Journal of Molecular Catalysis A: Chemical 336 (2011) 8–15

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Bi-functional modified-phosphate catalyzed the synthesis of α-α′-(*EE*)-bis(benzylidene)-cycloalkanones: Microwave versus conventional-heating

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ARTICLE INFO

Article history:
Received 23 June 2010
Received in revised form
13 November 2010
Accepted 27 November 2010
Available online 9 December 2010

Keywords:
Cross-aldol Condensation
α-α′-(*EE*)-bis(benzylidene)-cycloalkanones
Hydroxyapatite
Modified hydroxyapatite
Heterogeneous catalysis
Water
Conventional heating
Microwave irradiation

ABSTRACT

The impregnation of hydroxyapatite (HAP) by $NaNO_3$ leads to a modified-hydroxyapatite which has a bi-functional acid-base property. Sodium-modified-hydroxyapatite (Na-HAP) efficiently catalyzed the cross-aldol condensation of arylaldehydes and cycloketones to afford α-α′-(*EE*)-bis(benzylidene)-cycloalkanones in good yields under microwave irradiation. Moreover, the methodology described in this paper provides a very easy and efficient synthesis carried out in water as the greenest available solvent under conventional heating. A comparison study between these two different modes of heating was investigated. The catalyst was easily recovered and efficiently re-used.

1. Introduction

The use of microwaves has become a well established technique in chemistry that has found numerous applications in the laboratory as well as in industry [1]. It has been successfully used in areas such as drug discovery, polymer chemistry, material science, nanotechnology, and biochemical processes. Moreover, many articles have been published in the fast-moving field of microwave-assisted organic syntheses [2], since the appearance of the publication entitled: "The use of Microwave Ovens for Rapid Organic Syntheses" [3]. The main advantage of microwaves is to provide rapid-and-uniform heating as compared to classical oil or sand bath heating, resulting in a significant increase of reaction rates even when carried at the same temperature [4–7]. As a result, microwave-assisted chemistry has become an important tool in the green chemistry development [8]. Using microwaves to power chemical reactions enable chemists to completely eliminate solvents use completely in some instances. In other cases, water or the eco-friendly solvents including supercritical CO_2, perfluorinated solvents and ionic liquid could replace a variety of organic solvents [9–13]. The use of water as a medium for organic reactions presents a big challenge for modern organic chemistry and many reactions that were conventionally believed to occur only in organic solvents have been found to run in water with excellent conversion [14]. These techniques are completely coherent with the twelve principles of Green Chemistry, because they meet the advantages of protecting human health and the environment while simultaneously achieving commercial profitability [15,16]. The development of solid catalysts for the production of fine chemicals is nowadays a subject of increasing interest [17–20]. Indeed, hydroxyapatite has attracted a wide

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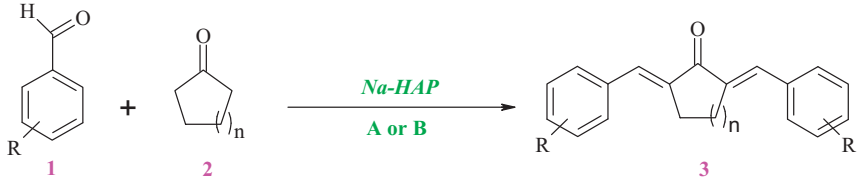
doi:10.1016/j.molcata.2010.11.032



Scheme 1. Cross-aldol condensation over sodium-modified hydroxyapatite.

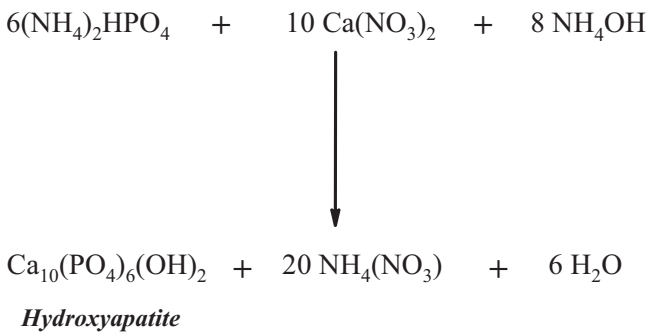
attention due to its use as inorganic macroligand for solid-base or acid catalysts [21]. Our research group has demonstrated the catalytic activity of this material, when used alone or modified being an efficient solid catalyst for many organic transformations [22,23].

