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# One-Pot and Green Procedure for the Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-(thio)ones Using ZnO Nanoparticles as a Solid Acid Catalyst

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**ABSTRACT.** A convenient and efficient method has been developed for the one-pot synthesis of dihydropyrimidinones (DHPMs) compounds. Dihydropyrimidinone derivatives were synthesized in good yields using ethyl acetoacetate, aldehyde (aromatic and aliphatic) and urea or thiourea in the presence of ZnO nanoparticles as a catalyst in $H_2O$ as solvent at 80 °C. This green chemistry procedure applied to the Biginelli reaction using ZnO nanoparticles as catalyst and illustrated as a rapid preparation of DHPMs in water as solvent. The products were identified by physical data (mp) by comparison with those reported in the literatures.

**Key words:** Biginelli reaction, Multicomponent reaction, ZnO nanoparticles, Dihydropyrimidinone

## 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 small heterocyclic molecules.[1] The combination of an aldehyde, enolizable ketones, and urea under acid catalysis to give a DHPMs was 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 catalyst have been reported by different research groups such as using of Brønsted acids,[3] Lewis acids,[4] microwave variants,[5] $Mn(OAc)^{3,6}$ LiBr,[7] ammonium salt,[8] solid support,[9] on reagents like CAN[10] and clay.[11] But some of the methods have their own limitations in terms of yields, catalyst load, stability of promoters, etc.

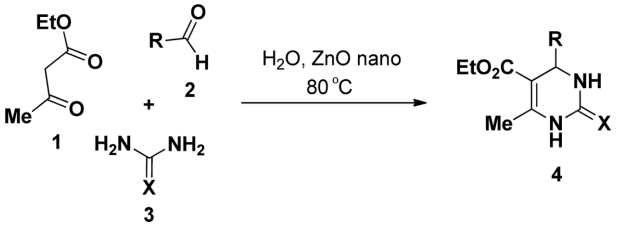
ZnO nanoparticles, is a very inexpensive and easily available Lewis acid catalyst. This catalyst has been widely used in organic reactions, but it has not been carefully studied as a catalyst in the Biginelli condensation in water as solvent until now.[12] Adsorption of the starting materials on the ZnO surface with the coordination of accessible zinc cation to functional groups led to the activation of substrates which enhanced the reactions rates and yields.[13–16] Due to the importance of Biginelli reaction products, the discovery and introduction of mild, economic and faster conditions using new catalytic methods are required.

We are interested in studying Biginelli reaction with the aim to develop an operationally simple method for the synthesis of a large range of DHPMs. During the course of our studies toward the development of new routes to the synthesis of organic compounds using green reaction mediums, herein, we report a novel approach for synthesis of 3,4-dihydropyrimidin-2(1*H*)- (thio)ones (**4**) via a one-pot condensation reaction between ethyl acetoacetate (**1**), aldehyde (aromatic and aliphatic) (**2**) and urea or thiourea (**3**) in the presence of ZnO nanoparticles as a non-toxic nanocatalyst in terms of green chemistry (*Scheme* 1).

## EXPERIMENTAL

### General Considerations

All the reagent and solvents were obtained from Merck (Germany) and were used without further purification.




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

Melting points were measured on an Electro Thermal 9100 apparatus.

### Preparation of ZnO Nanoparticles

Nano ZnO was prepared through the previously reported procedures.[12] In a typical procedure, 0.44 g (2.00 mmol) of $Zn(CH_3CO_2)_2$. $2H_2O$ was suspended in 220 mL of 2-propanol under vigorous stirring at 50 °C. A sodium hydroxide alcoholic solution was prepared by adding 0.16 g (4.00 mmol) NaOH to 60 mL of 2-propanol under vigorous stirring at 50 °C. The flasks containing $Zn(CH_3CO_2)_2$. $2H_2O$ and NaOH alcoholic solution were cooled in an ice-water bath. The sodium hydroxide solution was then added to zinc acetate solution under vigorous stirring to give a total volume of 300 mL. Final solution was heated in a controlled microwave cavity for 5 min. During the microwave irradiation the temperature of the solution reached up 80 °C. After 5 min, the transparent solution was obtained. The centrifugation of transparent solution yields white products, which were washed twice with absolute ethanol and dried at 70 °C for 4 h. Then white powders were calcined at 600 °C for 1 h. The results obtained from XRD pattern and SEM micrograph of the ZnO nanoparticles show that the mean particle size is 30 nm.

