

NanoZnO as an efficient & reusable catalyst for the preparation of 1,4-DHPs via Hantzsch reaction

Fatemeh Tamaddon*, Somayeh Moradi

Department of Chemistry, Faculty of Science, Yazd University, Yazd 89195-741, Iran

Received 5 February 2012; received in revised form 15 September 2012; accepted 15 October 2012

ABSTRACT

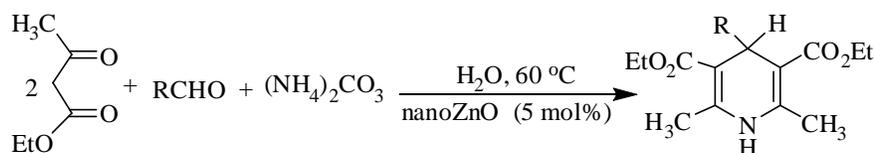
Easily prepared nanoZnO was found to be as an efficient catalyst in the synthesis of 1,4-DHPs via four-component reaction of 1,3-dicarbonyls, aldehydes and ammonium carbonate in water at 60 °C. The prepared nanoZnO was characterized by XRD and FT-IR analysis, while the determined specific surface area of nano catalyst by BET method was 33 m²/g.

Keywords: NanoZnO, Four-component reaction, DHPs, Ammonium carbonate.

1. Introduction

Preparation and application of metal oxide catalysts has been great interest for chemists and material scientists due to their advantages over other heterogeneous catalysts [1-6]. Metal oxides are non-corrosive, non-hygroscopic, and recoverable from the reaction mixture by a simple filtration. Nano metal oxides are more effective catalyst because of the small size and high surface area-to-volume ratio. Therefore nano-sized metal oxides have been extensively used as efficient heterogeneous catalysts in diverse organic transformations [7-10]. Metal oxide-catalyzed organic reactions in aqueous media without using harmful organic reagents or solvents are of even more desirable in green chemistry. Zinc oxide is a cost-effective metal oxide catalyst which as commercial form or nanoform has been used in eco-friendly and green organic synthesis. Preparation of nanoZnO is easier than other nano metal oxides and due to the effect of optional conditions such as pH, temperature, kind of surfactant, medium, and solvent on the crystallinity

and catalytic properties of nanoZnO, various types of nanosized ZnO can be easily prepared by changing the reaction conditions [7-12]. 1,4-Dihydropyridines are particular examples of natural products with biological properties and significant potentials which exhibit various pharmacological activities such as calcium channel antagonists [13-14], antihypertensive [15], antitumor [16], anti-inflammatory [17], antitubercular [18], antibacterial [19], and antioxidant activity [20]. 1,4-DHPs have been mainly prepared via the Hantzsch reaction [21] as a well-known multicomponent reaction (MCR), in which condensation of 2 mol 1,3-dicarbonyls, aldehydes and ammonia or ammonium salts results in the formation of these biologically active compounds. To improve the Hantzsch reaction various acidic and basic catalysts and energy sources have been used [22-27]. However synthesis of 1,4-DHPs in water and using a safe reusable catalyst is more desirable and in agreement with 12 principle of green chemistry. Recently, we have used ZnO and prepared nanoZnO in various organic transformations [8-10].



Scheme 1. NanoZnO-catalyzed synthesis of 1,4-DHPs.

* Corresponding author: E-mail: ftamaddon@yazduni.ac.ir.
Tel: 00983518122666; Fax: 00983518210644.

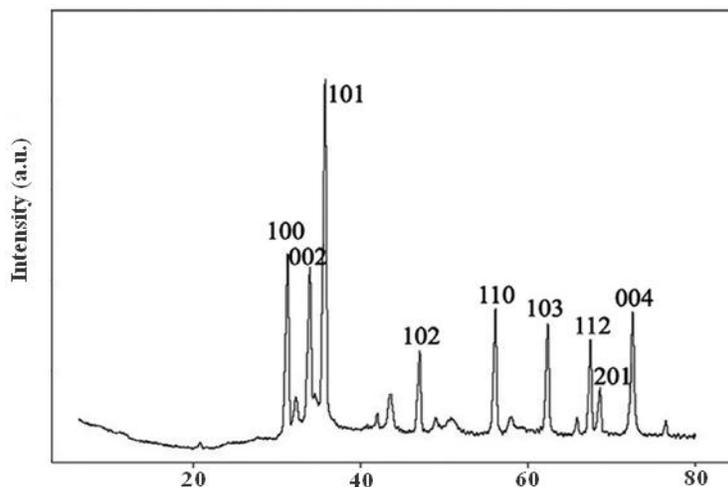


Fig. 1. XRD pattern for the prepared nanoZnO.

