

## Rapid and Efficient One-Pot Synthesis of 1,4-Dihydropyridine and Polyhydroquinoline Derivatives Through the Hantzsch Four Component Condensation by Zinc Oxide

F. Matloubi Moghaddam\*, H. Saeidian, Z. Mirjafary and A. Sadeghi  
*Laboratory of Organic Synthesis and Natural products, Department of Chemistry,  
Sharif University of Technology, Tehran, Iran, P. O. Box 11155-9516 Tehran, Iran*

*(Received 20 April 2008, Accepted 29 May 2008)*

A one-pot four-component reaction of aldehydes, ethyl acetoacetate/5,5-dimethyl-1,3-cyclohexanedione, ethyl acetoacetate and ammonium acetate in the presence of 10 mol% of ZnO as a heterogeneous catalyst for the synthesis of corresponding 1,4-dihydropyridine and polyhydroquinoline derivatives *via* the Hantzsch condensation is described. The present methodology offers several advantages such as simple procedure, excellent yields, and short reaction time.

**Keywords:** 1,4-Dihydropyridine and polyhydroquinolin, One-pot synthesis, Hantzsch condensation, Zinc oxide

---

### INTRODUCTION

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry allowing the facile creation of several new bonds in a one-pot reaction. Clearly, for multi-step synthetic procedures, the number of reactions and purification steps are among the most important criteria for the efficiency and practicability of the process and should be as low as possible. Therefore, in the last decade, research in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products [1].

On the other hand, in recent years, much attention has been directed towards the synthesis of 1,4-dihydropyridine compounds due to the wide range of biological activity associated with these compounds. 1,4-dihydropyridine derivatives possess a variety of biological activities such as vasodilator, bronchodilator, antiatherosclerotic, antitumor,

geroprotective, hepatoprotective and antidiabetic activity [2].

4-Aryl-1,4-dihydropyridines are analogues of NADH coenzymes, which have been explored for their calcium channel activity [3]. In addition, recently preceding studies have suggested that 1,4-dihydropyridine derivatives also provide an antioxidant protective effect that may contribute to their pharmacological activities [4]. Oxidation of 1,4-dihydropyridine to pyridines has also been extensively studied [5]. These examples clearly indicate the remarkable potential of novel 1,4-dihydropyridine and polyhydroquinoline derivatives as a source of valuable drug candidates and useful intermediates in organic chemistry. Thus, the synthesis of this heterocyclic nucleus is of much importance.

The known used route for synthesizing 1,4-dihydropyridine derivatives is the Hantzsch condensation, which involves the condensation of two molecules of a  $\beta$ -ketoester, one molecule of an aldehyde, and one molecule of ammonia in acetic acid or in refluxing alcohol [6]. This method, however, involves long reaction time and the use of a large quantity of volatile organic solvents and generally gives low yields. The preparation of 1,4-dihydropyridine and

---

\*Corresponding author. E-mail: matloubi@sharif.edu

polyhydroquinoline derivatives by ionic liquid [7] or microwave heating [8] has been reported.

Catalysts such as Sc(OTf)<sub>3</sub> [9], Silica gel/NaHSO<sub>4</sub> [10], heteropolyacid [11], I<sub>2</sub> [12], CAN [13], Yb(OTf)<sub>3</sub> [14] and Bakers' yeast [15] have also been used in this reaction. However, most of these methods employ expensive or poisonous catalysts, not commercially available catalysts, and long reaction times. Thus it is clearly evident that the development of new and flexible protocols is required.

Designing of new specific catalysts and exploring their catalytic activity has caused profound effects in optimizing the efficiency of a wide range of organic synthesis. Development of such catalysts has resulted in more economical and environmentally friendly chemistry through replacing nonselective, unstable, or toxic catalysts [16]. Surface of metal oxides exhibit both Lewis acid and Lewis base characters. This is characteristic of many metal oxides, especially TiO<sub>2</sub>, Al<sub>2</sub>O<sub>3</sub>, ZnO, *etc.*, and they are excellent adsorbents for a wide variety of organic compounds and increase reactivity of the reactants [17]. ZnO is certainly one of the most interesting of metal oxides, because it has surface properties which suggest that a very rich organic chemistry may occur there [18]. During our previous studies on the preparation of ZnO nanoparticles by controlled microwave heating and its application to *O*-acylation of alcohol, phenol [19] and for the synthesis of β-acetamido ketones/esters *via* a multi-component reaction [20] we became interested to explore further ZnO catalyzed organic reactions.

