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## $\text{Na}_2\text{CaP}_2\text{O}_7$ a new catalyst for the synthesis of $\alpha$ -amino phosphonates under solvent-free conditions at room temperature

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### Abstract

The synthetic diphosphate  $\text{Na}_2\text{CaP}_2\text{O}_7$  was found to be an efficient reagent for the synthesis of  $\alpha$ -amino phosphonates from imines and dialkyl phosphites. The addition of the dialkyl phosphite was carried out under mild conditions at room temperature without solvent. The catalyst was very stable and could be reused several times with high catalytic activity. **To cite this article:** A. Elmakssoudi et al., C. R. Chimie 8 (2005).

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### Résumé

Le diphosphate synthétique  $\text{Na}_2\text{CaP}_2\text{O}_7$  est un nouveau et puissant catalyseur pour la synthèse des  $\alpha$ -amino phosphonates à partir des imines et des phosphites de dialkyles. L'addition du phosphite de dialkyle est réalisée dans des conditions opératoires simples et douces à température ambiante et en absence du solvant. Notre catalyseur est stable et peut être utilisé plusieurs fois sans perdre son activité catalytique. **Pour citer cet article :** A. Elmakssoudi et al., C. R. Chimie 8 (2005).

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**Keywords:** Synthetic diphosphate;  $\alpha$ -Amino phosphonates; Heterogeneous catalysis; Recyclable catalyst

**Mots clés :** Diphosphate synthétique ;  $\alpha$ -Amino phosphonates ; Catalyse hétérogène ; Catalyseur recyclable

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## 1. Introduction

Surface-mediated solid phase reactions are of growing interest [1] because of their advantages of ease of set up, mild conditions, rapid reactions, selectivity, increased yields of the products and low cost compared with their homogeneous counterparts.

$\alpha$ -Amino phosphonates are an important class of compounds in modern pharmaceutical chemistry [2]. Peptido mimetics [3] made out of this class of compounds have shown promising pharmacological properties [4]. They also play an important role in hapten design for antibody generation [5] and enzyme inhibitors [6].

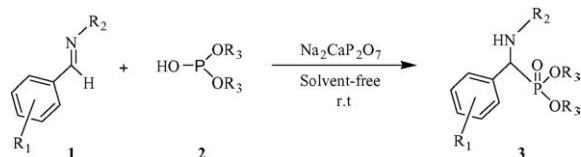
As a result, a variety of synthetic approaches have been developed for the synthesis of  $\alpha$ -amino phosphonates. Of these methods, the nucleophilic addition of phosphates with imines [7], catalysed by an acid or a base is one of the most convenient methods. Lewis acids [8] are known to catalyse these reactions under mild conditions. Interesting applications of this type of reactions have been reported by Simoni et al. [9], who has developed a procedure for the synthesis of  $\alpha$ -amino phosphonates using tetramethylguanidine as a catalyst. Recently,  $\text{CdI}_2$  [10] was also found to be effective for this transformation. However,  $\text{CdI}_2$  has been used in benzene and heating at 40–45 °C.

In this report, a new method for the synthesis of  $\alpha$ -amino phosphonates on a solid surface is described. It was found that synthetic diphosphate  $\text{Na}_2\text{CaP}_2\text{O}_7$  under solvent-free conditions at room temperature is capable of the synthesis of  $\alpha$ -amino phosphonates from imines and dialkyl phosphite under mild reaction conditions in few minutes (Scheme 1).

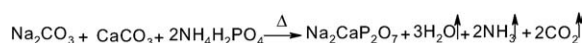
## 2. Experimental

### 2.1. Preparation of the catalyst and structural characteristics

The synthetic phosphate  $\text{Na}_2\text{CaP}_2\text{O}_7$  has been prepared by reaction between  $\text{Na}_2\text{CO}_3$ ,  $\text{CaCO}_3$  and



Scheme 1. Synthesis of  $\alpha$ -amino phosphonates in the presence the  $\text{Na}_2\text{CaP}_2\text{O}_7$  catalyst.



Scheme 2.

$\text{NH}_4\text{H}_2\text{PO}_4$  (Scheme 2) as described previously [11]. The final product is identified by X-ray powder diffraction using a Siemens D-500 diffractometer (Cu  $K\alpha$  radiation 1.5406 Å; Space group: triclinic  $P\bar{1}$ ;  $a = 5.361$  Å,  $b = 7.029$  Å and  $c = 8.743$  Å) and infrared spectroscopy.

