Natural Hydroxyapatite $Ca_5(PO_4)_3OH$: An Efficient Catalyst for the Chemo- and Regioselective Enamination of the β-Ketoesters

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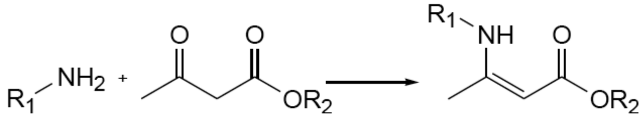
Abstract: Hydroxylapatite or hydroxyapatite $Ca_5(PO_4)_3OH$ (Hap), a natural mineral species of the family of phosphate, efficiently catalyzed the condensation of 1,3-ketoesters with primary amines under solvent-free conditions. The reaction was complete in 10 min, to afford β-enamino esters in a high yield and good selectivity. Moreover, the catalyst can be re-used for four times with good activities.

Keywords: Hydroxyapatite, Catalyst, Condensation, β-enaminoester, Solvent free.

INTRODUCTION

β-Enaminoesters are highly useful building blocks [1-3], which can be precursors for valuable natural therapeutic and biologically active compounds such as anticonvulsivant [4, 5], anti-inflammatory [6], and antitumor agents [7, 8]. Moreover, they are useful intermediates for the preparation of α, β aminoacids [9, 10], aminoesters [11], peptides [12], azocompounds [13, 14] quinolines [15, 16], and alkaloids [17-19]. Owning to their significances interest in organic synthesis, considerable efforts have been dedicated to study the synthesis of β-enaminones and β-enaminoesters. Various conditions and methods are reported in the literature [20-21]. However, these methods present some drawbacks such as long reaction time, expensive catalysts, high temperature and the use of hazardous solvent such as benzene [22].



Scheme 1: Condentation of β-ketoesters and primary amines

Other improved methods for this amination reaction were successively developed [23-28], such as the addition of zinc ester enolates or amide enolates to nitriles [29]. Some improved procedures have been also reported which use protonic acids such as PTSA [30]. Thus, a search for a new catalyst and simple procedure in mild and green conditions are of practical importance. Especially, catalysts which are a stable, inexpensive, non-toxic and readily producible from available materials.

Recently, we have reported a simple method for their preparation using $Ca(CF_3COO)_2$ as catalyst under solvent free conditions [31]. We have shown that the condensation of primary amines with cyclic and acyclic β-ketoesters occurs in mild conditions, with high yield and good selectivity [31-33].

In the course of our studies on the preparation of β-enaminoesters and following our objective on the use of available and eco-friendly catalyst, we focused our efforts on the use of hydroxyapatite $Ca_5(PO_4)_3OH$, as natural mineral species of the family of phosphate, to catalyze the desired reaction.

Our results show that the condensation of primary amines with β-ketoesters in solvent free conditions using natural hydroxyapatite as catalyst give the corresponding β-enaminoesters in good to excellent yields. Hence, this procedure provides in addition noticeable advantages in terms of economical, environmental and safety reasons.

Hydroxyapatites are very important inorganic materials in biology and chemistry [34]. The biological HAp is the most frequent crystalline phosphates of calcium [35], first mineral constituent of bones, tooth enamel and dentin; they are very flexible in term of composition and morphology. In chemistry, hydroxyapatite has received considerable attention due

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to its ion exchange ability, adsorption capacity, macroligand behaviour and acid-base properties [36].

EXPERIMENTAL SECTION

Materials

NMR studies were performed on a Bruker Avance 300 spectrometer in $CDCl_3$, chemicals shifts are given in ppm relative to external TMS and the coupling constant (J) in Hz. The reaction mixtures were analyzed on a Trace GC Shimadzu chromatograph equipped with an FID detector. GC parameters for capillary columns B5 (25 m x 0.25 mm, SGE): injector 240 °C; detector 240 °C; oven 70 °C for 5 min then 3 °C min^{-1} until 250 °C for 30 min; column pressure 20 kPa, column flow 6.3 mL min^{-1}, linear velocity 53.1 cm s^{-1}; total flow 138 mL min^{-1}. Liquid chromatography was performed on silica gel (Merck 60, 220-440 mesh). All the reagents and solvents used in the experiments were purchased from commercial sources as received without further purification (Aldrich, Acros).

General Procedure for the Catalytic Studies

In a typical experience, a mixture of 1.7 mmol of ketoester, 1.7 mmol of amines and 0.017 mmol of $Ca_5(PO_4)_3OH$ was stirred at room temperature for 10 min. The reaction was monitored by gas chromatography (GC). After completion of the reaction, 10 mL of distilled water was added and the product was extracted by ethyl acetate (3 x 25 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Pure β–enamioesters was obtained by silica gel column chromatography by using a mixture of hexane/ethyl acetate as eluent. All isolated pure products were characterized by ^1H and ^{13}C NMR and then compared with the known compounds [31].

RESULTS AND DISCUSSION

For optimization of the reaction conditions, a mixture of benzylamine and ethyl acetoacetate was reacted in different reaction conditions (Table **1**). The use of the catalyst is crucial for the reaction evolution; otherwise, without catalyst, high temperature is needed and low selectivity toward the β-enaminoester is obtained [31].

