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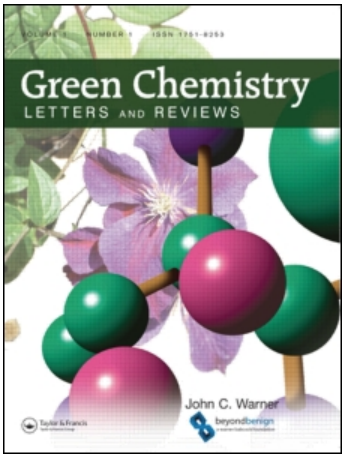

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RESEARCH LETTER

A new protocol for Biginelli (or like) reaction under solvent-free grinding method using Fe $(NO_3)_3.9H_2O$ as catalyst

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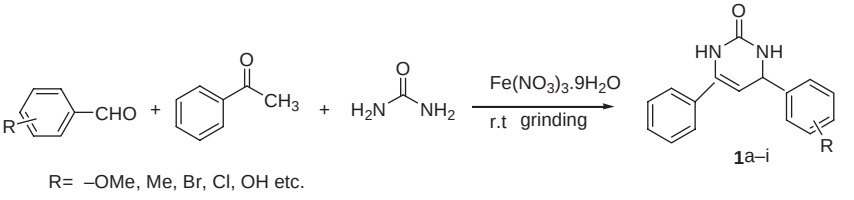
A new protocol for Biginelli (or like) reaction has been developed under solvent-free grinding method using catalytic amount of hydrated ferric nitrate or clayfen. The advantage of this novel protocol lies in the avoidance of organic solvent, high yield, energy efficiency, variation of substrates, and use of inexpensive catalyst. The recycling of catalyst is also possible with clayfen for more than three times. Furthermore, the catalytic activity of ferric nitrate retains its efficiency in methanol and acetone as reaction medium.



Keywords: dihydropyrimidinone; multicomponent; solid state; clayfen

1. Introduction

In recent years, the growing interest on exploitation of multicomponent reactions (MCR) (*1–4*) for the fast development of library of biologically active compounds is a promising greener route in terms of higher atom economy as compared to multistep reaction. One such MCR is the classical Biginelli (*5*) three-component reaction, which involves acid catalyzed one pot condensation of an aldehyde, a β-ketoester, and urea in ethanol for the synthesis of 3,4-dihydropyrimidinone derivatives (DHPM). A 3,4-DHPM derivatives exhibit excellent pharmacological and therapeutic properties such as antibacterial, antitumour, and antiinflammatory activities as well as behaving as calcium (*6–8*) channel blockers, α-1a-antagonists, and neuropeptides Y (NPY) antagonists. For the Biginelli reaction, a large number of new techniques (*9–14*) such as microwave-assisted synthesis, ultrasound irradiation, solvent-free condition, etc. and various Lewis acid catalysts (*15–19*) such as BF_3OEt_2, $InBr_3$, $LaCl_3.H_2O$, $Yb(OTf)_3$, $CuCl_2$, etc. were used to improve this conversion. Despite their potential utility, all these methods were limited to aromatic aldehydes, open chain β-dicarbonyl compound, and urea or thiourea. Very recently, the novel Biginelli like reaction (*20–24*) has been utilized to synthesize DHPM derivatives using various types of carbonyl compound such as acetophenone, cyclic ketone, cyclic-β-diketones, β-ketolactones, etc. However, many of these methods are low yields, very long reaction times, harsh reaction condition, and use of toxic solvent. Thus it becomes necessary to adopt experimental conditions which remove all these limitations to obtain a better yield of product under greener technique. Toda and his group (*25*) shown that many reactions such as Grignard reaction, Reformatsky reaction, and Aldol condensation can be conducted in high yield by just grinding solids together using mortar and pestle. Furthermore, these solid-state grinding reactions (or solvent-free reaction) have several advantages: more eco-friendly, low costs, higher yields, and simplicity in process and handling which are mainly important from the point of view of industrial manufacturing.

In continuation of our earlier work (*26–28*) on greener paths, we report herein, an efficient Biginelli (or like) reaction by using inexpensive Fe $(NO_3)_3.9H_2O$ as catalyst to synthesize large number of Biginelli

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products including 5-unsubstituted 3,4-dihydropyrimidinone **1** and 5-substituted 3,4-dihydropyrimidin-2(1H)-one **2** under solvent-free mechano-chemical mixing method using mortar and pestle.

