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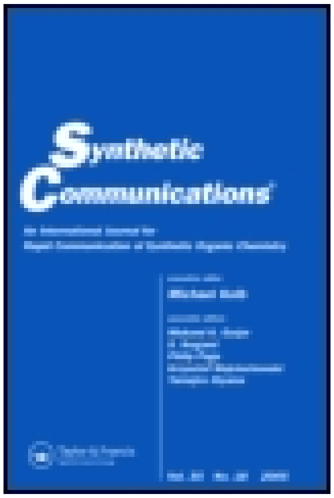

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ZnO Nanoparticles as an Efficient, Heterogeneous, Reusable, and Eco-Friendly Catalyst for One-Pot Three-Component Synthesis of 3,4-Dihydropyrimidin-2(1H)-(thio)one Derivatives in Water

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Accepted author version posted online: 02 Dec 2014.

To cite this article: Akbar Hassanpour, Rahim Hosseinzadeh Khanmiri & Jafar Abolhasani (2014): ZnO Nanoparticles as an Efficient, Heterogeneous, Reusable, and Eco-Friendly Catalyst for One-Pot Three-Component Synthesis of 3,4-Dihydropyrimidin-2(1H)-(thio)one Derivatives in Water, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, DOI: 10.1080/00397911.2014.987350

To link to this article: http://dx.doi.org/10.1080/00397911.2014.987350

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ZnO Nanoparticles as an Efficient, Heterogeneous, Reusable, and Eco-friendly Catalyst for One-Pot three-Component Synthesis of 3,4-dihydropyrimidin-2(1*H*)-(thio)one Derivatives in Water

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Abstract

An extremely efficient heterogeneous protocol is reported for the one-pot three-component synthesis of a series of dihydropyrimidinones (DHPMs) in the presence of ZnO nanoparticles in water as a green solvent. The ZnO nanoparticles exhibited excellent catalytic activity and the proposed methodology is capable to providing the desired products in high yield (65–94%) and short reaction time. After reaction course, ZnO nanoparticles can be recycled and reused without any apparent loss of activity which makes this ecofriendly process cost effective.

KEYWORDS: Biginelli reaction; Multicomponent reaction; ZnO nanoparticles; Green chemistry; Dihydropyrimidinone

1. INTRODUCTION

During the past decade, multicomponent reactions (MCRs) gained significant interest within the scientific community as an efficient, convenient, time-saving, and atom-economical approach to a variety of drug-like heterocyclic molecules.[1] The acid-catalyzed reaction of an aldehyde with enolizable ketones and urea to give a DHPM was

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first reported by Pietro Biginelli in 1893.[2] DHPMs compounds have a variety of pharmaceutical properties including calcium channel modulation, mitotic kinesin Eg5 inhibition, antiviral and antibacterial properties.[2] Because of the above mentioned properties of DHPMs, various synthetic methods with different catalysts have been reported by different research groups. These catalysts are Brønsted acids,[3] Lewis acids,[4] microwave variants,[5] $Mn(OAc)_2$[3,6] LiBr,[7] ammonium salt,[8] solid support,[9] CAN[10], NaCl,[11] and clay,[12] but some of the methods have their own limitations in terms of yields, catalyst load, stability of promoters, etc.

NanoZnO is a very inexpensive and easily available Lewis acid and base catalyst which has been widely used in organic reactions, especially as a catalyst in the Biginelli reaction in water as solvent until now.[13] The surface of ZnO nanoparticles activate the starting materials and coordination of accessible zinc cation to functional groups led to their activation and enhancement of the reaction rates and yields.[14, 15, 16, 17] Due to the importance of Biginelli products, the discovery and introduction of much mild, economic and faster conditions with nano-catalysts are required. With the aim to develop an operationally simple method for the synthesis of a large range of DHPMs, we report herein a novel approach for synthesis of 3,4-dihydropyrimidin-2(1*H*)- (thio)ones (**4**) via the one-pot reaction of ethyl acetoacetate (**1**), an aromatic or aliphatic aldehyde (**2**) and urea or thiourea (**3**) using ZnO nanoparticles as a non-toxic nanocatalyst (Scheme 1).

