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Short Communication

Efficient conversion of aldehydes and ketones into oximes using a nanostructured pyrophosphate catalyst in a solvent-free process

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ARTICLE INFO

Article history: Received 10 July 2012 Received in revised form 9 September 2012 Accepted 13 September 2012 Available online 20 September 2012

Keywords: Heterogeneous catalysis Nanostructured pyrophosphate Clean synthesis Oximes Microwave Conventional heating

ABSTRACT

A nanostructured pyrophosphate (Na₂CaP₂O₇) was synthesized by controlling the speed of its calcination, and then characterized by several methods including TGA, X-ray diffraction, FTIR, SEM, TEM and the determination of the surface area by the BET method. However, several aldehydes and ketones were efficiently and rapidly converted into the corresponding oximes by treatment with hydroxylamine hydrochloride in a solvent-free process under microwave irradiation using this nanostructured pyrophosphate as catalyst. The yields of the products were very high and the time required for their preparation was very short compared to conventional heating experiments and the catalyst was efficiently re-used.

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1. Introduction

One of the most important challenges for the modernization of organic synthesis is the preparation of active, selective, robust, and low-cost catalysts. Thus, the development of nanostructured catalysts for fine chemical production is currently a subject of increasing interest [1–4]. The second approach to achieve this target is to explore alternative reaction conditions and reaction media with minimal by-products [5]. Specifically, microwaves (MW) are an important alternate source of energy, which can accelerate reactions by the selective absorption of MW energy by polar molecules. The short reaction time and the expanded reaction range offered by MW assisted synthesis are suited to meet the increased demands in industry, particularly the pharmaceutical industry [6–8].

On the other hand, a large number of pharmaceutical oximes contain a group attached to a variable structure [9,10]. Furthermore, oximes are widely used as intermediates in fine organic synthesis [11–13]. The classical method for preparing them is the reaction of an aldehyde or ketone with hydroxylamine hydrochloride [14]. Several methods for their preparation have been reported in the literature including the use of formic acid [15], pyridine-chloroform [16], ethanol-pyridine [17], sulfuric acid [18], and NaOH with or without solvent [19–22]. However, the hazardous nature of these reagents results in many limitations. In order to avoid these limitations, many alternative strategies have recently been developed using solid catalysts such as alumina [23], silica gel [24], basic Al₂O₃ [25], resin (Amberlyst A-21) in ethanol [26], CaO [27], FeCl₃ [28], TiO₂/SO₄²⁻ without solvent [29], supported-POM [30], and Na₂SO₄ under ultrasound irradiation [31–33]. Recent literature has reported that high yields of hydroxyiminocycloalkanes could be achieved by either treating corresponding ketones with hydroxylamine or treating its salts in ionic liquids that contain sodium acetate or sodium bicarbonate [34]. Zang et al. have synthesized these products by the action of an ionic liquid under ultrasound irradiation [35]. More recently, Liao et al. have used the Pd/CNTs (carbon nanotubes) in the hydrogenation of nitrocyclohexane to cyclohexanone oxime [36].

Furthermore, many studies have been published describing the synthesis and use of the pyrophosphate $(Na_2CaP_2O_7)$ in various fields, particularly in heterogeneous catalysis [37]. Bennazha et al. were able to synthesize and characterize a series of pyrophosphates by adopting a dry technique [38]. Recently, we have developed a method to tailor the nanostructure of this pyrophosphate by focusing on reactant crashing and the speed of calcination. This nanostructured pyrophosphate has been used with great success to catalyze the synthesis of 2-amino-chromenes [39]. In this paper and in the continuity of our work we wish to report a new, simple,

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^{1566-7367/\$ -} see front matter © 2012 Elsevier B.V. All rights reserved. http://dx.doi.org/10.1016/j.catcom.2012.09.017



Scheme 1. Nanopyrophosphate catalyzed the synthesis of oximes under solvent-free conditions under microwave irradiation or conventional heating.

and green method for the solvent-free synthesis of oximes under microwave irradiation and via conventional heating using a nano-structured pyrophosphate (Na₂CaP₂O₇) catalyst (Scheme 1).