The structure is characterised by the presence of tunnels with similar dimension along the three directions [100], [010] and [001]. Fig. 1 gives a projection view of the structure along the crystallographic plane (100) [12]. Two kind of tunnels are present and both running along the [100] direction. They are built up from  $\text{P}_2\text{O}_7$  groups and  $\text{CaO}_6$  octahedra. Their dimension could be estimated by the respective distances ( $d_1 = 4.16$  Å,  $d_2 = 6.90$  Å) and ( $d_3 = 4.04$  Å,  $d_4 = 5.93$  Å). This space is not totally free because it is reduced by the presence of sodium cations which exhibit two kind of crystallographic sites (Fig. 1). The size distribution of the powder particles was determined. The result shows that all the sizes were statistically distributed below 50  $\mu\text{m}$ . The surface area of calcined  $\text{Na}_2\text{CaP}_2\text{O}_7$  was determined by the BET method from the adsorption–desorption isotherm of nitrogen at its boiling temperature, using a conventional volumetric apparatus and was equal to 2.4  $\text{m}^2 \text{g}^{-1}$ .

### 2.2. Preparation and characterisation of imine 1a–j

The imine **1a–j** were easily prepared by simple chemistry starting from the commercially available amines and aromatic aldehydes under standard conditions [13] (see Scheme 3 and Table 1).

### 2.3. Materials and methods

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker DRX-400 spectrometer in  $\text{CDCl}_3$ , using  $\text{CDCl}_3$  as internal standard. The chemical shifts ( $\delta$ ) are expressed in ppm relative to  $\text{CDCl}_3$  and coupling constant ( $J$ ) in Hertz. IR spectra were obtained on a FTIR (ATI Mattson-Genesis Series) and reported in wave numbers ( $\text{cm}^{-1}$ ). Surface area and pore size analysis were carried out at 77 K on a Micromeritics ASAP2010 instrument using nitrogen as adsorbent. X-ray diffraction patterns of the catalysts

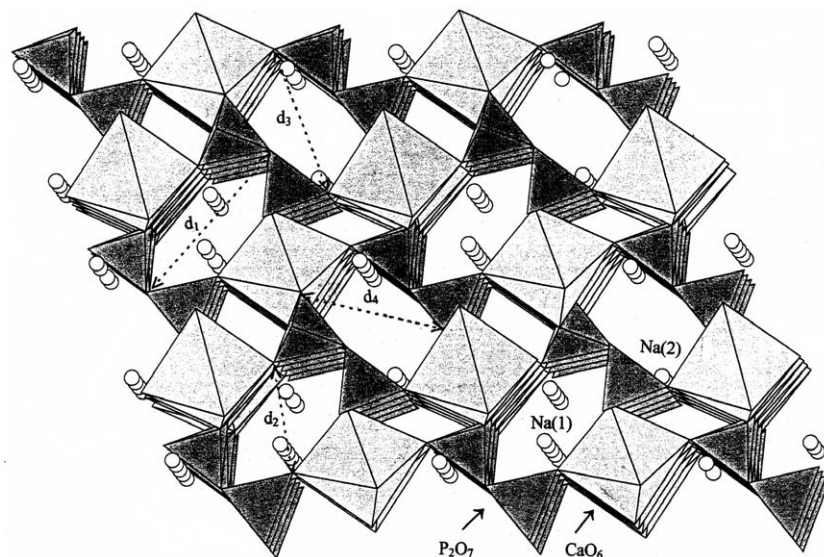
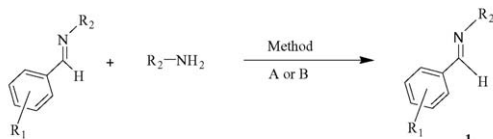


Fig. 1. Projection view of  $\text{Na}_2\text{CaP}_2\text{O}_7$  on the (100) plane ( $d_1 = 4.16 \text{ \AA}$ ,  $d_2 = 6.90 \text{ \AA}$  and  $d_3 = 4.04 \text{ \AA}$ ,  $d_4 = 5.93 \text{ \AA}$ ).

were obtained on a Philips 1710 diffractometer using  $\text{Cu-K}\alpha$  radiation. Melting points were determined with a “Thomas Hoover” melting (capillary method) apparatus and are uncorrected. Flash column chromatography was performed using Merck silica gel 60 (230–400 mesh ASTM).

