

Environmentally benign aqueous zinc tetrafluoroborate-catalyzed one-pot Biginelli condensation at room temperature

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Received 30 April 2008; accepted (revised) 17 December 2008

A trace amount (0.6 mole % with respect to aldehyde or 1,3-dicarbonyl compound) of an aqueous solution of zinc tetrafluoroborate has been used as a mild, efficient and almost neutral catalyst for a one-pot three component condensation of aldehydes, 1,3-dicarbonyl compound and urea or thiourea to afford the corresponding 3,4-dihydropyrimidin-2 (1*H*)-ones (DHPMs) and thiones in high yields at room temperature.

Keywords: Aqueous zinc tetrafluoroborate, Biginelli condensation, three-component reactions

At the beginning of the new century, organic solvent-free reactions have attracted considerable interest due to increasing awareness about environmental problems in chemical research and industry¹. Organic solvent-free reactions have many advantages such as reduced pollution, lower costs and simplicity. Another aspect which is receiving increasing attention is the use of water-accessible Lewis acid catalysts in various chemical transformations². Water as the reaction medium is generally considered as a cheap, safe, and environmentally benign alternative to 'synthetic' solvents³. This prompted the systematic investigation into the feasibility of organic solvent-less catalyzed reactions in aqueous media under mild conditions.

Dihydropyrimidinones and their derivatives are a very important class of bioactive compounds because of their pharmacological properties⁴. They are known to exhibit a wide range of biological activity such as calcium channel blockers⁵, antihypertensive agents⁶, α -adrenergic antagonists⁷ and neuropeptide Y (NPY) antagonists⁸. The biological activity of some recently isolated alkaloids has also been attributed to the presence of dihydropyrimidinone moiety in the molecules⁹. Notable among these are the batzelladine alkaloids, which have been found to be potent HIV gp-120-CD4 inhibitors¹⁰.

The Biginelli reaction, which was discovered more than a century ago is one of the most important reactions for the synthesis of dihydropyrimidinones

based on acid-catalyzed three-component condensation of 1,3-dicarbonyl compounds, aldehyde and urea¹¹. The major drawback of this protocol is the low yield of product in the case of both substituted aromatic and aliphatic aldehydes. Therefore, the search for finding milder and more convenient methods for the synthesis of these heterocyclic compounds has gained special urgency.

Results and discussion

Recently, many improved procedures have been reported for the preparation of DHPMs based on the modifications of classical Biginelli's reaction. These methods have been developed using different Lewis acids such as Sr(OTf)₂ (ref.12a), MgBr₂ (ref.12b), ZnCl₂ (ref.12c), In(OTf)₃ (ref.12d), LiBr (ref.12e), CeCl₃ (ref.12f), Cu(OTf)₂ (ref.12g), ZrCl₄ (ref.12h), FeCl₃-NiCl₂ (ref.12i), BiCl₃ (ref.12j), Mn(OAc)₂ (ref.12k), FeCl₃ (ref.12l), Ln(OTf)₃ (ref.12m), LaCl₃ (ref.12n), InCl₃ (ref.12o), BF₃ (ref.12p), *etc.* as well as protic acids such as H₂SO₄, HOAc, conc. HCl, *etc.* as promoters¹³. Several other catalysts, such as iodine¹⁴, N-bromosuccinimide¹⁵, polyphosphate ester (PPE)¹⁶ have been used to facilitate the reactions. An enantioselective Biginelli reaction catalyzed by Yb(OTf)₃ has been reported recently¹⁷. Many other methods including microwave irradiation, ionic liquids, clay, solvent-free and catalyst-free procedures are also reported¹⁸. However, many of

these methods are associated with harsh reaction conditions, expensive and toxic reagents, strongly acidic conditions, tedious work-up, stoichiometric amounts of catalysts, long reaction times, unsatisfactory yields, incompatibility with other functional groups, *etc.* Another important issue is that most of these methods involve either conventional heating or microwave-irradiation. Although the Biginelli reactions in pure water have been reported by several research groups, it has not been studied much at RT (ref.19). Very recently, Suzuki *et al.* reported that metal triflimides such as Ni(NTf₂)₂, Cu(NTf₂)₂, Yb(NTf₂)₂ in combination with HCl (acid additive) catalyzed the Biginelli reaction in water at RT affording moderate to high yields (25-88%) with longer reaction time (24 hr)²⁰. Thus, there is a scope for further innovation toward simple and general procedures for one-pot synthesis of dihydropyrimidinones and thiones under mild conditions at RT with shorter reaction time.

