

Highly Efficient One-Pot Three-Component Synthesis of Naphthopyran Derivatives in Water Catalyzed by Phosphates

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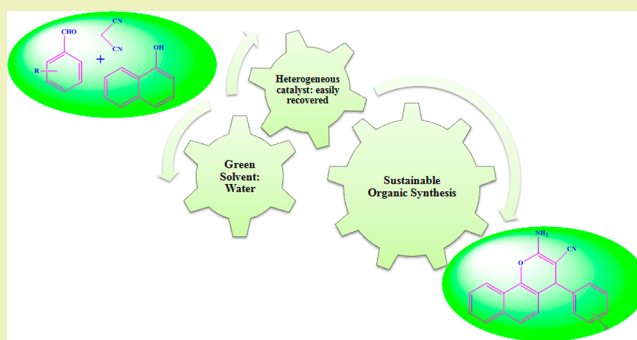
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S Supporting Information

ABSTRACT: An expeditious and efficient protocol for the synthesis of naphthopyrans has been developed that proceeds via a one-pot three-component sequential reaction in water catalyzed by phosphates (hydroxyapatite or sodium-modified hydroxyapatite). This is part of the mission to maximize valorization efforts of Moroccan natural phosphate resources. The title compounds have been obtained in high yield and purity. The catalyst can be reused several times, making this procedure facile, practical, and sustainable.

KEYWORDS: Three-component reactions, One-pot method, Heterogeneous catalysis, Phosphates, Sustainable chemistry



INTRODUCTION

Development of new synthetic routes,¹ especially cleaner ones, has become a necessity for the promotion of this field (fine chemicals) in view of environmental protection. Multi-component reactions (MCRs) have become an integral part of research in organic, combinatorial, and medicinal chemistry, as they are amenable to the production of a wide range of biologically active compounds.^{2–5} Thus, the success of combinatorial chemistry in the drug discovery process is considerably dependent on further advances in heterocyclic MCRs methodology and advancements in the development of environmentally benign multi-component procedures. The combinatorial synthesis of small-molecule heterocyclic libraries has emerged as a valuable tool in the search for novel lead structures.^{6,7} The MCRs strategy offers significant advantages over conventional linear-type synthesis because of its flexible, convergent, and atom-efficient nature.^{8,9} This is especially true if the reactions are conducted in the presence of a heterogeneous catalyst and in an eco-friendly solvent, such as water.^{10,11}

Naphthopyran and its derivatives have attracted considerable attention in medicinal and pharmacology research due to their large range of biological activities.^{12–17} The most straightfor-

ward synthesis of this heterocyclic system involves a three-component coupling of an aromatic aldehyde, malononitrile, and activated phenol. Traditionally, this reaction is catalyzed by a basic catalyst such as piperidine.¹⁸ Many homogeneous catalysts have been used for condensation reactions including ammonium salts,^{19–22} NaOH,²³ K₂CO₃,¹⁶ I₂/K₂CO₃,²⁴ TiCl₄,²⁵ InCl₃,²⁶ heteropolyacid,²⁷ and Et₃N.²⁸ However, some of the methods reported require prolonged reaction times and often the use of reagents in stoichiometric amounts and toxic solvents, and they generate moderate yields of final product.

On the other hand, a few heterogeneous catalysts have been used for this transformation. Among them, the use of the nanosized magnesium oxide and Mg/Al hydrotalcite have advanced as effective catalysts for this reaction.^{29,30} Our group has contributed to this field by developing a new sustainable process using a nanostructured pyrophosphate as a catalyst in water.³¹ More recently, Verma and Jain have used thiourea dioxide as an organocatalyst to catalyze this sequential MCR for the preparation of naphthopyrans and have shown the

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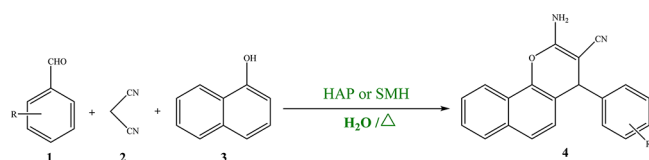
recyclability of their catalyst.³² Other mechanochemical methods have been developed using reagents such as NaHCO₃ and Na₂CO₃.^{33,34} In these two studies, the synthesis of 2-aminochromenes has been realized without solvent by grinding the reagents, except that in the later work, the reaction mixture was heated at 125 °C.