Herein, we wish to report a novel synthesis of polyhydroquinoline and 1,4-dihydropyridine derivatives using ZnO as an efficient, non-toxic and commercially available catalyst.

## EXPERIMENTAL

### General Procedure for Synthesis of Polyhydroquinoline and 1,4-Dihydropyridine Derivatives

To a stirred suspension of ZnO (10 mol%) in ethanol (1 ml) were added an aldehyde (1 mmol), ethyl acetoacetate/5,5-dimethyl-1,3-cyclohexanedione (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1 mmol). The reaction mixture was stirred at 80 °C for 60 min. The progress of the

reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure.

The solid residue was separated and dissolved in dichloromethane. The solution was filtered and zinc oxide was isolated and could be reused. Dichloromethane was evaporated under reduced pressure, which resulted in precipitation of the desired polyhydroquinoline and/or 1,4-dihydropyridine derivatives. The precipitated solid was washed with petroleum ether to remove any residual starting material and dried. The structure of the products was confirmed by <sup>1</sup>H NMR, <sup>13</sup>C NMR spectra and comparison with authentic samples prepared by reported methods.

### Representative Spectroscopic Data

Table 2, Entry 2: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.24 (d, J = 8.56 Hz, 2H), 6.86 (s, 1H), 6.76 (d, J = 8.56 Hz, 2H), 5.03 (s, 1H), 4.10 (q, J = 7.20 Hz, 2H), 3.75 (s, 3H), 2.36 (s, 3H), 2.27-2.18 (m, 4H), 1.25 (t, J = 7.20 Hz, 3H), 1.08 (s, 3H), 0.96 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 196.27, 168.03, 158.19, 149.24, 143.93, 140.16, 129.36, 113.66, 112.44, 106.61, 60.19, 55.52, 51.23, 41.22, 36.17, 33.06, 29.90, 27.55, 19.65, 14.68; Table 2, Entry 4: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.32 (d, J = 9.18 Hz, 1H), 7.17 (d, J = 8.80, 1H), 7.05 (t, J = 7.96, 1H), 6.95 (t, J = 8.36 Hz, 1H), 6.62 (s, 1H), 5.32 (s, 1H), 4.02-3.94 (m, 2H), 2.24-2.01 (m, 7H), 1.10 (t, J = 7.12 Hz, 3H), 0.98 (s, 3H), 0.86 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 196.01, 167.95, 149.60, 144.59, 144.35, 133.57, 132.45, 130.05, 127.69, 126.70, 111.47, 105.57, 60.23, 51.16, 41.34, 36.34, 32.92, 29.78, 27.59, 19.60, 14.64; Table 2, Entry 5: <sup>1</sup>H NMR (500 MHz, d<sub>6</sub>-DMSO): δ 7.87 (s, 1H), 7.05 (d, J = 7.97 Hz, 2H), 6.86 (d, J = 7.97 Hz, 2H), 4.86 (s, 1H), 3.93 (q, J = 7.13 Hz, 2H), 2.23-1.97 (m, 10H), 1.10 (t, J = 7.13 Hz, 3H), 0.95 (s, 3H), 0.82 (s, 3H); <sup>13</sup>C NMR (125 MHz, d<sub>6</sub>-DMSO): δ 195.73, 168.02, 149.57, 145.08, 144.80, 135.32, 128.77, 128.18, 111.85, 105.60, 59.80, 51.20, 36.33, 32.86, 29.84, 27.50, 21.34, 19.22, 14.59; Table 2, Entry 8: <sup>1</sup>H NMR (500 MHz, d<sub>6</sub>-DMSO): δ 8.11 (s, 1H), 7.97 (d, J = 8.15 Hz, 1H), 7.73 (d, J = 7.66 Hz, 1H), 7.50 (s, 1H), 7.36 (t, J = 7.90 Hz, 1H), 5.15 (s, 1H), 4.05 (q, J = 7.12 Hz, 2H), 2.40-2.11 (m, 7H), 1.19 (t, J = 7.12 Hz, 3H), 1.08 (s, 3H), 0.92 (s, 3H); <sup>13</sup>C NMR (125 MHz, d<sub>6</sub>-DMSO): δ 195.71, 167.48, 149.99, 149.69, 148.68, 145.59, 135.23, 128.86, 123.22, 121.51, 111.37, 104.98, 60.26, 51.04, 41.11, 37.35, 33.07, 29.82,