2. Experimental

2.1. Materials and apparatus

All commercial reagents were purchased from Aldrich Chemical Company and were used without further purification. Thermogravimetric analyses (TGA) were conducted under air in a TA Instrument Q500 apparatus with a 10 °C/min ramp between 25 and 1000 °C. 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 $(\theta - 2\theta)$. Fourier transform infrared (FT-IR) spectra of samples in KBr pellets were measured on a Bruker Vector 22 spectrometer. Scanning electron microscopy (SEM) pictures were recorded on a FEI Quanta 200 microscope after carbon metallization. The TEM micrographs were obtained on a Tecnai G2 microscope at 120 kV. Specific surface areas were determined from the nitrogen adsorption/desorption isotherms $(at - 196 \degree C)$ and measured with a Quantachrome Autosorb-1 automatic analyzer, using the BET equation at $p/p_0 = 0.98$. The microwave used was a StratSynth (Milestone S.r.l.); the wavelength of the microwave varied between 1 mm and 1 m, with a frequency that varied between 300 GHz to 300 MHz. NMR spectra were recorded on a Bruker ARX 300 spectrometer. Melting points were determined using a Stuart SN5228 apparatus.

2.2. Catalyst preparation

The synthesis of the pyrophosphate $(Na_2CaP_2O_7)$ in nanopowder form was carried out using Na_2CO_3 , $CaCO_3$ and $NH_4H_2PO_4$ in a 1:1:2 molar ratio respectively (purity of starting materials greater than 99%). These materials were mixed together in an agate mortar and heated progressively from 100 to 450 °C (Fig. S1 in Supplementary Data). Another sample has been prepared by adopting the conventional method described previously [38]. Thus, the same reagents were ground together and heated progressively to fusion (950 °C) in a porcelain crucible for 24 h with intermittent cooling and regrinding. The difference between these two methods is at the grinding velocity and the temperature of calcination.

2.3. General procedure for the synthesis of oximes

1 mmol of aldehyde or ketone and 2 mmol of hydroxylamine hydrochloride were mixed with 0.1 g of the nanostructured pyrophosphate (Na₂CaP₂O₇), and the mixture was heated classically at 80 °C or placed in a glass tube in a microwave reactor and then irradiated at 400 W (80 °C). After completion, CH₂Cl₂ was added, and the reaction mixture was filtered. The solution obtained was evaporated under reduced pressure. Further purification was accomplished by column chromatography on silica gel (200–300 mesh, eluted with petroleum ether or a mixture of petroleum ether and ethyl acetate). The products were identified by their melting points, ¹H NMR, and IR spectroscopies. The recovered nanostructured pyrophosphate was washed with acetone and calcined at 500 °C for 1 h before re-use.

3. Results and discussion

The synthesis of Na₂CaP₂O₇ was carried as it was described above (Section 2.2). In order to obtain a homogeneous single phase product, additional grinding and progressive heating steps were carried out. The details of the synthesis process of this catalyst and the adopted manner to control the nanostructuring are described in Figure S1. We note that the only difference with the method described in our previous work [39], is the velocity of heating and the affinity of the reagents mixture. The nanocrystal-size of the final product does depend not only on the quality of the starting products but also on the precision of the weighing and grinding. Thermogravimetric analysis (TGA) of a mixture of these three reagents showed that the thermal behavior of this blend was suitable to form the desired pyrophosphate (Figure S2 in ESI). Three major mass losses were observed and represented approximately 52% of loss, then these corresponded to the dehydration reaction (20%), the loss of NH_3 (17%) and CO_2 (5%) as well as the crystallization of this material (10%). X-ray diffraction (XRD) of Na₂CaP₂O₇ showed that this system crystallized in the



Fig. 1. SEM of Na₂CaP₂O₇.



Fig. 2. TEM images of Na₂CaP₂O₇ nanopowder (a) and (b), the conventionally prepared Na₂CaP₂O₇ (c) and (d).

triclinic system with the space group *P1bar* (Figure S3 in ESI). The lattice parameters of the prepared Na₂CaP₂O₇ were in excellent agreement with standard data: a = 5.361 Å, b = 7.029 Å and c = 8.743 Å, with the characteristic peaks of this pyrophosphate all present.

