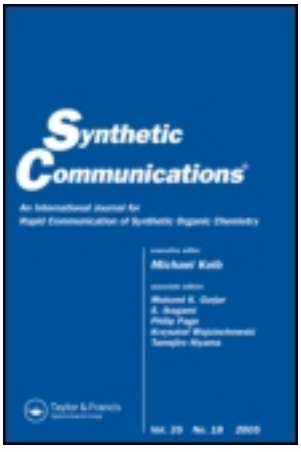


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Porous Calcium Hydroxyapatite as an Efficient Catalyst for Synthesis of Pyrazolines via 1,3-Dipolar Cycloaddition Under Solvent-Free Microwave Irradiation

R. Atir [a], S. Mallouk [a], K. Bougrin [a], M. Soufiaoui [a] & A. Laghzizil [b]
[a] Laboratoire de Chimie des Plantes et de Synthèse Organique et Bioorganique, Université Mohammed V-Agdal, Faculté des Sciences, Morocco
[b] Laboratoire de Chimie Physique Générale, Université Mohammed V-Agdal, Faculté des Sciences, Morocco
Published online: 21 Aug 2006.

To cite this article: R. Atir , S. Mallouk , K. Bougrin , M. Soufiaoui & A. Laghzizil (2006): Porous Calcium Hydroxyapatite as an Efficient Catalyst for Synthesis of Pyrazolines via 1,3-Dipolar Cycloaddition Under Solvent-Free Microwave Irradiation, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:1, 111-120

To link to this article: http://dx.doi.org/10.1080/00397910500330619

Synthetic Communications®, 36: 111–120, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500330619

Porous Calcium Hydroxyapatite as an Efficient Catalyst for Synthesis of Pyrazolines via 1,3-Dipolar Cycloaddition Under Solvent-Free Microwave Irradiation

R. Atir, S. Mallouk, K. Bougrin, and M. Soufiaoui
Laboratoire de Chimie des Plantes et de Synthèse Organique et Bioorganique, Université Mohammed V-Agdal, Faculté des Sciences, Morocco

A. Laghzizil
Laboratoire de Chimie Physique Générale, Université Mohammed V-Agdal, Faculté des Sciences, Morocco

Abstract: Adsorbed on porous calcium hydroxyapatite, 1,3-dipolar cycloaddition of diphenylnitrilimine on olefins is readily catalyzed under solvent-free microwaves irradiation. The pyrazolines are obtained in few minutes with high yields. Specific surface of porous calcium hydroxyapatite and microwaves effects are discussed.

Keywords: Microwave irradiation, porous hydroxyapatite, pyrazolines, solvent-free

INTRODUCTION

The 1,3-dipolar cycloaddition reaction is a powerful method for the preparation of five-membered heterocyclic compounds.[1] For example, pyrazolines are obtained by addition of nitrilimines with active alkenes. They are

Received in the UK May 23, 2005
Address correspondence to K. Bougrin, Laboratoire de Chimie des Plantes et de Synthèse Organique et Bioorganique, Université Mohammed V-Agdal, Faculté des Sciences, B.P. 1014, Morocco. Fax: (+212) 37 77 54 40; E-mail: kbougrin@yahoo.fr or bougrin@fsr.ac.ma

generally considered useful synthons in organic synthesis, and this heterocycle has often been used as a key intermediate for bioactive product synthesis.[2]

