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ORIGINAL PAPER

An efficient and environmentally friendly procedure for synthesis of pyrimidinone derivatives by use of a Biginelli-type reaction

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Abstract A Biginelli-type three-component reaction involving cyclopentanone, aromatic aldehyde, and urea or thiourea for preparation of pyrimidinone derivatives under neat conditions is described. This condensation reaction can also take place smoothly in the presence of vitamin B_1 in EtOH at 80 °C in good yield. The procedure is simple, high-yielding, time-saving, and environment friendly.

Keywords Multicomponent reactions · Aldehyde · Organocatalyst · Green chemistry

Introduction

Multicomponent reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yield of products, have attracted much attention [1–4]. The century-old Biginelli reaction as a classical multicomponent reaction has gained much importance in organic synthesis, partly because of the diverse types of physiological activity associated with the dihydropyrimidinones produced by this reaction [5–7].

The classical Biginelli reaction is a simple one-pot cyclocondensation of β-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of various catalysts [8–15]. Pan et al. [16] reported an efficient alternative for synthesis of fused pyrimidinones by a three-component condensation with aromatic aldehyde, cyclopentanone, and urea or thiourea. However, the use of stoichiometric amounts of TMSCl as additional reagent and mixed DMF/CH_3CN as reaction solvent seemed to be necessary to obtain satisfactory results. Furthermore, TMSCl is toxic, corrosive, and environmental unfriendly. More recently, Zhang described the three-component condensation of aromatic aldehyde, cyclopentanone, and urea or thiourea in the presence of $YbCl_3$ [17]. For conservation of the environment combined with economic aspects, the application of metal ion-free, environmentally safe, and convenient reagents in synthetic and medicinal chemistry is in demand [18–20].

Thus, the development of a simple, efficient, and environmentally friendly method for the Biginelli-type reaction is needed. Herein, we wish to report a novel and efficient procedure for synthesis of pyrimidinone derivatives via the three-component condensation of aromatic aldehyde, cyclopentanone, and urea or thiourea under neat conditions (Scheme 1) or in the presence of vitamin B_1 as an organocatalyst in EtOH (Scheme 2).

Results and discussion

Initially, we studied the Biginelli-type reaction of benzaldehyde (**1a**, 5 mmol), cyclopentanone (**2**, 5 mmol), and urea (**3a**, 6 mmol) under solvent-free conditions at 140 °C. To our delight, reaction was complete in 10 min, giving the desired product **4a** in 92% yield. Encouraged by the result, a series of aldehydes were selected to undergo the condensation under solvent-free conditions at 140 °C (Table 1).

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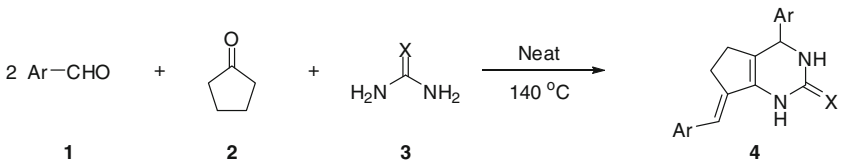
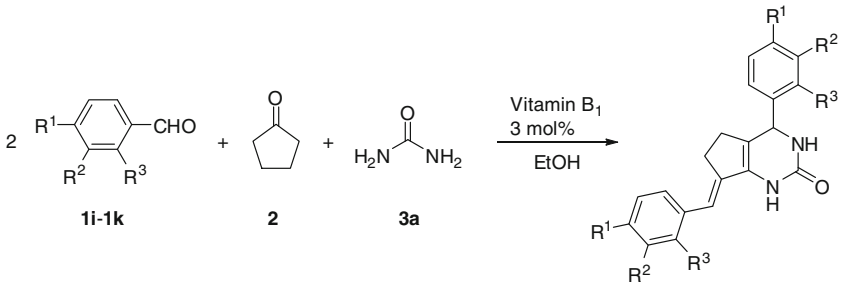
Scheme 1



Scheme 2



i: R^1 = OH, R^2 = CH_3O, R^3 = H
j: R^1 = Cl, R^2 = H, R^3 = Cl
k: R^1 = OBz, R^2 = R^3 = H