In addition to the challenge of finding a stable catalyst with high selectivity and reactivity, sustained efforts are devoted to the use of solid supports that enable fine dispersion and distribution of the catalyst. Among these, calcium phosphate such as hydroxyapatite (HAP) and its derivatives appear very appealing due to their ion-exchange capability, adsorption capacity, and acid–base properties.³⁵ HAP-based materials have been lately used in some important chemical transformations.^{36–39} Our group has also reported that the sodium-modified hydroxyapatite (SMH) is a valuable catalyst for several organic transformations.^{38–41}

The mining sector contributes to the development of the natural resources and industrial development in Morocco. The natural phosphates (NP) occupy a high priority in this field; the Moroccan soil contains three-quarters of the world's reserves with main deposits at in Khouribga, Youssoufia regions, and Boukraa in the south of Morocco (Supporting Information). Unfortunately, only the agricultural sector remains the most important user of these phosphates. Consequently, natural resource valorization becomes an urgent need and a logical extension of the value chain for this strategic sector. The valorization of natural phosphates (NP) is evaluated by developing industries for the manufacture of phosphate derivatives whose commercial value is high. This has stimulated the OCP Group in the Moroccan Kingdom to adopt pertinent R&D programs in which fundamental and industrial research are mutually reinforcing to develop new products with emerging applications. Among others, the most promising areas of the valorization of natural phosphate are the use of natural phosphate and its derivatives in applied heterogeneous catalysis in organic synthesis.³⁵ This is an area that has a vital role for the generation of value-added products for the national Moroccan economy.

The research work described herein addresses the national objective that not only valorizes the phosphate but also helps to develop efficient and environmentally benign protocols in aqueous organic synthesis in order to prepare a series of naphthopyrans, using phosphates such as hydroxyapatite and sodium-modified-hydroxyapatite (Scheme 1).

Scheme 1. Synthesis of Naphthopyrans in Water Using Phosphates



EXPERIMENTAL SECTION

Preparation of Catalysts. The experimental procedures and preparation of catalysts are described in the Supporting Information. The characterization of these catalysts (HAP and SMH) was accomplished as described already in published works.^{40–43}

General Procedure for the Synthesis of Naphthopyrans. To a stirred mixture of aldehyde **1** (1 mmol), malononitrile **2** (1 mmol),

and β -naphthol **3** (1 mmol) was added the catalyst [0.1 g of phosphate (HAP or SMH)]. The reaction mixture was refluxed in 10 mL of water. After an appropriate reaction time, the catalyst was removed by filtration and washed with acetone or ethyl acetate. After concentration of the filtrate, the residue was subjected to column chromatography leading to naphthopyrans, **4**. The structures of the prepared products were assigned on the basis of their spectral data in comparison with those reported in the literature. The recovered catalyst was calcined for 2 h at 450 °C under an air flow before being reused in subsequent reactions to demonstrate its prolonged activity.

RESULTS AND DISCUSSION


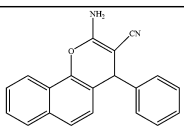
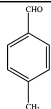
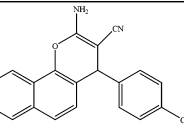
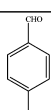
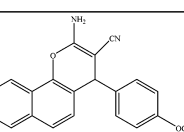
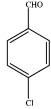
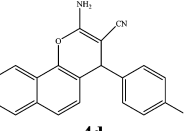
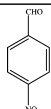
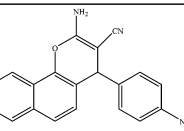
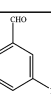
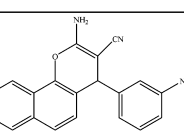
The synthesis of naphthopyrans was first carried out in water using HAP as a catalyst under conventional heating. In general, the yields obtained are privileged (61–87% for 6 h) (Table 1). To increase its catalytic activity, HAP was impregnated by sodium nitrate to generate a more efficient catalyst (SMH), as described previously.^{40–43} The resulting SMH material used in this study is a bifunctional catalyst because it has both basic sites and acidic sites.⁴² Initially, the influence of the solvent nature was studied on the synthesis of naphthopyran **4a** under classical heating. The condensation of benzaldehyde **1a**, malononitrile **2a**, and β -naphthol **3a**, was carried out in different solvents such as methanol, ethanol, and water. The obtained yields are 60%, 92%, and 95%, respectively, for methanol, ethanol, and water. It has been found that water is the most suitable solvent for this three-component reaction process. The reaction was quite sensitive to the reflux temperature.