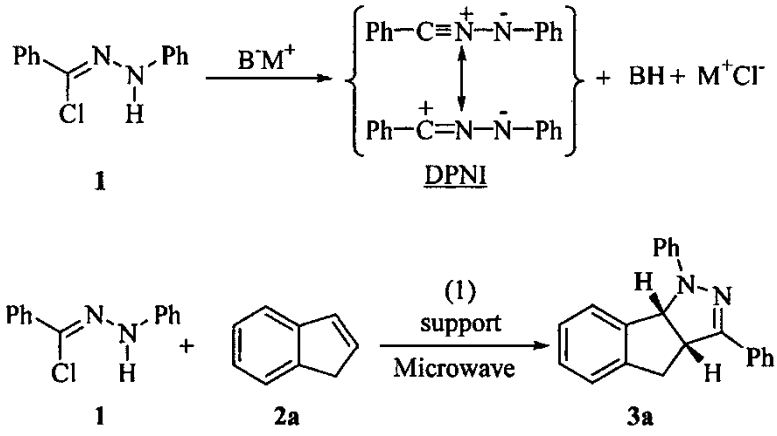
In recent years, it has been shown that various apatites have a catalytic application in organic synthesis[3] such as openings of epoxides and oxetanes,[3a] synthesis of phenol from benzene,[3b] oxidation of alcohols,[3c,3d] dehydrogenation of indolines,[3e] 2-butanol,[3f] and ethane,[3f] Knoevenagel condensation,[3g] Claisen–Schmidt condensation,[3h] and Friedel–Crafts alkylation.[3i] More recently, the hydroxyapatite has been used as excellent catalyst of three-component coupling reaction[3j] epoxidation of olefins under ultrasound irradiation.[3k] After revision of the literature, the applications on 1,3-dipolar cycloaddition reactions are not cited.

The application of microwave (MW) irradiation as a nonconventional energy source for activation of reactions has now become a very popular and useful technology in organic chemistry.[4] The combination of microwave irradiation and solvent-free reaction conditions leads to enhanced reaction rates, higher yields of pure products, easier workup, and, sometimes, to selective conversions with several advantages of the eco-friendly approach in the framework of green chemistry.[5]

Considering these reports and our continued interest in devising new solvent-free cyclization methods,[6] we report herein a microwave-enhanced method to obtain pyrazolines using a new catalyst and solvent-free conditions. Recently, we have developed an efficient method of 1,3-dipolar cycloaddition of diphenylnitrilimine (DPNI) with some alkenes using KF/γ-alumina[6a] or alumina,[6d] demonstrating its potential utility as a versatile protocol for the synthesis of pyrazolines. We were consequently encouraged to apply a solvent-free microwave-assisted procedure to this reaction for the sake of enhanced reactivity and environmental benefits. Herein, we report a microwave-assisted 1,3-dipolar cycloaddition of DPNI with alkenes catalyzed by porous calcium hydroxyapatite support [$Ca_{10}(PO_4)_6(OH)_2$] (p-HAP) (Scheme 1). The effects of microwave activation and surface of the support on the rate enhancement were also reported.

RESULTS AND DISCUSSION

In our experiment, in the absence of solvent, the reagents **1** and indene **2a** are previously impregnated on different supports including p-HAP100,[7] p-HAP300,[7] p-HAP800,[7] KF/NP (KF/natural phosphate),[8] KF/γ-alumina,[6a] and α-alumina under the same conditions, with the use of microwave heating for 3 min to afford 1,3-diphenyl-indano[3,2-d] pyrazoline **3a** (Scheme 1 and Table 1). The DPNI is generated in situ by heating hydrazonoyl chloride with support as base.[6a,9] The porous calcium hydroxyapatites used in our work were prepared by the chemical wet method and heated at different temperatures (100, 300, and 800°C) as reported elsewhere.[7] The



Scheme 1. 1,3-Dipolar cycloadditions reaction (1).

molar ratio of the reagents, irradiation time, and microwave power levels were optimized to achieve higher yields.

The best result of pyrazoline **3a** is obtained in the case of indene **2a**; the optimum conditions employed were 1 mmol of diphenylnitrilimine and 1 mmol of **2a** using 1 g of p-HAP300 or p-HAP100 as catalysts. However, under the same conditions used for p-HAP300 and p-HAP100, the catalyst KF/γ-Al_2O_3 is more reactive (Fig. 1). The power level of P_{max} (continuous irradiation) was found to be the most appropriate for cycloaddition reaction. The activity for reaction (1) was affected by two major factors, the effect of specific surface area and the chemical nature of surface (basic or acidic