#### 2.4. Typical experimental procedure

To a mixture of diphosphate catalyst 0.3 g and the imine **1** (1 mmol) was added dialkyl phosphite **2** (1.1 mmol). The mixture was stirred under solvent-free conditions at room temperature. The reaction progress was monitored by TLC (thin layer chromatography). The reaction mixture was diluted with dichloromethane, filtered out and the catalyst was washed with dichloromethane. After concentration of the filtrate under reduced pressure, the crude product was purified by silica gel column chromatography using *n*-hexane/ethyl acetate (80:20) as eluent. The product structure was analysed by  $^1\text{H}$ ,  $^{13}\text{C}$  NMR melting points and IR spectrometry.



Method A:  $\text{Na}_2\text{SO}_4/\text{Et}_2\text{O}/\text{r.t.}$ ; Method B: Dean Stark/Toluene

Scheme 3. Preparation of imine **1a–j** by two methods.

### 3. Result and discussion











To examine the catalytic activities of synthetic diphosphate  $\text{Na}_2\text{CaP}_2\text{O}_7$  [14] under solvent-free conditions at room temperature, we carried out the reaction of *N*-phenylbenzaldimine ( $\text{R}_1 = \text{H}$ ,  $\text{R}_2 = \text{Ph}$ , Scheme 1) and diethyl phosphite, in presence of various amount of catalyst. After 15 min of reaction the yields of product **3a** are summarised in Fig. 2. The best result was obtained with 0.3 g of  $\text{Na}_2\text{CaP}_2\text{O}_7$ .

In order to determine the scope and limitations associated with this catalyst, the optimum conditions for the reaction of *N*-phenylbenzaldimine ( $\text{R}_1 = \text{H}$ ,  $\text{R}_2 = \text{Ph}$ , Scheme 1) and diethyl phosphite were applied to other substrate (Table 2).

As shown in Table 2, the imines **1** react with dialkyl phosphites **2** in the presence of synthetic phosphate  $\text{Na}_2\text{CaP}_2\text{O}_7$  to afford the desired products **3** in good to excellent yields in few minute (10–15 min).

The imine, possessing a phenyl substituent ( $\text{R}_1 = \text{H}$ ,  $\text{R}_2 = \text{Ph}$ , Scheme 1) reacted effectively with diethyl phosphite to afford the  $\alpha$ -amino phosphonate **3a** in excellent yields. Aromatic bearing an electron-donating substituent ( $\text{R}_1 = p\text{-MeO}$ ,  $p\text{-Me}$ ) increase the reaction rate. Aromatic bearing an electron-withdrawing substituent ( $\text{R}_1 = p\text{-Cl}$ ,  $p\text{-NO}_2$ ) decrease the reaction rate. Steric hindrance at the *ortho* position of the *N*-aromatic ring seems to disfavour both kinetic and yield of the reaction (entries 3i/3a and 3j/3c).

Table 1  
Synthesis of imine **1a–j** by the amines and aromatics aldehydes under standard conditions

Entry	Imines	R <sub>1</sub>	R <sub>2</sub>	Yield(%) / Time(h) <sup>a</sup>
1	<b>1a</b>	H		91(12) <sup>b</sup>
2	<b>1b</b>	<i>p</i> -Me		84(12) <sup>b</sup>
3	<b>1c</b>	<i>p</i> -OMe		88(12) <sup>b</sup>
4	<b>1d</b>	<i>p</i> -Cl		83(12) <sup>b</sup>
5	<b>1e</b>	<i>p</i> -NO <sub>2</sub>		76(12) <sup>b</sup>
6	<b>1f</b>	<i>o</i> -OH		80(12) <sup>b</sup>
7	<b>1g</b>	H		86(24) <sup>c</sup>
8	<b>1h</b>	<i>p</i> -OMe		90(24) <sup>c</sup>
9	<b>1i</b>	H		84(24) <sup>c</sup>
10	<b>1j</b>	<i>p</i> -NO <sub>2</sub>		76(24) <sup>c</sup>

Thus, we estimate that the surface of Na<sub>2</sub>CaP<sub>2</sub>O<sub>7</sub> presents certainly multicatalytic active sites. The basic sites (oxygens of P<sub>2</sub>O<sub>7</sub> group and CaO<sub>6</sub> octahedra) abstract the proton from the phosphite. The acidic sites (phosphorus of P<sub>2</sub>O<sub>7</sub> group, Na<sup>+</sup> and Ca<sup>2+</sup> cations) coordinate with the nitrogen of imine and facilitate the nucleophilic addition of dialkyl phosphite. Consequently, the C–P bond formation is facilitated and the