In continuation of our research, we report in the present document our results on the use of ZnO nanoparticles as efficient and reusable catalysts for improvement of the Hantzsch reaction in water (Scheme 1)

2. Experimental

2.1. General

All chemical were commercial products. All melting points were obtained by Büchi Scientific apparatus and are uncorrected. All reactions monitored by TLC and all yields refer to isolated products. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker-Arance AQS at 500 MHz and 125MHz respectively in CDCl_3 . FT-IR spectra were recorded on a Bruker FT-IR spectrophotometer.

2.2. Preparation and characterization of nanoZnO

NanoZnO was prepared via the previously reported procedures [3,8]. Zinc acetate dihydrate (5.5 g) was dissolved in 50 mL of deionized water and then solid NaOH (16 g) was added slowly into the solution under magnetic stirring at room temperature. A transparent $\text{Zn}(\text{OH})_4$ solution was formed. Then 2 mL of ionic liquid 1-butyl-3-methylimidazolium bis (trifluoromethylsulfonyl) imide ([bmim][NTf₂]) was added to 3 mL of the above solution. The suspension was put into a domestic microwave oven (850 W) in air, 30% of the output power of the microwave was used to irradiate the mixture for 5 min (on for 10s, off for 5s). The white precipitate was collected by centrifugation, washed with deionized water and ethanol several times, and dried in vacuum oven at 40 °C for 10h. The sizes of particles were between 30-40 nm [3].

Crystalline structure of the prepared nanoZnO was determined by powder X-ray diffraction (XRD). The strong intensity and narrow width of diffraction peaks indicate the high crystallinity of the prepared nanoZnO and the peaks positioned at various 2θ s of prepared nanoZnO were related to wurtzitic structure (Fig. 1). These peaks and the strongest diffraction peak for the 101 plane which is characteristic of

the hexagonal wurtzite structure [28] are compatible with those in the standard XRD patterns (JCPDS 36-1451). According to the XRD, other ZnO phases or impurities were not observed in the prepared nanoZnO.

The surface area of the prepared nanoZnO was evaluated by following the BET method and was found 33 m^2/g .

The characteristic bands in FT-IR spectra of nanoZnO confirm its structure [29]. The diagnostic FT-IR absorption band at 500 cm^{-1} is respected to the Zn-O stretching band. A little adsorbed surface water was evidenced by the presence of the broad OH stretching at 3435 and bending mode of water at 1426 cm^{-1} . The medium absorption band at 876 cm^{-1} is maybe due to the non-fundamental combination frequencies (Fig. 2).

2.3. General procedure for the nanoZnO-catalyzed Hantzsch reaction

To a mixture of aldehyde (2 mmol), ethyl acetoacetate (4 mmol), and ammonium carbonate (2 mmol) in water (1 mL) was added nanoZnO (5 mol%) and the mixture was stirred at 60 °C for the given times (Table 1).

2.4. General procedure for the isolation and purification of products

After completion of the reaction (TLC monitoring), EtOAc ($2 \times 10\text{ mL}$) was added and the precipitated ZnO was centrifuged and filtered off. The resulting organic solution was washed with 10% NaHCO_3 and brine, dried over anhydrous Na_2SO_4 , and evaporated to give the desired DHP product. In some cases, the analytical pure products were obtained by recrystallization of the crude solid from EtOH:H₂O mixture (50:50). The structure of products was assigned by analysis of their IR, ^1H NMR, ^{13}C NMR spectra and comparison to authentic samples.