Table 1. Effect of several supports on 1,3-dipolar cycloaddition of hydrazonoyl chloride **1** with **2a** under microwave irradiation (max. power = 1250 W)

Support	t (min)	T_f (°C)[b]	Specific surface area ($m^2 \cdot g^{-1}$)	Basicity	Yield (%)[c]
p-HAP100[a]	3	142	235	Basic	88
p-HAP300[a]	3	181	159	Basic	98
p-HAP800[a]	3 (10)	95 (93)	89	Low	20 (25)[d]
KF/NP	3 (10)	86 (88)	8.9	Basic	8 (10)[d]
KF/γ-Al_2O_3	3	170	High	High	89
α-Al_2O_3	3	84	Low	Acid	0

[a]p-HAP is prepared and heated at different temperatures (100°C, 300°C, and 800°C) according to the described procedure.[7]

[b]Final temperature was measured by immersing the digital thermometric probe in the reaction mixture at the end of exposure during the microwave experiment.

[c]Isolated yield in pure product.

[d]Reaction is not complete after 10 min under microwave irradiation.

surfaces) (Table 1). The increase of p-HAP300 or p-HAP100 quantity in the cycloaddition reaction of **1** with **2a** decreases the reactivity. This phenomenon is probably related to the high dilution of reagents **1** and **2a** onto porous apatite surface. The use of p-HAP300 is particularly interesting because it is regenerated by heating at 300°C under reduced pressure for 20 min. After ten successive recoveries, product **3a** was obtained with the same yield. The best result for pyrazoline **3a** (89%) is also obtained with KF/γ-Al_2O_3, but this hyperbasic solid is very expensive and it is not regenerative. We notice that the existence of fluoride ions in KF/γ-Al_2O_3 caused a linkage of the solid on the recipient during its preparation or when it is used in the reaction.

Once suitable conditions have been determined, we extended this reaction to other olefins (**2a**–**h**) and the main results are summarized in Table 2. The reactions were carried out in a multimode domestic microwave oven. Reactions were monitored by TLC; the end of the reaction is indicated by the appearance of the pyrazolines **3** identified by its intense fluorescence at $\lambda = 365$ nm.

The pyrazolines **3** were obtained with a mixture of two regioisomers in the case of trans-olefins (**2e**–**h**), but only one regioisomer with the olefins (**2a**–**d**). In all cases, the important role of p-HAP300 in the reaction of **1** with **2** was confirmed by the result readily obtained with pyrazolines **3** to afford a good yield (87–95%) during a short reaction time (3 min). To check the possibility of intervention of specific microwave effects, the reaction of **1** with **2** using p-HAP300 was also examined using a preheated oil bath for the same time and final temperature (104–181°C), as measured at the end of exposure during the MW-assisted synthesis (Table 2). However, the adducts **3** were obtained only with poor yields (0–5%) after 3 min and with incomplete consumption of the starting materials.

We then turned our attention to more comprehensive MW-specific effect on the 1,3-dipolar cycloaddition reaction. For the sake of comparison and to

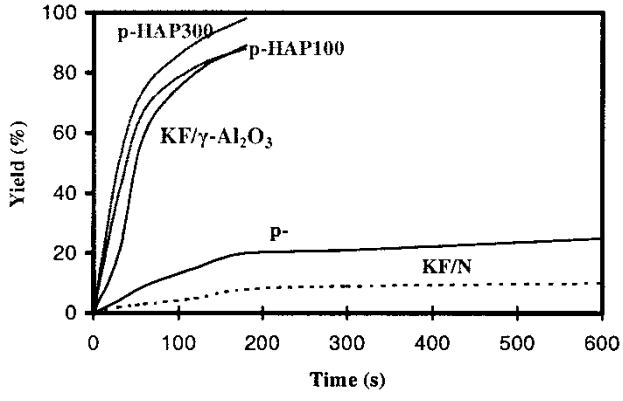
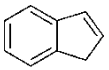
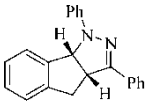
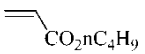
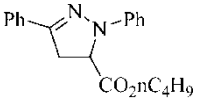
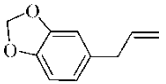
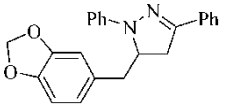
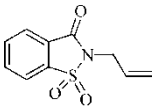
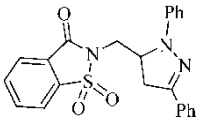
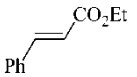
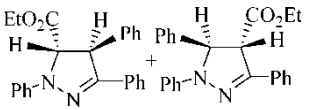