2. RESULTS AND DISCUSSION

ZnO nanoparticles is easily prepared from $Zn(CH_3CO_2)_2.2H_2O$.[13] In a model reaction, benzaldehyde, ethyl acetoacetate and urea were stirred in H_2O as solvent at 80 °C. It is important to note that this reaction does not proceed in the absence of catalyst. Stirring of the mixture of benzaldehyde, ethyl acetoacetate and urea at 80 °C for 28 h in H_2O gave a trace amount of the desired product (**4f**), while good results were obtained in the presence of ZnO nanoparticles after 30 min in H_2O as solvent at 80 °C (Table 1, entries **3**–**5**). We found that 4 mol% of ZnO nanoparticles could effectively catalyze the reaction for synthesis of the desired product, with 2 mol% of ZnO nanoparticles the reaction finished at longer time (Table 1, entry 2) and the yield and time of the reaction was not improved by more than 4 mol% of catalyst (Table 1, entry 4).

The effect of temperature was studied by carrying out the model reaction in the presence of ZnO nanoparticles (4 mol%) at 50 °C and 80 °C and it was observed (Table1, entries 5 and 6) that the yield was not increased by raising the reaction temperature. The bulk ZnO was also evaluated but the yield of reaction was clearly higher than ZnO bulk (91% versus 55%, Table 1, entries **3** and **7**).

The higher surface area, oxophilicity of zinc cation, amphoteric nature of nanoZnO together with the ability of the zinc cation for nearing of the activated starting materials supports its catalytic efficiency.

The effect of solvents was also examined for the above reaction and the results indicated the solvent efficiency on the reaction (Table 2). Performing the reaction of benzaldehyde,

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ethyl acetoacetate and urea in various protic and aprotic solvents showed the efficiency of polar solvents, and preferentially water as the reaction solvent (Table 2).

In order to explore the generality, we subjected various aldehydes **2** in the reaction with urea and thiourea at 50 °C in H_2O. As results show, electron-rich and electron-deficient substrates were reacted to synthesis the corresponding DHPM under the optimized reaction conditions. As indicated in Table 3, the reaction proceeds efficiently and led to the products **4a-z** in good yields.

Many of the pharmacological relevant substitution patterns on the aromatic ring could be introduced with high efficiency. Aromatic aldehydes carrying either electron donating or withdrawing substituents afforded high yields of products in high purity. Acid sensitive aldehydes such as furfural (**4k** and **4z**), which are normally observed either in the presence of protic or Lewis acids, is also worked well without the formation of any side products. In addition to its simplicity and milder reaction conditions, this method is effective even with aliphatic and unsaturated aldehydes which are normally produce poor yields in the presence of either protic or Lewis acids due to their decomposition or polymerization under acidic conditions. Also, water is a fully compatible medium with green chemistry.

Reusability is one of the important properties of this catalyst. For this reason, catalyst was recovered from the reaction between benzaldehyde, ethyl acetoacetate and urea by filtration. After washing with EtOAc and drying at 300 °C, the recovered NanoZnO was

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reused for three consecutive times in Biginelli reactions with no significant decreasing in the reaction yield. The changes in the structure of the recovered ZnO nanoparticles were determined by XRD and FT-IR methods. As can be seen in Figure 1, the structure of the recycled catalyst does not change and a very slight decrease in the reaction yield is may be due to the covering the surface of catalyst by impurities.

According to the established mechanism of the Biginelli reaction by Kappe, we also proposed that the key step in this cyclocondensation process should involve the formation of N-acyliminium ion intermediate.[25]

4. CONCLUSION

In conclusion, we have reported an efficient procedure for the synthesis of DHPMs using ZnO nanoparticles as a reusable, non-toxic and inexpensive nanocatalyst. Moderate to good yields of the corresponding DHPMs were obtained from readily available starting materials. 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 and it an attractive approach for the generation of different compounds with potential properties for medicinal chemistry programs.

ACKNOWLEDGMENTS

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The authors would like to thank Young Researchers and Elite Clube, Marand Branch, Islamic Azad University, Marand , Iran for the financial support of this research.

