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ZnO-NPs as an efficient reusable heterogeneous catalyst for synthesis of 1,4-Dihydropyrimidine derivatives in solvent-free conditions

ABSTRACT

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An efficient synthesis route to 1,4-dihydropyrimidine derivatives from reaction of divergent aldehydes with ethylacetoacetate and urea under solvent-free conditions by ZnO nanoparticles as a relative in expansive, eco-friendly, easy available, non-volatile, non-explosion, thermally robust, recyclable and easy to handle catalyst at 90°C with excellent yields is described. Unenhanced reaction times, simple reaction protocol and work-up, have been improved synthesis of these materials in the presence of this heterogeneous catalyst.

Keywords: *1,4-Dihydropyrimidinones; ZnO nanoparticles; Solvent-free conditions; Heterogeneous catalyst; H-NMR.*

INTRODUCTION

Recently, the use of solid-supported reagent has also received considerable important in organic synthesis because of their ease of handling, enhanced reaction rates, grater selectivity, simple work-up and reusability of catalyst [1]. The efficiency of heterogeneous catalysis has been improved by employing nano-sized catalyst [2] because of their extremely small size, high surface area, and reactive morphologies. Furthermore, the nano-catalyzed reactions provide the advantages of high atom efficiency, simplified isolation of product, and easy recovery and recyclability of the catalysts. In view of recent surge in the use of heterogeneous catalysis we have developed ZnO nano-particles employing. ZnO nano-particles as an inexpensive, non-volatile, recyclable, non-expensive, ease to handle and eco-friendly catalyst [3]. In the past decade, dihydropyrimidinones (DHPM_S) have exhibited important pharmacological and biological properties [4-14]. So the synthesis of DHPM_S has been revalued. The classical synthesis of dihydropyrimidinone was the Biginelli reaction of aldehyde, ethylacetoacetate, and urea or thiourea under acidic conditions [15].

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The method, however, requires harsh conditions leading often to low yields despite long reaction times. In order to circumvent these drawbacks many improvements and modifications have been developed, including microwave promotion [16-18], ultrasound irradiation [19-20], ionic liquids [21-22] and the use of Lewis acid catalyst, such as $N_6C_{15}/QN-NH_2$ [23, 24], $BF_3OEt_2/CuCl$ [25], formic acid [26], $Yb(OTf)_3$ [27], $InCl_3$ [28], NH_4Cl [29], $Cu(OTf)_2$ [30], $Cu(ClO_4)_2 \cdot 6H_2O$ [31], Trichloro acetic acid [32], $Fe(OTs)_3$ [33], $Zn((L)-proline)_2$ [34], MnO_2 -MWCNT [35], etc.

Chiral DHPM₅ via Biginelli condensation reaction have been realized [36-42]. A variety of substituent including N-substituted urea [43] and β -acylpyruvates [44] in the components have been investigated to produce differently substituted DHPM₅ for however most of these procedures have significant drawbacks such as high temperature, long reaction times, and low yields of products, harsh reaction conditions and difficult workup. Therefore, the development of simple, green, efficient, clean, high yielding and environmentally friendly have been approaches for the synthesis of these compounds in an important task for organic chemist.

In this research we want to report a new and efficient synthesis of 1,4-dihydropyrimidinones the presence of ZnO nano-particles as a Lewis acid catalyst under solvent-free conditions (Scheme 1).

EXPERIMENTAL

All reagents were purchased from Merck and used without further purification. The progress of reaction was monitored by TLC using 0.2 mm

Merck Silicagel 60 F 254 pre-coated plates. Melting points were measured on an Electrothermal 9100s apparatus and uncorrected. The IR spectra were recorded on FT-IR Shimadzu IR-470 spectrophotometer. The 1H -NMR spectra were determined on a Bruker Avance DRX-400 MHz instrument using TMS as the internal standard.

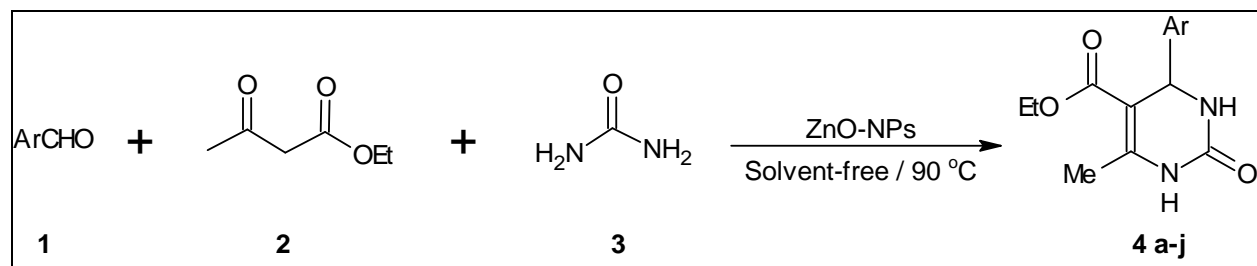
General procedure for the preparation of 1, 4-dihydropyrimidinones (4a-j)