2.5. Reusability of catalyst

ZnO or nanoZnO was regenerated, from the reaction of

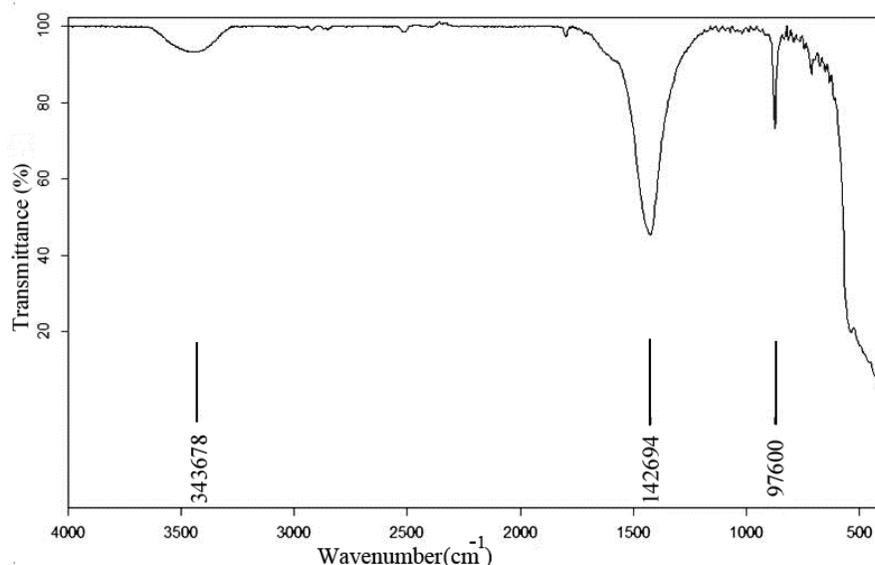


Fig. 2. FT-IR spectrum of the prepared nanoZnO.

benzaldehyde, ethyl acetoacetate, and ammonium carbonate with molar ratio of 1:2:1 by washing with EtOAc and drying at 300 °C or microwave irradiation. The recycled catalyst and reused for three consecutive times in Hantzsch reaction with no significant decreasing in reaction yields (Fig. 3).

Selected spectral data

Diethyl-2,6-dimethyl-4-(3-pyridyl)-1,4-dihydropyridine-3,5-dicarboxylate (Table 1, entry 12)
 Pale yellow solid, m.p. = 190-192 °C, IR (KBr, cm⁻¹): 3174 (NH stretching), 1688 (C=O) cm⁻¹. ¹H NMR (500 MHz,

CDCl₃, ppm) δ: 1.24 (t, *J* = 7.1 Hz, 6H, 2 × CH₃-CH₂), 2.36 (s, 6H, 2 × CH₃), 4.07-4.14 (m, 4H, O-CH₂CH₃), 5.01 (s, 1H, CH), 6.61 (s, 1H, NH), 7.19 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.64-7.66 (m, 1H), 8.39 (dd, *J* = 4.8, 1.6 Hz, 1H), and 8.55 (d, *J* = 1.9 Hz, 1H). ¹³C NMR (125 MHz, CDCl₃, ppm) δ: 14.68, 19.75, 38.23, 60.27, 103.57, 123.55, 136.27, 14, 4.00, 145.39, 147.40, 149.80, and 167.64. MS (EI): *m/z* : 330 (M⁺, 40), 301 (55), 285 (54), 252 (100), 224 (85), 196 (85), 150 (28), 106 (22), and 51 (18).

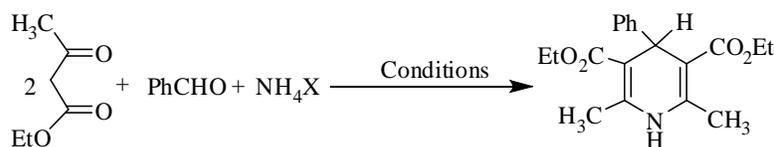


Table 1. NanoZnO-catalyzed synthesis of 1,4-dihydropyridine under different conditions via Hantzsch reaction.

