ACADEMIC PRESS

Application of natural phosphate modified with sodium nitrate in the synthesis of chalcones: a soft and clean method

Saïd Sebti,[a,*] Abderrahim Solhy,[a] Rachid Tahir,[a] Smahi Abdelatif,[a] Saïd Boulaajaj,[a]
José A. Mayoral,[b,*] José I. García,[b] José M. Fraile,[b] Abdelali Kossir,[c] and Hammou Oumimoun[c]

[a] *Laboratoire de Chimie Organique Appliquée et Catalyse, Université Hassan II, Faculté des Sciences Ben M'Sik, BP 7955, Casablanca, Morocco*
[b] *Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Facultad de Ciencias, Universidad de Zaragoza–C.S.I.C., E-50009 Zaragoza, Spain*
[c] *Centre d'Etudes et de Recherches sur les Phosphates Minéraux (CERPHOS), Groupe Office Chérifien des Phosphates (OCP), 37 Bd My Ismail, Casablanca, Morocco*

Abstract

The solid obtained by impregnation of natural phosphate (NP) with a solution of sodium nitrate, followed by calcination at 900 °C, is a strongly basic catalyst that is easily prepared from cheap precursors. The catalytic activity of this solid in the Claisen–Schmidt condensation was studied and high yields were obtained with small amounts of catalyst. The reaction rate depends on the substitution in both benzaldehyde and acetophenone derivatives. The effect of the solvent, as well as the addition of water and ammonium salt, was investigated as well. The catalyst can be easily recovered and efficiently reused.
© 2003 Elsevier Science (USA). All rights reserved.

Keywords: Natural phosphate; Sodium nitrate; Heterogeneous catalysis; Chalcones; Claisen–Schmidt condensation; Ammonium salt; Solvent effect; Water effect

1. Introduction

Heterogeneous catalysts are clearly advantageous over homogeneous ones in large-scale preparations. In this regard, catalysis of organic reactions by inorganic solids is an important new dimension in preparative organic chemistry. Among the different inorganic solids, natural phosphate (NP) has advantages in that it is cheap, readily available, nontoxic, and not a pollutant. During the past seven years we have studied the use of natural phosphate to promote organic transformations [1] and have shown that its mild basic and acidic properties can be exploited in many synthetic applications [2].

Chalcones represent one of the most abundant and ubiquitous groups of natural products [3]. In the last few years they have been shown to possess interesting biological properties, including anti-invasive [4], anticancer [5], inhibitory activation [6], antimalarial [7], antimicrobial [8], antimutagenic [9], radioprotective [10], and anti-inflammatory [11] effects. Furthermore, chalcones have attracted much attention as synthetic intermediates in the preparation of other compounds [12].

The Claisen–Schmidt condensation is the most useful reaction in the synthesis of chalcones and, for this reason, several excellent methods have been developed to carry out the reaction in the homogeneous phase. The use of heterogeneous basic catalysts, such as alumina [13], barium hydroxide [14], hydrotalcite and zeolite [15], facilitates the separation of the catalyst from the reaction medium. Furthermore, in many cases the catalyst may be reused. We previously reported that natural phosphate is capable of catalyzing the Claisen–Schmidt condensation, but that a large amount of catalyst is required [16]. We have also shown that doping with sodium nitrate increases the activity of natural phosphate [17].

In this paper we report a mild and convenient method for the heterogeneous catalysis of the Claisen–Schmidt condensation using NP modified by sodium nitrate.

* Corresponding authors.
 E-mail address: saidsebti@yahoo.fr (S. Sebti).

2. Methods

All commercial reagents and solvents were used without further purification. NP was purchased from CERPHOS (OCP). X-ray diffraction (XRD) patterns of the catalysts were obtained on a Philips 1710 diffractometer using Cu-K_α radiation. Surface areas were determined at 77 K using a Coulter SA 31000 instrument with an automated gas volumetric method employing nitrogen as the adsorbate. NMR spectra were recorded on a Bruker ARX 300 spectrometer. Mass spectra were recorded on a VG Autospec spectrometer. FTIR spectra were recorded on an ATI Mattson–Genesis Series spectrophotometer using the KBr disc method.