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REFERENCES

[1] (a) Dömling, A. Chem. Rev. **2006**, *106*, 17. (b) Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125. (c) Akritopoulou-Zanze, I. *Curr. Opinion Chem. Biol.* **2008**, *12*, 324. (d) Hulme, C. In Multicomponent Reactions; Zhu, J.; Bienayme, H., Eds.; Wiley-VCH, Verlag GmbH & Co. KgaA: Weinheim, **2005**, *311*. (e) Hulme, C.; Gore, V. *Current Med. Chem.* **2003**, *10*, 51. (f) Marcaccini, S.; Torroba, T. In Multicomponent Reactions; Zhu, J., Bienayme, H., Eds.; Wiley-VCH, Verlag GmbH & Co. KgaA: Weinheim, **2005**; *33*. (g) Zhu, J., *Eur. J. Org. Chem*. **2003**, 1133. (h) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899. (i) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (j) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463.

[2] Biginelli, P. *Gazz. chim. Ital.* **1893**, *23*, 360.

[3] (a) Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Brosse, C. De.; Mai, S.; Truneh, A.; Faulkner, D. J. *J. Org. Chem.* **1995**, *60*, 1182. (b) Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. *Tetrahedron Lett.* **1996**, *37*, 6977. (c) Heys, L.; Moorea, C. G.; Murphy, P. J. *J. Chem. Soc. Rev.* **2000**, *29*, 57. (d) Tu, S.; Fang, F.; Miao, C.; Jiang, H.; Feng, Y.; Shi, D.; Wang, X. *Tetrahedron Lett.* **2003**, *44*, 6153.

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[4] (a) Hu, E. H.; Sidler, D. R.; Dolling, Ulf-H. *J. Org. Chem.* **1998**, *63*, 3454. (b) Ranu, B. C.; Hazra, A.; Jana, U. *J. Org. Chem.* **2000**, *65*, 6270. (c) Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Venugopal, C.; Ramalingam, T. *Synthesis* **2001**, *1341*. (d) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Synlett* **2001**, *863*. (e) Reddy, V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N. *Tetrahedron Lett.* **2002**, *43*, 2657. (f) Fu, N. Y.; Yuan, Y. F.; Cao, Z.; Wang, S. W.; Wang, J. T.;

Peppe, C. *Tetrahedron* **2002**, *58*, 4801. (g) Fan, X.; Zhang, X.; Zhang, Y. *J. Chem. Res.* (S) **2002**, *436*. (h) Lu, J.; Bai, Y. *Synthesis* **2002**, *466*. (i) Varela, R.; Alam, M. M.; Adapa, S. R. *Synlett* **2003**, *67*. (j) Bose, D. S.; Fatima, L. Meryala, H. B. *J. Org. Chem.* **2003**, *68*, 587. (k) Sabitha, S.; Reddy, G. S. K. K.; Reddy, Ch. S.; Yadav, J. S. *Synlett*, **2003**, *858*. (l) Paraskar, A. S.; Dewkar, G. K.; Sudalai, A. *Tetrahedron Lett.* **2003**, *44*, 3305.

[5] (a) Yadav, J. S.; Reddy, B. V. Subba; Reddy, E. Jagan; Ramalingam, T. *J. Chem. Res.* (S) **2000**, *354*. (b) Stadler, A.; Kappe, C. O. *J. Chem. Soc. Perkin Trans*. 1, **2000**, *1363*. (c) Kappe, C. O.; Kumar, D; Varma, R. *Synthesis* **1999**, *1799*. (d) Kidwai, M.; Saxena, S.; Mohan, R.; Venkataramanan, R. *J. Chem. Soc. Perkin Trans.* 1, **2002**, *1845*.

[6] Dondoni, A.; Massi, A. *Tetrahedron Lett.* **2001**, *42,* 7975.

[7] (a) Maiti, G.; Kundu, P.; Guin, C. Tetrahedron Lett. **2003**, *44*, 2757. (b) Baruah, P. P.; Gadhwa, S.; Prajapati, D.; Sandhu, J. S. *Chem. Lett.* **2002**, *10*, 1038.

[8] Reddy, K. R.; Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Reddy, N. *Tetrahedron Lett.* **2003**, *44*, 8173.

[9] (a) Bigi, F.; Carloni, S.; Frullanti, B.; Maggi, R.; Sartori, G. *Tetrahedron Lett.* **1999**, *40*, 3465. (b) Dondoni, A.; Massi, A. *Tetrahedron Lett.* **2001**, *42*, 7975. (c) Wipf, P.

