laboratory of Inorganic Materials, Tallinn University of Technology, Ehitajate tee 5, 19086 Tallinn, Estonia

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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 a 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]

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*".

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* Corresponding author. CNRS, UMR 8232, Institut Parisien de Chimie Moléculaire, F-75005 Paris, France.
E-mail address: michel.gruselle@upmc.fr (M. Gruselle).

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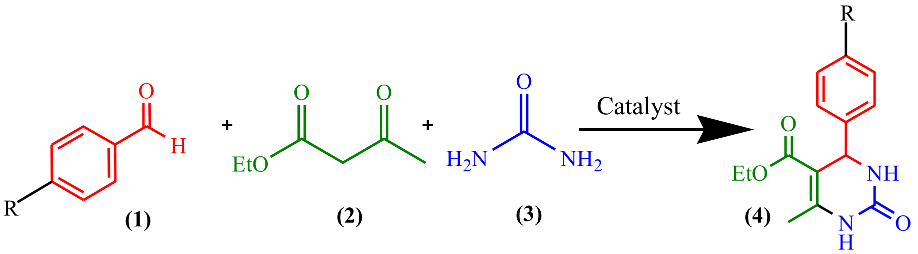

4a) R= H

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.

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,[35] 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).

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

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	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.