## Rapid and Efficient One-Pot Synthesis of 1,4-Dihydropyridine

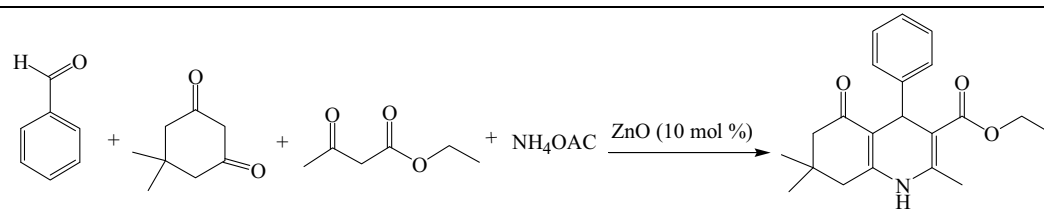
27.51, 19.54, 14.59; Table 2, Entry 10:  $^1\text{H}$  NMR (500 MHz,  $d_6$ -DMSO):  $\delta$  8.90 (s, 1H), 7.22 (m, 1H), 6.12 (m, 1H), 5.73 (d,  $J = 3.01$  Hz, 1H), 4.94 (s, 1H), 4.02-3.93 (m, 2H), 2.40-1.95 (m, 7H), 1.09 (t,  $J = 6.75$  Hz, 3H), 0.93 (s, 3H), 0.84 (3H);  $^{13}\text{C}$  NMR (125 MHz,  $d_6$ -DMSO):  $\delta$  194.93, 167.54, 159.34, 151.28, 146.69, 141.57, 110.98, 107.53, 104.79, 101.52, 59.95, 51.12, 33.64, 30.42, 30.01, 27.25, 22.79, 19.11, 15.11; Table 3, Entry 1:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.21 (d,  $J = 7.43$  Hz, 2H), 7.13 (t,  $J = 7.45$  Hz, 2H), 7.05 (t,  $J = 7.10$  Hz, 1H), 5.59 (s, 1H), 4.92 (s, 1H), 4.07-3.97 (m, 4H), 2.26 (s, 6H), 1.15 (t,  $J = 7.12$  Hz, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.02, 148.16, 144.19, 128.41, 128.23, 126.49, 104.64, 60.10, 40.07, 19.98, 14.65; Table 3, Entry 3:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.14 (d,  $J = 8.35$  Hz, 2H), 7.09 (d,  $J = 8.35$  Hz, 2H), 5.70 (s, 1H), 4.89 (s, 1H), 4.04-3.99 (m, 4H), 2.25 (s, 6H), 1.15 (t,  $J = 7.12$  Hz, 6H);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  167.86, 146.75, 144.42, 132.11, 129.82, 128.35, 104.30, 60.22, 39.68, 19.96, 14.67; Table 3, Entry 6:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.14 (d,  $J = 1.98$  Hz, 1H), 6.14 (t,  $J = 2.43$  Hz, 1H), 5.87 (d,  $J = 3.10$  Hz, 1H), 5.79 (s, 1H), 5.13 (s, 1H), 4.14-4.05 (m, 4H), 2.26 (s, 6H), 1.19 (t,  $J = 7.12$  Hz, 6H); 167.89, 159.11, 145.48, 141.26, 110.40, 104.85, 101.16, 60.23, 33.84, 19.93, 14.74.

## RESULTS AND DISCUSSION

To find the optimal conditions, the synthesis of 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester was used as a model reaction. A mixture of benzaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol), ethyl acetoacetate (1 mmol) and ammonium acetate (1 mmol) was stirred under various reaction conditions (Table 1). In the absence of the catalyst, product was obtained in low yield after 5 h, while good results were obtained in the presence of ZnO (Table 1, entries 2-6).

On the optimized of amount of catalyst, we found that 10 mol% of ZnO could effectively catalyze the reaction for the synthesis of the desired product. With inclusion of 5 mol% of ZnO the reaction took longer time. Using more than 10 mol% ZnO has less effect on the yield and time of the reaction (Table 1, entry 4). The effect of temperature was also studied by carrying out the model reaction in the presence of ZnO (10 mol%) at room temperature (25 °C), 40 °C and 80 °C. It was observed that the yield was increased as the reaction temperature was raised (Table 1, entries 3, 5 and 6). We then continued to optimize the model reaction by detecting the efficiency of polar and non-polar solvents. The polar solvent

