

# An Eco-Friendly Paradigm for the Synthesis of $\alpha$ -Hydroxyphosphonates Using Sodium-Modified Fluorapatite under Solventless Conditions

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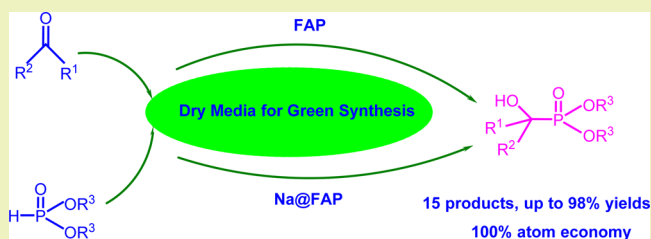
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**ABSTRACT:** A versatile and environmentally friendly method for the synthesis of various organophosphorus compounds have been developed using a heterogeneous catalysis technology. We have synthesized a series of the  $\alpha$ -hydroxyphosphonates, a biologically important class of compounds, via the Pudovik reaction between dialkylphosphite and aldehydes or ketones using sodium-modified fluorapatite (Na@FAP) as a highly efficient basic solid catalyst under solventless conditions at room temperature. Catalyst reuse, ease of separation of the pure product, and high yields are some of the unique features of this process.

**KEYWORDS:** Green Synthesis,  $\alpha$ -Hydroxyphosphonates, Fluorapatite, Sodium-modified fluorapatite, Heterogeneous catalysis, Without solvent



## INTRODUCTION

The synthesis of  $\alpha$ -hydroxyphosphonates have received a lot of attention due to their biological activities especially as chiral derivatives,<sup>1</sup> such as antiviral, antibacterial, anticancer, pesticides, renin inhibitors, HIV protease, and enzyme inhibitor properties.<sup>2</sup> The relatively inert nature of the C–P bond and the physical and structural similarity of phosphonic and phosphinic acids to the biologically important phosphate ester and carboxylic acid functionality<sup>3</sup> are the characteristics that give these derivatives multiple activities and thus a wide range of applications. It should be noted that there is a crucial role of this class of products as starting materials for the synthesis of many interesting and useful products.<sup>4</sup> Various methods have been used to synthesize the  $\alpha$ -hydroxyphosphonates, and the most versatile of them are inspired by old methods described by Pudovik<sup>5</sup> and Abramov.<sup>6</sup> There are direct pathways for the formation of C–P bonds, involving the addition of organophosphorus compounds containing a labile P–H bond to unsaturated systems (i.e., aldehydes or ketones). In homogeneous media, a variety of catalysts such as sodium alkoxide,<sup>5,6</sup> triethylamine,<sup>7</sup> ethyl magnesium bromide,<sup>8</sup> potassium cesium fluoride,<sup>9</sup> quinine,<sup>10</sup> LDA,<sup>11</sup> TMG,<sup>12</sup> DBU (1,8-diazabicyclo[5.4.0]undec-7-ene),<sup>13</sup> boron trifluoride etherate,