The reactions were examined in dichloromethane with 0.5 mol %, 0.68 mol %, and 1 mol % successively and we have found that 1 mol % catalyst is a sufficient amount for complete conversion as well as to obtain the best yield (entries 1).

The effect of different solvents has been studied at room temperature using 1 mol % of catalyst. All the solvents tested led to the desired product with low to moderate yield (Table **1**, entries 1, 4-7). The water, as green solvent, led to uncompleted reaction, only 40 % yield and low conversion are achieved (entry 7). The best result is obtained in free solvent conditions at room temperature, and the corresponding product was obtained in 96% yield (entry 8). At high temperature, the conversion increased while low selectivity is observed (entry 11).

Table 1: Optimization of the Condensation of Benzylamine and Ethyl-Acetoacetate Catalyzed by Hydroxyapatite

Entry	Solvent	Temperature (°C)	Molar ratio Substrate/Catalyst	Conversion[a] (%)	Yield[b] (%)
1	Dichloromethane	RT	100	71	68
2	Dichloromethane	RT	150	62	57
3	Dichloromethane	RT	200	47	43
4	Methanol	RT	100	58	56
5	Acetonitrile	RT	100	58	43
6	Acetone	RT	100	72	64
7	H_2O	RT	100	44	40
8	Free-solvent	RT	100	98	96
9	Free-solvent	40	100	97	91
10	Free-solvent	60	100	97	82
11	Free-solvent	80	100	99	61

[a] The conversion was determined by gas chromatography.
[b] Isolated yield.

After optimizing the reaction conditions, the catalyst was recovered for successive condensation showing an appreciable catalytic activity (Table **2**). The yields of corresponding β-enaminoester after 10 min at room temperature were still reasonably good after fourth run.

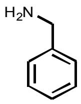
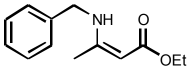
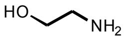
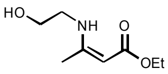
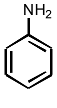
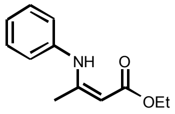
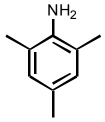
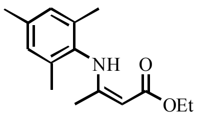
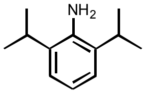
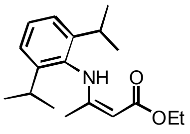
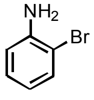
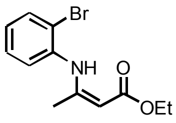
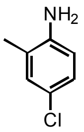
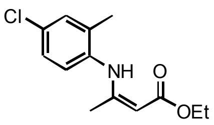
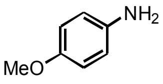
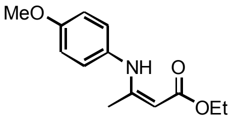
Tables 2: Condensation of Acetoacetate with Benzylamine Catalyzed by $Ca_5(PO_4)_3(OH)$

Recycling	Conversion[a] (%)	Yield[b] (%)
1	95	92
2	93	88
3	89	85
4	87	82

[a] The conversion was determined by gas chromatography.
[b] Isolated yield.

With the optimized conditions in hand, we next investigated a wide variety of primary amines with ethylacetoacetate using 1 mol % of hydroxyapatite at room temperature under free solvent condition. The desired products were obtained in good to excellent yields (Table **3**). The reaction proceeded well with aromatic and aliphatic amines giving the corresponding β-enamino-ester in excellent yields. As shown in Table **3**, reaction of various aryl amines carrying either electron-donating or electron withdrawing substituents were successfully reacted with ethyl acetoacetate to produce their corresponding β-enamino-ester in good yields with short reaction time (10 min). However, with aromatic amines possessing sterically hindering groups, reasonable yield were obtained with respect to aniline (Table **3**, entries 15-16).

Table 3: Condensation of Ethyl-Acetoacetate with Primary Amines Catalyzed by $Ca_5(PO_4)_3(OH)$

Entry	Amine	Product	Conversion[a] (%)	Yield[b] (%)
12			98	96
13			97	94
14			95	92
15			90	88
16			87	83
17			79	76
18			83	80
19			93	91

[a] The conversion was determined by gas chromatography.
[b] Isolated yield.

The ^{1}H NMR spectra analyses of the isolated products showed the formation of (Z)-enaminoester derivatives by the chemical shift of the -NH- group which appeared in the region of 8-10.9 ppm [31]. The X-ray study of a similar compounds shows that molecule assumes a Z conformation about the C=C bond. An S(6) ring motif is formed due to an intramolecular N-H···O hydrogen bond [32, 33].

CONCLUSION

In conclusion, we have described a simple, efficient, and cost effective protocol for the preparation of β-enaminoesters from β-ketoesters by their reaction with both aromatic and aliphatic amines using HAp ($Ca_5(PO_4)_3(OH)$) as naturally available and inexpensive catalyst. The reaction processes in short reaction time, at room temperature under solvent free conditions to afford the expected products in good to excellent yields. Moreover, the catalyst could be re-used at least four times, maintaining good activity for the selected reaction. The reaction gave exclusively the (Z) β-enaminoester derivatives which can be explained by the presence of intramolecular hydrogen bonding. The use of both natural hydroxyapatite and solvent-free conditions constitutes a sustainable and environment-friendly approach for the synthesis the target compounds.

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