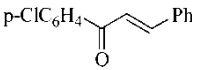
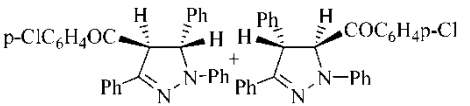
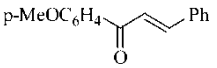
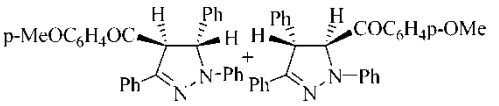
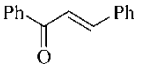
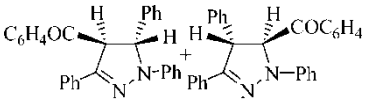
Figure 1. Catalytic activity of p-HAP100, p-HAP300, p-HAP800, KF/γ-Al_2O_3, and KF/NP in the synthesis of pyrazoline **3a** via reaction (1).

Table 2. 1,3-Dipolar cycloaddition of hydrazonoyl chloride **1** with olefin **2** (via Scheme 1) on p-HAP300 during 3 min under microwave irradiation (power = 1250 W)

Olefin (**2**)		T (°C)[a]	Adduct (**3**)		Isolated yield (%) MW[b]	Isolated yield (%) Δ[c]	Regioisomers ratio
	**2a**	181		**3a**	94	5	100/0
	**2b**	112		**3b**	92	5	100/0
	**2c**	104		**3c**	94	4	100/0
	**2d**	116		**3d**	87	0	100/0
	**2e**	132		**3e**	95	0	93/7

(continued)

Table 2. Continued

Olefin (**2**)		T (°C)[a]	Adduct (**3**)		Isolated yield (%) MW[b]	Isolated yield (%) Δ[c]	Regioisomers ratio
	**2f**	115		**3f**	95	0	95/5
	**2g**	145		**3g**	89	0	95/5
	**2h**	123		**3h**	90	0	91/9

[a]Final temperature was measured by immersing a digital thermometric probe in the reaction mixture immediately after microwave irradiations.
[b]Yields in pure products obtained under microwave irradiation.
[c]Yields determined by classical heating in the same reaction conditions (3 min, final temperature, vessel).

check the efficiency of MW activation in 1,3-dipolar cycloaddition reactions as well as the possible intervention of nonthermal MW-specific effects, control experiments were conducted using a thermostatted oil bath ($\Delta =$ conventional heating) under identical reaction conditions (time, temperature, vessel). The main results are given in Table 2. As illustrated in Table 2, nonthermal microwave specific effects were revealed in all cases; for instance, the reaction (1) was conducted under the same reaction conditions in the preheated oil bath, comparing the temperature profiles during the reaction (Fig. 2 and Table 2) to afford **3a** with only 5% yield. Microwave irradiation can therefore improve this reaction by enhancement of the dipole–dipole stabilization of the transition state when compared to the ground state.[10] In addition, it was observed that 120 min were required to achieve the adduct **3** by classical heating with the same yield, compared to 3 min under MW irradiation. This phenomenon can be explained with the weak thermal conductivity of p-HAP300 observed under classical heating. The same observation is described in the literature with other oxydes in dry media[11] such as silica, alumina, KF-alumina, and clay supports.

Although most experiments were performed on a 1-mmol scale, these reactions can also be performed with higher amounts of reagents (up to 5 mmol) with comparable yields. Additionally, we found that the MW-assisted reactions are more efficient, more convenient, and cleaner.