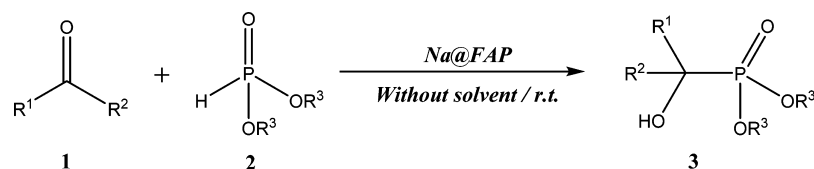
$\text{AlCl}_3$  or  $\text{HCl}$ ,<sup>14</sup> TFA or  $\text{TfOH}$ ,<sup>15</sup>  $\text{Ti}(\text{O}^i\text{Pr})_4$ ,<sup>16</sup>  $\text{TMSCl}$ ,<sup>2,17</sup>  $\text{LiClO}_4 \cdot \text{Et}_2\text{O}$ ,<sup>18</sup>  $\text{NH}_4\text{VO}_3$ ,<sup>19</sup> guanidine hydrochloride,<sup>20</sup> and  $\text{MoO}_2\text{Cl}_2$ <sup>21</sup> have been employed to carry out this condensation. However, these methodologies suffer from disadvantages such as toxicity of reagents, corrosiveness due to acid or basic reagents employed, moisture sensitivity of the catalyst, requirement of high temperatures, use of hazardous organic solvents, and inconvenient handling procedures.<sup>22</sup> Heterogeneous catalysis is one of the technological pillars of green chemistry allowing the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.<sup>23,24</sup> The use of heterogeneous catalysts provides a perfect solution to overcome the above limitations, and there are many reports on solid catalysts for this reaction, including  $\text{Al}_2\text{O}_3$ ,<sup>25</sup>  $\text{KF}/\text{Al}_2\text{O}_3$ ,<sup>26</sup>  $\text{K}_2\text{CO}_3$ ,<sup>27</sup> polymer-supported 1,5,7-triazabicyclo[4.4.0]dec-1-ene (TBD) (P-TBD),<sup>28</sup> polystyrenetetraalkylammonium hydroxide ion-exchange resin [Rexyn 201(OH)],<sup>29</sup>  $\text{CaO}$ ,<sup>30</sup> and  $\text{MgO}$ .<sup>31</sup> Shinde et al. have used an organocatalyst (Camphos sulfonic acid, CSA) assisted

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## Scheme 1. Addition of Dialkylphosphite to Aldehydes or Ketones



by an ultrasound technique.<sup>32</sup> More recently, G. Keglevich et al. have synthesized a series of  $\alpha$ -hydroxyphosphonates under microwave conditions using  $\text{Na}_2\text{CO}_3$  as such a catalyst.<sup>33</sup> Our group also contributes to the development of new methods of synthesis of the  $\alpha$ -hydroxyphosphonates. We use catalysts based on natural or synthetic phosphate for condensation of the dialkylphosphites to the aldehyde or ketone in dry media without any solvent.<sup>34</sup>

Fluorapatite (FAP,  $\text{Ca}_{10}(\text{PO}_4)_6(\text{F})_2$ ) is one of the most promising materials for bone replacement because of its osteoconductive and biocompatibility properties.<sup>35</sup> When used as a catalyst, FAP has the unusual property of containing both acid and basic sites in a single crystal lattice. Many organic reactions have been achieved using FAP as a catalyst or for supporting a catalyst, for example, in the Knoevenagel reaction,<sup>36</sup> Michael addition,<sup>37</sup> Friedel crafts alkylation reaction,<sup>38</sup> trans-esterification reaction,<sup>39</sup> synthesis of 3,4-dihydropyrimidin-2-ones,<sup>40</sup> synthesis of 5-arylhydantoins,<sup>41</sup> allylation of aldehydes,<sup>42</sup> synthesis of trisubstituted olefins,<sup>43</sup> and Suzuki and Heck coupling reactions.<sup>44</sup> Recently, we have reported the hydration of nitriles to the corresponding amides catalyzed by the sodium-modified fluorapatite in water.<sup>45</sup> On the basis of these results, we report herein a new application of the sodium-modified fluorapatite for the catalysis of the addition of dialkylphosphate to aldehydes or ketones with good yields under mild conditions (Scheme 1).

## EXPERIMENTAL SECTION

**Materials and Apparatus.** All commercial reagents were purchased from Aldrich Chemical Co. Elemental analysis (Ca, P, Na) was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) from Yvan Jobin (Ultimate 2). Thermogravimetric analyses (TGA) were conducted under air using a TA Instruments Q500 apparatus with  $10^\circ\text{C}/\text{min}$  ramp between 25 and  $1000^\circ\text{C}$ . Fourier Transform Infrared (FT-IR) spectra of samples in KBr pellets were measured on a Bruker Vector 22 spectrometer. X-ray diffraction (XRD) patterns of the catalyst were obtained at room temperature on a Bruker AXS D-8 diffractometer using  $\text{Cu K}\alpha$  radiation in Bragg–Brentano geometry ( $\theta$ – $2\theta$ ). Scanning electron microscopy pictures were recorded on a FEI Quanta 200 microscope after carbon metallization. The specific surface areas were determined from the nitrogen adsorption/desorption isotherms (at 77 K) measured with a Quantachrome Autosorb-1 automatic analyzer, using the BET equation at  $p/p_0 = 0.98$ . NMR spectra were recorded on a Bruker ARX 300 spectrometer.

