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# Oxalic acid dihydrate catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*) -one derivatives under thermal and solvent-free conditions

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ABSTRACT

Oxalic acid dihydrate as a green, mild and efficient catalyst for the one-pot three-component Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives from the reaction between β-keto esters (methyl or ethyl acetoacetate), aromatic aldehyde (benzaldehye derivatives) and urea or thiourea under thermal and solvent-free conditions with excellent yields and short reaction time is studied. The most remarkable benefits of this synthetic method include the green methodology, an eco-friendly, inexpensive and non-toxic catalyst, solvent-free conditions, the availability of materials, and a simple operational procedure with no column chromatographic separation. The products were characterized by melting points, IR and $^1$H NMR spectroscopy.

***Keywords**: Oxalic acid.2H$_2$O, Green methodology, Biginelli reaction, 3, 4-Dihydropyrimidinone.*

## 1. Introduction

In recent years, multicomponent domino reactions (MCRs) [1-6] have become useful tools for the synthesis of heterocyclic compounds because a wide range of their properties such as atom-economy, mild and environmentally-friendly, low-cost and one-pot operation. Recently, advances in multi-component reactions have resulted in the development of using green catalysts [7-10].

Organic compounds containing nitrogen-heterocyclic rings are important compounds in medicinal chemistry. Recently, Biginelli reactions [11] have attracted much interest in the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones derivatives because of their specially pharmaceutical and biological activities. For example, these compounds have been used as calcium channel blockers, α-1a-antagonists [12], and anti-HIV agents [15]. They also have antihypertensive [13], anticancer [14], antibacterial, antifungal [16], antiviral [17], antioxidative [18] and anti-inflammatory [19] effects.

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In recent years, several protocols for the preparation of these compounds have been reported. They include Brønsted or Lewis acid catalysts such as Calcium Fluoride [20] cellulose sulfuric acid [21], bioglycerol-based sulfonic acid functionalized carbon [22], p-sulfonic acid calixarenes [23], copper(II)sulfamate [24], triphenylphosphine [25], melamine trisulfonic acid [26], bakers' yeast [27], hydrotalcite [28], hexaaquaaluminium (III) tetrafluoroborate [29], TBAB [30] and copper (II) tetrafluoroborate [31]. Some of the limitations of these methodologies are low yields, toxic organic solvents and catalysts, harsh reaction conditions and expensive materials.

Because of special pharmaceutical and biological properties 3,4-dihydropyrimidin-2-(1*H*)-ones derivatives, the development of a green, simple as well as environmentally safe methodology for the synthesis of these compounds was the major aim of our research. In addition, oxalic acid dihydrate was examined as a green, efficient and mild catalyst. The advantages of oxalic acid dihydrate as a catalyst in organic compound synthesis include green, friendly environment, mild, inexpensive, non-toxic. Also, oxalic acid dihydrate can be successfully used in the carbon-carbon bond type as a mild and efficient catalyst in organic synthesis.

Finally, in this procedure, a green, simple and mild one-pot approach was followed for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives using oxalic acid dihydrate as a green, mild and efficient catalyst by means of three component Biginelli reaction between β-keto esters, aldehyde derivatives and urea/thiourea under thermal and solvent-free conditions with excellent yields.

## 2. Experimental

### *2.1. General*

Melting points of all compounds were determined using an Electro thermal 9100 apparatus. $^1$HNMR spectra were recorded on a Bruker DRX-400 Avance instrument with DMSO-$d_6$ as solvents. All reagents and solvents were purchased from Merck, Fluka and Acros chemical companies were used without further purification.

### *2.2. General procedure for preparation of 3,4-dihydropyrimidin-2-(1H)-one derivatives (**4a- l**)*

A mixture of aldehydes derivatives (**1**, 1.0 mmol) and urea/thiourea (**2**, 1.5 mmol), ethyl/methyl acetoacetate (**3**, 1.0 mmol) was heated under solvent free conditions at 80 °C for appropriate time in the presence of oxalic acid dihydrate (20 mol %). After completion of the reaction (by thin layer chromatography TLC), the mixture was cooled to rt and cold water was added. Then, the precipitated was separated with filtration and recrystallized from ethanol to afford the pure products (**4a- l**). Some of spectra data of products are represented below.