Entry	NH ₄ X	Conditions		Time (h)	Yield (%) ^a
		Catalyst (mol %)/°C/Solvent			
1	NH ₄ OAc	NanoAl ₂ O ₃ (10)/80/EtOH		2.5	80
2	NH ₄ OAc	NanoSiO ₂ (10)/80/EtOH:H ₂ O		3	65
3	NH ₄ OAc	CaO (10)/80/EtOH		2.45	73
4	(NH ₄) ₂ CO ₃	NanoZnO (10)/80/EtOH:H ₂ O		2	91
5	NH ₄ OAc	ZnO (10)/80/EtOH:H ₂ O		2	90
6	NH ₄ OAc	NanoZnO (5)/60/EtOH:H ₂ O		3	92
7	NH ₄ OAc	ZnO (10)/60/H ₂ O		>3	89
8	NH ₄ OAc	NanoZnO (5)/60/H ₂ O		2	89
9	(NH ₄) ₂ CO ₃	NanoZnO (5)/60/H ₂ O		2	95
10	NH ₄ OAc	ZnO (10)/80/EtOH		4	85 [12]
11	(NH ₄) ₂ CO ₃	ZrO ₂ (5)/60/H ₂ O		4	83

^aIsolated yield.

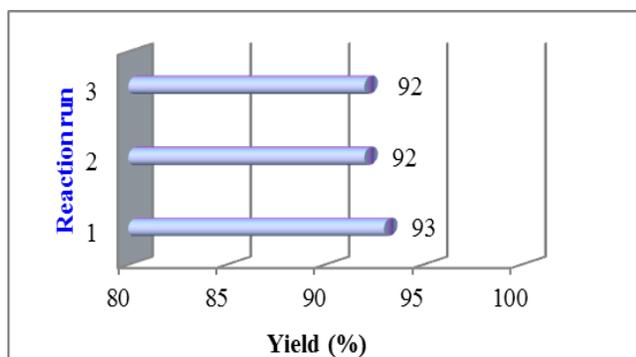


Fig. 3. The reusability of nanoZnO.

Diethyl-2,6-dimethyl-4-(3-hydroxyphenyl)-1,4-dihydropyridine-3,5-dicarboxylate (Table 1, entry 7)

Pale yellow solid, m.p. = 180-182 °C, IR (KBr, cm^{-1}): 3349 (OH and NH stretching), 1648 (C=O) cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , ppm) δ : 1.26 (t, $J = 7.1$ Hz, 6H, $2 \times \text{CH}_3\text{-CH}_2$), 2.33 (s, 6H, $2 \times \text{CH}_3$), 4.09-4.18 (m, 4H, O- CH_2CH_3), 5.00 (s, 1H, CH), 5.13 (br s, 1H, OH), 5.70 (br s, 1H, NH), 6.63 (dd, $J = 7.95, 2.39$ Hz, 1H_{arom}), 6.80 (s, 1H_{arom}), 6.89 (d, $J = 7.69$ Hz, 1H_{arom}), and 7.09 (t, $J = 7.8$ Hz, 1H_{arom}). ^{13}C NMR (125 MHz, CDCl_3 , ppm) δ : 14.62, 19.22, 39.44, 59.64, 103.22, 113.36, 115.39, 119.43, 149.97, 157.07, and 168.15. Anal. Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_5$: C, 66.07; H, 6.71; and N, 4.06. Found: C, 66.04; H, 6.67; and N, 4.00.

3. Results and discussion

Our study began with the reaction between benzaldehyde, ethyl acetoacetate, and ammonium salts, in the presence of metal oxide catalysts under various conditions. The optimization of reaction conditions was reached by carrying the reaction in different temperatures and utilizing different catalyst loadings (Table 1).

The metal oxides screened were effective catalysts for the Hantzsch reaction, but as shown in Table 1, the excellent yields of desired 1,4-DHP was achieved using 5 mol% of nanoZnO as catalyst, ammonium carbonate as nitrogen source, and water as solvent at 60 °C after 2h (Table 1, entry 9). In order to extend this environmentally benign methodology for the synthesis of 1,4-DHPs, we examined the efficiency of nanoZnO-catalyzed Hantzsch reaction of various aldehydes, ethyl acetoacetate and ammonium carbonate in water under optimized conditions (Table 2).