**Catalysts Preparation.** The synthesis of fluorapatite [ $\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$ ] is carried out by a co-precipitation method. An amount of 250 mL of an aqueous solution containing 7.92 g of diammonium phosphate and 1.00 g of  $\text{NH}_4\text{F}$ , maintained at a pH greater than 12 by addition of ammonium hydroxide (15 mL), was dropped under constant stirring into 150 mL of an aqueous solution containing 23.6 g of calcium nitrate [ $\text{Ca}(\text{NO}_3)_2 \cdot \text{H}_2\text{O}$ ]. The suspension was then refluxed for 4 h. The obtained FAP was filtered, washed with doubly distilled water, dried overnight at  $80^\circ\text{C}$ , and calcined at  $700^\circ\text{C}$ .

$\text{Na@FAP}$  was prepared by adding 10 g of FAP to an aqueous solution of sodium nitrate (50 mL, 1.17 M). The mixture was then

stirred, evaporated to dryness, and calcined under open air for 1 h at  $650^\circ\text{C}$  before use.

**General Procedure for the Synthesis of the  $\alpha$ -Hydroxyphosphonates.** To a flask containing an equimolar mixture (2.5 mmol) of aldehyde or acetophenone 1 and dialkylphosphite 2 (Scheme 1), the catalyst (1 g) was added, and the mixture was vigorously stirred with a spatula at room temperature ( $20$ – $25^\circ\text{C}$ ) and left for the appropriate time (Tables 1 and 2).  $\text{CH}_2\text{Cl}_2$  (20 mL) was

**Table 1.** Data of Porosity of FAP and  $\text{Na@FAP}$

	surface area ( $\text{m}^2/\text{g}$ )	total pore volume ( $\text{cc/g}$ )
FAP	15.4	0.058
$\text{Na@FAP}$	5.4	0.0032


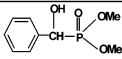

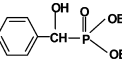

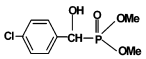

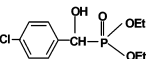
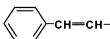
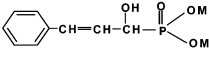
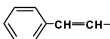
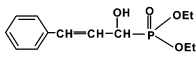

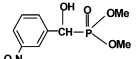

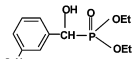

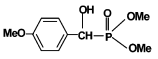

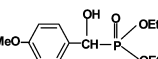

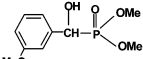
added, and the catalyst was filtered off. The solution was concentrated to give a residue, which was purified by recrystallization. The products were identified by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, IR spectroscopy, and mass spectrometry. The recovered  $\text{Na@FAP}$  was reactivated by calcination at  $500^\circ\text{C}$  for 1 h after being acetone washed.