*Selected spectral data*

*5- Ethoxycarbonyl- 6- methyl- 4- phenyl- 3,4-dihydro pyrimidin-2(1H)-one (**4a**)*:

m.p.= 198-200°C. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 1.10 (3H, t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (3H, s, $CH_3$), 3.99 (2H, q, *J*=7.2 Hz, $CH_2O$), 5.15 (1H, s, CHN), 7.26 (3H, d, *J*= 7.2 Hz, ArH), 7.33 (2H, t, *J*=7.2 Hz, ArH), 7.76 and 9.21 (2H, 2s, 2NH) ppm.

*5- Ethoxycarbonyl- 6- methyl- 4- (4- methylphenyl)- 3,4-dihydropyrimidin-2(1H)-one (**4e**)*:

m.p.= 202-204°C. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 1.11 (3H, t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.26 (6H, d, *J*=9.2 Hz, $2CH_3$), 3.99 (2H, q, *J*=7.2 Hz, $CH_2O$), 5.11 (1H, s, CHN), 7.13 (4H, s, ArH), 7.70 and 9.17 (2H, 2s, 2NH) ppm.

*5- Methoxycarbonyl- 6- methyl- 4- (4- nitrophenyl)- 3,4-dihydropyrimidin-2(1H)-one (**4g**)*:

m.p.= 216-218°C. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 2.28(3H, s, $CH_3$), 3.55 (3H, s, $OCH_3$), 5.28 (1H, s, CHN), 7.52 (2H, d, *J*= 8.4Hz, ArH), 7.22 (2H, d, *J*= 8.8Hz, ArH), 7.93 and 9.40 (2H, 2s, 2NH) ppm.

*5- Methoxycarbonyl- 6- methyl- 4- (2- chlorophenyl)- 3,4-dihydropyrimidin-2(1H)-one (**4h**)*:

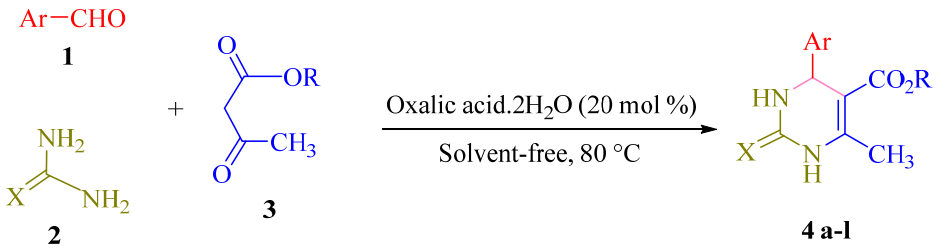
m.p.= 250-252°C. $^1$HNMR (400 MHz, DMSO-$d_6$): δ= 2.31 (3H, s, $CH_3$), 3.46 (3H, s, $OCH_3$), 5.62 (1H, s, CHN), 7.28-7.34 (3H, m, ArH), 7.42 (1H, d, *J*=7.2 Hz, ArH), 7.72 and 9.36(2H, 2s, 2NH) ppm.

*5- Ethoxycarbonyl- 6- methyl- 4- phenyl- 3,4-dihydro pyrimidin-2(1H)-thione (**4k**)*:

m.p.= 208-210°C. $^1$HNMR (400 MHz, DMSO-$d_6$): 1.11 (3H, t, *J*= 7.2 Hz, $\underline{CH_3}CH_2$), 2.31 (3H, s, $CH_3$), 4.02 (2H, q, *J*=7.2 Hz, $CH_2O$), 5.19 (1H, s, CHN), 7.23 (2H, d, *J*=7.2 Hz, ArH), 7.28 (1H, t, *J*=7.2 Hz, ArH), 7.36(2H, t, *J*=7.2 Hz, ArH), 9.68 and 10.36 (2H, 2s, 2NH) ppm.

## 3. Results and Discussion

A green, mild and efficient catalyst for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones derivatives by means of one-pot three component condensation Biginelli reaction of aldehydes derivatives (**1**, 1.0 mmol), urea/ thiourea (**2**, 1.5 mmol) and ethyl/methyl acetoacetate (**3,** 1.0 mmol) in the presence of oxalic acid dihydrate under solvent free and thermal conditions is reported (Scheme 1).




**Scheme 1.** Synthesis of 3, 4-dihydropyrimidin-2-(1*H*)-one derivatives.

In order to optimize the reaction conditions, the synthesis of compound **4a** (Table 3, entry 1) was used as a model reaction. The effects of different amounts of the catalyst on the reaction were studied. No product could be detected in the absence of the catalyst even after 9h (Table 1, entry 1). The best amount of the catalyst was 20 mol % (0.025 g, Table1, entry 5). The higher amount of the catalyst did not increase the yield products (Table 1, entry 6).

