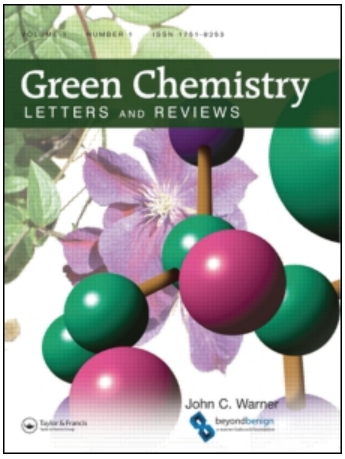

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Zinc perchlorate catalyzed one-pot synthesis of 3,4-dihydropyrimidinones under solvent-free conditions

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ORIGINAL ARTICLE

Zinc perchlorate catalyzed one-pot synthesis of 3,4-dihydropyrimidinones under solvent-free conditions

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In this paper, we report zinc perchlorate hexahydrate [$Zn(ClO_4)_2 \cdot 6H_2O$] as a highly effective catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions. These improved reaction conditions allow the preparation of a wide variety of substituted dihydropyrimidinones in high yields and purity under mild reaction conditions. Compared with the classical Biginelli reaction, this method has the advantage of excellent yields and short reaction time in solvent-free conditions.

Keywords: Biginelli reaction; 3,4-dihydropyrimidin-2(1H)-ones; zinc perchlorate catalyst; solvent-free condition

Introduction

Organic synthesis involving environmentally clean protocols under solvent-free conditions has emerged as an area of great interest from both environmental and economical points of view (*1,2*). Many conventional chemical processes make use of large amounts of toxic reactants and or volatile solvents. Replacement of such hazardous reagents is one of the main goals of green chemistry. Synthesis of organic molecules from easily available substrates via atom-efficient reactions such as multicomponent reactions (MCR) are of special importance to the organic chemists (*3*). The Biginelli reaction (*4*) is one of the most useful examples of MCR, gaining increasing importance in organic and medicinal chemistry due to its capacity to generate multifunctionalized products including 3,4-dihydropyrimidin-2-(1H)-ones (DHPM) and their thione analogs. Such heterocycles show a wide range of pharmacological properties including antiviral, antitumor, antibacterial and anti-inflammatory activities (*5*). They have emerged as integral backbones and calcium channel blockers, α-1a-antagonists and neuropeptide Y-(NPY) antagonists (*6,7*). Several alkaloids containing the DHPM as core unit have been isolated from marine sources having interesting biological properties (*8*). For example, batzelladine alkaloids are potent HIV gp-120-CD4 inhibitors (*9*).

The original Biginelli protocol for the preparation of DHPM was conducted in boiling ethanol in the presence of catalytic amounts of concentrated hydrochloric acid. This simple procedure has been effective in a number of the Biginelli reactions with simple unsubstituted, or para and meta-substituted aldehydes and acetoacetate esters (*10–16*). However, in the cases of significant steric hindrance in both counterparts, the reaction yields drop drastically (*17*). So as to improve the yield of dihydropyrimidinones, a few other multistep approaches using aldehyde (*18*) or acetoacetate (*19*) equivalents have been developed in modified Biginelli reactions. Nevertheless, the original Biginelli reaction offers the most simple, cost-effective and reasonable access to these important compounds.

In the last two decades, more efficient conditions have been found for the Biginelli reaction using Lewis acid as catalyst (*20*). Microwave irradiation (*21*) as well as solid-phase and fluoro-phase techniques (*22*) facilitating this synthesis have also become increasingly widespread. Additionally, the Biginelli reaction can be strongly accelerated by various ionic liquids in catalytic amounts, e.g., 1-n-butyl-3-methylimidazolium tetrafluoroborate ($BMImBF_4$) (*23*). These catalysts have been efficiently used both on solid support and in solutions. Some of these catalyzed conditions have drawbacks like, the need of strong and protic acids (*4,24a*), anhydrous conditions, (*24b–f*) high temperature and prolonged reaction times (*25,26*). The requirement of large amount of moisture sensitive/hazardous/costly catalyst, halogenated solvents, special apparatus, and the unsatisfactory yields due

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to undesirable side reactions achieved with existing protocols makes it necessary to search for improved and more efficient catalytic condition for the Biginelli reaction.