**Table 1.** Optimization of the ZnO Catalyzed Model Reaction



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	Yields (%)
1	No catalyst	$\text{C}_2\text{H}_5\text{OH}$	80	7	57
2	ZnO (5%)	$\text{C}_2\text{H}_5\text{OH}$	80	4	78
3	ZnO (10%)	$\text{C}_2\text{H}_5\text{OH}$	80	1	92
4	ZnO (20%)	$\text{C}_2\text{H}_5\text{OH}$	80	1	95
5	ZnO (10%)	$\text{C}_2\text{H}_5\text{OH}$	40	4	81
6	ZnO (10%)	$\text{C}_2\text{H}_5\text{OH}$	25	4	64
7	ZnO (10%)	$\text{CH}_3\text{CN}$	80	1	73
8	ZnO (10%)	$\text{C}_6\text{H}_5\text{CH}_3$	80	1	36
9	ZnO (10%)	$\text{CH}_2\text{Cl}_2$	55	4	32
10	ZnO (10%)	$\text{C}_2\text{H}_5\text{OH}$	80	1	78 <sup>a</sup>

<sup>a</sup>Yield after three runs of recycling catalyst.

such as ethanol and acetonitrile were much better than non-polar solvent (Table 1, entries 8-9). To check the reusability of the catalyst, the recycled catalyst was used and after three runs, the yield was still high (Table 1, entry 10).

To generalize this methodology, we subjected a series of

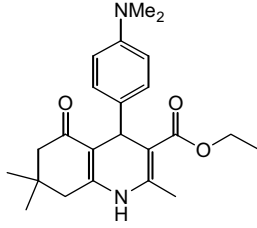
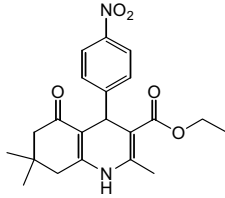
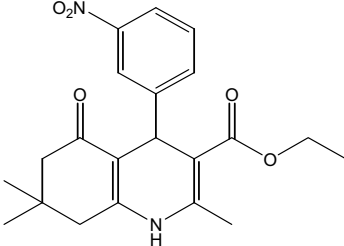
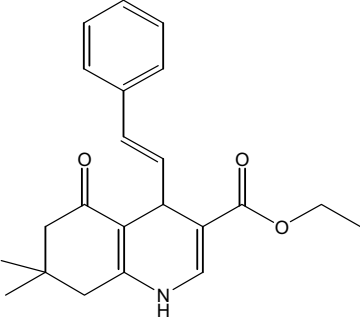
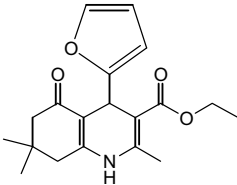
other aldehydes having electron-donating as well as electron-withdrawing substituents to obtain the corresponding polyhydroquinoline and/or 1,4-dihydropyridine derivatives under the optimized reaction conditions (Tables 2 and 3). It could be seen that the variations in the yields were very little

**Table 2.** ZnO-Catalyzed the Synthesis of Polyhydroquinoline Derivatives *via* Hantzsch Reaction

Entry	R	Product	Yield (%)
1	C <sub>6</sub> H <sub>5</sub>		92
2	<i>p</i> -OMeC <sub>6</sub> H <sub>5</sub>		84
3	<i>p</i> -ClC <sub>6</sub> H <sub>5</sub>		92
4	<i>o</i> -ClC <sub>6</sub> H <sub>5</sub>		81
5	<i>p</i> -MeC <sub>6</sub> H <sub>5</sub>		90