2. Results and discussion

We first started to investigate the reaction (Scheme 1) of anisaldehyde (1 mmol), acetophenone (1 mmol), and urea (1.5 mmol) in presence of different catalysts (0.1 mmol) (Table 1) under solvent-free grinding method and in presence of various solvents. From these results, it was observed that except hydrated ferric nitrate and clayfen, all others catalysts were found to be inactive for this reaction. The hydrated ferric nitrate took less reaction time (Table 1, Entry 8) as compared (Table 1, Entry 9) to supported catalyst (clayfen). Furthermore, the catalyst ferric nitrate retained its activity in methanol and acetone as reaction medium (Table 1, Entries 14, 15).

The above optimized condition of the Biginelli like reaction of acetophenone under solvent-free method, extended to other aromatic aldehydes with different substituents and the results are summarized in Table 2, Entries 1–9. All aromatic aldehydes containing different substituent reacted efficiently to form the corresponding 5-unsubstituted 3,4-dihydropyrimidinone **1** derivatives.

Finally, we applied this method for the synthesis of 5-substituted 3,4-dihydropyrimidone derivatives **2** using acetoacetic ester (Scheme 2) as carbonyl compound (Table 2) with different aldehydes and urea (or thiourea).

In our overall study on the different types of experimentations to come up with a simple and environmentally benign reaction system, we explored efficacy of ferric nitrate in synthesizing more importantly 5-unsubstituted 3,4-dihydropyrimidinone **1** compounds employing green method. However, problem regarding the regeneration of the catalyst is a hindrance in assigning it as green catalyst. This problem can also be solved by using clay supported ferric nitrate (clayfen) as catalyst. Although, the catalytic activity of clayfen is less than ferric nitrate, it can be easily regenerated by altering the aqueous work up with hot ethanol solvent. The insoluble clayfen residue washed several times with hot ethanol and dried in a vacuum desicator. The regenerated clayfen can be reused three times without appreciable loss of catalytic activity.

The good performance of hydrated iron (III) nitrate as catalyst may be ascribed to its easy electron accepting property as a strong oxidant which catalyzes the formation of iminium intermediate **3** in the slowest step as well as activating β-ketoester **4** in the process of Biginelli reaction based on the proposed mechanism by Kappe (*29*) shown in Scheme 3.

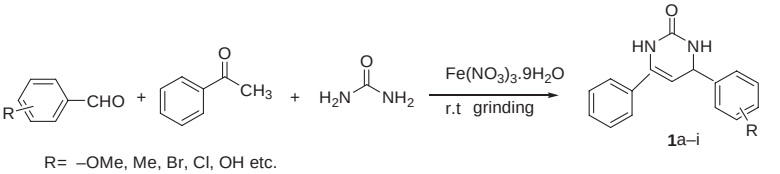
The progress of these solid-state reactions was further monitored by measurement of the IR spectrum of the reaction mixture of acetophenone, anisaldehyde, and urea (Scheme 1) at various time intervals (Figure 1a) using clayfen as catalyst where gradual change of N–H and C=O stretching frequencies represents the completion of reaction into Biginelli product. The IR spectra of regenerated clayfen shown similar absorptions peak with clayfen catalyst (Figure 1b).

We have developed a general and efficient greener path for the synthesis of 5-unsubstituted 3,4-dihydropyrimidinone **1** and 5-substituted 3,4-dihydropyrimidinone **2** under solvent-free grinding condition using hydrated ferric nitrate/clayfen as catalyst. The advantage of this novel protocol lies in the avoidance of organic solvent, high yield, energy efficiency, variation of substrates, and cheaper catalyst.

3. Experimental

3.1. General

All reactions were monitored by TLC using silica gel (Merck, 60–120 mesh). ^{1}HNMR spectra were recorded on a Varian 400 MHz FT-NMR spectrometer using $CdCl_3$ as solvent and TMS as internal standard. The elements analyses were performed on a Perkin–Elmer 20 Analyzer. IR data were recorded at Nicolet instruments 410-FTIR spectrophotometer using KBr optics. All products were characterized by comparison of their IR, ^{1}HNMR, and mass spectra with those of authentic samples (*20–24,30–35*). The starting chemicals were obtained from commercial suppliers and used without further purification.



Scheme 1. Synthesis of 5-unsubstituted 3, 4-dihydropyrimidinone 1.