## RESULTS AND DISCUSSION

Initially, we synthesized and then characterized the catalytic materials by several analytical techniques. FAP was prepared by reaction between diammonium phosphate, calcium nitrate, and ammonium fluoride in the presence of ammonia as described previously.<sup>36</sup> The FAP was calcined at  $700^\circ\text{C}$  before use.  $\text{Na@FAP}$  was prepared by impregnation of the FAP with a solution of sodium nitrate ( $\text{NaNO}_3/\text{FAP} = 1/2$  w/w) followed by drying and calcination at  $650^\circ\text{C}$ . The Ca/P ratio was determined by elemental analysis, and the obtained results matched the expected ratio for FAP (1.65). X-ray diffraction of the FAP powder confirmed the apatitic-type structure for this material, with the peaks matching the ASTM file (ICPDS Cards No. 15-876). The sharp and distinct peaks indicate a high degree of crystallinity (Figure 1). The lattice parameters for the fluorapatite were  $a = 9.37 \pm 0.01 \text{ \AA}$  and  $c = 6.88 \pm 0.005 \text{ \AA}$ , respectively. The XRD patterns of calcined  $\text{Na@FAP}$  show evidence of new phases, among which the CaO phase ( $2\theta = 32.2, 37.5, \text{ and } 54.0$ ) was clearly identified. Two other new phases are probably  $\text{CaNaPO}_4$  and  $\text{Na}_2\text{Ca}_4(\text{PO}_4)_3\text{F}$  obtained by an exchange of sodium with calcium. No crystalline phases of  $\text{Na}_2\text{O}$  and  $\text{CaF}_2$  were observed nor were  $\text{Ca}(\text{OH})_2$  or  $\text{CaCO}_3$ .

From IR analysis, broad absorption bands in the range  $965$ – $1100 \text{ cm}^{-1}$  were observed, indicating the presence of  $\text{PO}_4$  (Figure 2). Hydroxyl bands are not evident. For  $\text{Na@FAP}$ , the OH bond in the IR spectrum has been reported to be in the region of  $3500 \text{ cm}^{-1}$  along with a broad peak at around  $1460 \text{ cm}^{-1}$ . The calcination of  $\text{NaNO}_3$ -impregnated material leads to thermal decomposition of nitrate,<sup>45</sup> which is expected to lead to sodium oxide. The highly reactive oxide is unlikely to ever exist as such, and therefore, we believe that the thermal decomposition is accompanied by a structural rearrangement, leading to a material with  $\text{Ca}(\text{OH})_2$  units as part of its structure. It may be that the CaO phase is formed by the decomposition of  $\text{Ca}(\text{OH})_2$  at  $650^\circ\text{C}$  forming also by the

Table 2. Addition of Aldehydes on the Alkylphosphites over Apatite as Catalyst without Any Solvent

Entry	R <sup>1</sup>	R <sup>3</sup>	Product	Yields (%) <sup>a</sup>	
				FAP	Na@FAP
1		-Me		51 (60)	98 (1)
2		-Et		50 (60)	94 (1)
3		-Me		35 (30)	97 (1)
4		-Et		34 (30)	90 (1)
5		-Me		40 (30)	95 (1)
6		-Et		40 (30)	93 (1)
7		-Me		67 (60)	89 (1)
8		-Et		60(60)	90 (1)
9		-Me		20 (60)	80 (1)
10		-Et		15 (60)	83 (1)
11		-Me		17 (60)	80 (1)

<sup>a</sup>Values given in parentheses denote the time in minutes.

substitution of Na by Ca of the apatitic structure. The mixture of all phases (CaNaPO<sub>4</sub>, Na<sub>2</sub>Ca<sub>4</sub>(PO<sub>4</sub>)<sub>3</sub>F, and CaO) leads to a material that may be responsible for the catalytic activity.

TGA studies were carried out to analyze weight loss during the thermal processing of the powder after drying. A typical TGA curve is shown in Figure 3. It can be observed that there are two major weight losses. The first weight loss, below 250 °C, corresponds to the removal of water and the next one between 250 and 650 °C is due to the decomposition of the nitrate. The surface areas of calcined FAP and Na@FAP were determined by the BET method (Figure 4), and total pore volumes were calculated by the BJH method. The results are shown in Table 1. Figure 5 shows electron micrographs of samples of FAP and Na@FAP. Their comparison reveals a slight difference in the shape as well as in the arrangement of the crystals. To determine the basic properties of those catalysts, we have previously studied<sup>45</sup> the adsorption of those

materials with a molecule of acid character like phenol ( $pK_a = 9.9$ ). The amount of basic centers in the FAP and Na@FAP were determined by adsorption of phenol at different initial concentrations. The extrapolation at zero concentration was carried out to minimize the effect of physisorption. Values of 0.44 and 0.57 mmol/g were obtained, respectively, for FAP and Na@FAP.