A projection view of the structure along the crystallographic plan (100) is shown in Figure S4 (see ESI). Channels of similar dimensions running along three directions [100], [010] and [001] can be observed. Two kinds of channels were present, both running along the [100] axis. They were constructed from the P₂O₇ groups and the CaO₆ octahedra (Figure S5). Their dimensions were estimated by their respective distances (d_1 =4.16 Å, d_2 =6.90 Å) and (d_3 =4.04 Å, d_4 =5.93 Å). The channels were only partially open due to the presence of sodium cations which were located on two different crystallographic sites. The existence of P₂O₇ units was confirmed by the symmetrical vibration bands of P–O–P at 720 cm⁻¹ as well as the anti-symmetric vibration bands at 893 cm⁻¹ (Figure S6). The related vibrations of the PO₄ groups were shared between two fields: a field of symmetrical vibrations at



Fig. 3. Influence of catalyst weight on the synthesis yield of product 3a.

996 cm⁻¹ and 1031 cm⁻¹ and another that ranged from 1130 to 1278 cm⁻¹. Scanning Electronic Microscopy (SEM) was used to study the morphology of the surface of Na₂CaP₂O₇ (Fig. 1). This micrograph shows a homogeneous microstructure that consisted of layers of various sizes and forms. In addition, the specific surface area of Na₂CaP₂O₇, as determined by the BET method, was found to be $S = 4 \text{ m}^2 \text{ g}^{-1}$. The total pore volume, calculated by the BJH method at P/Po=0.12-0.25, was V_T=0.021 cm³ g⁻¹. The shape, size, and morphology of Na₂CaP₂O₇ particles were revealed by TEM. The micrograph shows nanoparticles that are rod-like which agglomerate to form superstructures with different aspect ratios of grain crystals (i.e. length/diameter) (Fig. 2). Na₂CaP₂O₇ is characterized by an average grain diameter and length of 15 nm and 40 nm, respectively.

After characterization of the Na₂CaP₂O₇ catalyst, we have tested its catalytic activity in the synthesis of oximes, which has been carried out in a solvent-free process under microwave irradiation. The comparison between conventional heating versus microwave heating was investigated. The details of these reactions are described as below. The synthesis of oximes was initially carried out without solvent using nanostructured pyrophosphate as a catalyst under conventional heating. Overall, obtained yields were good after only 10-min and the isolated yields of oximes range from 50 to 83%. The only reaction that required more time corresponds to product 3a. However, under solvent-free microwave conditions, nanostructured pyrophosphate can easily catalyze the transformation of various aldehydes and ketones into the corresponding oximes. Our initial study focused on the influence of catalyst weight. Decreasing the catalyst's mass beyond a certain threshold resulted in a decreased efficiency. This threshold mass corresponded to 0.1 g of catalyst. This decrease in efficiency can be explained by the dispersion of the organic substrates on the surface of the catalyst (Fig. 3). We note that the obtained yields are 15, 59, 82, 87 and 94% corresponding to the used weights: 0.01, 0.05, 0.1, 0.2 and 0.3(g), respectively. Thereafter, we fixed the weight at 0.1 g. It was important to note that the obtained yield from the synthesis of 3a, catalyzed by the conventionally prepared pyrophosphate [38], was 47%. However, a yield of 82% was obtained when the same catalyst was prepared by the

Table 1

Synthesis of the oximes from aldehydes and ketones using nanostructured phosphate
Comparison between conventional heating and microwave irradiation. ^a

Entry	Aldehyde		Product ^b	Isolated yield (%) (time (min))	
				Δ	MW
1	O H		N_OH	27 (4) 83 (10)	82 (4) 47 (4) ^c
2	ОН	3b	H ₃ C	78 (10)	80 (4)
3	H H	3с	MeO N-OH	81 (10)	86 (4)
4	MeO'	3d	CI N OH	66 (10)	73 (4)
5	CI ² V H	Зе	O2N OH	71 (10)	69 (4)
6		3f	O2N OH	80 (10)	77 (4)
7	O H	3g	OH OH	76 (10)	84 (4)
8		3h	(CH ₃) ₂ N	63 (10)	75 (4)
9		3i	^O , ^O , ^{OH}	80 (10)	80 (4)
10	CH3	3j	CH3	56 (10)	52 (4)
11		3k	N ^{OH}	50 (30)	62 (15)
12	° –	31	N ^{OH}	74 (10)	82 (4)
13		3m	N ^{OH}	70 (10)	83 (4)

^a Solvent-free synthesis under microwave irradiation: aldehyde or ketone (1 mmol) and hydroxylamine hydrochloride (2 mmol), $Na_2CaP_2O_7$ (0.1 g), classical heating or MW (80 °C).