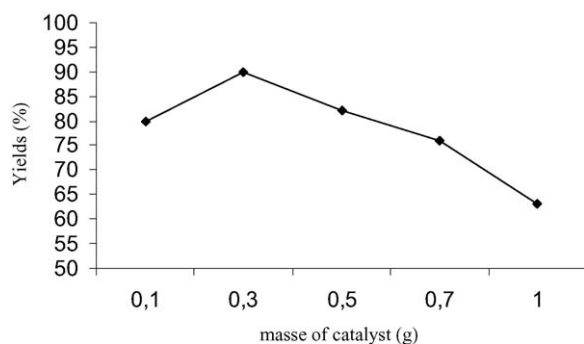


Fig. 2. Influence of amount of Na<sub>2</sub>CaP<sub>2</sub>O<sub>7</sub> in the synthesis of  $\alpha$ -amino phosphonate **3a**, time of reaction 15 min.

final  $\alpha$ -amino phosphonate is obtained by transfer of a proton.













We next investigated the stability of the catalyst in order to recycle it. The used and recovered Na<sub>2</sub>CaP<sub>2</sub>O<sub>7</sub> has been shown to be reusable after drying at 150 °C under vacuum, and more efficiently after washing with acetone followed by calcinations at 600 °C (Fig. 3). In the last case, the catalyst can be recovered and reused at least five times without appreciable loss of activity.

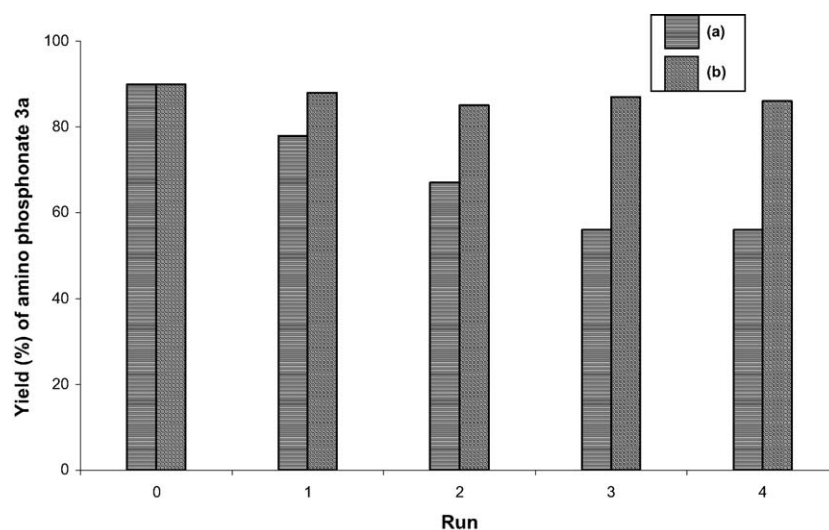
#### 4. Conclusion

We have developed a novel and effective route to  $\alpha$ -amino phosphonate derivatives **3** by the addition reaction of the dialkyl phosphites **2** to imines **1** using the synthetic diphosphate Na<sub>2</sub>CaP<sub>2</sub>O<sub>7</sub>. This catalyst brings advantages such as high catalytic activity and selectivity under mild conditions avoiding toxic solvents and easy separation of the catalyst by simple filtration.

Table 2

Synthesis of  $\alpha$ -amino phosphonates **3** in the presence the  $\text{Na}_2\text{CaP}_2\text{O}_7$  under solvent-free conditions at room temperature

$\alpha$ -amino phosphonate	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield(%) / Time(min) <sup>a</sup>
<b>3a</b>	H		Et	75(10) / 90(15)
<b>3b</b>	<i>p</i> -Me		Et	79(10) / 90(15) / 93(20)
<b>3c</b>	<i>p</i> -OMe		Et	84(10) / 92(15)
<b>3d</b>	<i>p</i> -Cl		Et	62(10) / 81(15)
<b>3e</b>	<i>p</i> -NO <sub>2</sub>		Et	51(10) / 69(15) / 86(25)
<b>3f</b>	<i>o</i> -OH		Et	87(20)
<b>3g</b>	H		Me	88(15)
<b>3h</b>	<i>p</i> -OMe		Me	81(15)
<b>3i</b>	H		Et	80(90)
<b>3j</b>	<i>p</i> -OMe		Et	84(90)
<b>3k</b>	H		Et	78(60)
<b>3l</b>	<i>p</i> -NO <sub>2</sub>		Et	70(60)

Fig. 3. Recycling of the  $\text{Na}_2\text{CaP}_2\text{O}_7$  catalyst in the synthesis of **3a**: (a) catalyst recoverable dried at 150 °C for 1 h; (b) catalyst recoverable, washed with acetone, dried and calcined at 600 °C for 30–60 min.

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