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Cunningham, A. A. *Tetrahedron Lett.* **1995**, *36*, 7819. (d) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Fard, M. A. B. *Tetrahedron Lett.* **2003**, *44*, 2889.

[10] Yadav, J. S.; Subba Reddy, B. V.; Reddy, K. B.; Raj. K. S.; Prasad, A. R. *J. Chem. Soc. Perkin Trans.* 1, **2001**, *1939*.

[11] Kolosov Maksim, A.; Orlov Valeriy, D.; Beloborodov Dmitriy, A.; Dotsenko Victor, V. *Mol. Divers.* 2009, *13*, 5.

[12] Mitra, A. K.; Banerjee, K. *Synlett* **2003**, *10*, 1509.

[13] Tamaddon, F.; Moradi, S. *J. Mol. Catal. A: Chem.* **2013**, *370*, 117.

[14] Tamaddon, F.; Amrollahi, M. A. Sharafat, L. *Tetrahedron* Lett. **2005**, *46*, 7841.

[15] Tamaddon, F.; Sabeti, M. R.; Jafari, A. A.; Tirgir, F.; Keshavarz, E. *J. Mol. Catal. A: Chem*. **2011**, *351*, 41.

[16] Tamaddon, F.; Nasiri, A.; Farokhi, S. *Catal. Commun.* **2011**, *12*, 1477.

[17] Tamaddon, F.; Tavakoli, F. *J. Mol. Catal. A: Chem.* **2011**, *337*, 52.

[18] Tamaddon, F.; Razmi, Z.; Jafari, A. A. *Tetrahedron Lett.* **2010**, *51*, 1187.

[19] Ghosh, R.; Maiti, S.; Chakraborty, A. *J. Mol. Catal. A: Chem,* **2004**, *217*: 47.

[20] Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2004**, *6*, 147.

[21] (a) Liu, C.; Wang, J.; Li, Y. *J. Mol. Catal. A: Chem.* **2006**, *258*, 367. (b) Reddy, C. V.; Mahesh, M.; Raju, P. V. K.; Babu, T. R.; Reddy, V. V. N. *Tetrahedron Lett.* **2002**, *43*, 2657.

[22] Nandurkar, N. S.; Bhanushali, M. J.; Bhor, M. D.; Bhanage, B. M. *J. Mol. Catal. A: Chem.* **2007**, *271*, 14.

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[23] Slimi, H.; Moussaoui, Younes.; Ben Salem, R. *J. de la Société Chimi. de Tunisie,* **2012**, *14*, 1.

[24] Suman, L.; Jain, J. K.; Joseph, S. S.; Bir, S. *J. Mol. Catal. A: Chem.* **2007**, *268*, 134.

[25] Kappe, C. O. *Molecules* **1998**, *3*, 1.

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Table 1. Optimization of the ZnO nanoparticles catalyzed model reaction for synthesis of DHPMs

Entry	Catalyst (mol%)	Time (min)	Yields (%)[a]
1	No catalyst	28 h	12
2	ZnO nano (2)	90	67
3	ZnO nano (4)	30	91
4	ZnO nano (7)	30	94
5	ZnO nano (4)	30	90 [b]
6	ZnO nano (4)	30	90 [c]
7	ZnO bulk (4)	180	55

[a] Isolated yield. [b]Reaction was carried out at 80 ºC. [c] Reaction was carried out at 50 °C.

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Table 2. The influence of the solvent on the yield of model 3,4-DHPM **3f**[a]

Entry	solvent	Time (min)	Yields[b] (%)
1	Water	30	91
2	Ethanol	30	87
3	Acetonitrile	30	89
4	Toluene	30	5
5	Dichloromethane	30	24
6	Chloroform	30	18
7	THF	30	45

[a] Reaction conditions: benzaldehyde (1.00 mmol), ethyl acetoacetate (1.10 mmol) and urea (3.00 mmol) in solvent and nano ZnO (4 mol%) as catalyst at 50 ℃. [b] Isolated yield

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Table 3. ZnO nanoparticles catalyzed one-pot synthesis of DHPMs in H_2O as solvent[a]