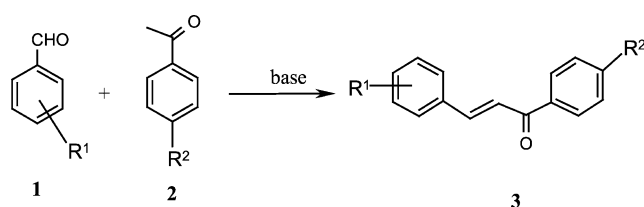### 2.1. General procedure for the Claisen–Schmidt condensation with NaNO₃/NP catalyst

NaNO₃/NP was prepared by addition of natural phosphate (10 g) to an aqueous sodium nitrate solution (50 ml, 1.17 M). The mixture was stirred at room temperature for 30 min and the water was evaporated under reduced pressure. The resulting solid was calcined under air at different temperatures for 2 h. NaNO₃/NP (0.1 g) was added to a solution of aldehyde **1** (2.5 mmol) and acetophenone **2** (2.5 mmol) in methanol (1 to 3 ml) and the mixture was stirred at room temperature for the appropriate time. CH₂Cl₂ (20 ml) was added, the catalyst was filtered off, and the solution concentrated to give a residue, which was purified by distillation under vacuum and recrystallisation. The products **3** (Scheme 1) were identified by ¹H NMR, ¹³C NMR, and IR spectroscopy and by mass spectrometry. The catalyst was reactivated by drying at 150 °C or, alternatively, by washing with acetone, drying at 100 °C and calcination at 900 °C for 1 h.

The same procedure was used for the reactions carried out in presence of BTEAC (0.03 g). The products were washed with water to eliminate the ammonium salt before purification.

3. Results and discussion

3.1. Effect of catalyst preparation and reaction conditions

Natural phosphate exists under several mineralogical classes [18] which generally belong to the family of phosphocalcic apatites ($Ca_{10}(PO_4)_6F_2$ for fluoroapatite in its pure state). In sedimentary rocks, phosphates are formed from compounds derived from apatite by partial isomorphic substitution: Ca^{2+} ions by Na^+, Mg^{2+}, Co^{2+}, Fe^{3+}, or Al^{3+}, PO_4^{3-} ions by VO_4^{3-}, SO_4^{2-}, CO_3^{2-} or MnO_4^-, and F^- by ^-OH or Cl^-. These different substitutions cause distortions of the structure which depend on the nature and the radii of the ions involved. Natural phosphate used in this work was obtained from the Khouribga region (Morocco). Prior to use this material requires initial treatments such as crushing and washing. For use in organic synthesis, the natural phosphate is treated by techniques involving attrition, sifting, calcinations (900 °C), washing, and recalcinations [19]. These treatments lead to a fraction between 100 and 400 μm that is rich in phosphate and has the following chemical composition: P_2O_5 (34.24%), CaO (54.12%), CO_2 (1.13%), MgO (0.68%), SiO_2 (2.24%), Al_2O_3 (0.46%), Fe_2O_3 (0.36%), F^- (3.37%), SO_3 (2.21%), Na_2O (0.92%), K_2O (0.04%) and several metals (Cd, Zn, Cu, U, Cr, V) in the ppm range. The surface area of NP is 1.4 m²/g and its total pore volume is $V_T = 0.0055$ cm³/g.

The modified natural phosphate (NaNO₃/NP) was prepared by adding NP (m_1) to an aqueous solution of sodium nitrate (m_0), followed by low-pressure water evaporation and calcination. The catalysts were tested in the Claisen–Schmidt condensation of arylaldehydes **1** with acetophenones **2**, a reaction that gives chalcones **3** (Scheme 1).

