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

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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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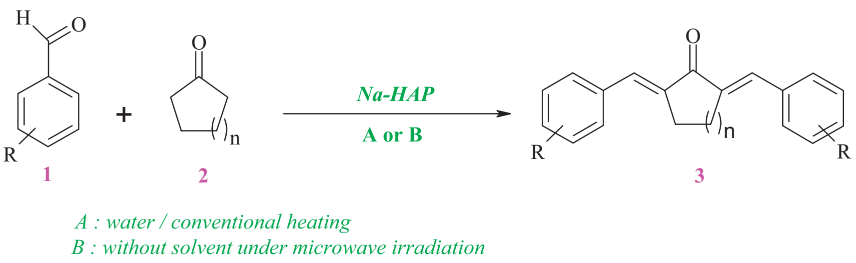


Scheme 1. Cross-aldol condensation over sodium-modified hydroxyapatite.

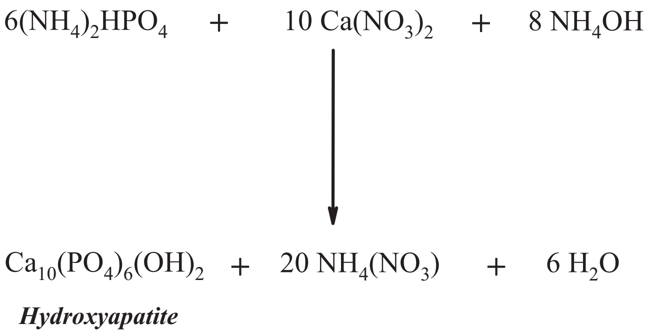
attention due to its use as inorganic macroligand for solid-base or acid catalysts [21]. Our research group has demonstrated the catalytic activity of this material, when used alone or modified being an efficient solid catalyst for many organic transformations [22,23].

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).



$$6(NH_4)_2HPO_4 \quad + \quad 10\,Ca(NO_3)_2 \quad + \quad 8\,NH_4OH$$
$$\downarrow$$
$$Ca_{10}(PO_4)_6(OH)_2 \quad + \quad 20\,NH_4(NO_3) \quad + \quad 6\,H_2O$$

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*-