The α-α′-bis(substituted-benzylidene) cycloalkanones are important pharmacophores and are widely found in many biologically active compounds such as HIV-1 integrase inhibitory [24], cytotoxic [25], cancer chemopreventive [26] and have anti-oxidant properties [27]. Cross-aldol condensation of aromatic aldehydes with cyclic ketones is an important protocol for the synthesis of these compounds. This reaction is classically carried out using strong acid or base [28]. Indeed, different organometallic complexes [29], Lewis acid such as $RuCl_3$ [30], SmI_3 [31], BF_3 Et_2O [32], $FeCl_3$ $6H_2O$ [33], $Mg(HSO_4)_2$ [34], $Yb(OTf)_3$ [35], $InCl_3$ $4H_2O$ [36], $Cu(OTf)_2$ [37], and other catalysts such as, SiO_2–Pr–SO_3H [38], CH_3CO_2Na/CH_3CO_2H under microwave [39], under micellar medium [40], Polymer-supported sulfonic acid (NKC-9) [41] $SOCl_2$/EtOH [42], $TiCl_3(SO_3CF_3)$ [43], I_2 [44], TMSCl/NaI [45], LiOH [46], BMPTO [47], and KF/Al_2O_3 [48] are found to be able to catalyze this reaction. However, these methods of synthesis suffer from some drawbacks such as the use of toxic reagents, unfeasibility of recovering the catalyst, modest yields and long reaction time. The development of safer, more efficient and more eco-friendly chemical technologies is a major need for the humanity in the 21st century. For these reasons and since the last decade, our research work was focused to develop clean organic syntheses [22,23,49]. Thus, we present here a new application of the sodium-modified-hydroxyapatite for the catalysis of the cross-aldol condensation in water under conventional heating (Method A) and/or in a solventless system under microwave irradiation (Method B) (Scheme 1).

2. Experimental

2.1. Materials and apparatus

All commercial reagents were purchased from Aldrich Chemical Company and were used without further purification. X-ray diffraction (XRD) patterns of the catalyst were obtained at room temperature on a Bruker AXS D-8 diffractometer using Cu-K_α radiation in Bragg–Brentano geometry (θ–2θ). The specific surface areas were determined from the nitrogen adsorption/desorption isotherms (at −196 C) measured with a Quantachrome Autosorb-1 automatic analyzer, using the BET equation at $p/p_0 = 0.98$. Fourier transform infrared (FT-IR) spectra of samples in KBr pellets were measured on a Bruker Vector 22 spectrometer. NMR spectra were recorded on a Bruker ARX 300 spectrometer. Melting points were determined using a Stuart SN5228 apparatus. Differential Scanning Calorimetry (DSC) was conducted under air in a Q100 apparatus. Elemental analysis (Ca, Na, and P concentrations) was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) from Jabin Yvan (Ultimate 2).



Scheme 2. Synthesis of hydroxyapatite.

2.2. Catalysts preparation

2.2.1. Preparation of HAP catalyst

The synthesis and characterisation of HAP were already described [22,23]. The synthesis of HAP [$Ca_{10}(PO_4)_6(OH)_2$] was carried out by the co-precipitation method. 250 mL of a solution containing 7.92 g of diammonium hydrogen phosphate, maintained at a pH higher than 12, by addition of ammonium hydroxide (BDH) (60–70 mL), were dropped under constant stirring into 150 mL of a solution containing 23.6 g of calcium nitrate [$Ca(NO_3)_2{\cdot}4H_2O$]. The suspension was refluxed for 4 h and doubly distilled water (DDW) was used to prepare the solutions. The HAP crystallites were filtered, washed with DDW, dried overnight at 80 °C and calcined in an open air at 800 °C for 30 min before use (Scheme 2).

2.2.2. Preparation of Na-HAP catalyst

The modified HAP (Na-HAP = 1/2, w/w) was prepared by addition of HAP (0,1 g) to an aqueous solution of sodium nitrate (50 mL, 1.17 M). The resulting mixture was stirred at room temperature for 30 min, and then the water was evaporated under vacuum. The resulting solid was calcined in an open air at 700 °C.

2.3. General procedure for the synthesis of the α-α′-(EE)-bis(benzylidene)-cycloalkanones

The typical reaction procedure for the cross-aldol condensation of aldehydes with cycloalkanones catalyzed by hydoxyapatite alone or modified was as follows.

Method A: to a 6 mL of distilled water in a round bottom flask, was added arylaldehydes **1** (4 mmol), cycloalkones **2** (2 mmol) and 100 mg of the catalyst, and the mixture was refluxed in water.