Aqueous solution of zinc tetrafluoroborate is a very cheap, commercial and readily available reagent. It has been used as an efficient catalyst in a number of useful synthetic transformations²¹. As a part of the ongoing studies to test the effectiveness of aq. Zn(BF₄)₂ as catalyst in various chemical transformations²², herein is described aq. zinc tetrafluoroborate catalyzed one pot Biginelli condensation under organic solvent-free conditions at RT (Scheme I).

In a typical experimental procedure, a mixture of 1,3-dicarbonyl compound (1 mmole), aldehyde (1 mmole), and urea or thiourea (1.2 mmole) was stirred at RT in the presence of a catalytic amount of an aqueous solution (40% w/v) of zinc tetrafluoroborate (0.6 mole % with respect to aldehyde) for a certain period of time as required for completion of the reaction (TLC). After completion of reaction, the reaction mixture was poured into water and the solid product was separated, filtered and purified by recrystallization from ethanol. Large scale (100 mmole) reactions were also carried out without any difficulty following the same procedure. A wide range of structurally diverse aldehydes, 1,3-dicarbonyl compounds and urea were subjected to reaction under

this procedure to get the corresponding dihydropyrimidinones as summarized in Table I.

All these reactions were carried out at RT and afforded the desired products in high yield. Several sensitive functionalities such as -OH, -OMe, -NO₂, -CO₂Et remained unaffected under the present reaction conditions. Aromatic, aliphatic and heterocyclic aldehydes reacted well to give the desired product in excellent yield. The present procedure was equally effective for thiourea also. In general, the reactions were fast. No organic solvents were required to isolate the product from the reaction mixture. Only ethanol was employed for recrystallization to provide analytically pure samples.

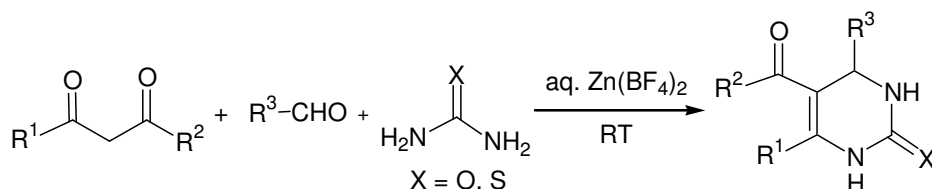
Experimental Section

Melting points were determined on a glass disk with an electrical bath and are uncorrected. ¹H (300 MHz) and ¹³C NMR (75 MHz) spectra were run in DMSO-*d*₆. IR spectra were taken as KBr discs. Elemental analyses were carried out on a Perkin-Elmer autoanalyzer. Aq. Zn(BF₄)₂ was purchased for Aldrich. 1,3-Dicarbonyl compounds, aldehydes, urea and thiourea were all commercial materials. All liquid reagents were distilled before use.

General procedure for the synthesis of dihydropyrimidinones

Representative procedure for 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (1). A mixture of ethyl acetate (260 mg, 2 mmole), benzaldehyde (212 mg, 2 mmole) and urea (144 mg, 2.4 mmole) was stirred at RT in presence of a catalytic amount of an aqueous solution (40% w/v) of zinc tetrafluoroborate (0.6 mole % with respect to aldehyde or 1,3-dicarbonyl compound) for 3 hr (TLC). After completion of the reaction, the reaction mixture was poured into water (20 mL) and the solid product was filtered under suction. Recrystallization from hot ethanol afforded the pure product (380 mg, 73 %), m.p. 201-02°C (lit.^{7p} m.p. 202-04°C).