Product	R	R^1	R^2	X	Time (min)	Yields[b] (%)	Reference[c]
4a	4-MeO-C_6H_4	CH_3	OEt	O	25	94	[18]
4b	3-MeO-4-HO-C_6H_3	CH_3	OEt	O	20	98	[19]
4c	4-HO-C_6H_4	CH_3	OEt	O	20	93	[20]
4d	4-CH_3-C_6H_4	CH_3	OEt	O	30	92	[18]
4e	4-Cl-C_6H_4	CH_3	OEt	O	25	90	[18]
4f	C_6H_5	CH_3	OEt	O	30	91	[18]
4g	C_3H_7	CH_3	OEt	O	40	85	[21]
4h	$C_6H_5CH= CH$	CH_3	OEt	O	30	80	[20]
4i	3-NO_2-C_6H_4	CH_3	OEt	O	30	79	[18]
4j	4-NO_2-C_6H_4	CH_3	OEt	O	30	78	[18]
4k	2-Furyl	CH_3	OEt	O	40	85	[18]
4l	Cyclohexyl	CH_3	OEt	O	40	74	[21]
4m	CH_3	CH_3	OEt	O	40	65	[21]
4n	C_2H_5	CH_3	OEt	O	40	70	[21]
4o	C_6H_5	CH_3	OCH_3	O	35	88	[22]
4p	4-MeO-C_6H_4	Et	OEt	O	25	86	[23]
4q	2-pyridyl	CH_3	OEt	O	35	84	[24]
4r	4-MeO-C_6H_4	CH_3	OEt	S	25	94	[18]
4s	3-MeO-4-HO-	CH_3	OEt	S	20	98	[19]

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	C_6H_3						
4t	4-HO-C_6H_4	CH_3	OEt	S	25	91	[20]
4u	4-Cl-C_6H_4	CH_3	OEt	S	25	92	[18]
4v	C_6H_5	CH_3	OEt	S	30	90	[18]
4w	$C_6H_5CH= CH$	CH_3	OEt	S	30	78	[20]
4x	3-NO_2-C_6H_4	CH_3	OEt	S	30	77	[18]
4y	4-NO_2-C_6H_4	CH_3	OEt	S	30	75	[18]
4z	2-Furyl	CH_3	OEt	S	40	80	[18]

[a] Reaction conditions: aldehyde (1.00 mmol), ethyl acetoacetate (1.10 mmol), urea or thiourea (3.00 mmol), ZnO nanoparticles (4 mol%), 50 °C. [b] Isolated yield. [c] Products were characterized by comparison of their spectroscopic data with those reported in the literature.

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Scheme 1. Synthesis of dihydropyrimidinones/thiones catalyzed by ZnO nanoparticles in H_2O as solvent

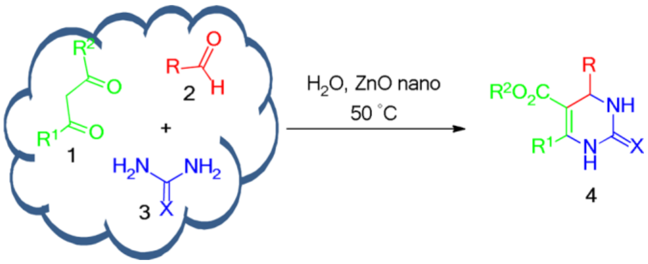

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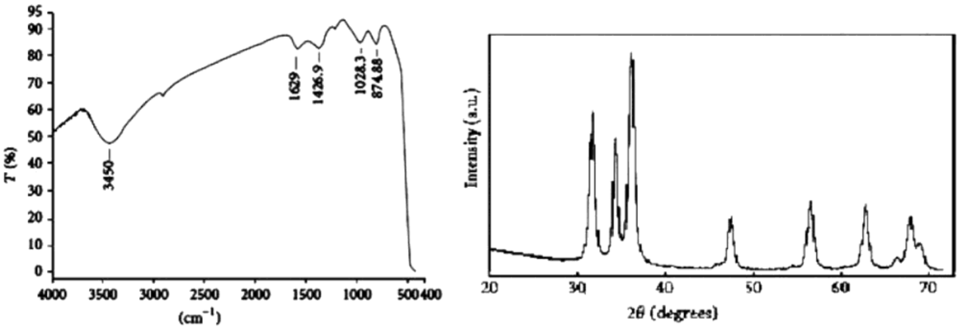
Figure 1. FTIR spectrum and XRD pattern of ZnO nanoparticles



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