Method B: to a solution of aldehydes **1** (4 mmol) and cycloalkanes **2** (2 mmol), 100 mg of the Na-HAP was added and the mixture was stirred with a spatula at room temperature and was irradiated by microwave for the appropriate time at (450 W). Hot water (2 × 20 mL) was added, followed by simple filtration. For both methods, after filtration and extraction with hot water, the solutions were concentrated and purified by silica gel chromatography (*n*-

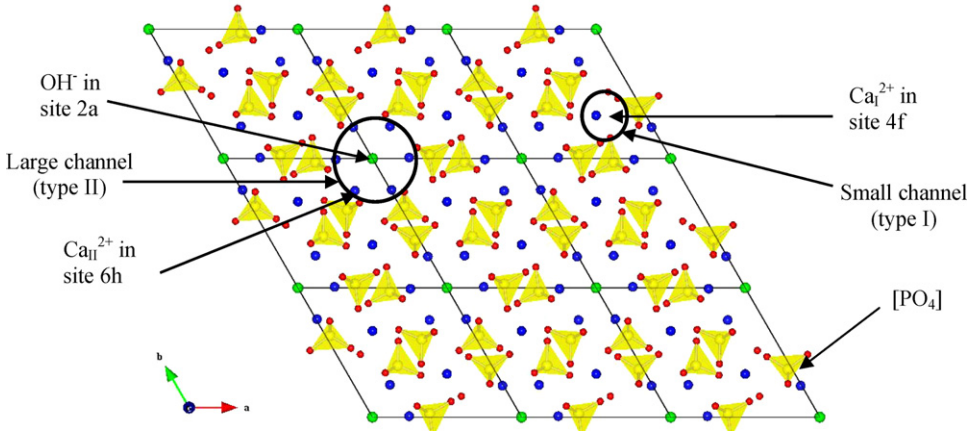


Fig. 1. Projection of the hydroxyapatite structure according to the *c* axis.

hexane/ethyl acetate: 7/3). The products were identified by melting points, ^{1}H NMR, ^{13}C NMR, and IR spectroscopies. Na-HAP was reactivated by drying at 150 °C or, alternatively washed with acetone and calcined at 600 °C for 1 h.

3. Results and discussion

3.1. Catalyst characterization

The preparation of this material was carried out by co-precipitation method. Hydroxyapatite crystallizes in the hexagonal system with the space group *P*63/*m*. The lattice parameters of the prepared HAP are in excellent agreement with standard data: $a = 6.883$ Å and $c = 9.422$ Å, with all the registered characteristic peaks of hydroxyapatite being present. The framework of the stoichiometric calcium hydroxyapatite can be described as a compact assemblage of tetrahedral PO_4 groups, where the P^{5+} ions are in the centre of the tetrahedrons whose tops are occupied by 4 oxygen atoms, each PO_4 tetrahedron is shared by one column and delimits two types of unconnected channels (Fig. 1) [50]. The first channel has a diameter of 2.5 Å and is surrounded by Ca^{2+} ions, denoted Ca_I or 4f (4 per unit cell). They are in coordination 9 with the oxygen atoms of the PO_4 tetrahedrons resulting in the formation of a polyhedron as shown in Fig. 2. The second type plays an important role in the properties of the apatites. It has a diameter larger than the previous one (3–4.5 Å), and contains six other Ca^{2+} ions, referred to as Ca_{II} or 6 h. The latter are located at the periphery of the channel. These ions are located two dimensions 1/4 and 3/4 of the unit cell along the *c axis* and form alternate equilateral triangles around the helicoidal senary axis, their coordination is 7. They are surrounded by six atoms of oxygen [1 O(I), 1 O(II), 4 O(III)] belonging to $[XO_4]$ tetrahedrons and one OH^- anion in position 2a (Fig. 3) [51]. The existence of two different calcium sites is of special interest because the material properties can be tuned by specific modification of the site [52]. These channels host OH^- groups along the c axis to balance the positive charge of the matrix. The OH^- ions are located in columns perpendiculars to the unit cell face, at the centre of the large channels type II. The oxygen of the hydroxyl group is located at 0.4 Å out of the plane formed by the calcium ion, and the hydrogen at 1 Å farther, almost on the triangle plane of calcium. The dimension of the tunnel confers certain mobility to these ions and allows consequently their circulation along the tunnels in the direction of O_Z axis (Fig. 4). The HAP is a highly non-stoichiometric calcium phosphate compound with a Ca/P molar ratio ranging from 1.50 to 1.67 [53]. The Ca/P molar ratio of a stoichiometric form of hydroxyapatite is 1.67. The preparation of the nonstoichiometric hydroxyapatite can be explained by the fact that the loss of Ca^{2+} ions and the resulting electrical imbalance are corrected by the introduction of H^+ ions and depletion of OH^- ions, denoting this by the formula $Ca_{10-Z}(HPO_4)_Z(PO_4)_{6-Z}(OH)_{2-Z}$; $0 < Z \leq 1$ [54]. Moreover, the environment around the OH^- sites is very attractive for substitutions because it allows one to control the ratio between acid-base sites. It is well known that at a Ca/P ratio of 1.50, HAP acts as an acid catalyst with the existence always of basic sites. In contrast, at a Ca/P ratio of 1.67, it acts as a basic catalyst while acid sites are still present [55]. To sum up, the hydroxyapatite is con-