Also, the effect of temperature on the reaction was studied. No product could be detected in room temperature (Table 2, entry 1). The reaction was investigated by changing temperature from 40-100°C. The best yield was obtained in 80°C (Table 2, entry 4).

To examine the efficiency and the applicability of this three-component reaction, different aldehydes and ethyl/methyl acetoacetate were tested. Aromatic aldehydes bearing either electron-withdrawing functional groups, such as nitro and halo substituents, or electron-donating groups, such as methyl and methoxy were converted into the corresponding products with good yields. We also applied thiourea. The results are summarized in Table 3.

The proposed mechanism for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones is shown in Scheme 2. In this transformation, the first step can be the condensation between urea/thiourea and aldehyde and generates iminium intermediate **A**. Iminium intermediate **A** undergoes nucleophilic addition with enol **B** to form **C**. Finally, the ring closure results in the Biginelli product **4**, via the nucleophilic attack by the amine onto the carbonyl group [32].

Comparison of the catalytic ability of some catalysts reported in the literature for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives are shown in Table 4. This study revealed that oxalic acid dehydrate showed an extraordinary potential to be an alternative cheap, cost- effective, green, eco-friendly, efficient catalyst for the Biginelli reaction. In addition, the use of solvent-free conditions with excellent yields and short reaction time in the reaction with both urea and thiourea are the notable advantages of this present methodology.

**Table 1.** Optimization of the reaction condition in the synthesis of **4a** [a]

| Entry | Oxalic acid.2$H_2O$ (mol %) | Time (min) | Isolated Yields (%) |
|---|---|---|---|
| 1 | Catalyst free | 540 | Not product |
| 2 | 5 | 60 | 28 |
| 3 | 10 | 60 | 46 |
| 4 | 15 | 35 | 65 |
| **5** | **20** | **35** | **86** |
| 6 | 25 | 35 | 88 |

[a]Reaction conditions: benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), urea (1.5 mmol) and oxalic acid dihydrate was heated at 80°C for the appropriate time.

**Table 2**. Effect of temperature on the synthesis of **4a**. [a]

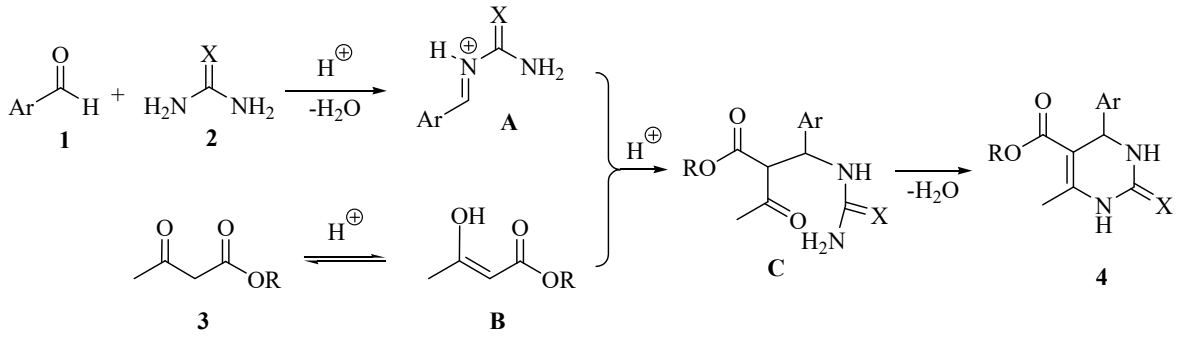
| Entry | Temperature (°C) | Time (min) | Product | Isolated Yields (%) |
|---|---|---|---|---|
| 1 | rt | 540 | 4a | Not product |
| 2 | 40 | 120 | 4a | 31 |
| 3 | 60 | 60 | 4a | 57 |
| 4 | 80 | 35 | 4a | 86 |
| 5 | 100 | 35 | 4a | 87 |

[a]Reaction conditions: benzaldehyde (1.0 mmol); ethyl acetoacetate (1.0 mmol); urea (1.5 mmol) and oxalic acid dihydrate (20 mol %) was heated under various temperatures for the appropriate time.