This procedure is followed for the synthesis of all the dihydropyrimidinones listed in Table I. The



Scheme I — Aq. Zn(BF₄)₂ catalyzed synthesis of dihydropyrimidinones

Table I — Aq. $\text{Zn}(\text{BF}_4)_2$ catalyzed synthesis of dihydropyrimidinones

Compd.	R ¹	R ²	R ³	X	Time (h)	Yield (%) ^a	Ref
1	Me	OEt	Ph	O	3	73	12p
2	Me	OEt	4-(Cl)-C ₆ H ₄	O	5	61	12p
3	Me	OEt	4-OMe-C ₆ H ₄	O	4	71	12p
4	Me	OEt	2-OH-C ₆ H ₄	O	4	75	12q
5	Me	OEt	4-OH-C ₆ H ₄	O	6	81	12q
6	Me	OEt	PhCH=CH ₂	O	5	70	12q
7	Me	OEt	1-Naphthyl	O	5	70	
8	Me	OEt	<i>n</i> -C ₃ H ₇	O	3.5	90	12r
9	Me	OEt	<i>n</i> -C ₇ H ₁₅	O	4	90	
10	Me	Me	Ph	O	2.5	93	12s
11	Me	Me	4-OMe-C ₆ H ₄	O	3	84	12t
12	Me	OEt	Ph	S	6	65	12o
13	Me	Me	Ph	S	3	85	12o
14	Me	Me	2-furfuryl	O	4	80	12o
15	Me	Ph	4-OMe-C ₆ H ₄	O	7	65	12o
16	Me	Ph	Ph	O	2.5	93	12s
17	Me	OEt	4-NO ₂ -C ₆ H ₄	O	5	84	12p

^aYields refer to pure solid products, properly characterized by m.p. spectral (IR, ¹H, ¹³C NMR), and analytical data.

known compounds have been identified by comparison of spectral data (IR and ¹H NMR) and m.p. with those reported. The m.p., spectral, and analytical data of the new compounds have been presented below in order of their entries in **Table I**.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one, 1: Colorless solid; m.p. 201-02°C (lit.^{12p} 202-204°C); IR (KBr): 3240, 1722, 1705, 1649 cm⁻¹; ¹H NMR: δ 9.12 (s, 1H), 7.66 (s, 1H), 7.28-7.16 (m, 5H), 5.10(d, *J* = 3.3 Hz, 1H), 3.94 (q, *J* = 7.1 Hz, 2H), 2.18 (s, 3H), 1.04 (t, *J* = 7.1 Hz, 3H).

4-(4-chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 2: Colourless solid; m.p. 212-14°C (lit.^{12p} 213-15°C); IR (KBr):

3242, 1723, 1704, 1649 cm⁻¹; ¹H NMR: δ 9.20 (s, 1H), 7.82 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.11(d, *J* = 1.6 Hz, 1H), 3.96 (q, *J* = 7.1 Hz, 2H), 2.23 (s, 3H), 1.06 (t, *J* = 7.2 Hz, 3H).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 3: Colourless solid; m.p. 200-01°C (lit.^{12p} 200-01°C); IR (KBr): 3246, 1700, 1642 cm⁻¹; ¹H NMR: δ 9.20 (s, 1H), 7.69 (s, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.09 (d, *J* = 2.6 Hz, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 2.26 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H).

5-Ethoxycarbonyl-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 4: Colourless solid; m.p. 199-200°C (lit.^{12q} 201-02°C); IR (KBr): 3224, 3084, 2926, 1748, 1705, 1644 cm⁻¹; ¹H NMR: δ 9.31 (s, 1H), 9.02 (s, 1H), 7.62 (s, 1H), 7.23-7.14 (m, 2H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 4.49-4.42 (m, 1H), 4.18-4.13 (m, 2H), 1.72 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H).

5-Ethoxycarbonyl-4-(4-hydroxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 5: m.p. 226-27°C (lit.^{12q} 222-29°C); IR (KBr): 3290, 2982, 1690, 1641 cm⁻¹; ¹H NMR: δ 9.31 (s, 1H), 9.06 (s, 1H), 7.60 (s, 1H), 7.00 (d, *J* = 6.9 Hz, 2H), 6.67 (d, *J* = 6.9 Hz, 2H), 5.05 (d, *J* = 2.7 Hz, 1H), 3.96 (q, *J* = 7.2 Hz, 2H), 2.20 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 3H).