In order to determine the best ratio of $r = $ NaNO₃/NP, we carried out the synthesis of chalcone **3a** ($R^1 = R^2 = H$) by condensation between benzaldehyde and acetophenone at room temperature in methanol (1 ml) using NaNO₃/NP (0.1 g) as a catalyst. The yields obtained after reaction times of 24 h were 98, 78, 67, 8, and 2% on using NaNO₃/NP with weight ratio $r = 1/2$, $1/3$, $1/5$, $1/8$, and $1/15$, respectively (Fig. 1). The best result was obtained when $r = 1/2$. We also investigated the use of other calcination temperatures. Treatment at 150, 300, and 500 °C led to catalysts with poor activities (Table 1). This is in agreement with the results of thermal analysis, with a weight loss between 600 and 800 °C indicating that the solid phase reaction takes only place at high temperature. With regard to the sodium salt, solids
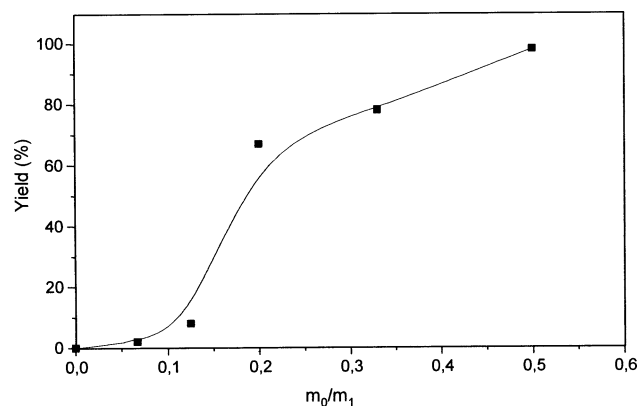
Scheme 1.

Fig. 1. Effect of m_0/m_1 ratio on the yield of **3a**.

Table 1
Condensation of benzaldehyde and acetophenone catalyzed by 0.1 g of solid (various catalysts)

Entry	Catalyst	Calcination temp. (°C)	Reaction time (h)	Yield (%)
1	Without	–	48	0
2	$NaNO_3$	–	48	0
3	NP	900	24	2
4	$NaNO_3/NP$	150	24	4
5	$NaNO_3/NP$	300	24	3
6	$NaNO_3/NP$	500	24	2
7	$NaNO_3/NP$	900	18	98
8	NaCl/NP	150	24	0
9	Na_2SO_4/NP	150	24	0
10	Na_2CO_3/NP	150	24	0
11	NaCl/NP	900	24	0
12	Na_2SO_4/NP	900	24	0
13	Na_2CO_3/NP	900	24	0

Table 2
Most intense diffraction lines for $NaNO_3/NP$ calcined at 900 °C in comparison with reference CaO

$NaNO_3/NP$ (900 °C)		Calcium oxide	
2θ (°)	Intensity	2θ (°)	Intensity
32.21	78[a]	32.23	36
37.37	100	37.38	100
53.87	60	53.90	54
64.16	21	64.21	16
67.37	14	67.44	16

[a] Line overlapped with that of NP at 32.27°.

prepared by doping NP with NaCl, Na_2SO_4, and Na_2CO_3 did not promote the reaction (Table 1).

The best catalyst ($NaNO_3/NP$ calcined at 900 °C) was studied further. The FT-IR spectrum of $NaNO_3$ shows a very strong and broad band with a maximum around 1375 cm^{-1}. The same intense band is present at 1365 cm^{-1} in the spectrum of $NaNO_3/NP$ calcined at 500 °C, demonstrating the stability of the nitrate species under those conditions. However, this band almost disappears after calcination at 900 °C, because of the decomposition of nitrate.