The results showed that aromatic aldehydes bearing both electron-deficient and electron-rich substituent, aliphatic aldehydes, and even heteroaryl aldehydes afforded the desired 1,4-DHPs in good yield (Table 2).

Table 3 demonstrates that the catalyst loading in our method were significantly lower than the reported methods, whereas higher yield in the shorter reaction time was obtained in water without using any organic solvent.

4. Conclusion

In summary, we have demonstrated an efficient one-pot synthesis of desired 1,4-dihydropyridines from various aldehydes, ethyl acetoacetate, and $(\text{NH}_4)_2\text{CO}_3$ using nanoZnO in water. The present work is an efficient simple, eco- friendly, and commercially procedure for the Hantzsch reaction using a catalytic amount of nanoZnO as a reusable moderate Lewis acid and water as a green solvent. The products were also obtained in shorter times and higher yields without any purification compared with previous methods.

Acknowledgements

We acknowledge the research council of Yazd University.

References

- [1] G. Sartori, R. Maggi, Chem. Rev. 113 (2010) PR1–PR54.
- [2] B. Karimi, J. Maleki, J. Org. Chem. 68 (2003) 4951–4954.
- [3] E.K. Goharshadi, Y. Ding, P.J. Nancarrow, Phys. Chem. Solids 69 (2008) 2057–2060.
- [4] Y.J. Kim, R.S. Varma, Tetrahedron Lett. 45 (2004) 7205–7208.
- [5] M.F. Garca, A.M. Arias, J.C. Hanson, J.A. Rodriguez, Chem. Rev. 104 (2004) 4063–4104.
- [6] M. Hosseini-Sarvari, H. Sharghi, J. Org. Chem. 71 (2006) 6652–6654.
- [7] R. Jalal, E.K. Goharshadi, M. Abareshi, M. Moosavi, A. Yousefi, P. Nancarrow, Mater. Chem. Physic. 121 (2010) 198–201.
- [8] F. Tamaddon, M.R. Sabeti, A.A. Jafari, F. Tirgir, E. Keshavarz, J. Mol. Catal. A: Chem. 351 (2011) 41–45.
- [9] F. Tamaddon, A. Nasiri, S. Farokhi, Catal. Commun. 12 (2011) 1477–1482.
- [10] F. Tamaddon, M.A. Amrollahi, L. Sharafat, Tetrahedron Lett. 46 (2005) 7841–7844.
- [11] S. Ashoka, P. Chithaiah, K.V. Thipperudraiah, G.T. Chandrappa, Chim. Acta 363 (2010) 3442–3447.
- [12] F. Matloubi Moghaddam, H. Saeidian, Z. Mirjafary, A. Sadeghi J. Iran. Chem. Soc. 6 (2009) 317–324.
- [13] B. Bülbül, G. S. Oztürk, M. Vural, R. Şimşek, Y. Sarioğlu, A. Linden, M. Ülgen, C. Şafak, Eur. J. Med. Chem. 44 (2009) 2052–2058.
- [14] R. Miri, K. Javidnia, H. Sarkarzadeh, B. Hemmateenejad, Bio. Med. Chem. 14 (2006) 4842–4849.
- [15] J. Safari, S.H. Banitaba, S.D. Khalili, J. Mol. Catal. A: Chem. 335 (2011) 46–50.
- [16] G.M. Reddy, M. Shiradkar, A.K. Chakravarthy, Curr. Org. Chem. 11 (2007) 484–487.
- [17] M. Khoshneviszadeh, N. Edraki, K. Javidnia, A. Alborzi, B. Pourabbas, J. Mardaneh, R. Miri, Bioorg. Med. Chem. 17 (2009) 1579–1586.
- [18] K. Sirisha, D. Bikshapathi, G. Achaiah, V.M. Reddy, Eur. J. Med. Chem. 46 (2011) 1564–1571.