**Table 3.** Oxalic acid dihydrate catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one derivatives.

| Entry | Ar | R | X | Product [a] | Time (min) | Yield (%) [b] | m.p. (°C) | | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Found | Reported | |
| 1 | $C_6H_5$ | $C_2H_5$ | O | **4a** | 35 | 86 | 198-200 | 200-202 | [24] |
| 2 | 4-OMe-$C_6H_4$ | $C_2H_5$ | O | **4b** | 30 | 85 | 202-204 | 202-203 | [28] |
| 3 | 4-$(Me)_2N$-$C_6H_4$ | $C_2H_5$ | O | **4c** | 40 | 77 | 252-254 | 255-257 | [28] |
| 4 | 4-F-$C_6H_4$ | $C_2H_5$ | O | **4d** | 25 | 83 | 174-176 | 174-176 | [30] |
| 5 | 4-Me-$C_6H_4$ | $C_2H_5$ | O | **4e** | 30 | 86 | 202-204 | 204-205 | [27] |
| 6 | 2-Cl-$C_6H_4$ | $C_2H_5$ | O | **4f** | 45 | 80 | 217-219 | 220-223 | [24] |
| 7 | 4-$O_2N$-$C_6H_4$ | $CH_3$ | O | **4g** | 25 | 79 | 216-218 | 214-216 | [24] |
| 8 | 2-Cl-$C_6H_4$ | $CH_3$ | O | **4h** | 30 | 84 | 250-252 | 248-252 | [24] |
| ]9 | 4-F-$C_6H_4$ | $CH_3$ | S | **4i** | 35 | 80 | 210-212 | 208-210 | [30] |
| 10 | 4-OMe-$C_6H_4$ | $C_2H_5$ | S | **4j** | 35 | 82 | 151-153 | 150-152 | [24] |
| 11 | $C_6H_5$ | $C_2H_5$ | S | **4k** | 40 | 84 | 208-210 | 208-210 | [24] |
| 12 | 4-Cl-$C_6H_4$ | $C_2H_5$ | S | **4l** | 55 | 78 | 192-194 | 191-195 | [20] |

[a]Isolated yield.
[b]Reaction conditions: benzaldehyde (1.0 mmol), ethyl/methyl acetoacetate (1.0 mmol), urea/thiourea (1.5 mmol) and oxalic acid dihydrate (20 mol %) was heated at 80 °C.




**Scheme 2.** Proposed mechanistic route for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones.

## 4. Conclusions

In summary, a green protocol was studied for Biginelli synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones via one-pot three component reaction of aldehydes, urea/thiourea and ethyl/methyl acetoacetate in the presence of oxalic acid dihydrate as the catalyst under thermal and solvent-free conditions. The notable advantages of the present methodology are low-cost, non-toxic catalyst, high catalytic activity, eco-friendly, excellent yields, short reaction times, environmentally benign nature and solvent-free conditions.

## Acknowledgments

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**Table 4.** Comparison of catalytic ability some of catalysts reported in the literature for synthesis of **4a.**

| Entry | Catalyst | Conditions | Time/Yield (%) | Refrences |
|---|---|---|---|---|
| 1 | Bakers' yeast | Room temperature | 24h/84 | [27] |
| 2 | Hydrotalcite | Solvent-free, 80°C | 35 min/84 | [28] |
| 3 | $[Al(H_2O)_6](BF_4)_3$ | MeCN, Reflux | 20 h/81 | [29] |
| 4 | $Cu(BF_4)_2.xH_2O$ | Room temperature | 30 min/90 | [31] |
| 5 | [Btto][*p*-TSA] | Solvent-free, 90°C | 30 min/96 | [33] |
| 6 | Triethylammonium acetate | 70°C | 45min/90 | [34] |
| 7 | *p*-Dodecylbenzenesulfonic acid | Solvent-free, 80°C | 3 h/94 | [35] |
| 8 | Oxalic acid dihydrate | Solvent-free, 80°C | 35 min/86 | This work |