In the X-ray diffraction pattern of $NaNO_3/NP$ calcined at 500 °C, lines corresponding to NP and pure $NaNO_3$ ($2\theta = 29.36$, 38.96 and 47.90°) are present. These lines disappear after calcination at 900 °C (Fig. 2), showing again the decomposition of nitrate, whereas a large number of new lines appears with modification in the intensity of the NP lines. The most intense new lines correspond to CaO, as shown in Table 2, demonstrating that a solid phase reaction takes place between the supported sodium nitrate and the calcium phosphate of the support during the nitrate decomposition process. It is assumed that sodium phosphate or any type of calcium sodium mixed phosphate is the resulting species when part of the calcium is released from the crystalline framework to form CaO. However, the remaining lines do not fit with any reference composed by Na, Ca, P, N, H, and O. The only remarkable fact is that
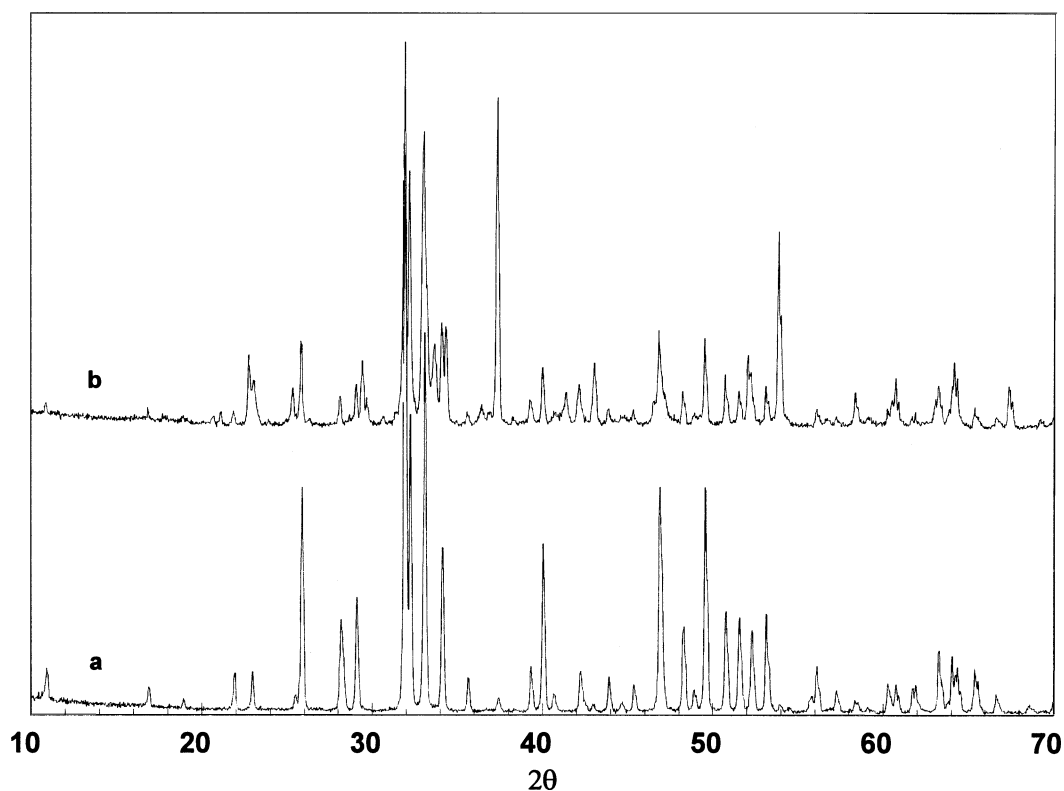

Fig. 2. X-ray diffraction patterns of (a) NP and (b) $NaNO_3/NP$ calcined at 900 °C.

the main modifications in the pattern are produced in the range of $2\theta = 32–35°$, with new lines at 33.68° and 34.34° together with an increase in the intensity of other lines in that zone. These lines may correspond to sodium phosphate species, given that the most intense lines in the references are 34.1° for γ-Na$_3$PO$_4$, 34.2° for β-Na$_3$PO$_4$, and 31.9° for Na$_2$HPO$_4$. The formation of very small crystals, partially amorphous materials or mixed phosphates with different stoichiometry may account for the lack of intense bands of sodium phosphate species. It has been shown that in other base-catalyzed reactions [17b] this insoluble sodium phosphate may be the active species.