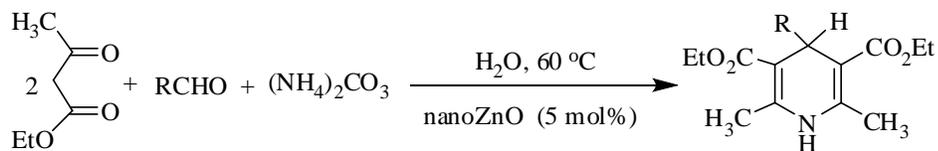
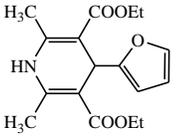
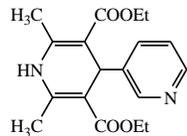


Table 2. Zinc oxide-catalyzed synthesis of 1,4-DHPs via the four-component reaction.

Entry	R	Product	Yield (%) ^a	Time (h)	m.p. (°C)	
					Found	(Reported) [22]
1	C ₆ H ₅		95	2	157–160	(157–159)
2	4-MeOC ₆ H ₄		95	2.5	156–158	(158–160)
3	4-MeC ₆ H ₄		94	2.5	136–138	(137–139)
4	4-ClC ₆ H ₄		93	1.5	156–158	(158–161)
5	4-O ₂ NC ₆ H ₄		90	1.5	131–132	(129–131)
6	4-HOC ₆ H ₄		89	2.5	226–229	(226–228)
7	3-HOC ₆ H ₄		86	2	180–183	(180–182)
8	4-FC ₆ H ₄		92	2	155–158	(155–157)
9	<i>n</i> -Propyl		85	2.5	125–127	(125–127)
10	<i>iso</i> -Propyl		90	2.5	95–97	(95–97)

Table 2. (Continued)

11	2-Furyl		90	2.5	159–162 (160–162)
12	3-Pyridyl		95	2	189–193 (190–192)

^aIsolated yield.

Table 3. Comparison of the nanoZnO-catalyzed Hantzsch reaction with literature reported methods.

Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (h)	Isolated yield (%)	Reference
1	MgAl ₂ -HT (2.9)	CH ₃ CN	25	6.5	61	[30]
2	PPh ₃ (20)	EtOH	Reflux	5	72	[25]
3	ZnO (10)	EtOH	80	1	85	[12]
4	nanoZnO (5)	H ₂ O	50-60	2	95	Present work

[19] A.M. Vijesh, A.M. Isloor, S.K. Peethambar, K.N. Shivananda, T. Arulmoli, N.A. Isloor, *Eur. J. Med. Chem.* 46 (2011) 5591–5597.
 [20] D. Shahabi, M.A. Amrollahi, A.A. Jafari, *J. Iran. Chem. Soc.* (2011) 1052-1057.
 [21] A. Hantzsch, *Justus Liebigs Ann. Chem.* 215 (1882) 1–82.
 [22] F. Tamaddon, Z. Razmi, A. A. Jafari, *Tetrahedron Lett.* 51 (2010) 1187–1189.
 [23] J.L. Wang, B-K. Liu, C. Yin, Q. Wu, X.-F. Lin, *Tetrahedron* 67 (2011) 2689–2692.
 [24] M.A. Chari, K. Syamasundar, *Catal. Commun.* 6 (2005) 624–626.

[25] S. Sueki, R. Takei, J. Abe, I. Shimizu, *Tetrahedron Lett.* 52 (2011) 4473–4477.
 [26] A. Debache, W. Ghalem, R. Boulcina, A. Belfaitah, S. Rhouati, B. Carboni, *Tetrahedron Lett.* 50 (2009) 5248–5250.
 [27] E. Rafiee, S. Eavani, S. Rashidzadeh, M. Joshaghani, *Inorg. Chim. Acta.* 362 (2009) 3555–3562.
 [28] M. Muruganandham, J.J. Wu, *Appl. Catal. B: Environ.* 80 (2008) 32–41.
 [29] N. Faal Hamedani, F. Farzaneh, *J. Sci.* 17 (2006) 231–234.
 [30] C. A. Antonyraj, S. Kannan, *Appl. Catal.* 338 (2008) 121–129.