A mixture of aromatic aldehyde (1mmol), ethylacetoacetate (1 mmol), urea (1.3 mmol) and ZnO nano-particles (0.25 mmol) was heated in oil bath at 90 °C. The progress of reaction was monitored by TLC. After completion the reaction after 50 min, the mixture was cooled to room temperature, water was added and the mixture stirred for 30 min. The precipitate was filtered off and recrystallized from ethanol to give compound 4a-j in high yields. (See Table 1)

RESULTS AND DISCUSSION

In this paper, we report a new, simple, mild and effective procedure for the one-pot, three component reaction of aromatic aldehyde, and urea, ethylacetoacetate and ZnO nano-particles as a recyclable catalyst. The catalyst is safe, easy to handle, mild, environmentally favorable. The optimization of the reaction with different amounts of catalyst was carried out and was found that at 25 mol% the yield was good (Table 1, entry 7). The result of the synthesis of 1,4-dihydropyrimidin - ones are summarized in Table 2.

The effect of solvent and reusability of catalyst in synthesis has been explored. The results are summarized in Table 3.



Scheme 1. Synthesis of 1,4-dihydropyrimidinones the presence of ZnO nano-particles as a Lewis acid catalyst

Table 1. Effect of ZnO-NPs catalyst amount on the model reaction^a

Entry	Catalyst (mol%)	t (°C)	Time (min)	Yield (%) ^b
1	None	80	100	trace
2	5	80	80	45
3	15	85	70	76
4	20	80	70	80
5	20	90	70	82
6	25	80	70	84
7	25	90	50	92
8	25	100	50	90
9	30	90	50	91

a) Reaction condition: Benzaldehyde (1mmol), ethylacetoacetate (1mmol), urea (1.3 mmol) and ZnO-NPs (different amount) under solvent-free conditions at different temperature. b) Isolated yields

Table 2. Synthesis of 1,4-dihydropyrimidinones 4a-j^a

Entry	Aromatic aldehyde	Product	Yield (%) ^b	mp °C	
				Found ^c	Reported [Ref]
1	C ₆ H ₅ CHO	4a	92	207-209	207 [40]
2	4-ClC ₆ H ₄ CHO	4b	95	214-216	212 [24]
3	4-MeOC ₆ H ₄ CHO	4c	88	203-204	202 [24]
4	4-NO ₂ C ₆ H ₄ CHO	4d	96	208-210	207 [30]
5	3-NO ₂ C ₆ H ₄ CHO	4e	93	225-226	226-228 [30]
6	3-ClC ₆ H ₄ CHO	4f	93	196-198	200-201 [31]
7	3-MeOC ₆ H ₄ CHO	4g	88	202	203-204 [31]
8	4(CH ₃) ₂ NC ₆ H ₄ CHO	4h	84	256-257	256-258 [31]
9	3-HOC ₆ H ₄ CHO	4i	92	164-165	167-170 [31]
10	Salicylaldehyde	4j	88	205	201-203 [31]

a) Reaction condition: Aromatic aldehyde (1mmol), ethylacetoacetate (1mmol), urea (1.3 mmol) and ZnO-NPs (0.25 mmol) under solvent-free conditions at 90 °C. b) Isolated yields c) Uncorrected

Table 3. The effect of solvent on model reaction at refluxing conditions^a

Entry	Solvent	T (min)	Yield ^b
1	CH ₂ Cl ₂	180	trace
2	CHCl ₃	150	trace
3	CH ₃ OH	100	70
4	CH ₃ CH ₂ OH	100	46
5	CH ₃ CN	80	66
6	Toluene	80	70
7	Solvent-free	50	92

a) Reaction condition: Benzaldehyde (1mmol), ethylacetoacetate (1mmol), urea (1.3 mmol) and ZnO-NPs (0.25 mmol) b) Isolated yields