5-Ethoxycarbonyl-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1H)-one, 6: Colourless solid; m.p. 232-34°C (lit.^{12q} 238-39°C); IR (KBr): 3245, 1724, 1700, 1650 cm⁻¹; ¹H NMR: δ 8.93 (s, 1H), 7.33 (s, 1H), 7.20-6.99 (m, 5H), 6.14 (d, *J* = 15.9 Hz, 1H), 5.99 (dd, *J* = 15.9 Hz, 6.0 Hz, 1H), 4.52 (d, *J* = 3.6 Hz, 1H), 3.93-3.81 (m, 2H), 2.00 (s, 3H), 0.98 (t, *J* = 7.1 Hz, 3H).

5-Ethoxycarbonyl-6-methyl-4-naphthyl-3,4-dihydropyrimidin-2(1H)-one, 7: Colourless solid; m.p. 210-11°C; IR (KBr): 3373, 3332, 2986, 1701, 1648 cm⁻¹; ¹H NMR: δ 9.25 (s, 1H), 8.31(d, *J* = 8.09 Hz, 1H), 7.93 (d, *J* = 7.75 Hz, 1H), 7.84 (d, *J* = 7.84, 1H), 7.74 (s, 1H), 7.40-7.58 (m, 4H), 6.06 (s, 1H), 3.75-3.84 (m, 2H), 2.36 (s, 3H), 0.81(t, *J* = 7.04 Hz, 3H); ¹³C NMR: δ 166.2, 152.5, 149.6, 141.3, 134.3, 130.9, 129.3, 128.7, 126.9, 126.6, 126.5, 125.1, 124.5, 100.0, 59.9, 50.6, 28.6, 14.7. Anal. Calcd for C₁₈H₁₈N₂O₃: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.63; H, 5.83; N, 9.01%.

5-Ethoxycarbonyl-6-methyl-4-propyl-3,4-dihydropyrimidin-2(1H)-one, 8:

Colourless solid; m.p. 167-69°C (lit.^{12r} 168-70°C); IR (KBr): 3250, 1724, 1705, 1748 cm⁻¹; ¹H NMR :

8.92 (s, 1H), 7.31 (s, 1H), 4.09-3.98 (m, 3H), 2.14 (s, 3H), 1.42-1.38 (m, 7H), 0.81 (t, $J = 6.3$ Hz, 3H).

5-Ethoxycarbonyl-6-methyl-4-heptyl-3,4-dihydropyrimidin-2(1H)-one, 9: Colourless solid; m.p. 178-89°C; IR (KBr): 3307, 3244, 2925, 1704, 1662, 1654, 1224, 1085 cm^{-1} ; ^1H NMR: δ 8.91 (s, 1H), 7.30 (s, 1H), 4.05-4.01 (m, 3H), 2.14 (s, 3H), 1.36-1.14 (m, 15H), (0.86-0.82 (m, 3H); ^{13}C NMR: δ 171.1, 158.7, 153.5, 105.2, 64.4, 55.7, 42.2, 36.8, 34.5, 34.3, 34.1, 29.3, 27.7, 23.3, 19.4. Anal. Calcd for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_3$: C, 63.80; H, 9.28; N, 9.92. Found: C, 63.77; H, 9.26; N, 9.89%.

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one, 10: Colourless solid; m.p. 233-35°C (lit.^{12s} 233-35°C); IR (KBr): 3255, 1702, 1665, 1596 cm^{-1} ; ^1H NMR: δ 9.19 (s, 1H), 7.82 (s, 1H), 7.30-7.17 (m, 5H), 5.24 (d, $J = 3.3$ Hz, 1H), 2.28 (s, 3H), 2.08 (s, 3H).

5-Ethoxy-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 11: Colourless solid; m.p. 167-69°C (lit.^{12t} 166-68°C); IR (KBr): 3232, 3123, 2957, 1715, 1700, 1597, 1509 cm^{-1} ; ^1H NMR: δ 9.10 (s, 1H), 7.77 (s, 1H), 7.17 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 5.21 (d, $J = 3.0$ Hz, 1H), 3.71 (s, 3H), 2.27 (s, 3H), 2.06 (s, 3H).