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Table 1. Synthesis of 5-unsubstituted 3,4-dihydropyrimidinone **1** using 0.1 mmol of different catalysts.

Entry	Catalyst	Solvent	Time (hr)	Yield[a] (%)
1	Borax	–	2	5
2	$BF_3.(OEt)_2$	–	1.5	10
3	H_3BO_3	–	2	NR
4	Sulfamic acid	–	1.5	10
5	Oxalic acid	–	1.5	8
6	NH_4Cl	–	1	NR
7	CAN	–	1	NR
8	$FeNO_3.9H_2O$	–	1.5	92
9	Clayfen	–	3	80
10	$Mn(OAc)_2.4H_2O$	–	1.5	NR
11	P-TsOH	–	1.5	NR
12	Monmorillonite-KSF	–	1.5	NR
13	I_2	–	1.5	NR
14	$FeNO_3.9H_2O$	MeOH	12	90
15	$FeNO_3.9H_2O$	CH_3COCH_3	12	75
16	$FeNO_3.9H_2O$	CH_2Cl_2	12	NR
17	$FeNO_3.9H_2O$	$CHCl_3$	12	NR
18	$FeNO_3.9H_2O$	H_2O	12	NR

[a]All solvent-free reactions were carried out under grinding method.

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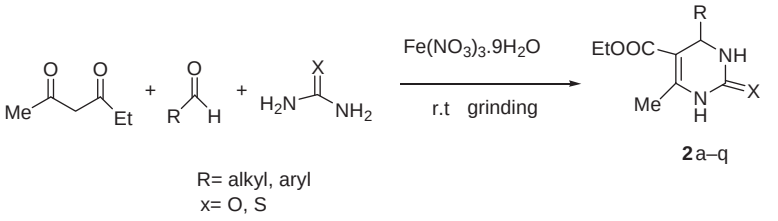
Table 2. Synthesis of 5-unsubstituted 3,4-dihydropyrimidinone **1** and 5-substituted 3,4dihydropyrimidinone **2** derivatives.

						Melting point (°C)	
Entry	R	Product[a]	X	Yield[b] (%)	Time (min)	Found reported (*20,30–37*)	
1	C_6H_5	1a	O	90	35	244	245–246
2	$4\text{-}ClC_6H_4$	1b	O	95	75	266	267–269
3	$4\text{-}MeOC_6H_4$	1c	O	92	1.5 h	258	259–261
4	$2\text{-}ClC_6H_4$	1d	O	85	25	261–62	260–263
5	3-Br C_6H_4	1e	O	80	40	257–58	256–58
6	$4\text{-}OHC_6H_4$	1f	O	90	25	256	255–257
7	$3\text{-}MeOC_6H_4$	1g	O	92	55	256	257–258
8	$4\text{-}MeC_6H_4$	1h	O	88	45	249	248–250
9	$3,4\text{-}(OMe)_2\ C_6H_3$	1i	O	93	60	244	243–245
10	C_6H_5	2a	O	95	1 h	202–203	202–204
11	$4\text{-}NO_2C_6H_4$	2b	O	89	2 h	206–208	208–209
12	$2\text{-}NO_2C_6H_4$	2c	O	90	1.5 h	220	218–220
13	$3\text{-}NO_2C_6H_4$	2d	O	93	75	226–227	226–227
14	$4\text{-}ClC_6H_4$	2e	O	83	45	211–212	213–215
15	$4\text{-}MeOC_6H_4$	2f	O	98	55	201–202	201–203
16	$4\text{-}MeC_6H_4$	2g	O	90	1 h	169–170	168–170
17	$C_6H_5\ CH=CH$	2h	O	94	75	242–243	241–242
18	$CH_3(CH_2)_3$	2i	O	65	1 h	156–157	157–158
19	$CH_3(CH_2)_2$	2j	O	70	2 h	153–155	152–154
20	Furyl	2k	O	75	45	202–203	204.5–205
21	C_6H_5	2l	S	87	30	200–205	205–206
22	$4\text{-}MeOC_6H_4$	2m	S	83	45	150	152–154
23	$3\text{-}NO_2C_6H_4$	2n	S	80	80	204–206	206–207
24	$4\text{-}NO_2C_6H_4$	2o	S	85	2	108–110	109–111
25	$4\text{-}ClC_6H_4$	2p	S	81	75	191–192	192–193
26	$3,4,5\text{-}(OMe)_3\ C_6H_4$	2q	S	80	1.5	203–205	202–204

[a]All products were characterized by FT-IR, ^{1}HNMR, CHN analyzer, and also their melting points with that of previous literature.
[b]Isolated yield.
[c]Melting points are uncorrected.