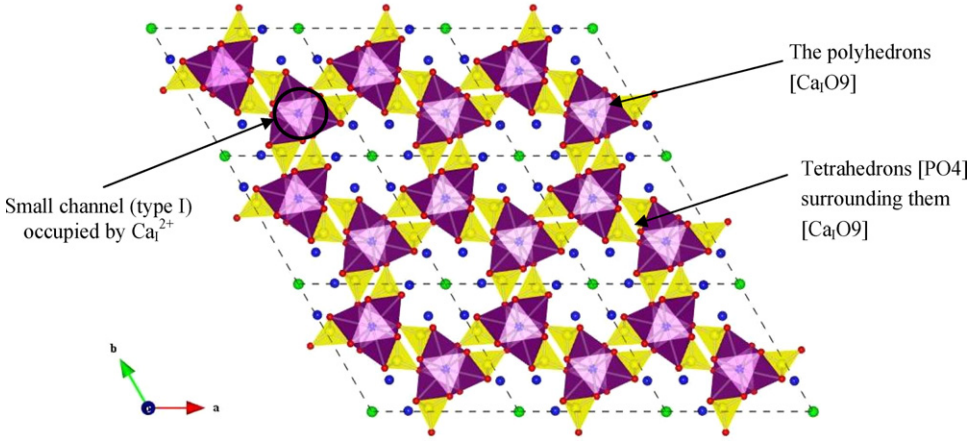


Fig. 2. Projection showing the arrangement of tetrahedrons $[PO_4]$ and the polyhedrons $[CaIO_9]$ by giving place to two channels.

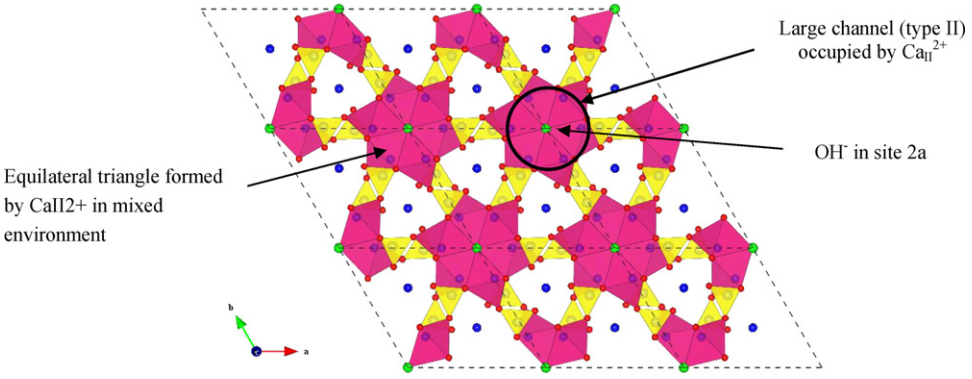


Fig. 3. Projection showing the two channels feature of hydroxyapatite as well as the alternate equilateral triangles formed by Ca_{II}^{2+} having a mixed environment.

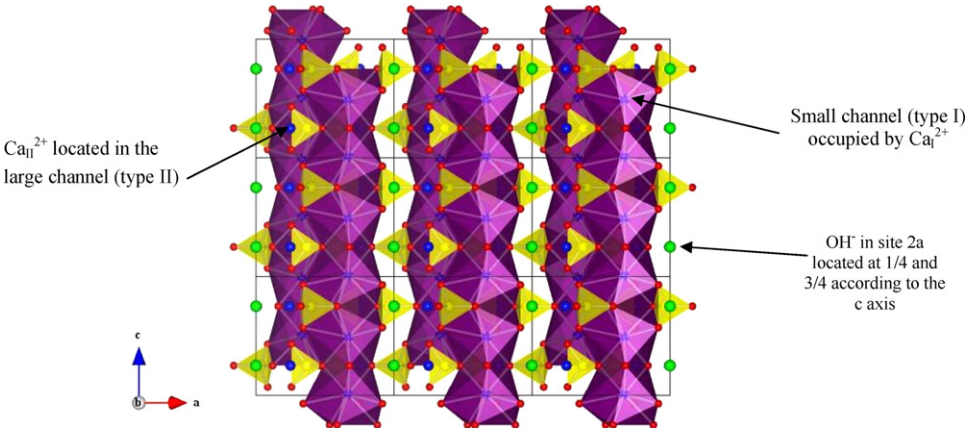


Fig. 4. Projection of the structure $Ca_4(I)Ca_6(II)(PO_4)_6(OH)_2$ along the *b*-axis.