The natural phosphate shows a very low surface area (1.4 m^2/g) together with a low total pore volume (0.0055 cm^3/g). In the case of NaNO$_3$/NP calcined at 900 °C the surface area is even lower (0.66 m^2/g) with similar total pore volume. It is then rather surprising that this solid has a very high catalytic activity and basicity was determined by phenol adsorption. Solutions of phenol were prepared in cyclohexane with concentrations in the range 5–200 mM and n-octane was added as internal standard. Variable amounts of the solids (15–45 mg) were stirred at room temperature with different volumes of those solutions (3–9 ml) in order to study the adsorption equilibrium. The phenol remaining in solution was analyzed by GC. Values of adsorbed phenol were in the range of 0.5–1.8 mmol/g. These values are surprisingly high for a solid with such a low surface area; in fact they represent a surface concentration of 4.5–16.4 molecules/Å^2. This concentration cannot be due to chemisorption and it is difficult to find an explanation. However, the high polarity of the surface might be the origin of this behavior. In any case, it is clear that the solid is basic, as indicated by its catalytic activity, observed in the epoxidation of electron-deficient alkenes with H$_2$O$_2$ [17b], a reaction that needs the presence of basic centers.

The condensation of the benzaldehyde and the acetophenone was used as a benchmark reaction to study the influence of the volume of the methanol. The best yield (98%) is obtained after 24 h with a volume of 1–3 ml. An increase in the volume up to 5 ml slightly decreases the reaction yield (88%), and this drops further to 40% when a volume of 10 ml is used. In absence of the solvent, only a 10% yield is obtained. This behavior indicates that some solvent is needed to facilitate the contact between the reagents and the active sites, but a large volume reduces the concentration and, as a consequence, the reaction rate.

We proceeded to study the solvent effect in the synthesis of chalcone **3a** using the NaNO$_3$/NP catalyst. In dichloromethane, THF, hexane, and butanol the reaction did not take place. The use of isopropanol gave only a 12% yield of **3a** after 24 h, but 63% of **3a** was isolated when the reaction was carried out in ethanol. It can be concluded that methanol is the best solvent for this reaction.

To complete this preliminary study, the issue of catalyst recovery was also considered. When the catalyst was separated by filtration and dried at 150 °C, a rapid decrease of

the catalytic activity was observed in subsequent reactions. The yields obtained are 98, 75, 60, and 35% using the fresh catalyst, cycles 1, 2, and 3, respectively. However, the activity was almost completely recovered when the catalyst was washed with acetone and calcined at 900 °C. Thus, the yields obtained are 98, 94, and 92% with fresh catalyst, cycles 1 and 2, respectively. The strong adsorption of some byproducts may be responsible for this behavior.

3.2. Scope of NaNO$_3$/NP

In order to determine the scope and limitations associated with this new catalyst, the optimum conditions for the Claisen–Schmidt condensation between benzaldehyde and acetophenone were applied to other substrates (Table 3). All of the reactions proceeded efficiently at room temperature. Although all products are obtained in high isolated yields, longer reaction times are required in the synthesis of some chalcones. The presence of an electron-donor group in the aldehyde (entry 4) or the ketone (entry 6) made the reaction less favorable. The worst result was obtained when both reagents contained donor methoxy groups (entry 8).

3.3. Effect of addition of water

Having shown that NaNO$_3$/NP is an active catalyst for a wide variety of Claisen–Schmidt condensations, we tried to further improve the catalytic activity of this solid. We have reported previously that addition of small amounts of water to reaction mixtures can increase the catalytic activity of natural and synthetic phosphates [16,20–22]. We tested this approach in the synthesis of chalcone **3a** using NaNO$_3$/NP in the presence of different amounts of water in conjunction with methanol or ethanol as solvents. When the reaction was carried out with 1 ml of methanol, the addition of water led to a decrease in the yield. Thus, the yields obtained after 6 h are 65, 57, 47, 35, and 28% in the presence of 0.05, 0.1, 0.3, 0.5, and 1 ml of water, respectively, whereas the yield is 57% with anhydrous solvent. In contrast, the behavior in ethanol is completely different in that the addition of small amounts of water has a positive effect. The yields obtained are 13, 21, 55, 42, and 23% using 0.05, 0.1, 0.3, 0.5, and 1 ml of water respectively. Only 4% of product was isolated with the anhydrous solvent. The best result was then obtained with 0.3 ml of water in 1 ml of ethanol.