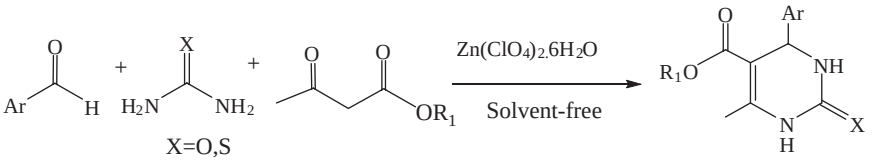
Results and discussion

In search of less costly but more effective catalysts, we thought that it should be a compound of group I/II metal with strong oxophilic central metal ion and strong electron-withdrawing counter anion. Metal perchlorates are strong contenders as catalysts for industrial use (*27*). We studied the three component Biginelli condensation catalyzed by zinc perchlorate examining the conditions for the reaction involving benzaldehyde, urea and ethyl acetoacetate to afford the DHPM **4** (Scheme 1). A summary of the optimization experiments is shown in Table 1. The optimum amount of catalyst (2 mol%) was determined from the experiments. With increase in catalyst concentration up to 2 mol%, the yield increased upto 95% in solvent-free condition in just 15 min. Beyond 2 mol% catalyst concentration, yield of DHPM increases marginally. When the reaction was carried out in different solvents under optimized catalyst concentration of 2 mol%, the yields obtained were much lower than those in neat condition, that too with longer reaction time. The lowest yield of 46% was obtained with dichloromethane (DCM), whereas maximum was 80% in ethanol. The Biginelli reaction could be carried out under neat conditions in excellent yield (95%). The difference in yields between the reactions ran in solvent versus solvent-free conditions can be due to an increase in the electrostatic effect of the ionic aggregates in the solid state to activate the electrophile. DHPM **4** was isolated by pouring reaction mass into ice water followed by filtration. Moreover, the best results were observed when the molar ratio of aldehyde **1**, β-diketoester **2** and urea **3** was 1:1:1.5. The three component condensation reactions proceeded smoothly at 100°C and were complete in 15–30 min. The yields were significantly increased from 20–50% of the classical Biginelli method to 80–95%, and the reaction time was drastically shortened from 18 h to 15 min. (*28*) Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2(1H)-thiones, which are also of much interest with regard to biological activity. For example, monastrol is a new class of anticancer agents acting as cell division (mitosis) blockers (*29*).

Likewise, to study generality of this process, a variety of substituted aromatic and heterocyclic aldehydes carrying either electron-donating or electron-withdrawing substituents were examined. Acid-sensitive aldehydes such as furfural worked well without the formation of any side products, which are normally observed in the presence of protic acids due to their polymerization under acidic conditions. In all the cases, high yields of products with high purity were achieved. These results are shown in Table 2, which encouraged us to explore the potential of this catalytic system for the synthesis of various DHPM. The efficiency of this reaction is substrate dependent with the use of more highly functionalized or sterically hindered keto esters leading to severely reduced yield (*30*).

Zinc perchlorate can be applied as an efficient catalyst not only for synthesis of the open chain 1,3-dicarbonyl compounds, but also for cyclic 1,3-dicarbonyl compounds. We have used dimedone **5** as a cyclic 1,3-dicarbonyl compound, urea and substituted aromatic aldehyde for the synthesis of DHPM derivatives (Scheme 2). These results are shown in Table 3.

Better catalytic activity of zinc perchlorate may be attributed to: (i) higher charge with respect to size (Z^2/r) value of Zn^{2+} ion (5.33 e^2m^{-10}) (*31*) making Zn^{2+} ions significantly more oxophilic; and (ii) lower hydrolysis constant (pKh value) of 9.6 of Zn^{2+} ion (*32*) helping to hold oxophilic property in the presence of water of hydration and trace of moisture. Thus, zinc perchlorate was more effective in inducing "electrophilic activation." It is anticipated that the strong electron-withdrawing nature of the ClO^{4-} counter anions in zinc perchlorate make Zn^{2+} sufficiently electrophilic. With zinc perchlorate as a catalyst, the proposed mechanism (Scheme 3) for the synthesis of DHPM involves the acid catalyzed formation of N-acyliminium ion intermediate (shown in Scheme 3) formed from the aldehyde and urea as per the mechanism assumed by Kappe (*33*). Interception of the iminium ion by keto ester produces an



Scheme 1. Synthesis of 3,4-dihydropyrimidin-2(1H)-ones/thiones.