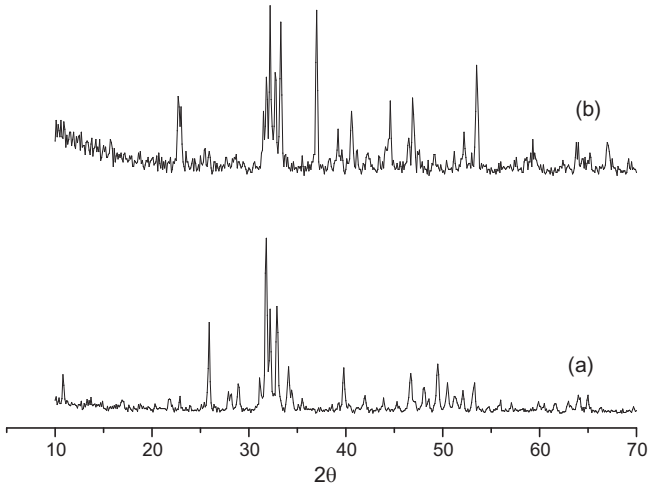


Fig. 5. XRD patterns of HAP (a) and Na-HAP (b).

sidered as a bi-functional catalyst and the control of its acid-base character depends primarily on the Ca/P molar ratio.

The basic properties of the HAP have been determined by the adsorption of phenol which give a value of 0.3 (mmol g^{-1}) for 2 h. To increase its basic property, HAP was modified by sodium to provide a catalyst (Na-HAP). Indeed, the value of the adsorbed phenol on the Na-HAP at the same time (2 h) is 1.6 (mmol g^{-1}). This modification gives a new strong active catalyst, as it was previously described [22]. The X-ray diffraction pattern of the calcined Na-HAP (w/w = 1/2) showed the apparition of new solid phases namely $NaCaPO_4$, CaO, and Na_2O (Fig. 5). The bulk composition of the HAP and Na-HAP is summarized in Table 1. Elemental analysis by ICP-AES (after dissolution in diluted HNO_3) indicated that the Ca/P ratio in HAP corresponded to the theoretical value of stoichiometric hydroxyapatite (1.67) [55]. The inclusion of sodium affects the hydroxyapatite structure, and the ratio of Ca/P increases to reach a value of 2.489, which does not correspond to the hydroxyapatite stoichiometric structure. This confirms the observations we observed by XRD. The percentage of sodium in the analyzed sample is 9.7%. The specific surface area was determined by the BET method ($S = 1.55\ m^2\ g^{-1}$). The TD/DTA analysis of the non-calcined Na-HAP showed an endothermic behavior at 290–306 °C without loss of weight (melting point of $NaNO_3$) and an endothermic behavior at 600–725 °C with 22.5% drop of weight, indicating the decomposition of $NaNO_3$ (Fig. 6). The basic properties of HAP and sodium-modified-hydroxyapatite (Na-HAP) have been determined by the adsorption of phenol (0.6 and 1.6 mmol g^{-1} in 2 h for HAP and Na-HAP respectively).

3.2. α-α′-(EE)-bis(benzylidene)-cycloalkanones synthesis over Na-HAP under conventional heating and/or microwave irradiation

Cross-aldol condensation was first carried out in water using HAP as a catalyst under conventional heating. In general, the

Table 1
The composition of the catalysts are determined by ICP-AES, and the ratios are calculated as molar ratios.

Catalyst	Ca/P	(Ca + Na)/P	Na/P	Na (wt%)
HAP	1.67	–	–	–
Na-HAP	2.489	3.009	0.52	2.98

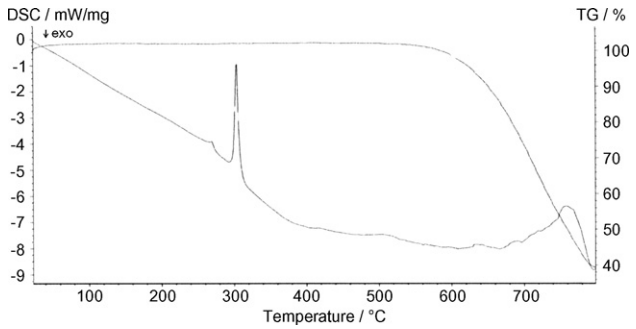


Fig. 6. Sodium nitrate thermogram carried out under nitrogen.