3.4. Effect of addition of an ammonium salt

In previous work it was shown that the addition of an ammonium salt to natural phosphate [16], fluorapatite [20], or hydroxyapatite [21] increases the activity of these catalysts. Therefore, we carried out the synthesis of chalcone **3a** with NaNO$_3$/NP in methanol using different amounts of benzyltriethylammonium chloride (BTEAC). The results obtained after 6 h show that the best yields are obtained with 0.03–0.06 g of BTEAC. Moreover, the kinetic curves for the syn-

Table 3
Synthesis of chalcones by Claisen–Schmidt condensation using $NaNO_3$/NP in methanol

Entry	Substituents in reagents		Product		Yield[a] (%) [time (h)]	
	R^1	R^2			Without BTEAC	With BTEAC
1	H	H	**3a**		73(10) 98(18)	95(10)
2	*p*-Cl	H	**3b**		30(6) 94(16)	90(6)
3	*m*-NO$_2$	H	**3c**		38(6) 94(16)	95(6)
4	*p*-MeO	H	**3d**		40(12) 84(24) 91(36)	84(12) 94(24)
5	H	*p*-MeO	**3e**		37(12) 90(24)	82(12) 93(24)
6	*p*-Cl	*p*-MeO	**3f**		74(24) 93(48)	97(24)
7	*m*-NO$_2$	*p*-MeO	**3g**		55(24) 81(48)	92(24)
8	*p*-MeO	*p*-MeO	**3h**		40(24) 70(48)	93(24)
9	H	*p*-NO$_2$	**3i**		72(6)[b] 92(16)[b]	98(6)[b]
10	*p*-Cl	*p*-NO$_2$	**3j**		80(6)[b] 94(16)[b]	94(6)[b]
11	*m*-NO$_2$	*p*-NO$_2$	**3k**		58(6)[b] 70(12)[b] 95(24)[b]	84(6)[b] 98(12)[b]
12	*p*-MeO	*p*-NO$_2$	**3l**		74(6)[b] 93(16)[b]	89(6)[b]

[a] Isolated yields.
[b] Reaction carried out in the presence of 3 ml of methanol.

thesis of chalcone **3a** with or without BTEAC clearly show the enhancement of the catalytic activity of $NaNO_3$/NP by the addition of the ammonium salt. The yields obtained after 1, 6, 12, and 16 h are 10, 58, 81, and 92% without BTEAC and 27, 85, 98, and 98% in the presence of BTEAC, respectively.

Finally, this method was extended to the synthesis of several chalcones (Table 3). In all cases the reaction afforded the product **3** in high yields. The addition of BTEAC caused a significant increase in the reaction rate. For example, after 6 h the yield in **3b** (entry 2) ranged from 30% without BTEAC to 90% with the ammonium salt. Similar effects were observed for the other chalcones, even in the synthesis of **3h**, the worst case without BTEAC. It is important to note that BTEAC itself has not catalytic activity, so that it seems to act as a phase transfer catalyst.

4. Conclusions

Natural phosphate modified by impregnation with sodium nitrate and calcination at 900 °C is an efficient basic catalyst for the Claisen–Schmidt condensation. Several chalcones can be synthesized with high yields using catalytic amounts of $NaNO_3/NP$. The results depend on several factors, with the nature and amount of solvent playing a decisive role. The advantages of this solid over other basic heterogeneous catalysts are the high activity, the simplicity of the preparation method, the ready availability, the low price of the precursors, and the ease of reuse. The presence of an ammonium salt increased the reaction rate for all chalcones synthesized and the products were obtained in high yields. These results open the way to the use of this inexpensive solid as a basic catalyst for other applications.

Acknowledgments

References

[1] (a) S. Sebti, A. Saber, A. Rhihil, Tetrahedron Lett. 35 (1994) 9399;
(b) S. Sebti, A. Rhihil, A. Saber, N. Hanafi, Tetrahedron Lett. 37 (1996) 6555;
(c) S. Sebti, A. Rhihil, A. Saber, M. Laghrissi, S. Boulaajaj, Tetrahedron Lett. 37 (1996) 3999;
(d) S. Sebti, A. Rhihil, A. Saber, Chem. Lett. 8 (1996) 721.