### General Procedure for the Preparation of 3,4-Dihydropyrimidin-2(1*H*)-(thio)ones 4a–w

General procedure for one-pot preparation of 3,4-dihydropyrimidin-2(1*H*)-(thio)ones using ZnO nanoparticle as a catalyst is that to a stirred suspension of ZnO nanoparticles (4 mol%) in water (5 ml) were added an aldehyde (1.00 mmol), ethyl acetoacetate (1.10 mmol), urea or thiourea (3.00 mmol), and then heated in water as solvent at 80 °C while being stirred for 20–40 min. The completion of the reaction was monitored by TLC. After completion of the reaction, which resulted in precipitation of the desired 3,4-dihydropyrimidin-2(1*H*)-(thio)ones **4a–w**. The precipitated solid was filtered, dried, washed with petroleum ether to remove any residual starting material and then recrystallized from ethanol to afford the pure product. The catalyst could be recovered after evaporation of the aqueous layer, the reused in subsequent reaction without losing any significant activity. The products were identified by physical data (mp) by comparison with those reported in the literatures.

## RESULTS AND DISCUSSION

ZnO nanoparticles is easily prepared from $Zn(CH_3CO_2)_2 \cdot 2H_2O$.[12] In a model reaction, benzaldehyde, ethyl acetoacetate and urea were stirred in $H_2O$ as solvent at 80 °C.

***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 °C. [c]Reaction was carried out at 50 °C.

It is important to note this point that this reaction does not proceed in the absence of catalyst. Stirring 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**).

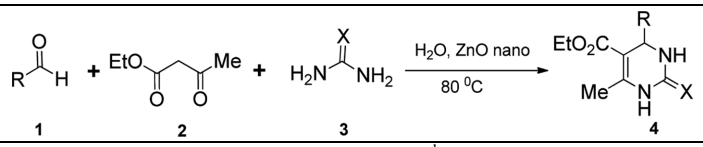
At this point, we started to investigate different amount of catalysts for this reaction (*Table* 1). In order to obtain the best conditions, on the optimized of amount of catalyst, we found that 4 mol% of ZnO nanoparticles could effectively catalyze the reaction for synthesis of the desired product. With inclusion of 2 mol% of ZnO nanoparticles the reaction took longer time (*Table* 1, entry 2). Using more than 4 mol% ZnO nanoparticles has less effect on the yield and time of the reaction (*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. It was observed (*Table* 1, entries 5 and 6) that the yield was not increased as the reaction temperature was raised. Commercially available ZnO bulk also was evaluated for the synthesis of DHPMs. Clearly, the reaction time using ZnO nanoparticles has been reduced by six times with higher yield than ZnO bulk (91% versus 55%, Table 1, entries **3** and **7**).

As results show, among the verified metal oxides, 4 mol% of ZnO were highly effective catalysts. The oxophilicity of zinc cation, amphoteric nature of ZnO together with the ability of the zinc cation for nearing of the activated starting materials via an extra template affect supports the efficiency of ZnO catalysts.