CONCLUSION

We have demonstrated that it is possible to perform the synthesis of pyrazolines via 1,3-dipolar cycloaddition on the surface of porous calcium

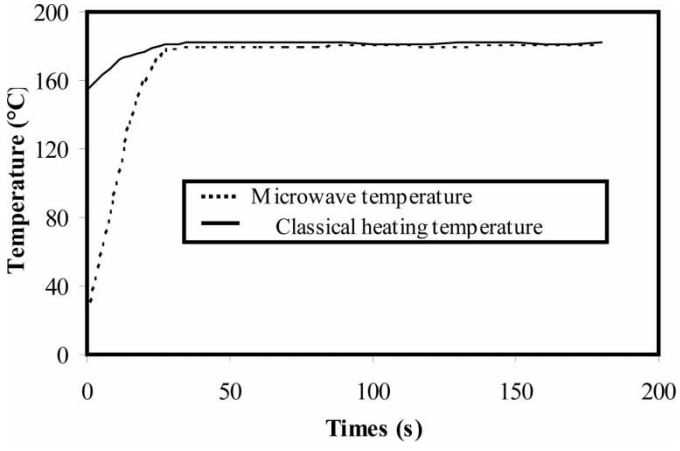


Figure 2. Temperature profiles monitored during the reaction of **1** and **2a** under microwave irradiation or classical heating at 181°C.

hydroxyapatite under solvent-free conditions with the help of MW irradiation from a domestic microwave oven. The method is fast, operationally simple, and allows rapid access to a variety of pyrazoline derivatives. Nonthermal MW-specific effects were also demonstrated. Efforts to extend this catalyst to other heterocyclic reactions are in progress.

EXPERIMENTAL

General Methods

A microwave of frequency 2.45 GHz, 1250 W, equipped with thermometer and timer (Philco) was used in all irradiation experiments. Melting points were determined on a Kofler melting-point apparatus and are uncorrected. Reactions were monitored by TLC on 0.2-mm silica-gel plates (Merck) using hexane/ethylacetate (80/20 v/v) mixtures as eluents, and compounds were visualized with UV light (254 and 365 nm) and iodine. Elemental analyses were performed by an LEO CHNS-93S apparatus. NMR spectra were determined on Bruker WP spectrometer at 250 MHz (^{1}H NMR) and at 62.89 MHz (^{13}C NMR). Chemical shifts are reported as δ values relative to the solvent peak of $CDC1_3$ set at $\delta = 7.27$ (^{1}H NMR) or $\delta = 77$ (^{13}C NMR) with tetramethylsilane as internal standard (δ) and were measured in ppm. Mass spectra (MS) were obtained with AEI MS-50 spectrometer by chemical ionization (IC) using isobutane as the reagent gas. All solvents used in reactions were freshly distilled from appropriate drying agents. All other reagents were recrystallized or distilled when necessary. Column flash chromatography was carried out on silica gel 60 (70–230 mesh). Completion of the reaction was generally revealed by TLC and indicated by the appearance of the pyrazolines **3**, identified by its intense fluorescence at $\lambda = 365$ nm. The resulting solid is analytically pure pyrazoline derivatives **3a–d** and the mixture of the two regioisomeric cycloadducts **3e–h**. Most adducts described herein were previously reported in the literature,[6a,12] with exception of adducts **3c** and **3d**.

General Procedure for the Synthesis of Pyrazolines 3

A mixture of hydrazonoyl chloride (0.230 g; 1 mmol) and olefin (1 mmol) was added to p-HAP300 (1 g) in CH_2Cl_2 (10 mL). The whole mixture was stirred for 1 min. The solvent was evaporated under reduced pressure in moderate condition (40°C) and then was irradiated by microwave (Philco, operating at 2.45 GHz, $P_{max} = 1250$ W) for the period of time and temperature (in Tables 1 and 2). The reaction progress was followed by TLC using n-hexane/ethyl acetate (8 : 2) as eluent. After 3.0 min, the reaction vessel was cooled, and the product was washed with 2×10 mL of CH_2Cl_2 or