After synthesis and characterization of fluorapatite and Na@FAP, we tested these two materials as catalysts in the synthesis of  $\alpha$ -hydroxyphosphonates in dry media without solvent (Tables 2 and 3), which tends to a green synthesis strategy, going from modernization of organic synthesis toward sustainability.

Initially, we studied the influence of several parameters on a model condensation (synthesis of  $\alpha$ -hydroxyphosphonate, **3a**), specifically: (i) optimal catalyst preparation conditions (Na@FAP), (ii) quantity of catalyst, and (iii) kinetics of the reaction.

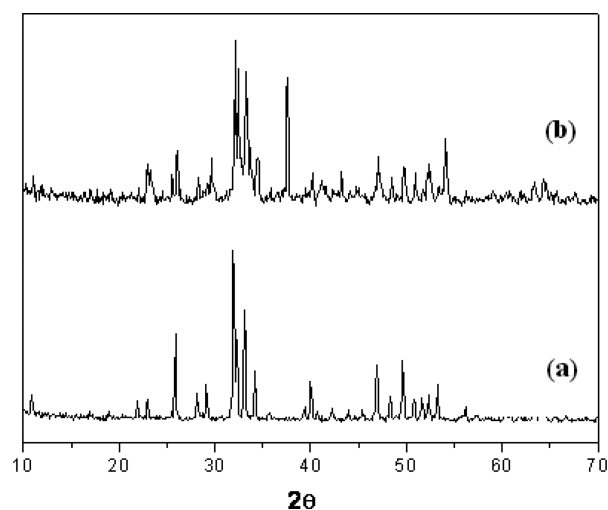


Figure 1. X-ray diffraction of FAP (a) and Na@FAP (b).

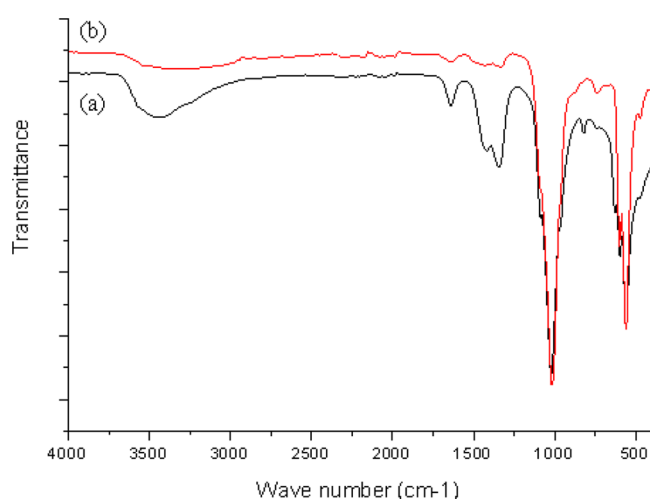


Figure 2. FT-IR spectra of noncalcined Na@FAP (a) and calcined Na@FAP at 650 °C.

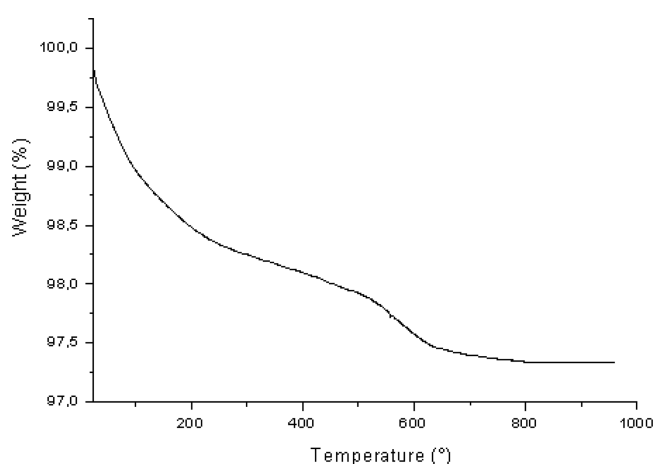


Figure 3. Thermal gravimetric analysis (TGA) of fresh Na@FAP.