To understand the effect of water volume on the three-component reaction catalyzed by SMH, different volumes of water were tested in this process (Figure 1). The experiments carried out do not provide a rationalization of results but establish the best quantities to use. When using 1 mL of water, only 35% of the desired product was obtained in 3 h of reaction time. The yield was increased significantly with increasing volumes of water. Thus, in the presence of 10 mL of water, the yield reached 95% in **4a**, as clearly shown in Figure 1. Beyond this quantity, a sharp decrease in yield was observed. This phenomenon can be due to the better and more efficient dispersion of the reagents when a large volume of water is used. The optimum volume of water was determined to be 10 mL (Figure 1).

Heterogeneous catalysis is more interesting because of profound advantages of straightforward recovery and reuse of the catalyst from the reaction mixture by simple filtration or decantation and recently by magnetic alterations. After recovery of SMH by simple filtration followed by calcination at 450 °C for 2 h, we established a set of experiments using the recycled catalyst in the synthesis of **4a**. The reactions were carried out in exactly the same adopted conditions above. Recycling studies have shown that the catalyst can be readily recovered and reused at least five times without any loss of activity (Figure 2).

The scope of this protocol was further demonstrated by studying the reaction of various aromatic aldehydes with malononitrile and β -naphthol under described reaction conditions. The products were isolated, purified by column chromatography, and analyzed by IR, ¹H, and ¹³C NMR spectroscopies and melting points. The previous reagents, reaction time, and product yields for the three-component reaction are given in Table 1. In almost all cases, the reaction was found to be selective and afforded excellent yields (72–96%) of the desired products in a shorter time than the

Table 1. One-pot Multi-Component Aqueous Reaction of Aromatic Aldehydes, Malononitrile, and 1-Naphthol for the Synthesis of Naphthopyrans in the Presence of HAP and SMH

Entry	Aldehyde	Product	Isolated yield (%) ^a	
			HAP	SMH
1		 4a	74 (6)	95 (3)
2		 4b	71 (6)	79 (3)
3		 4c	61 (6)	72 (3)
4		 4d	75 (6)	96 (3)
5		 4e	87 (6)	93 (2)
6		 4f	82 (6)	92 (2)

^aAll compounds were identified by melting points, ¹H NMR, ¹³C NMR, IR, and MS. Values given in parentheses denote the reaction time in hours.

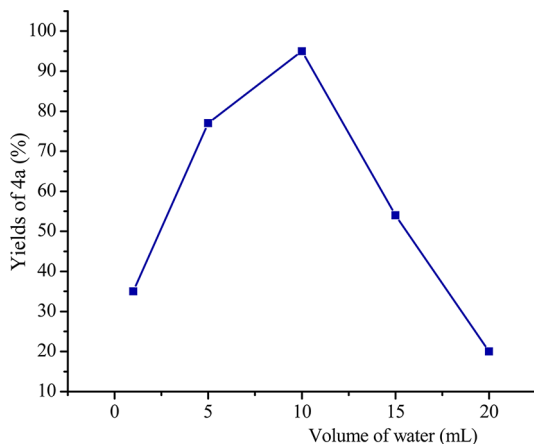


Figure 1. Effect of the quantity of water in the synthesis of naphthopyran **4a** catalyzed by SMH.