^b All products are reported in the literature.

^c Reaction carried out in the presence of the conventionally prepared pyrophosphate.

method reported herein. Analysis of the conventionally prepared pyrophosphate by TEM (Fig. 2(b)) showed that the crystallite size of this material was larger than the one prepared in this work.

The results presented in Table 1 demonstrated the scope of oxime synthesis. In general, excellent recoveries were obtained after 4 min reaction times, except for product **3k** that required 15 min irradiation. When acetophenone and benzophenone were used, poor recoveries were achieved compared to other reagents (52 and 62% for **3j** and **3k**, respectively). This can be explained by a steric hindrance effect. However, all aldehydes and ketones possessing electron-withdrawing (EWG)



Fig. 4. Recycling of Na₂CaP₂O₇ catalyst in the synthesis of oxime **3a**, under the same experimental conditions.

and/or electron-donating (EDG) groups on the phenyl ring were easily converted to the corresponding aldoximes or ketoximes. The nature of these substituents (EDG or EWG) did not have a major influence on the transformation yield. Importantly, good yields were obtained even in the presence of non-activated cycloketones. This demonstrated how catalytically effective the system is. The use of microwaves was very helpful not only in improving reaction yields but also in decreasing the reaction time. In the absence of a catalyst, reactions under microwave irradiation did not occur. This demonstrated a certain synergy between the catalysts and the microwave. Thus, it was reasonable to associate temperature as being a determining factor for promoting condensation. The purified products were analyzed by melting points, ¹H NMR and IR spectroscopies. Analysis of the spectral data of ¹H NMR showed that for all the products prepared, only *E* isomers were formed.

The catalyst was recovered by simple filtration from the reaction mixture, washed with acetone, and then calcined. We note that the study of the influence of the calcination temperature of the recovered catalyst revealed that the ideal temperature is 500 °C for 1 h, so that the recovered catalyst can have its initial activity. Indeed, the re-activated catalyst was successfully re-used seven times without losing its activity as shown in Fig. 4. The principal question in fundamental catalysis research is what are the mechanism (on the atomic scale) by which the catalytic reaction occurs. The key points to understand a mechanism in heterogeneous catalysis is the determination the active surface sites, the activation processes, the intermediates, and conversion rates towards reaction products. Because of the complex and dynamic character of the surface and interface phenomena taking place during a catalytic reaction this is not an easy task [40]. In this case, the catalyst had a low specific surface area; this implied that the catalytic process was a surface phenomenon. The presence of a large population of electron pairs on the surface (the loads: $P_2O_7^{4-}$, PO_4^{3-} , Ca^{2+} , Na^+) maybe explained that this catalyst has of acid sites and also base. The synthesis mechanism of oxime formation was mostly based on an addition-elimination process (Fig. 5). The reaction rate of hydroxylamine with acetone was greatest when the catalyst had a low acidity. This reaction requires a low acidity to selectively protonate the oxygen of the carbonyl group and to avoid the nitrogen of NH₂OH, which would remove its nucleophilic property. Thus, the oximes were formed by nucleophilic attack of hydroxylamine at the carbonyl carbon of aldehydes or ketones. This gave an unstable carbinolamine intermediate, which was acid-catalyzed because it formed a leaving group (H₂O) and then subsequently formed the oxime by dehydration.

4. Conclusion

In conclusion, different oximes were synthesized using a simple and environmentally benign method from the reaction of aldehydes or ketones with hydroxylamine hydrochloride using nanostructured



Fig. 5. Synthesis mechanism of oximes.

pyrophosphate as an efficient heterogeneous catalyst under microwavesolvent-free conditions. The prepared catalyst by the conventional method is less active than the other that has been prepared by our method, which proves that the nanostructuration of the material is an asset to have more important properties. A comparison study between the two modes of heating (traditional and microwave irradiation) was achieved. Good to excellent yields were obtained in a short reaction time using microwaves. The current method offers many obvious advantages compared with those reported in the literature. These include high efficiency, high yields, operational simplicity, and low environmental impact. Moreover, the nanostructured pyrophosphate catalyst used in the first cycle of the reaction was successfully recovered and re-used in seven-cycle runs.

Acknowledgment

The authors thank Centre National de la Recherche Scientifique et Technique (CNRST) for funding this project under the RS program. We also thank the technical and administrative support teams of the MAScIR Foundation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2012.09.01.

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