For the first study, we have adopted a mass ratio,  $r = m(\text{NaNO}_3)/m(\text{FAP}) = 1/2$  because we have already demonstrated in previous and similar works that the best mass ratio of  $\text{NaNO}_3/\text{support}$  (natural phosphate or hydroxyapatite) is  $r = 1/2$ .<sup>46,47</sup> Then, we optimized the ideal

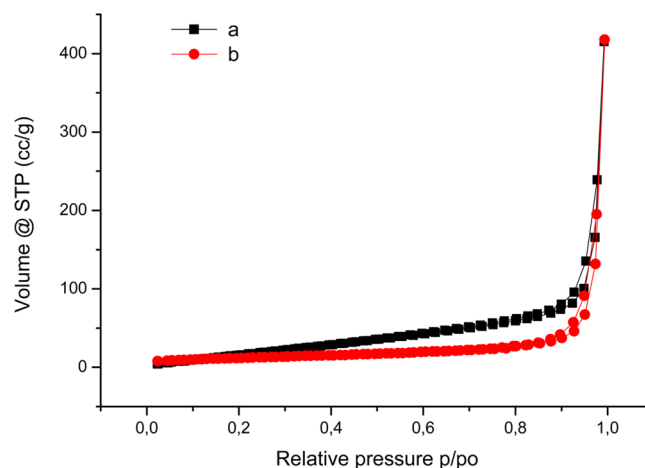


Figure 4. Nitrogen adsorption/desorption isotherm of sodium-modified FAP (a) and FAP (b).

temperature of the calcination of this material ( $r = m(\text{NaNO}_3)/m(\text{FAP}) = 1/2$ ), and thus, we studied the influence of calcination temperature on the activity of this catalyst toward synthesis of product 3a chosen as a model reaction for this study. We therefore reacted benzaldehyde and dimethyl phosphite in dry conditions in the presence of 1 g of calcined  $\text{NaNO}_3/\text{FAP}$  at different temperatures, namely, 150, 300, 500, and 650 °C, respectively. The obtained yields are, respectively, 6%, 11%, 14%, and 98%. This study clearly demonstrates that the origin of the catalytic property of the prepared materials is dependent on the calcination temperature. Subsequently, we adopted 650 °C as the calcination temperature for obtaining Na@FAP. Nevertheless, a series of  $\alpha$ -hydroxyphosphonate compounds have been synthesized. The condensation of the carbonyl compounds (2.5 mmol) with dialkylphosphites (2.5 mmol) was carried out in the presence of 1 g catalyst (FAP, Na@FAP) at room temperature without solvent. The products were isolated at the end of the reaction and were purified by recrystallization in cyclohexane and then analyzed by  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR. The results are summarized in Tables 1 and 2.

It is clear that FAP alone can catalyze these condensations and yields increase with longer reaction times providing that there is no poisoning of the surface of the FAP; only the slowness of the kinetics of the reaction led to poor yields in short periods of time. The use of Na@FAP led to a significant improvement in yields as well as in (reduced) reaction times. The impregnation of FAP by sodium is an interesting method that has already proven to give a very active catalyst but not for this type of application.<sup>45</sup> Here, 15 products were easily prepared with yields exceeding 90% in the majority of cases. The condensation is more rapid with aldehydes than with ketones. However, for both sets of aldehydes and ketones, we note a difference in reactivity due to the influence of substituent's aromatic ring.