Table 2
Solvent effect on the synthesis of **3a** catalyzed by Na-HAP under conventional heating.

Solvent	*n*-Butanol	Ethanol	Methanol	Water
Dipole moment, μ (Debye)	1.66	1.69	1.7	1.8
Yield (%) in **3a**	30	40	70	96

obtained yields are poor. Thus, in 24 h reaction, the obtained recoveries in **3a**, **3b**, **3c**, **3d**, **3e**, **3f**, **3 g**, **3 h**, **3i**, **3j**, **3k** and **3l**, were 25, 30, 27, 25, 30, 35, 24, 35, 25, 20, 28 and 30% respectively. HAP was then activated by sodium nitrate as previously published. The resulting Na-HAP catalyst used in this study is prepared according to the method described above. Initially, the influence of the solvent nature was studied on the synthesis of α-α′-(*EE*)-bis(benzylidene)-cyclopentane **3a** under classical heating. The condensation of cyclopentanone (2 mmol) and benzaldehyde (4 mmol) (Scheme 1), was carried out in different solvents such as *n*-butanol, ethanol, methanol and water (Table 2). The obtained yields are 30, 40, 70 and 96% respectively. It has been found that water was the most suitable solvent for the cross-aldol condensation. The reaction was quite sensitive to the temperature of the solvents, but especially to the polarity, thus, the yield increases accordingly.

Afterwards, the reaction was carried out in various quantities of water. In all cases, water seems to positively activate the reaction; however, at higher volume of water the yields start dropping significantly. The optimum volume of water was determined at 6 mL (Fig. 7). To determine the scope and the limitation of this reaction, the optimum conditions for the synthesis of the product **3a** were applied to other substrates. The previous reagents, reaction time, and product yields for the cross-aldol condensation are given in Table 3. Different cyclic ketones such as cyclopentanone and cyclohexanone were condensed with various aryl and heteroaryl aldehydes in water catalyzed by Na-HAP under conventional heating. Excellent results (85–96% yields) were obtained and the reactions were completed after 0.5–2 h (TLC). It can be noticed that the condensation of various aldehydes with cyclopentanone is faster than the condensation with cyclohexanone. This may be due to the removal of the eclipsing effect of adjacent hydrogen atoms in cyclopentanone after the formation of arylmethylidene derivative [56]. Moreover, the electron-releasing group (ERG) of aldehydes (Cl, CH_3, OMe), seem to slow down their condensations with cyclopentanone as will as cyclohexanone (entries 2–4 and 8–10), and that would be because of the decrease in electrophilicity of the active centre of aldehyde. In the case of NO_2 which is an electron-withdrawing group (EWG), the same effect was noted. This may be due to the steric hindrance of this voluminous group in *meta* position. On the other hand, the effect of conventional heating versus microwave was investigated on the synthesis of α-α′-(*EE*)-bis-(benzylidene)-cycloalkanones. The cross-aldol condensation of different aldehydes on cycloalkanones was carried out under microwave irradiation using 10 mol% of catalyst (Na/HAP). Excellent recoveries were obtained (81–97%) in a relatively short time period (4–10 min). After reaction, the product is filtered, washed with hot water followed by drying and purification. The use of microwave is very helpful to improve the yields and to decrease the reaction time in comparison to classical thermal reflux. It was noticed that there was no reaction under microwave without catalyst, and to what was observed in traditional heating without solvent. This shows a certain synergy between catalyst and the microwave. It is thus completely reasonable to think that the effect of the temperature is a determining factor to promote this condensation. Unfortunately, domestic microwave was used and therefore it was impossible to measure the exact temperature during the reaction. The structures of α-α′-(*EE*)-bis-(benzylidene)-cycloalkanones (**3a**–**3l**) were characterized by comparison of their spectroscopic data (^{1}H NMR and IR) and melting points with those reported in the literature. The *EE* geometry of the double bonds in the above compounds (**3a**–**3l**) was based on earlier literature reports [57]. As noted before, Na-HAP as its homologue HAP is a bifunctional catalyst which contain at the same time acid and basic sites. In addition, we believe that the reaction is occurring over both sites (acid or base) making the catalyst of special interest. Moreover the bi-functional nature (acid/base) of the catalyst as well as the cooperative effect of the other phases (CaO and Na_2O) which exist with the $NaCaPO_4$ phase contribute significantly to its highly observed activity. To this end we carried out the reaction of the synthesis of 3 h under conventional heating in the presence of 0.1 g of the following catalysts: CaO, Na_2O and $NaCaPO_4$. In general, the obtained yields are poor. Thus, in 3 h reaction, in presence of CaO, Na_2O or $NaCaPO_4$ the yields in product **3 h** were 2, 24 and 25% respectively.