Table 1 Synthesis of Biginelli-type product **4**

Entry	Ar	X	Time (min)	Product	Yield (%)[a]	Ref.
1	C_6H_5 (**1a**)	O	10	**4a**	92	[16]
2	4-MeC_6H_4 (**1b**)	O	15	**4b**	95	[16]
3	4-$MeOC_6H_4$ (**1c**)	O	25	**4c**	85	[16]
4	3-$NO_2C_6H_4$ (**1d**)	O	15	**4d**	86	[16]
5	4-$NO_2C_6H_4$ (**1e**)	O	15	**4e**	86	[17]
6	4-ClC_6H_4 (**1f**)	O	10	**4f**	90	[16]
7	4-FC_6H_4 (**1g**)	O	15	**4g**	90	[16]
8	4-CNC_6H_4 (**1h**)	O	15	**4h**	88	[17]
9	3-MeO-4-OHC_6H_3 (**1i**)	O	20	**4i**	–[b]	
10	2,4-$Cl_2C_6H_3$ (**1j**)	O	20	**4j**	20	
11	4-$BzOC_6H_4$ (**1k**)	O	20	**4k**	25	
12	C_6H_5 (**1a**)	S	60	**4l**	82	[16]
13	4-MeC_6H_4 (**1b**)	S	60	**4m**	84	[17]
14	4-$MeOC_6H_4$ (**1c**)	S	60	**4n**	80	[16]
15	4-$NO_2C_6H_4$ (**1d**)	S	60	**4o**	82	[16]
16	4-ClC_6H_4 (**1f**)	S	60	**4p**	86	[16]

Conditions: aromatic aldehyde (**1**, 5 mmol), cyclopentanone (**2**, 5 mmol), and urea (**3a**) or thiourea (**3b**) (6 mmol), 140 °C

[a] Isolated yield

[b] Several side reactions were observed and the desired product could not be isolated

As shown in Table 1, aromatic aldehydes bearing functional groups (for example –H, $–CH_3$, $–OCH_3$, –Cl, –F, $–NO_2$, and –CN) react smoothly to give the corresponding products in good yields (80–95%). We also found that this condensation reaction was complete within 60 min, much quicker than reported methods (3–10 h) [16, 17].

However, several side reactions were observed when aromatic aldehydes bearing the –OH were used as a starting material and the desired product could not be isolated (Table 1, entry 9). In addition, very low yields of the target products were obtained when using **1j** and **1k** as substrates because the reaction mixture could not be efficiently stirred (Table 1, entries 10 and 11). Hence, we turned our attention towards the synthesis of pyrimidinone derivatives **4i–4k** by condensation of cyclopentanone (**2**), urea (**3a**), and aromatic aldehydes **1i–1k**.

As shown in Table 2, the mixture of 4-hydroxy-3-methoxybenzaldehyde (**1i**), cyclopentanone (**2**), and urea (**3a**) was chosen as the model reaction under different reaction conditions. First, we changed the reaction temperature from 20 to 140 °C (Table 2, entries 1–4), because, unfortunately, no desired product **4i** was observed when the mixture was stirred at 20 °C for 10 h (Table 2, entry 1). In addition, several side reactions were observed, as indicated by TLC, when the three-component condensation reaction took place at 80–140 °C under solvent-free conditions (Table 2, entries 2–5). We also carried out the condensation reaction at 80 °C in various solvents (Table 2, entries 5–10), for example MeOH, EtOH, THF, DMF, CH_3CN, and DMSO. Unfortunately, only trace amounts of the target product were observed when the mixture was stirred at 80 °C in these solvents.

In our previous study, we found that several multi-component reactions proceeded smoothly in the presence of vitamin B_1 as catalyst [21]. Therefore, we carried out the reaction in EtOH at 80 °C, taking a 1:1:1.2 mol ratio of 4-hydroxy-3-methoxybenzaldehyde (**1i**), cyclopentanone (**2**), and urea (**3a**) in the presence of 3 mol% vitamin B_1 for 3 h. To our delight, the desired product **4i** was obtained in 86% yield (Scheme 2). We changed the amount of vitamin B_1 from 1 to 10 mol%, and found use of 3 mol% was optimum to ensure

Table 2 Synthesis of Biginelli-type product **4i** under various conditions

Entry	Solvent	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield (%)[a]
1	None	0	20	10	NR[b]
2	None	0	80	1	–[c]
3	None	0	120	0.3	–[c]
4	None	0	140	0.3	–[c]
5	MeOH	0	80	3	Trace
6	EtOH	0	80	3	Trace
7	THF	0	80	3	Trace
8	DMF	0	80	3	Trace
9	CH_3CN	0	80	3	Trace
10	DMSO	0	80	3	Trace
11	EtOH	Vitamin B_1 (1)	80	3	45
12	EtOH	Vitamin B_1 (3)	80	3	86
13	EtOH	Vitamin B_1 (5)	80	3	86
14	EtOH	Vitamin B_1 (10)	80	3	85