## References


[1] A. Strecker, Leibigs. Ann. Chem. 75 (1850) 27-45.
[2] M. Abaszadeh, M. Seifib, M. Ghashang. Iran. J. Catal. 5 (2014) 113-117.
[3] N. Hazeri, M.T. Maghsoodlou, S. Mohamadian Souri, M. Lashkari, M. Ghashang, Iran. J. Catal. 5 (2015) 9-14.
[4] L. Moradi, G.R. Najafi, H. Saeidiroshan. Iran. J. Catal. 5 (2015) 357-364.
[5] H. Eshghi, M. Rahimizadeh, S.M. Mousavi. Iran. J. Catal. 4 (2014) 235-239.
[6] S.S. Sajadikhah, M.T. Maghsoodlou, N. Hazeri, Chin. Chem. Lett. 25 (2014) 58-60.
[7] S.S. Sajadikhah , N. Hazeri, M.T. Maghsoodlou, S.M. Habibi-Khorassani, Kh. Khandan-Barani, J. Chem. Res. 37 (2013) 40-42.
[8] Z. Madanifar, M.T. Maghsoodlou, M. Kangani, N. Hazeri, Res. Chem. Int. 41 (2015) 9863-9869
[9] N. Hazeri, S.S. Sajadikhah, M.T. Maghsoodlou, S. Mohamadian-Souri, M. Norozi, M. Moein, J. Chin. Chem. Soc. 61 (2014) 217-220.
[10] H. Zang, Y. Zhang, B. Cheng, W. Zhang, X. Xu, Y. Ren. Chin. J. Chem. 30 (2012) 362-366.
[11] P. Biginelli, Gazz. Chim. Ital. 23 (1893) 360-413.
[12] O. Prakash, R. Kumar, V. Parkash, Eur. J. Med. Chem. 43 (2008) 435-440.
[13] K.Sujatha, P. Shanmugam, P.T. Perumal, D. Muralidharan, M. Rajendran, Bioorg. Med. Chem. Lett. 16 (2006) 4893-4897.
[14] S. Wisen, J. Androsavich, C.G. Evans , L. Chang, J.E. Gestwicki , Bioorg. Med. Chem. Lett. 18 (2008) 60-65.
[15] L. Heys, C.G. Moore, P. Murphy, J. Chem. Soc. Rev. 29 (2000) 57-67.
[16] M. Ashok, B.S. Holla, N.S. Kumara, Eur. J. Med. Chem. 42 (2007) 380-385.
[17] E.W. Hurst, R. Hull, J. Med. Pharm. Chem. 3 (1961) 215-219.
[18] A.M. Magerramow, M.M. Kurbanova, R.T. Abdinbekova, I.A. Rzaeva, V.M. Farzaliev, M.A. Allokhverdiev, Russ. J. Appl. Chem. 79 (2006) 787-790.
[19] S.S. Bahekar, D.B. Shinde, Bioorg. Med. Chem. Lett. 14 (2004) 1733-1736.
[20] S. Chitra, K. Pandiarajan, Tetrahdron Lett. 50 (2009) 2222-2224.
[21] A. Rajack, K. Yuvaraju, C. Praveen, Y.L.N. Murthy, J. Mol. Catal. A: Chem. 370 (2013) 197-204.
[22] K. Konkala, N.M. Sabbavarapu, R. Katla, N.Y.V. Durga, T.V.K. Reddy, L.A.P.D. Bethala , R.B.N. Prasad, Tetrahedron Lett. 53 (2012) 1968-1973.
[23] D.L. Silva, S.A. Fernandes, A.A. Sabino, A. Fatima, Tetrahedron Lett. 52 (2011) 6328-6330.
[24] C.J. Liu, J.D. Wang, Molecules 14 (2009) 763-770.
[25] A. Debache, M. Amimour, A. Belfaitah, S. Rhouati, B. Carboni, Tetrahedron Lett. 49 (2008) 6119-6121.
[26] F. Shirini, M.A. Zolfigol, A. Albadi. Chin. Chem. Lett. 22 (2011) 318-321.
[27] A. Kumar, R.A. Maurya, Tetrahedron Lett. 48 (2007) 4569-4571.
[28] J. Lai, M. Sharma, S. Gupta, P. Parashar, P. Sahu, D.D. Agarwal, J. Mol. Catal. A: Chem. 352 (2012) 31-37.
[29] M. Litvic, I. Vecenaj, Z.M. Ladisic, M. Lovric, V. Vinkovic, M. Filipan-Litvic, Tetrahedron 66 (2010) 3463-3471.
[30] B. Ahmad, R.A. Khan, Habibullah, M. Keshai, Tetrahydron Lett. 50 (2009) 2889-2892.
[31] A. Kamal, T. Krishnaji, M.A. Azhar, Catal. Commun. 8 (2007) 1929-1933.
[32] Kappe, C.O.J. Org. Chem. 62 (1997) 7201-7204
[33] Y. Zhang, B. Wang, X. Zhang, J. Huang, C. Liu, Molecules 20 (2015) 3811-3820.
[34] P. Attri, R. Bhatia, J. Gaur, B. Arora, A. Gupta, N. Kumar, E.H. C hoi, Arab. J. Chem. (2014) doi: 10.1016/j.arabjc.2014.05.007.
[35] K. Aswin, S.S. Mansoor, K. Logaiya, P.N. Sudhan, R.N. Ahmed, J. Taibah University Sci. 8 (2014) 236-247.