Scheme 2. Synthesis of 5-substituted 3, 4-dihydropyrimidinone 2.

3.2. General method for the synthesis of Biginelli (or like) product under solvent-free grinding technique

A mixture of acetophenone (1 mmol), aldehyde (1 mmol), urea (1.5 mmol), and hydrated ferric nitrate (or clayfen) (0.1 mmol) was gently ground by hand using mortar and pestle of appropriate size. The progress of the reaction was monitored by TLC which indicates the formation of single product. The mixture becomes a sticky paste during the course of reaction which finally solidifies on completion of reaction. Finally, it was washed with a cold saturated solution of $NaHCO_3$ (5 ml) and then filtered through a sintered funnel to afford the crude product which was further purified by recrystallization (ethanol). With clayfen catalyst, the reaction mixture was dissolved in hot ethanol and filtered. The insoluble clayfen residue washed several times with hot ethanol and dried in a vacuum desicator for reuse.

3.3. Spectral data of selected compounds

3.3.1. 4-(4-Chlorophenyl) 3,4-dihydro-6-phenylpyrimidin-2(1H)-one 1b

Melting point 266°C; ^{1}HNMR (400 MHz, DMSO-d_6); δ 8.67 (s, 1H, NH), 8.10 (s, 1H, NH), 7.52–7.30 m, (m, 9H, Ar–H), 5.46(d, $J = 2.8$ Hz, 1H, CH), 5.16 (d, 1H, $J = 2.8$ Hz, CH); IR (KBr) cm^{-1} 3230, 2934, 1682, 1575, and 1467; CHN Anal. Cal. $C_{16}H_{13}ClN_2O$; C 67.48, H 4. 56, N 9.84; Found C 66.75, H 4.55, N 10.00.

3.3.2. 3,4-Dihydro-4-(4-methoxyphenyl)-6-phenylpyrimidin-2(1H)-one 1c

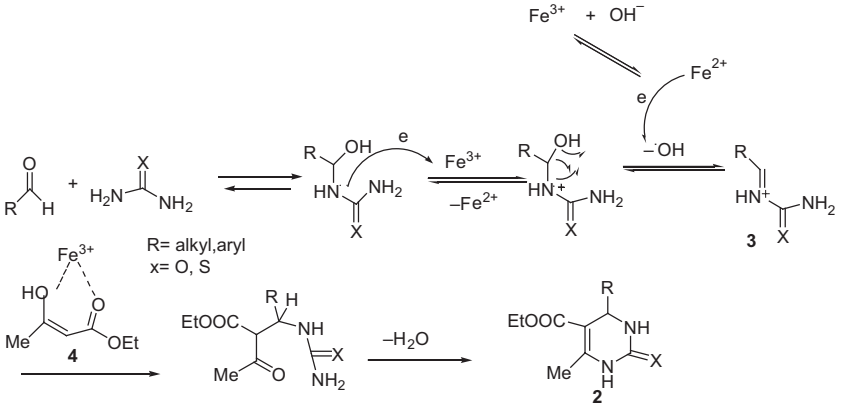
Melting point 258°C; ^{1}HNMR (400 MHz, DMSO-d_6); δ 12.00 (s, 1H, NH), 9.30 (s, 1H, NH), 8.35–7.28 (m, 9H, Ar–H), 6.94 (d, $J = 8.7$ Hz, 1H, CH), 5.42 (d, 1H, $J = 8.7$ Hz, CH), 3.76 (s, 3H, OCH_3); IR (KBr) cm^{-1} 3384, 2935, 1615, 1520, 1410; CHN Anal. Cal. $C_{17}H_{16}N_2O_2$; C 72.85, H 5.71, N 10.00; Found C 72.60, H 5.73, N 10.10.

3.3.3. 3,4-Dihydro-4-(4-hydroxyphenyl)-6-phenylpyrimidin-2(1H)-one 1f

Melting point 256°C; ^{1}HNMR (400 MHz, DMSO-d_6); δ 9.22 (s, 1H, NH), 8.16–7.54 (m, 9H, Ar–H), 7.36–7.32 (s, 1H, NH), 7.25 (d, $J = 8.8$ Hz, 1H, CH), 5.52 (s, 1H, OH) 5.12 (d, 1H, $J = 8.8$ Hz, CH); IR (KBr) cm^{-1} 3387, 2920, 1628, 1517, and 1448; CHN Anal. Cal. $C_{16}H_{14}N_2O_2$; C 72.17, H 5.26, N 10.50; Found C 72.30, H 5.33, N 10.40.