THF. The solvent was evaporated under reduced pressure and the residue was purified by recrystallization in EtOH. The product was analysed by ^{1}H NMR, ^{13}C NMR, IR, and mass spectrometry, and compared to samples cited in literature.[6a,12]

5-(1,3-benzodioxol-5-ylmethyl)-1,3-diphenyl pyrazoline (3c): Mp 114–116°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 3.1 (m, 2H, CH_2), 3.4 (m, 2H, CH_2-C = N), 4.2 (m, 1H, CH), 5.8 (s, 2H, OCH_2O), 6.7–7.4 (m, 13H, Harm). ^{13}C NMR ($CDCl_3$): d 37.0 (CH_2), 44.3 (CH_2-C = N), 64.6 (CH), 101.0 (OCH_2O), 108.5–147.7 (Carm), 162.0 (C = N). CIMS (isobutane, reagent gas): m/z 357 [M + H]. Anal. calcd. for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found C, 77.45; H, 5.60; N, 7.89.

***N*-[1,3-diphenyl-pyrazolinyl methyl] saccharin (3d):** Mp 110–112°C (EtOH). ^{1}H NMR ($CDCl_3$): δ 3.9 (m, 2H, CH_2-C = N), 4.2 (m, 1H, CH-N), 4.5 (m, 2H, CH_2-N-SO_2), 5.8 (s, 2H, OCH_2O), 6.9–8.0 (m, 14H, Harm). ^{13}C NMR ($CDCl_3$): δ 36.3 (CH_2-N-SO_2), 42.7 (CH_2-C = N), 63.8 (CH-N), 111.9–148.3 (Carm), 164.8 (C = N), 166.0 (C = O). CIMS (isobutane, reagent gas): m/z 418 $[M + H]^+$. Anal. calcd. for $C_{23}H_{20}N_2O_2$: C, 66.17; H, 4.59; N, 10.07. Found C, 66.48; H, 4.55; N, 10.13.

ACKNOWLEDGMENTS

Financial assistance of Ministry of Education, Government of Morocco (PROTARS III, D13/57) and CNRST-Morocco are gratefully acknowledged.

REFERENCES

1. (a) Cinquini, M.; Cozzi, F. *Methoden der Organische Chemie (Houben-Weyl)*; Stereoselective Synthesis., G. Thieme: Stuttgart, 1995; Vol. E 21c, 2953; (b) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863; (c) Kunz, H.; Rüch-Braun, K. *Chiral Auxiliaries in Cycloadditions*; Wiley-VCH: Weinheim, 1999; (d) Karlsson, S.; Högberg, E.-H. *Org. Prep. Proc. Int.* **2001**, *33*, 1032; (e) Conti, P.; Roda, G.; Barberis Negra, F. F. *Tetrahedron Asym.* **2001**, *12*, 1363.
2. (a) Palaska, E.; Aytemir, M.; Uzbay, T.; Erol, D. Eur. *J. Med. Chem.* **2001**, *36*, 539; (b) Sharma, S.; Srivastava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2002**, *37*, 689; (c) Tabarelli, Z.; Rubin, M. A.; Berlese, D. B.; Sauzem, P. D.; Missio, T. P.; Teixeira, M. V.; Sinhorin, A. P.; Martins, M. A.; Zanatta, N.; Bonacorso, H. G.; Mello, C. F. *Braz. J. Med. Biol. Res.* **2004**, *37*, 1531; (d) Rani, P.; Srivastava, V. K.; Kumar, A. *Eur. J. Med. Chem.* **2004**, *39*, 449; (e) Berghot, M. A.; Moawad, A. B. *Eur. J. Pharm. Sc.* **2003**, *20*, 173.
3. (a) Onaka, M.; Ohta, A.; Sugita, K.; Izumi, Y. *Appl. Catal. A* **1995**, *125*, 203; (b) Liptáková, B.; Hronec, M.; Cvengro Ová, Z. *Catal. Today* **2000**, *61*, 143; (c) Maeda, Y.; Washitake, Y.; Nishimura, T.; Iwai, K.; Yamauchi, T.; Uemura, S. *Tetrahedron* **2004**, *60*, 9031; (d) Muzart, J. *Tetrahedron* **2003**, *59*, 5789; (e) Hara, T.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2003**, *44*, 6207; (f) Elkabouss, K.; Kacimi, M.; Ziyad, M.; Ammar, S.;