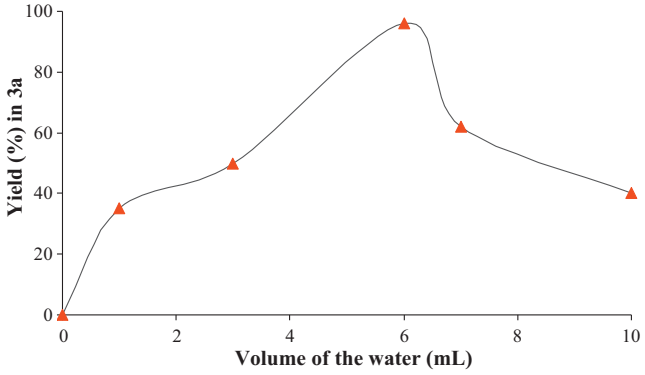


Fig. 7. Effect of the volume of water on the synthesis of the product **3a** catalyzed by Na-HAP under conventional heating.

Therefore, the proposed reaction mechanism is accordingly illustrated in Scheme 3. In the first step, the carbonyl group of cycloalkones **2** is activated by acid site and the proton in position α of carbonyl by the basic site to give a nucleophilic compound on the level of carbon. This can in turn attack particularly the carbonyl of the aldehyde which is activated by acid site, making it highly electrophilic, to give the aldol **4**, which then would be dehydrated to give the product 5. The resulting product would reacts with a second aldehyde molecule to form α,α′-bis(substituted benzylidene)cycloalkanone **3**. It is though very important to mention that the catalyst is involved in all these steps by weakening chemical bonds of the reactants and by consequent lowering the activation energy.

It is only in theory that the catalyst is found intact at the end of reaction. All catalysts are exhausted, and when their activities or selectivities become insufficient, they then have to regenerate them under appropriate treatment that will allow them to recover partially or completely their initial properties. When cycle-

Table 3
Comparison between conventional heating (method A) and solvent-free microwave methodology (method B), in presence of Na-HAP.

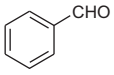
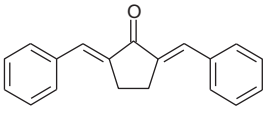
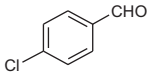
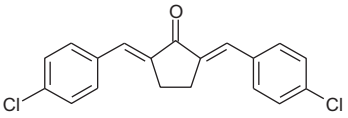
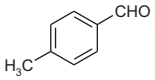
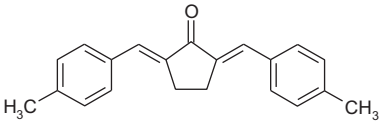
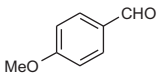
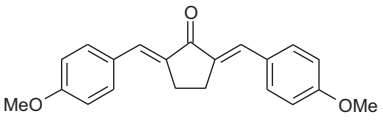
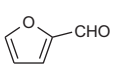
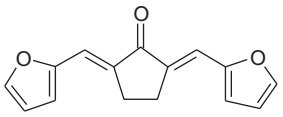
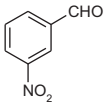
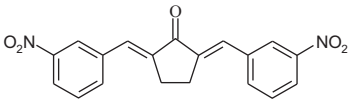
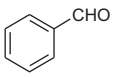
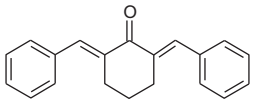
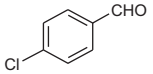
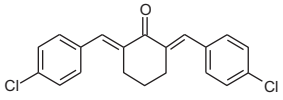
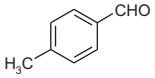
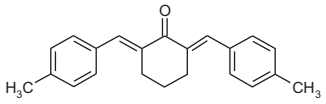
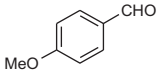
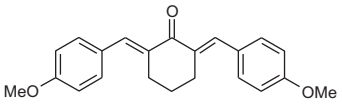
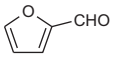
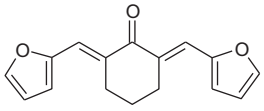
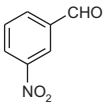
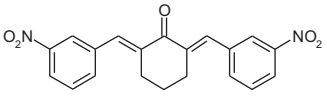
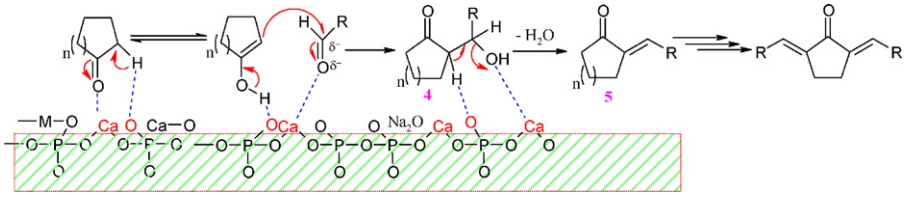
Entry	Cyclo-alkanone	Aldehyde	Product[d]	Isolated yield (%)[a]	
				Method A[b]	Method B[c]
1			 **3a**	96 (30)	95 (4)
2			 **3b**	95 (90)	96 (8)
3			 **3c**	91 (90)	97 (10)
4			 **3d**	90 (60)	96 (10)
5			 **3e**	96 (30)	95 (6)
6			 **3f**	92 (90)	92 (8)
7			 **3g**	95 (60)	86 (4)
8			 **3h**	95 (120)	81 (8)
9			 **3i**	91 (120)	90 (10)
10			 **3j**	85 (120)	92 (10)