In order to explore the range of this extension, we subjected a series of various aldehydes **2** with urea at 80 °C in $H_2O$. As a results show, electron-releasing substituents as well as electron-withdrawing for the synthesis of corresponding DHPM under the optimized reaction conditions. As indi-

***Table* 2.** ZnO nanoparticles catalyzed one-pot synthesis of DHPMs in $H_2O$ as solvent[a]




1 2 3 4

| Product | R | X | Time (min) | Yields[b] (%) | Found mp (°C) | Reported (Ref.) |
|---|---|---|---|---|---|---|
| **4a** | 4-MeO−$C_6H_4$ | O | 25 | 94 | 201–203 | 202–204[17] |
| **4b** | 3-MeO−4-HO−$C_6H_3$ | O | 20 | 98 | 233–235 | 231–233[18] |
| **4c** | 4-HO−$C_6H_4$ | O | 20 | 93 | 226–228 | 226–228[19] |
| **4d** | 4-$CH_3$−$C_6H_4$ | O | 30 | 92 | 215–217 | 215–216[17] |
| **4e** | 4-Cl−$C_6H_4$ | O | 25 | 90 | 210–213 | 209–211[17] |
| **4f** | $C_6H_5$ | O | 30 | 91 | 199–201 | 200–203[17] |
| **4g** | $C_3H_7$ | O | 40 | 85 | 179–181 | 178–180[20] |
| **4h** | $C_6H_5$CH= CH | O | 30 | 80 | 234–236 | 237–239[19] |
| **4i** | 3-$NO_2$−$C_6H_4$ | O | 30 | 79 | 231–233 | 230–232[17] |
| **4j** | 4-$NO_2$−$C_6H_4$ | O | 30 | 78 | 206–208 | 207–209[17] |
| **4k** | 2-Furyl | O | 40 | 85 | 206–208 | 208–209[17] |
| **4l** | Cyclohexyl | O | 40 | 74 | 237–239 | 236–238[20] |
| **4m** | $CH_3$ | O | 40 | 65 | 192–194 | 193–195[20] |
| **4n** | $C_2H_5$ | O | 40 | 70 | 179–181 | 179–181[20] |
| **4o** | 4-MeO−$C_6H_4$ | S | 25 | 94 | 150–153 | 152–154[17] |
| **4p** | 3-MeO−4-HO−$C_6H_3$ | S | 20 | 98 | 147–149 | 147–149[18] |
| **4q** | 4-HO−$C_6H_4$ | S | 25 | 91 | 199–201 | 198–200[19] |
| **4r** | 4-Cl−$C_6H_4$ | S | 25 | 92 | 192–194 | 190–192[17] |
| **4s** | $C_6H_5$ | S | 30 | 90 | 206–208 | 205–207[17] |
| **4t** | $C_6H_5$CH=CH | S | 30 | 78 | 243–245 | 244–246[19] |
| **4u** | 3-$NO_2$−$C_6H_4$ | S | 30 | 77 | 203–205 | 201–203[17] |
| **4v** | 4-$NO_2$−$C_6H_4$ | S | 30 | 75 | 108–110 | 107–109[17] |
| **4w** | 2-Furyl | S | 40 | 80 | 183(dec.) | 184(dec.)[17] |

[a]Reaction conditions: aldehyde (1.00 mmol), ethyl acetoacetate (1.10 mmol), urea or thiourea (3.00 mmol), ZnO nanoparticles (4 mol%), 80 °C. [b]Isolated yield.

cated in *Table* 2, the reaction proceeds very efficiently and led to afford the corresponding DHPM **4a–w** in fairly good yields.

In general, electron-donating substituents furnished higher reaction rates, affording DHPM in good yields. On the other hand, electron-withdrawing substituents decreased the rate of the reaction and moderate yields of DHPM were obtained (*Table* 2).

Recyclability of the catalyst was examined, too. For this reason, catalyst which was recovered from reaction between 3-methoxy-4-hydroxy-benzaldehyde, ethyl acetoacetate and urea by filtration; after drying the catalyst, it was reused Nano ZnO was regenerated by washing with EtOAc and drying at 300 °C or microwave irradiation and reused for three consecutive times in Biginelli reactions with no significant decreasing in reaction yields. This procedure was carried out for three times. Results of these successive reactions are shown in *Figure* 1. It is clear that by successive use of catalyst no decrease in reactivity or performance can be seen (*Figure* 1). After the fourth run the turnover number (TON) was 96.