Table 1. Formation of dihydropyrimidinones in different solvents[a] and solvent-free condition.[b]

Entry	Solvent	Catalyst conc. (mol%)	Time (h)	Yield[c] (%)
1	Ethanol	2	4	80
2	Toluene	2	6	65
3	Acetonitrile	2	5	62
4	Benzene	2	5	52
5	THF	2	6	58
6	DCM	2	5	46
7	Neat	2	0.25	95
8	Neat	1	0.25	86
9	Neat	0.5	0.25	82

[a]Reflux temperature.
[b]The reaction was carried out in presence of benzaldehyde (1 mmol), urea (1.5 mmol), ethyl acetoacetate (1 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (2 mol%) 100°C.
[c]Isolated yield.

open chain ureide, which subsequently cyclizes to DHPM.

Physical and spectral data of synthesized known compounds are in good agreement with those reported in the literature. Spectral data of new compounds are shown.

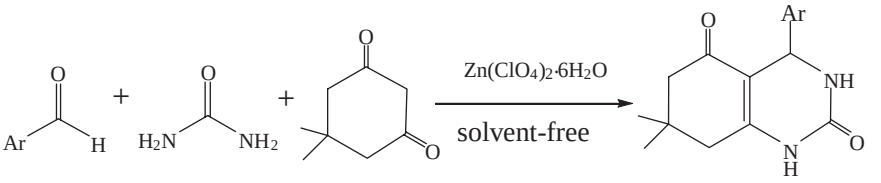
Conclusion

We have described herein a highly efficient catalyst for synthesis of substituted DHPM in a solvent-free condition. The advantages include: (i) the use of small amount (2.0 mol%) of cheap, easy to handle and commercially available catalyst; (ii) short reaction times; and (iii) high yields. With increasing environmental concerns (*34*) the solvent-free reaction conditions should make this methodology environmentfriendly and applicable for large-scale operations. The applicability of this catalyst resulted in decreased reaction time and increased yields of the biologically active dihydropyrimidone derivatives. The industrial utility of this methodology has been demonstrated by an improved synthesis of the key intermediate.

Table 2. Zinc perchlorate catalyzed synthesis of dihydropyrimidinones under solvent-free conditions.[a]

Entry	Ar	R_1	X	Time (min)	Yield[b] (%)
1	Ph	Et	O	15	95
2	4-Cl–C_6H_4	Et	O	20	88
3	4-OH–C_6H_4	Et	O	15	90
4	4-OMe–C_6H_4	Et	O	15	92
5	4-Me_2N–C_6H_4	Et	O	20	89
6	3,4-$(OMe)_2$–C_6H_3	Et	O	25	91
7	4-NO_2–C_6H_5	Et	O	20	88
8	$C_6H_5CH=CH$	Et	O	15	84
9	2,6-Cl_2–C_6H_3	Et	O	20	80
10	2-Furyl	Et	O	25	82
11	Ph	Me	O	15	95
12	4-OH–C_6H_4	Me	O	15	90
13	4-Cl–C_6H_4	Me	O	20	89
14	4-Me_2N–C_6H_4	Me	O	20	90
15	4-OMe–C_6H_4	Me	O	15	93
16	3-OMe,4-OH–C_6H_3	Me	O	20	85
17	Ph	Et	S	15	93
18	4-Cl–C_6H_4	Et	S	20	84
19	4-OH–C_6H_4	Et	S	15	87

[a]Reaction condition: aldehyde (1 mmol), β-diketoester (1 mmol), urea or thiourea (1.5mmol), ethyl acetoacetate (1 mmol), $Zn(ClO_4)_2 \cdot 6H_2O$ (2 mol%) at 100°C.
[b]Isolated yield.



5 **6a-b**

6a:Ar=2-Cl-C $_6H_4$
6b:Ar=4-OCH $_3$-C_6H_4

Scheme 2. Synthesis of DHPM from cyclic 1,3-dicarbonyl compound.