Table 3 (*Continued*)

Entry	Cyclo-alkanone	Aldehyde	Product[d]	Isolated yield (%)[a]	
				Method A[b]	Method B[c]
11			 **3k**	95 (60)	90 (6)
12			 **3l**	85 (120)	87 (8)

[a] Values given in parentheses denote the time in minutes.
[b] Reaction carried out in water under conventional heating.
[c] Solvent-free synthesis under microwave irradiation
[d] All products are reported in the literature.



Scheme 3. Proposed mechanism of cross-aldol condensation over sodium-modified-hydroxyapatite.

use (number of regenerations) is bigger, the catalyst becomes more important. However, it is not sufficient that the catalyst recovers its activity and selectivity; it must also keep up its stability and strength in successive regenerations, as well as all its physical and chemical characteristics. The study of the regeneration and re-use of Na-HAP was carried out for the microwave-assisted synthesis of 3a. We note that the analysis of the recovered catalyst (Na-HAP) after second-cycle by ICP-AES shows that the concentrations of the elements Ca, Na, and P is almost constant compared with baseline concentrations. Thus, after each cycle, the initial catalyst was removed, dried and reused in this condensation. The catalyst was recycled four times, and the activity of the catalyst was found to be decreasing with each reuse. However, when the recovered catalyst was washed with acetone and then calcined at 600 °C, its catalytic activity seems to be unchanged for 5-cycle run (Fig. 8). This can be explained by the fact that after the reaction, a small amount of reagents remain adsorbed on the dried catalyst, thereby blocking accessibility of reagents and molecular traffic. This results in a decrease of the performance after using this catalyst several times. But, when we washed and calcined the recovered catalyst, it had its original activity because this treatment frees the pores which were blocked and the reagents were made more accessible to the active sites.

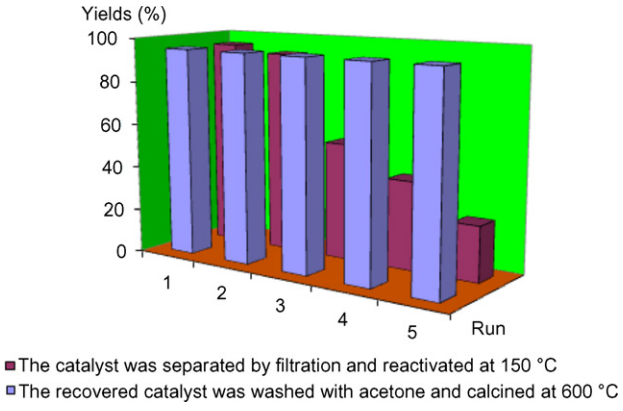


Fig. 8. Recycling of Na-HAP catalyst in the synthesis of α-α′-(*EE*)-bis(benzylidene)-cycloalkanone **3a**.

4. Conclusion

In this work, we have developed an efficient and convenient protocol for the synthesis of α-α′-(*EE*)-bis(benzylidene)-cycloalkanones via cross-aldol condensation between arylaldehydes and cycloalkanones catalyzed by sodium-modified-hydroxyapatite. The reaction can be carried out in water under classical heating. The microwave-assisted procedure in solvent-free system has provided a soft and cleaner approach for the cross-aldol condensation. Compared to conventional heating, the main advantages of the microwave procedure include mild conditions, higher yields, shorter reaction period, and catalyst re-use. Other applications of this method are underway in our laboratory.

Acknowledgements

Thanks are due to Hassan II Academy of Science and Technology and Centre National de la Recherche Scientifique et Technique (CNRST), for their financial support.

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