In order to ascertain the effect of solvent on reaction, the reaction was carried out using different solvents of varied dielectric constants. The result summarized (Table 3) which suggested that solvents with high dielectric constant produced high yield of 4a products as in EtOH (Table 3, entry 4) and that with low dielectric constant formed low yield of 4a product as in the case of CH₂Cl₂. It is observed that the excellent results were obtained in solvent-free conditions at 90 °C using ZnO-NPs as catalyst. (Table 3, entry 7). Thus, the EtOH or MeOH stabilized ZnO nano-particles may facilitate the deprotonation/enolate equilibrium of ethylacetoacetate, thereby reactive enolate is

formed which later reacts with aromatic aldehyde and complete the catalytic cycle by reductive elimination of the product 4a. The efficiency of the recovered catalyst in this reaction has been explored. To evaluate the catalytic activity and the potential of recycling, we completed several catalytic cycle. In each cycle, ZnO nanoparticles was washed with ethanol and dried under vacuum to remove the residual solvent. The catalyst could be reused for four times with a minimal loss of activity. These experimental observations suggest the eco-friendly and environmentally benign nature of the reusable ZnO nano-catalyst.

CONCLUSIONS

In conclusion we have demonstrated that nano-ZnO is a new, efficient and green catalyst for the synthesis of 1,4-dihydropyrimidinones. The one-pot three component condensation of aldehydes, urea and ethylacetoacetate in the presence of ZnO-NPs afforded 1,4-dihydropyrimidinones under thermal solvent-free conditions. Salient feature of this method are mild reaction conditions, environmental compatibility, easy of isolation of product, and excellent reusability of the catalyst. The present procedure gave the products in excellent yields at reduced reaction time, which might be due to the increased reactivity of the reactants on high surface area of ZnO nanoparticles.

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REFERENCES

- [1] Kaneva N. V., Yordanov G. G., Dushikin C. D., (2010), Manufacturing of patterned ZnO films with application for photo initiated decolorization of malachite green in aqueous solutions. *Bull. Master. Sci.* 33: 111-117.
- [2] Xia Y. N., Yang P. D., Sun Y. G., Wu Y. Y., Mayers B., Caters B., (2003), Solvothermal synthesis of Boehmite and γ -Alumina Nanorods. *Adv. Mater.* 15: 353-358.
- [3] Gouvea C. A. K., Wypych F., Moraes S. G., Duran N., (2000), Photo degradation of direct red-81 (5-Solamine) by using Zinc Oxide nanoparticles on glass granule substrate in acidic pH and various atmospheres. *Chemosphere.* 40: 433-439.
- [4] Aly A. A., (2006), Synthesis and pharmacological activity of annelated pyrimidine derivatives. *Phosph. Sulf. Silicon Relat. Elem.* 181: 1285-98.
- [5] Pinna C., Glass R., Knight G. E., Bolego C., Puglisi L., Burnstock G., (2005), Purine and pyrimidine-induced responses and P₂Y receptor characterization in the hamster proximal urethra. *Br. J. Pharmacol.* 144: 510-8.
- [6] Reznik V. S., Pashkurov N. G., Mikhailov A. S., Akamsin V. D., Galyamctdinova I. V., Zobov V. V., (2004), Synthesis and pharmacological activity of ω -(4-phenylpiperazin-1-yl) alkylthiopyrimidine. *Pharm. Chem. J.* 38: 654-8.
- [7] Sondhi S. M., Singh N., Johar M., Kumar A., (2005), Synthesis, anti-inflammatory and analgesic activities evaluation of some mono, bi and tricyclic pyrimidine derivatives. *Bioorg. Med. Chem.* 13: 6158-66.
- [8] Bruno O., Brullo C., Ranise A., Schenone S., Bondavalli F., Barocelli E., (2001), Synthesis and pharmacological evaluation of 2,5-cycloamino-5H-[1] benzopyrano[4,3-d] pyrimidines endowed with in vitro antiplatelet activity. *Bioorg. Med. Chem. Lett.* 11: 11397-400.
- [9] Gangjcc A., Vidwans A., Elzcin E., Mc Cuire J. J., Quccner S. F., Kisliuk R. L., (2001), Synthesis, antifolate, and antitumor activities of classical and nonclassical 2-amino-4-oxo-5 substituted pyrrolo[2,3-d] pyrimidines. *J. Med. Chem.* 44: 1993-2003.
- [10] Banjanac M., Tatic I., Ivezic Z., Tomic S., Dumic J., (2009), Pyrimidopyrimidines: a novel class of dihydrofolate reductase