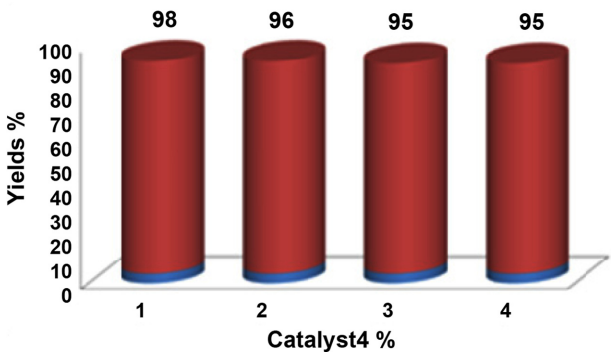
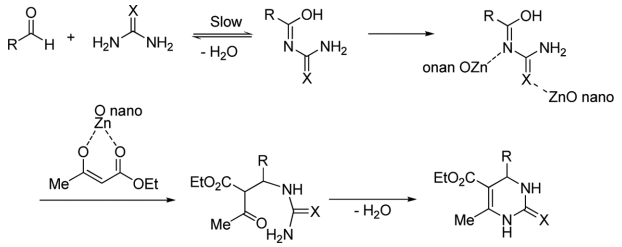



***Figure* 1.** Recycle of the catalyst.

The mechanism of the Biginelli reaction established by Kappe proposed that the key step in this cyclocondensa-




***Scheme* 2.** Suggested mechanism for the Biginelli reaction catalyzed by ZnO nanoparticles in $H_2O$ as solvent.

tion process should involve the formation of N-acyliminium ion intermediate.[21]

A proposed reaction mechanism of Biginelli condensation via acyl imine intermediate is presented in *Scheme* 2. It seems that ZnO may stabilize the acylimine intermediate due to the presence of vacant d-orbital. This intermediate is formed by the reaction of the aldehyde and urea or thiourea and then stabilized by ZnO nanoparticles. Subsequent addition of ethyl acetoacetate enolate to the acylimine, followed by cyclization and dehydration, afforded the corresponding 3,4-dihydropyrimidin-2(1*H*)-(thio)ones.

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 aldehyde such as furfural (**4k** and **4w**) is also worked well without the formation of any side products, which are normally observed either in the presence of protic or Lewis acids. 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 medium that is fully compatible with green chemistry.

## CONCLUSIONS

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.

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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; p 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; p 33. (g) Jieping Zhu. *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.
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. 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. Mitra, A. K.; Banerjee, K. *Synlett* **2003**, *10*, 1509.
12. Tamaddon, F.; Moradi, S. *J. Mol. Catal. A: Chem.* **2013**, *370*, 117.
13. Tamaddon, F.; Amrollahi, M. A. Sharafat, L. *Tetrahedron Lett*. **2005**, *46*, 7841.
14. Tamaddon, F.; Sabeti, M. R.; Jafari, A. A.; Tirgir, F.; Keshavarz, E. *J. Mol. Catal. A: Chem*. **2011**, *351*, 41.
15. Tamaddon, F.; Nasiri, A.; Farokhi, S. *Catal. Commun.* **2011**, *12*, 1477.
16. Tamaddon, F.; Tavakoli, F. *J. Mol. Catal. A: Chem.* **2011**, *337*, 52.
17. Tamaddon, F.; Razmi, Z.; Jafari, A. A. *Tetrahedron Lett.* **2010**, *51*, 1187.
18. Ghosh, R.; Maiti, S.; Chakraborty, A. *J. Mol. Catal. A: Chem,* **2004**, *217*, 47.
19. Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2004**, *6*, 147.
20. (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.
21. Kappe, C. O. *Molecules* **1998**, *3*, 1.