Rapid and Efficient One-Pot Synthesis of 1,4-Dihydropyridine

Table 2. Continued

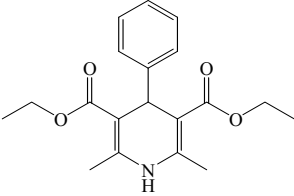
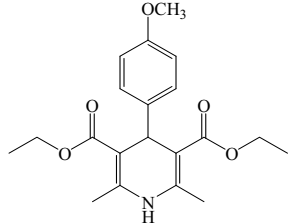
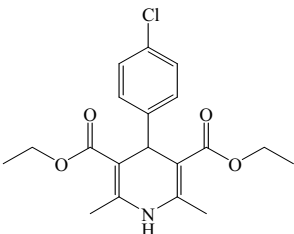
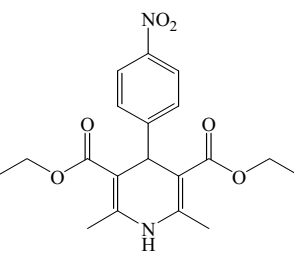
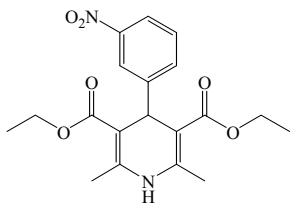
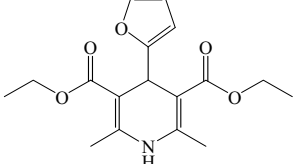
6	$p\text{-NMe}_2\text{C}_6\text{H}_5$		85
7	$p\text{-NO}_2\text{C}_6\text{H}_5$		94
8	$m\text{-NO}_2\text{C}_6\text{H}_5$		90
9	$\text{C}_6\text{H}_5\text{CH}=\text{CH}$		85
10	2-Furyl		88

and both electron-rich and electron-deficient aldehydes as well as heterocyclic ones such as furfural worked well, giving excellent yields of the substituted polyhydroquinoline and/or 1,4-dihydropyridine derivatives.

The superiority of the present protocol over reported methods can be seen by comparing our results with those of

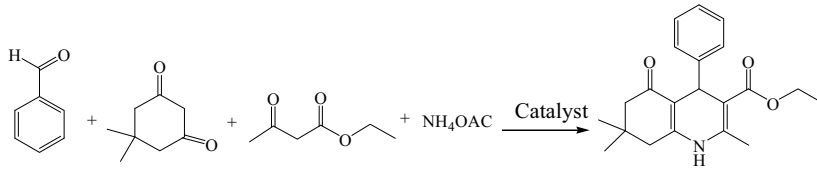
some recently reported procedures, as shown in Table 4. The synthesis of 2,7,7-trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic acid ethyl ester was used as a model reaction and the comparison is in terms of mol% of the catalysts, temperature, reaction time and percentage yields. Some catalysts such as  $\text{AlCl}_3$ ,  $\text{ZnCl}_2$  and  $\text{FeCl}_3$  required 100

**Table 3.** ZnO-Catalyzed the Synthesis of 1,4-Dihydropyridine Derivatives *via* Hantzsch Reaction

Entry	R	Product	Yield (%)
$\text{RCHO} + 2 \text{CH}_3\text{COCH}_2\text{CO}_2\text{Et} + \text{NH}_4\text{OAc} \xrightarrow{\text{ZnO (10 mol\%)}} \text{Product}$			
1	C <sub>6</sub> H <sub>5</sub>		85
2	<i>p</i> -OMeC <sub>6</sub> H <sub>5</sub>		79
3	<i>p</i> -ClC <sub>6</sub> H <sub>5</sub>		82
4	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>		87
5	<i>m</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>		80
6	<i>2-Furyl</i>		86

## Rapid and Efficient One-Pot Synthesis of 1,4-Dihydropyridine

**Table 4.** Effect of Catalysts on the Synthesis of 2,7,7-Trimethyl-5-oxo-4-phenyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylic Acid Ethyl Ester



Entry	Catalyst (mol %)	Temperature (°C)	Time (h)	Yield (%) [Lit.]
1	No catalyst	70	7	57
2	Heteropolyacid (1 mol %)	81	35 min	80 [11]
3	I <sub>2</sub> (30 %)	25	1.5	93 [12]
4	Yb(OTf) <sub>3</sub> (5 mol %)	25	5	90 [9]
5	AlCl <sub>3</sub> (100 %)	25	24	48 [9]
6	ZnCl <sub>2</sub> (100 %)	25	24	42 [9]
7	FeCl <sub>3</sub> (100 %)	25	24	38 [9]
8	ZnO (10 %)	70	1	92

mol%, while a low (10 mol%) of ZnO is used in this methodology.

In Conclusion, we have reported an efficient procedure for the synthesis of polyhydroquinoline and 1,4-dihydropyridine derivatives using ZnO as a reusable, non-toxic, non-corrosive, inexpensive and commercially available heterogeneous catalyst. The major advantage of this method is the ease of the work-up; *i.e.*, the products can be isolated without chromatography. The method also offers some other advantages such as clean reaction, low loading of catalyst, high yields of products, short reaction times and use of various substrates, which make it a useful and attractive strategy for the synthesis of polyhydroquinoline and 1,4-dihydropyridine derivatives.