Experimental section

Material and methods

Melting points was determined in an open capillary. IR spectra were recorded on a Shimadzu IR-470 spectrophotometer and reported in wave numbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 and 100 MHz, respectively. NMR spectra were obtained in solutions of dimethylsulfoxide (DMSO) (d_6) and chemical shifts reported in parts per million (ppm). Analytical thin layer chromatography (TLC) of all reactions was performed on Merck prepared plates. Column chromatography was performed using silica gel (100–200 mesh).

General procedure for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones (DHPM) (4)

A mixture of aldehyde (1 mmol), β-keto ester (1 mmol), urea or thiourea (1.5 mmol) and $Zn(ClO_4)_2{\cdot}6H_2O$ (2 mol%) was heated with stirring at 100°C for an appropriate time (Table 2). After completion of reaction (TLC), the reaction mixture was cooled and poured into cold water and stirred for 5 min. The solid was suction filtered, washed with cold water (20 mL × 2), filtered and recrystallized from ethanol to afford pure product.

Selected physical data or compounds

5-(Ethoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Entry 1)
m.p. 200–202°C; IR (KBr): ν_{max} (in cm^{-1}) = 3244, 3189, 2979, 2939, 2812, 1731, 1701, 1647, 1515; ^1H NMR (δ in ppm, DMSO-d_6): δ 9.18(s, 1H, NH), 7.73 (s, 1H, NH), 7.33 (m, 5H, arom CH), 5.14(s, 1H, CH), 3.98 (q, J = 8 Hz, 2H, OCH_2), 2.24 (s, 3H, CH_3), 1.10 (t, J = 8 Hz, 3H, CH_3); ^{13}C (δ in ppm, DMSO-d_6): δ 165.45,152.25, 148.45, 144.92, 128.51, 127.39, 126.33, 99.37, 59.32, 54.03, 17.86, 14.15.

4-(4-Chlorophenyl)-5-(Ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Entry 2)
m.p. 211–213°C; IR (KBr): ν_{max}(in cm^{-1}) = 3242, 3114, 2981, 2956, 2835, 1680, 1669, 1650, 1575; ^1H NMR (δ in ppm, DMSO-d_6): δ 9.25(s, 1H, NH), 7.77 (s, 1H, NH),7.40 (d, J = 8 Hz, 2H, arom CH), 7.25 (d, J = 8.4 Hz, 2H, arom CH), 5.13(s, 1H, CH), 3.98 (q, J = 8 Hz, 2H, OCH_2), 2.24 (s, 3H, CH_3), 1.09 (t, J = 8 Hz, 3H, CH_3); ^{13}C (δ in ppm, DMSO-d_6): δ 165.21, 151.94, 148.76, 143.80, 131.79, 128.42, 128.20, 98.80, 59.28, 53.41, 17.82, 14.09.

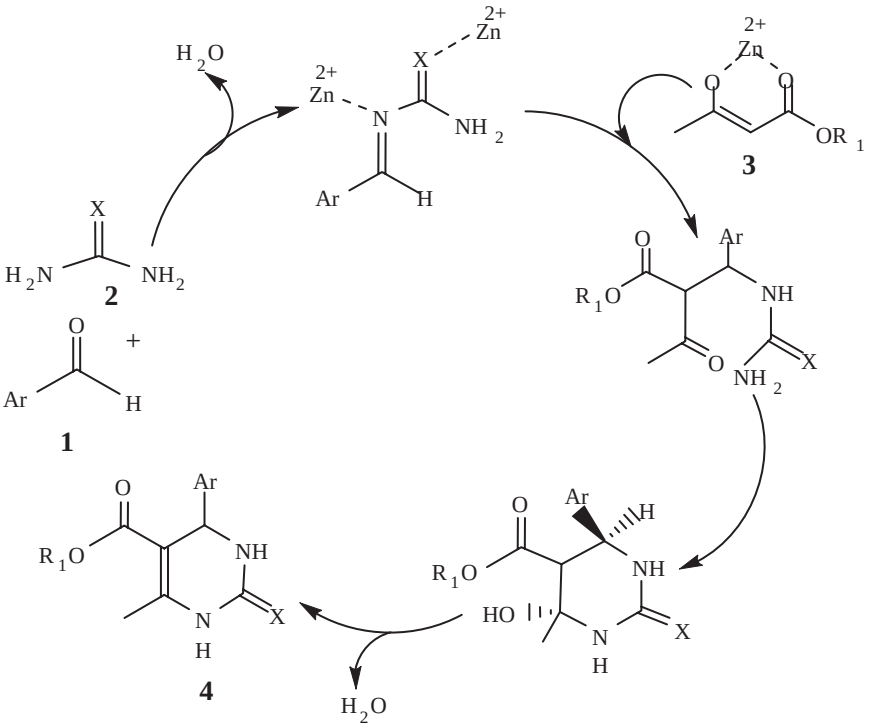
5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Entry 4)
m.p. 198–200°C; IR (KBr): ν_{max}(in cm^{-1}) = 3234, 3176, 2983, 2946, 2835, 1730, 1650, 1605, 1548; ^1H NMR (δ in ppm, DMSO-d_6): δ 9.15(s, 1H, NH), 7.67 (s, 1H, NH), 7.14 (d, J = 8 Hz, 2H, arom CH), 6.88 (d, J = 8.4 Hz, 2H, arom CH), 5.05(s, 1H, CH), 3.98 (q, J = 8 Hz, 2H, OCH_2), 2.23 (s, 3H, CH_3), 1.10 (t, J = 8 Hz, 3H, CH_3).