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione, 12: Colourless solid; m.p. 202-04°C (lit.^{12o} 204-06°C); IR (KBr): 3180, 2988, 1705, 1652, 1571, 1467, 1186 cm^{-1} ; ^1H NMR: δ 10.32 (s, 1H), 9.66 (s, 1H), 7.28-7.18 (m, 5H), 5.19 (s, 1H), 3.96 (q, $J = 6.0$ Hz, 2H), 2.28 (s, 3H), 1.09 (t, $J = 6.0$ Hz, 3H).

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione, 13: Colourless solid; m.p. 219-20°C (lit.^{12o} 220-22°C); IR (KBr): 3283, 2999, 1615, 1575, 1456 cm^{-1} ; ^1H NMR: δ 10.05 (s, 1H), 9.51 (s, 1H), 7.06-6.97 (m, 5H), 5.07 (s, 1H), 2.02 (s, 3H), 1.90 (s, 3H).

5-Acetyl-4-(2-furfuryl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one, 14: Colourless solid; m.p. 210-12°C (lit.^{12o} 210-12°C); IR (KBr): 3278, 2950, 1711, 1682, 1591, 1330 cm^{-1} ; ^1H NMR: δ 9.20 (s, 1H), 7.82 (s, 1H), 7.53 (s, 1H), 6.35 (s, 1H), 6.10 (d, $J = 2.7$ Hz, 1H), 5.30 (d, $J = 2.7$ Hz, 1H), 2.21 (s, 3H), 2.14 (s, 3H).

5-Benzoyl-4-(3-methoxyphenyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one, 15: Colourless solid; m.p. 218-20°C (lit.^{12o} 218-19°C); IR (KBr): 3285, 2930, 1709, 1675, 1598, 1569 cm^{-1} ; ^1H NMR: δ

9.12 (s, 1H), 7.74 (s, 1H), 7.53-7.43 (m, 5H), 7.12 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 5.27 (d, $J = 2.4$ Hz, 1H), 3.70 (s, 3H), 1.67 (s, 3H).

5-Benzoyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one, 16: Colourless solid, m.p. 160-61°C (lit.^{12s} 260-61°C); IR (KBr): 3300, 1705, 1672, 1651 cm^{-1} ; ^1H NMR: δ 9.18 (s, 1H), 7.80 (s, 1H), 7.51-7.19 (m, 10H), 5.31 (s, 1H), 1.66 (s, 3H).

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one, 17: Colourless solid, m.p. 207-09°C (lit.^{12p} 208-11°C); IR (KBr): 3244, 1726, 1702, 1647 cm^{-1} ; ^1H NMR: δ 9.31 (s, 1H), 8.20 (d, $J = 8.7$ Hz, 2H), 7.87 (s, 1H), 7.50 (d, $J = 8.7$ Hz, 2H), 5.24 (d, $J = 1.6$ Hz, 1H), 3.95 (q, $J = 7.1$ Hz, 2H), 2.21 (s, 3H), 1.04 (t, $J = 7.1$ Hz, 3H).

Conclusion

In this paper it has been demonstrated that aqueous zinc tetrafluoroborate is an effective catalyst for the synthesis of dihydropyrimidines at RT. Operational simplicity, aqueous media, mild reaction conditions, environment friendly, compatibility with various functional groups, high yields, and application of inexpensive and easily available reagents as catalyst are the advantages of the present procedure. It is important to note that the present modified Biginelli condensation is carried out at RT and in aqueous conditions. It is believed that all these advantages make this process useful for the synthesis of dihydropyrimidinones.

Acknowledgement

AH is pleased to acknowledge the financial support from DST (Grant No. SR/FTP/CS-107/2006). The authors are thankful to the Department of Chemistry, Visva-Bharat, DST-FIST and UGC-SAP. The authors also express their sincere thanks to Prof. B. C. Ranu, Department of Chemistry, Indian Association for the Cultivation of Science for his constant encouragement and useful suggestions.

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