## REFERENCES

- [1] a) A. Domling, I. Ugi, *Angew. Chem Int. Ed.* 39 (2000) 3168; b) L. Yu, B. Chen, X. Huang, *Tetrahedron Lett.* 48 (2007) 925.
- [2] a) M. Kawase, A. Shah, H. Gaveriya, N. Motohashi, H. Sakagami, A.V. Molnar, *J. Bioorg. Med. Chem.* 10 (2002) 1051; b) R. Mannhold, B. Jablonka, W. Voigt, K. Schoenafinger, K. Schraun, *Eur. J. Med. Chem.* 27 (1992) 229.
- [3] S. Visentin, B. Rolando, D.A. Stilo, R. Fruttero, M. Novara, E. Carbone, C. Roussel, N. Vanthuynne, A. Gasco, *J. Med. Chem.* 475 (2004) 2688.
- [4] R. Toniolo, D.F. Narda, G. Bontempelli, F. Ursini, *Bioelectro Chem.* 51 (2000) 193.
- [5] H. Adibi, R.A. Hajipour, *Bioorg. Med. Chem. Lett.* 17 (2007) 1008.
- [6] B. Love, M.K. Sander, *J. Org. Chem.* 30 (1965) 1914.
- [7] S.J. Yadav, S.V.B. Reddy, K.A. Basak, V.A. Narasaiah, *Green Chem.* 5 (2003) 3; b) R. Sridhar, T.P. Perumal, *Tetrahedron* 61 (2005) 2465.
- [8] a) A. Agarwal, S.M.P. Chauhan, *Tetrahedron Lett.* 46 (2005) 1345; b) L. Ohberg, J. Westman, *Synlett* (2001) 126.
- [9] L.J. Donelson, A.R. Gibbs, K.S. De, *J. Mol. Catal. A.* 256 (2006) 309.
- [10] A.M. Chari, K. Syamasundar, *Catal. Commun.* 6 (2005) 624.
- [11] M.M. Heravi, K. Bakhtiari, M.N. Javadi, F.F. Bamoharram, M. Saeedi, A.H. Oskooie, *J. Mol. Catal. A.* 264 (2007) 50.
- [12] S. Ko, V.N.M. Sastry, C. Lin, F.C. Yao, *Tetrahedron Lett.* 46 (2005) 5771.
- [13] S. Ko, F.C. Yao, *Tetrahedron* 62 (2006) 7293.
- [14] M.L. Wang, J. Sheng, L. Zhang, W.J. Han, Y.Z. Fan, H.

- Tian, T.C. Qian, *Tetrahedron* 61 (2005) 1539.
- [15] A. Kumar, A.R. Maurya, *Tetrahedron Lett.* 48 (2007) 3887.
- [16] a) R. Singh, M.R. Kissling, A.M. Letellier, P.S. Nolan, *J. Org. Chem.* 69 (2004) 209; b) T.P. Anastas, B.L. Bartlett, M.M. Kirchof, C.T. Williamson, *Catal. Today* 55 (2000) 11.
- [17] K. Tanabe, *Solid Acids and Bases*, Academic Press, New York, 1970.
- [18] a) F. Tamaddom, A.M. Amrollahi, L. Sharafat, *Tetrahedron Lett.* 46 (2005) 7841; b) M. Gupta, S. Paul, R. Gupta, A. Loupy, *Tetrahedron Lett.* 46 (2005) 4957; c) M. Hosseini-Sarvari, H. Sharghi, *J. Org. Chem.* 71 (2006) 6652; d) M. Hosseini-Sarvari, H. Sharghi, *Tetrahedron* 61 (2005) 10903; e) H. Sharghi, M. Hosseini-Sarvari, *Synthesis* 8 (2002) 1057; f) M. Hosseini-Sarvari, *Synthesis* 5 (2005) 787; g) M. Hosseini-Sarvari, H. Sharghi, *Phos. Silicon. Sulf.* 182 (2007) 2125; h) M. Hosseini-Sarvari, *Synth. Commun.* 16 (2008) 832; i) M. Hosseini-Sarvari, S. Etemad, *Tetrahedron* (2008) 5519; j) M. Hosseini-Sarvari, H. Sharghi, S. Etemad, *Helv. Chim. Acta.* 91 (2008) 715.
- [19] M.F. Moghaddam, H. Saeidian, *Mater. Sci. Eng. B.* 139 (2007) 265.
- [20] Z. Mirjafary, H. Saeidian, A. Sadeghi, M.F. Moghaddam, *Catal. Commun.* 9 (2008) 299.