- inhibitors. *Food Technol. Biotechnol.* 47: 236-45.
- [11] Mangalagiu G., Ungureanu M., Grosu G., Mangalagiu I., Petrovanu M., (2001), New pyrrolopyrimidine derivatives with antifungal or antibacterial properties. *Ann. Pharm. Fr.* 59: 139-40.
- [12] Wamhoff H., Dzenis J., Hirota K., Katritzky A. R., Advances in heterocyclic chemistry, vol. 55, 2nd ed. New York: Academic Press Inc. 1992. P. 163-5.
- [13] Kappe C. O., (1993), 100 Years of Biginelli dihydropyrimidine synthesis. *Tetrahed.* 49: 6937-6963.
- [14] Kappe C. O., (2000), Recent advances in the Biginelli dihydropyrimidine synthesis. New tricks from an old dog. *Acc. Chem. Res.* 33: 879-888.
- [15] Biginelli P., (1893), Aldehyde-urea derivatives of aceto- and oxaloacetic acids. *Gazz. Chim. Ital.* 23: 360-413.
- [16] Li Y. X., Bao W. L., (2003), Microwave-assisted Solventless Biginelli Reaction Catalyzed by Montmorillonite Clay-SmCl₃. 6H₂O System. *Chin. Chem. Lett.* 14: 93-995.
- [17] Yadav J. S., Reddy B. V., Reddy E. J., Ramalingam T., (2000), Microwave-assisted efficient synthesis of dihydropyrimidines: improved high yielding protocol for the Biginelli reaction. *J. Chem. Res. (S)*. 7: 354-355.
- [18] Stefani H. A., Gatti P. M., (2000), 3,4-Dihydropyrimidin-2(1H)-Ones: fast synthesis under microwave irradiation in solvent free conditions. *Synth. Commun.* 30: 165-2173.
- [19] Yadav J. S., Reddy K. B., (2001), Ultrasound-accelerated synthesis of 3,4-dihydropyrimidin-2(1H)-ones with ceric ammonium nitrate. *J. Chem. Soc.* 16: 1939-1941.
- [20] Li J.T., Han J.F., Yang J.H., Li T.S., (2003), An efficient synthesis of 3,4-dihydropyrimidin-2-ones catalyzed by NH₂SO₃H under ultrasound irradiation. *Ultrason. Sonochem.* 10: 119-122.
- [21] Peng J. J., Deng Y. Q., (2001), Ionic liquids catalyzed Biginelli reaction under solvent-free conditions. *Tetrahed. Lett.* 42: 5917-5919.
- [22] Shao G.Q., (2004), Biginelli Condensation Assisted by Microwave Irradiation in Ionic Liquids. *Chin. J. Synth. Chem.* 12: 325-328.
- [23] Niralwad K. S., Shingate B. B., Shingare M. S., (2010), Ultrasound-assisted One-Pot Synthesis of Octahydroquinazolinone Derivatives Catalyzed by Acidic Ionic Liquid [tbmim] Cl₂/AlCl₃. *J. Chin. Chem. Soc.* 57: 89-92.
- [24] Cai Y. F., Yang H. M., Li L., Jiang K. Z., Lai G.Q., Jiang J. X., Xu L.W., (2010), Cooperative and Enantioselective NbCl₅/Primary Amine Catalyzed Biginelli Reaction. *Eur. J. Org. Chem.* 26: 4986-4990.
- [25] Hu E. H., Sidler D. R., Dolling U. H., (1998), Unprecedented Catalytic Three Component One-Pot Condensation Reaction: An Efficient Synthesis of 5-Alkoxy carbonyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones. *J. Org. Chem.* 63: 3454-3457.
- [26] Cheng J., Qi D. Y., (2007), An efficient and solvent-free one-pot synthesis of dihydro-pyrimidinones under microwave irradiation. *Chin. Chem. Lett.* 18: 47-650.
- [27] Ma Y., Qian C. T., Wang L. M., Yang M., (2000), Lanthanide triflate catalyzed Biginelli reaction. One-pot synthesis of dihydropyrimidinones under solvent-free conditions. *J. Org. Chem.* 65: 3864-3868.
- [28] Ranu B. C., Hajra A., Jana U., (2000), Indium (III) Chloride Catalyzed One-Pot Synthesis of Dihydropyrimidinones by a Three-Component Coupling of 1,3-Dicarbonyl Compounds, Aldehydes, and Urea: An Improved Procedure for the Biginelli Reaction. *J. Org. Chem.* 65: 6270-6272.
- [29] Shaabani A., Bazgir A., Teimouri F., (2003), Ammonium chloride-catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions. *Tetrahed. Lett.* 44: 857-859.
- [30] Paraskar A. S., Dewkar G. K., Sudalai A., (2003), Cu(OTf)₂: A reusable catalyst for high-yield synthesis of 3, 4-dihydropyrimidin-2(1H)-ones. *Tetrahed. Lett.* 44: 3305-3308.