3.3.4. 3, 4-Dihydro 4-(3, 4-dimethoxyphenyl)-6-phenylpyrimidin-2(1H)-one 1i

Melting point 244°C; ^{1}HNMR (400 MHz, DMSO-d_6); δ 11.92 (s, 1H, NH), 8.55 (s, 1H, NH), 8.52–7.50 (m, 8H, Ar–H), 7.45 (d, $J = 8.3$ Hz, 1H, CH), 7.08 (d, 1H, $J = 8.3$Hz, CH), 3.90 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3); IR (KBr) cm^{-1} 3277, 2930, 1617, 1515, and 1462; CHN Anal. Cal. $C_{18}H_{18}N_2O_3$;



Scheme 3. Possible reaction mechanism

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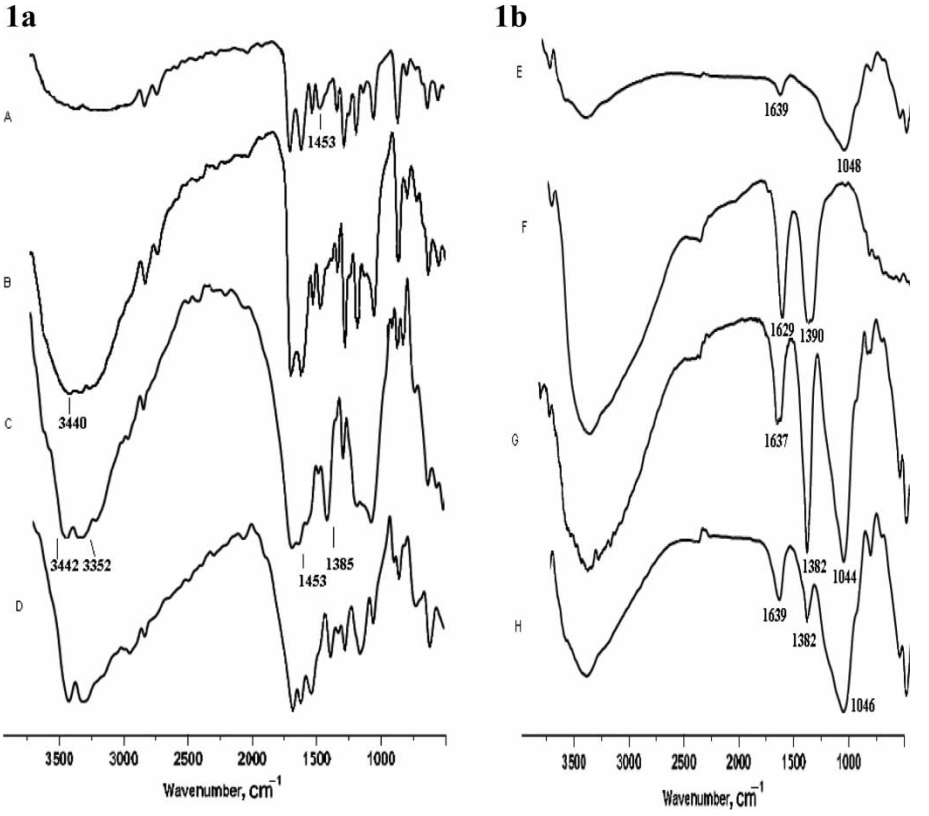

Figure 1. (a) IR spectra of reaction mixture (acetophenone, anisaldehyde, and urea) at various time intervals, 60 mins (A), 120 mins (B), 3 hr (C), and pure product (D) where region 3000–3500 cm^{-1} represents splitting of ν_{N-H} stretching into two peaks and region 1500–1700 cm^{-1} shows gradual change of $\nu_{C=O}$ stretching frequencies. (b) IR spectra of Monmorillonite K-10 (E), Fe $(NO_3)_3.9H_2O$ (F), clayfen (G), and regenerated clayfen (H).

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C 69.67, H 5.85, N, 9.03; Found C 69.60, H 5.78, N 9.00.

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