4-(2,6-Dichlorophenyl)-5-(Ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Entry 9)
m.p. 255–257°C; IR (KBr): ν_{max}(in cm^{-1}) = 3353, 3233, 2982, 3123,1696, 1542, 1445; ^1H NMR (δ in

Table 3. Zinc perchlorate catalyzed synthesis of DHPM using cyclic 1,3-dicarbonyl compounds under solvent-free condition[a]

Entry	Ar–CHO	Time (min)	Yield[b] (%)	M.P (°C)
6a	2-Cl–C_6H_4–CHO	15	83	182–184
6b	4-OCH_3–C_6H_4–CHO	20	88	228–230

[a]The reaction was carried out in presence of aldehyde (1 mmol), urea (1.5 mmol), dimedone (1 mmol), $Zn(ClO_4)_2{\cdot}6H_2O$ (2 mol%) at 100°C.
[b]Isolated yield.



Scheme 3. Proposed mechanism for one-pot synthesis of DHPM Biginelli condensation protocol.

ppm, DMSO-d_6): δ 9.28(s, 1H, NH), 7.59 (s, 1H, NH), 7.20 (d, J = 8 Hz, 2H, arom CH), 7.0 (d, J = 8.4 Hz, 2H, arom CH), 6.75 (d, J = 8.4 Hz, 2H, arom CH), 5.0 (s, 1H, CH), 3.86 (q, J = 8 Hz, 2H, OCH_2), 2.17 (s, 3H, CH_3), 0.90 (t, J = 8 Hz, 3H, CH_3). ^{13}C (δ in ppm, DMSO-d_6): δ 164.86, 150.5, 149.35, 137.55, 135.08, 129.29, 94.02, 58.70, 52.18, 17.78, 13.67.

4-(2-chlorophenyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (Entry 6a)
m.p. 182–184°C; IR (KBr): ν_{max}(in cm^{-1}) = 3234, 3176, 2983, 2946, 2835, 1730, 1650, 1605, 1548; ^1H NMR (δ in ppm, DMSO-d_6): δ 9.34(s, 1H, NH), 8.68 (s, 1H, NH), 7.34 (m, 4H, arom CH), 5.05(s, 1H, CH), 2.44 (s, 2H, CH_2), 2.15 (s, 2H, CH_2), 0.98 (s, 6H, CH_3).

4-(4-methoxyphenyl)-7,7-dimethyl-3,4,7,8-tetrahydroquinazoline-2,5(1H,6H)-dione (Entry 6b)
m.p. 228–230°C; IR (KBr): ν_{max}(in cm^{-1}) = 3234, 3176, 2983, 2946, 2835, 1730, 1650, 1605, 1548; ^1H NMR (δ in ppm, DMSO-d_6): δ 9.22(s, 1H, NH), 7.68 (s, 1H, NH), 7.04 (dd, J = 8.4 Hz, 2H, arom CH), 6.7 (dd, J = 8.4 Hz, 2H, arom CH), 5.05(s, 1H, CH), 3.72 (s, 3H, CH_3), 2.47 (s, 2H, CH_2), 2.20 (s, 2H, CH_2), 0.98 (s, 6H, CH_3).

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