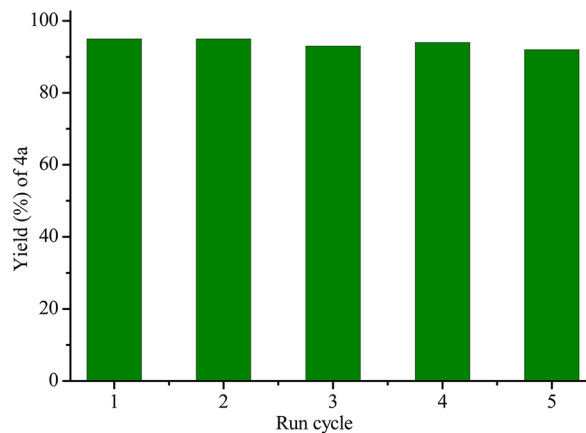
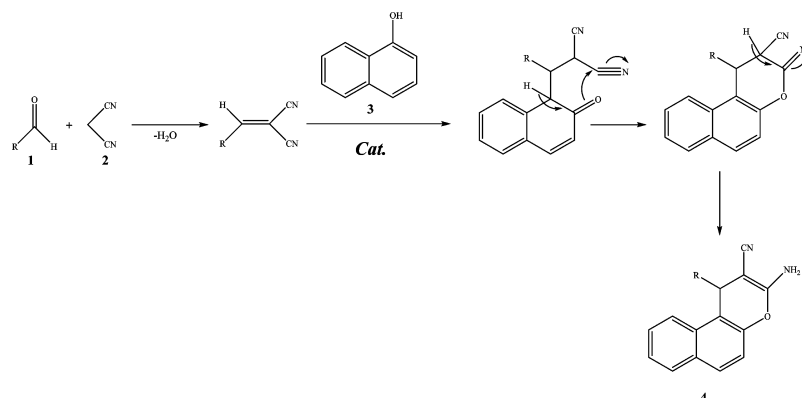


Figure 2. Results of recycling over five consecutive recycling experiments.

reactions catalyzed by HAP without any evidence of the formation of any side product. It can be noticed that the

presence of electron-releasing groups on the aldehydes (CH_3 , OCH_3) seem to slow down the three-component condensations (entries 2 and 3) presumably because of the decrease in

Scheme 2. Mechanism for SMH-Catalyzed Synthesis of Naphthopyrans in Water



electrophilicity of the active center of aldehyde. In the case of Cl, which is an electron-withdrawing group, the similar effect was noted (entry 4).

These reactions typically involve a bifunctional catalyst (acid/base). However, hydroxyapatite is a highly nonstoichiometric calcium phosphate compound with a Ca/P molar ratio ranging from 1.50 to 1.67.⁴⁴ 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 Ca²⁺ 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*}(HPO₄)_{*Z*}(PO₄)_{6-*Z*}(OH)_{2-*Z*}; 0 < *Z* ≤ 1.⁴⁵ 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 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.⁴⁶ To sum up, the hydroxyapatite is considered as a bifunctional catalyst, and the control of its acid–base character depends primarily on the Ca/P molar ratio. To increase its catalytic activity, sodium nitrate was used to modify HAP in order to obtain a more efficient catalyst (SMH), as it was previously described.⁴⁰ The basic properties of HAP and SMH have been determined by the adsorption of phenol. The catalyst had a large population of electron pairs on the surface (the loads: PO₄³⁻, Ca²⁺, Na⁺) and also contained acid and base sites, which makes for an easily achievable reaction. The reaction mechanism gives a description of how reactants are converted to products at the molecular level and consists of one or more elementary reactions, which in the case of a complex mechanism consists of more than one elementary sequential step. The mechanism of this reaction can be seen as sequential reactions involving the Knoevenagel reaction, Michael addition, and an intramolecular cyclization that may take place in the formation of the final product (Scheme 2). The overall reaction cannot give us the rate equation because the overall conversion tells us nothing about the mechanism by which reactants are converted to products. The first step, which is not limiting, is the formation of the alkene. Indeed, it is well known that the first step, if carried out in protic solvents like water, does not require any catalyst.⁴⁷ The second step is the ortho C-alkylation of 1-naphthol, which is a rate-limiting step. The last step is completely regio-selective; it requires the action of the catalyst (SMH)^{32,48} to produce the desired regioisomer product 4.

CONCLUSIONS

In summary, phosphates such as hydroxyapatite and sodium-modified hydroxyapatite are suitable catalysts for one-pot three-component synthesis of naphthopyran derivatives. Thus, a series of naphthopyrans were synthesized in water as a green solvent, which gives credence to this eco-friendly procedure. Specifically, the SMH catalyst showed excellent yields and stability through five cycles. The methodology developed is highly efficient and environmentally benign in terms of product recoveries, atom economy, and solvent usage. The novelty of the catalytic system lies in its low cost and availability that can contribute to generate a strong synergy between industry and academia and between private and public bodies in Morocco. Further studies in the sustainable applications of this catalyst to other chemical reactions are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Materials and apparatus, localization of phosphate deposits in the Moroccan Kingdom, preparation of the catalysts (HAP and SMH), catalyst characterization (XRD, DSC, FTIR, and nitrogen adsorption/desorption isotherm of HAP and SMH). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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