- [31] Lei M., Ma L., Hu L.H., (2011), Cu(ClO₄)₂·6H₂O as an Efficient Catalyst for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Under Solvent-Free Conditions. *Synth. Commun.* 41: 3071–3077.
- [32] Karimi-Jaberi Z., Moaddeli M. S., (2012), Synthesis of 3, 4-Dihydropyrimidin-2(1H)-ones and their corresponding 2(1H) thion using Trichloro acetic acid as a catalyst under solvent-free conditions. *ISRN Org. Chem.* Vol 2012.[Article ID. 474626].
- [33] Starcevich J. T., Laughlin T. J., Mohan R. S., (2013), Iron (III) tosylate catalyzed synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones via the Biginelli reaction. *Tetrahed. Lett.* 54: 983-985.
- [34] Siddiqui Z. N., (2013), Bis(*L*)prolinato-*N,O*] Zn-water: A green catalytic system for the synthesis of 3,4-dihydropyrimidin-2(1H)ones via the Biginelli reaction. *Compt. Rendus. Chime.* 16: 183-188.
- [35] Safari J., Gandomi-Ravandi S., (2013), MnO₂-MWCNT nano composites as efficient catalyst in the synthesis of Biginelli-type compounds under microwave radiation. *J. Molec. Cat. A: Chemical.* 3: 73-77.
- [36] Yu J.; Shi F.; Gong L.-Z., (2011), Brønsted-Acid-Catalyzed Asymmetric Multicomponent Reactions for the Facile Synthesis of Highly Enantioenriched Structurally Diverse Nitrogenous Heterocycles. *Acc. Chem. Res.* 44: 1156–1171.
- [37] Saha S.; Moorthy J. N., (2011), Enantioselective Organocatalytic Biginelli Reaction: Dependence of the Catalyst on Sterics, Hydrogen Bonding, and Reinforced Chirality. *J. Org. Chem.* 76: 396–402.
- [38] Shen Z.-L., Xu X.-P., Ji S.-J., (2010), Brønsted Base-Catalyzed One-Pot Three-Component Biginelli- Type Reaction: An Efficient Synthesis of 4,5,6-Triaryl-3,4-dihydropyrimidin-2(1H)-one and Mechanistic Study. *J. Org. Chem.* 75: 1162–1167.
- [39] Nandi G. C., Samai S., Singh M. S., (2010), Biginelli and Hantzsch-Type Reactions Leading to Highly Functionalized Dihydropyrimidinone, Thiocoumarin, and Pyridopyrimidinone Frameworks via Ring Annulation with β-Oxodithioesters. *J. Org. Chem.* 75: 7785–7795.
- [40] Wang Y., Yu J., Miao J., Chen R., (2011), Bifunctional primary amine-thiourea-TfOH (BPAT·TfOH) as a chiral phase-transfer catalyst: the asymmetric synthesis of dihydropyrimidines. *Org. Biomol. Chem.* 9: 3050–2054.
- [41] Isambert N., Duque M. M. S., Plaquevent J. C., Genisson Y., Rodriguez J., Constantieux T., (2011), Multicomponent reactions and ionic liquids: a perfect synergy for eco-compatible heterocyclic synthesis. *Chem. Soc. Rev.* 40: 1347–1357.
- [42] Salehi H., Guo Q. X., (2005), Efficient Magnesium Bromide-Catalyzed One-pot Synthesis of Substituted 1,2,3,4-Tetrahydropyrimidin-2-ones Under Solvent-free Conditions. *Chin. J. Chem.* 23: 91–97.
- [43] Ryabukhin S. V., Plaskon A. S., Bondarenko S. S., Ostapchuk E. N., Grygorenko O. O., Shishkin O. V., Tolmachev A. A., (2010), Acyl pyruvates as synthons in the Biginelli reaction. *Tetrahed. Lett.* 51: 4229–4232.
- [44] Jun L., Yinjuan B., Zhenjun W., Bingqin Y., Huairang M., (2000), One-pot synthesis of 3,4-dihydropyrimidine-2(1H)ones using Lanthanum chloride as a catalyst. *Tetrahed. Lett.* 41: 9075-78.