Bozon-Verduraz, F. *J. Catal.* **2004**, *226*, 16; (g) Sebti, S.; Tahir, R.; Nazih, R.; Saber, A.; Boulaajaj, S. *Appl. Catal. A* **2002**, *228*, 155; (h) Sebti, S.; Solhy, A.; Tahir, R.; Smahi, A. *Appl. Catal. A* **2002**, *235*, 273; (i) Saber, A.; Smahi, A.; Solhy, A.; Nazih, R.; Elaabar, B.; Maizi, M.; Sebti, S. *J. Mol. Catal. A* **2003**, *202*, 229; (j) Choudary, B. M.; Sridhar, C.; Kantam, M. L.; Sreedhar, B. *Tetrahedron Lett.* **2004**, *45*, 7319; (k) Pillai, U. R; Sahle-Demessie, E. *Appl. Catal. A* **2004**, *261*, 69.

4. (a) De la Hoz, A.; Diaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659. For recent reviews on microwave chemistry, see; (b) Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984; (c) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199; (d) Lidström, P.; Tierney, J. P.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225; (e) Hayes, B. L. *Microwave Synthesis: chemistry at the Speed of Light*; CEMPublishing: Matthews, NC, 2002; (f) Loupy, A. *Microwaves in Organic Synthesis*; Wiley-VCH: Weinheim, 2002; (g) Mingos, M. D.P. *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell: Oxford, 2004, Chap. 1; (h) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.
5. (a) Bougrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055; (b) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe', D. *Synthesis* **1998**, 1213; (c) Varma, R. S. *Green Chem.* **1999**, *1*, 43.
6. (a) Bougrin, K.; Soufiaoui, M.; Loupy, A.; Jacquault, P. *New J. Chem.* **1995**, *19*, 213; (b) Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett.* **1995**, *36*, 3683; (c) Syassi, B.; Bougrin, K.; Soufiaoui, M. *Tetrahedron Lett.* **1997**, *38*, 8855; (d) Ben Alloum, A.; Bakkas, S.; Bougrin, K.; Soufiaoui, M. *New J. Chem.* **1998**, 809; (e) Louërat, F.; Bougrin, K.; Loupy, A.; Retana, A. M. O.; Pagaladay, J.; Palacios, F. *Heterocycles* **1998**, *48*, 161; (f) Bougrin, K.; Loupy, A.; Petit, A.; Daou, B.; Soufiaoui, M. *Tetrahedron* **2001**, *57*, 163.
7. El Hammari, L.; Laghzizil, A.; Barboux, P.; Saoiabi, A.; Lahlil, K. *J. Solid State Chem.* **2004**, *177*, 134.
8. Abrouki, Y.; Zahouily, M.; Rayadh, A.; Bahlaouan, B.; Sebti, S. *Tetrahedron Lett.* **2002**, *48*, 8951.
9. (a) El-Abadelah, M. M.; Hussein, A. Q.; Kamal, M. R.; Al-Adhami, K. H. *Heterocycles* **1988**, *27*, 917; (b) Garanti, L.; Molteni, G.; Pilati, T. *Tetrahedron Asym.* **2002**, *13*, 1285.
10. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.
11. (a) Bram, G.; Loupy, A.; Majdoub, M.; Petit, A. *Chem. Ind.* **1991**, *11*, 396; (b) Bougrin, K.; Loupy, A.; Petit, A.; Daou, B.; Soufiaoui, M. *Tetrahedron* **2001**, *57*, 163.
12. Mallouk, S.; Bougrin, K.; Doua, H.; Benhida, R.; Soufiaoui, M. *Tetrahedron Lett.* **2004**, *45*, 4143.