One of the most important features of a heterogeneous catalyst is the ease of the recovery and reuse. Na@FAP was recovered and dried at 150 °C before being tested for the synthesis of 3a. After a 4 cycle run, a progressive decrease in yield was observed as shown in Figure 1, indicating catalyst exhaustion. This behavior can be explained by the accumulation of organic substrates over the active sites of the catalyst. However, we were able to achieve a complete regeneration of the catalyst when washed by acetone and then calcined at 500 °C before its reuse. Figure 6 shows the activity profile of the



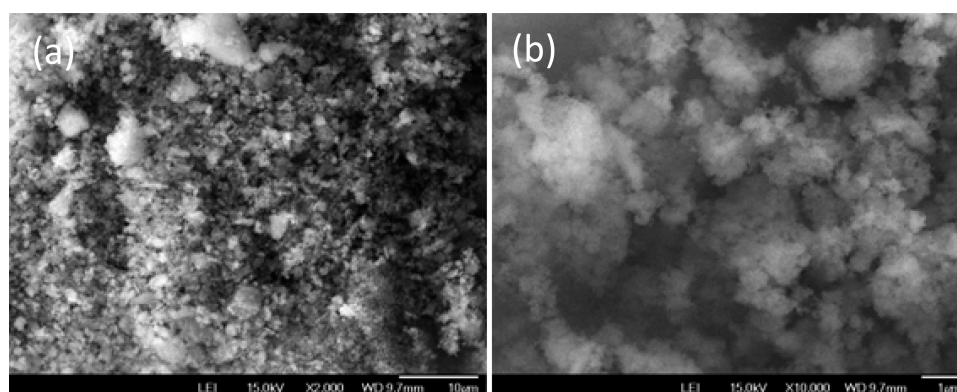


Figure 5. Scanning electron microscope (SEM) pictures of FAP (a) and Na@FAP (b).

Table 3. Addition of Ketones on Alkylphosphites over Phosphate-Based Catalysts without Any Solvent

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Product	Yields (%) <sup>a</sup>	
					FAP	Na@FAP
1		CH <sub>3</sub>	-Me		41 (12)	94 (1)
2		CH <sub>3</sub>	-Me		32 (12)	75 (1) 98 (1.5)
3		CH <sub>3</sub>	-Me		45 (12)	97 (1)
4		CH <sub>3</sub>	-Et		40(12)	98 (1)

<sup>a</sup>Values given in parentheses denote the time in hours.

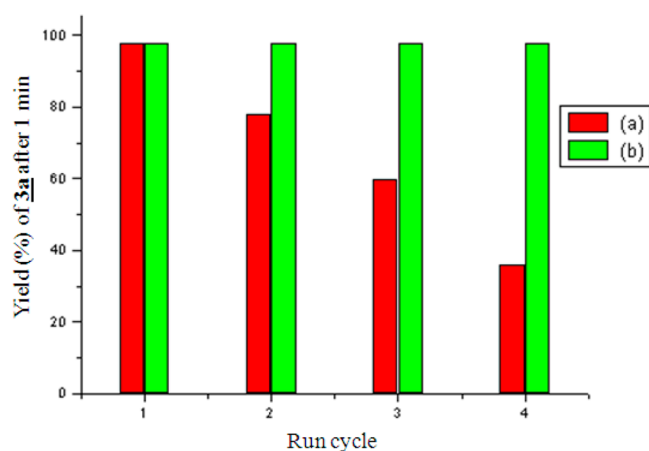


Figure 6. Reuse of Na@FAP catalyst in the synthesis of  $\alpha$ -hydroxyphosphonate 3a.

catalyst after a 4 cycle run. On the other hand, the analysis of the reaction mixture by ICP-OES showed the complete absence of sodium, which clearly demonstrated that not leaching this element occurred from the catalyst.

## CONCLUSIONS

In conclusion, we have developed a clean and easy method for the synthesis of  $\alpha$ -hydroxyphosphonates using an inexpensive, reusable, easy to handle, noncorrosive, and environmentally benign catalysts, fluorapatite and especially sodium-modified fluorapatite, in dry media. The use of these catalysts offers diverse advantages including simplicity of operation due to the heterogeneous nature of reaction, easy workup, high yields, and catalyst reusability.

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### Notes

The authors declare no competing financial interest.

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