[2] (a) S. Sebti, H. Boukhal, N. Hanafi, S. Boulaajaj, Tetrahedron Lett. 40 (1999) 6207;
(b) H.B. Lazrek, A. Rochdi, Y. Kabbaj, M. Taourirte, S. Sebti, Synth. Commun. 29 (1999) 1057;
(c) A. Alahiane, A. Rochdi, M. Taourirte, N. Redwane, S. Sebti, H.B. Lazrek, Tetrahedron Lett. 42 (2001) 3579.

[3] D.M. Tomazela, M.T. Pupo, E.A.P. Passador, M.F.d.G.F. da Silva, P.C. Vieira, J.B. Fernandes, Fo.E. Rodrigues, G. Oliva, J.R. Pirani, Phytochemistry 55 (2000) 643.

[4] S. Mukherjee, V. Kumar, A.K. Prasad, H.G. Raj, M.E. Bracke, C.E. Olsen, S.C. Jain, V.S. Parmar, Bioorg. Med. Chem. 9 (2001) 337.

[5] N.J. Lawrence, A.T. McGown, S. Ducki, J.A. Hadfield, Anti-Cancer Drug Des. 15 (2000) 135.

[6] F. Bois, A. Boumendjel, A.M. Mariotte, G. Conseil, A. Di Petro, Bioorg. Med. Chem. 7 (1999) 2691.

[7] V.J. Ran, A.S. Saxena, S. Srivastava, S. Chandra, Bioorg. Med. Chem. Lett. 10 (2000) 2159.

[8] M. Kidwai, P. Sapra, P. Misra, R.K. Saxena, M. Singh, Bioorg. Med. Chem. 9 (2001) 217.

[9] R. Edenharder, R. Ranscher, K.L. Platt, Mutat. Res. 379 (1997) 21.

[10] R.T. Blickenstaff, W.R. Hanson, S. Reddy, R. Witt, Bioorg. Med. Chem. 3 (1995) 917.

[11] H.-K. Hsieh, L.-T. Tsao, J.-P. Wang, C.-N. Lin, J. Pharm. Pharmacol. 52 (2000) 163.

[12] B.M. Choudary, K.M. Lakshmi, R.C.R. Venkat, R.K. Koteswara, F. Figueras, J. Mol. Catal. A 146 (1999) 279.

[13] R.S. Varma, G.W. Kabalka, L.T. Evans, R.M. Pagni, Synth. Commun. 15 (1985) 279.

[14] M.S. Climent, J.M. Marinas, Z. Mouloungui, Y. LeBigot, M. Delmas, A. Gaset, J.V. Sinisterra, J. Org. Chem. 54 (1989) 3695.

[15] (a) M.J. Climent, A. Corma, S. Iborra, J. Primo, J. Catal. 151 (1995) 60;
(b) A. Guida, M.H. Lhouty, D. Tichit, F. Figueras, P. Geneste, Appl. Catal. A 164 (1997) 251.

[16] S. Sebti, A. Saber, A. Rhihil, R. Nazih, R. Tahir, Appl. Catal. A 206 (2001) 217.

[17] (a) S. Sebti, A. Solhy, R. Tahir, S. Boulaajaj, J.A. Mayoral, J.M. Fraile, A. Kossir, H. Oumimoun, Tetrahedron Lett. 42 (2001) 7953;
(b) J.M. Fraile, J.I. Garcia, J.A. Mayoral, S. Sebti, R. Tahir, Green Chem. 3 (2001) 271.

[18] A.G. Fischer, D. Jérôme, in: Environmental Phosphorus Handbook, Wiley, New York, 1973, p. 141.

[19] S. Sebti, A. Saber, A. Rhihil, R. Nazih, R. Tahir, N. Hanafi, S. Boulaajaj, Recent Res. Dev. Org. Chem. 4 (2000) 335.

[20] S. Sebti, R. Nazih, R. Tahir, L. Salhi, S. Saber, Appl. Catal. A 197 (2000) L187.

[21] S. Sebti, R. Tahir, R. Nazih, S. Saber, S. Boulaajaj, Appl. Catal. A 228 (2002) 155.

[22] J. Bennazha, M. Zahouily, S. Sebti, A. Boukhari, E.M. Holt, Catal. Commun. 2 (2001) 101.