Conditions: 4-hydroxy-3-methoxybenzaldehyde (**1i**, 5 mmol), cyclopentanone (**2**, 5 mmol), and urea (**3a**, 6 mmol), solvent-free or solvent 3 cm^3

[a] Isolated yield

[b] No reactions were observed

[c] Several side reactions were observed and the desired product could not be isolated

high reaction efficiency (Table 2, entries 11–14). Then, we carried out the three-component condensation reaction using aromatic aldehydes **1i–1k** in the presence of 3 mol% vitamin B_1 in EtOH for 3 h and obtained the desired products **4i–4k** in 86, 83, and 90% yield, respectively (Scheme 2).

In conclusion, this method is a new and simple modification of the Biginelli-type reaction of aromatic aldehyde, cyclopentanone, and urea or thiourea. The three-component condensation reaction can proceed under solvent-free conditions at 140 °C without any catalysts in excellent yields (80–95%). In addition, the condensation reaction can also take place smoothly in the presence of 3 mol% vitamin B_1 in EtOH at 80 °C in good yields (83–90%). It is important to note that the reaction can proceed smoothly in good yield by employing a catalytic amount of vitamin B_1 as the catalyst when using an aldehyde carrying a hydroxy group as the starting material, which normally gives an extremely poor yield under catalyst-free conditions. This one-pot synthesis of hydropyrimidinone derivatives is therefore simple, high yielding, time saving, and environmentally friendly. It is an useful addition to existing methods.

Experimental

Reagents and all solvents were analytically pure grade and were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer at 400 and 100 MHz, with TMS as an internal standard. Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. Melting points were determined with an X-4 apparatus and are corrected. Mass spectra were measured with a Thermo Finnigan LCQ-Advantage. Elemental analyses (C, H, N, S) were performed on a Fisons EA 1110 CHNS elemental analyzer; results agreed favorably with calculated values.

*General procedure for synthesis of compounds **4a–4h** and **4l–4p***

An aldehyde (**1a–1h**, 5 mmol), cyclopentanone (**2**, 5 mmol), and urea (**3a**) or thiourea (**3b**) (3.6 mmol) were mixed in a round-bottomed flask. The mixture was stirred at 140 °C for the time needed to complete the reaction (monitored by TLC). After cooling to room temperature, the reaction was quenched with 20 cm^3 H_2O and stirred for 10 min. The pure product **4** was isolated by filtration, followed by washing with EtOAc.

*General procedure for the synthesis of compounds **4i–4k***

A mixture of aldehyde (**1i–1k**, 5 mmol), cyclopentanone (**2**, 5 mmol), urea (**3a**, 3.6 mmol), and vitamin B_1 (0.15 mmol) in 3 cm^3 ethanol was heated to 80 °C, with stirring, for 3 h to complete the reaction (monitored by TLC). After cooling to room temperature, the reaction was quenched with 20 cm^3 H_2O and stirred for 10 min. The pure product was isolated by filtration, followed by washing with EtOAc.

1,3,4,5,6,7-Hexahydro-7-(4-hydroxy-3-methoxybenzylidene)-4-(4-hydroxy-3-methoxyphenyl)-2H-cyclopenta[d]pyrimidin-2-one (**4i**, $C_{22}H_{22}N_2O_5$)

Yellow solid, yield 86%; m.p.: 241–244 °C; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 9.03$ (brs, 1H), 8.93 (brs, 1H), 8.60 (brs, 1H), 7.04 (s, 1H), 6.88 (s, 1H), 6.81 (d, $J = 2$ Hz, 1H), 6.75–6.78 (m, 3H), 6.67 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, 1H), 6.52 (brs, 1H), 5.04 (brs, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.77–2.85 (m, 2H), 2.32–2.41 (m, 1H), 2.02–2.11 (m, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 153.7, 148.0, 147.9, 146.4, 145.7, 136.5, 136.3, 134.9, 129.9, 121.6, 119.4, 117.6, 117.2, 116.1, 115.9, 112.3, 111.3, 57.6, 56.1, 55.9, 28.9, 28.7$ ppm; MS (ESI): $m/z = 417$ ($[M + Na]^+$).

7-(2,4-Dichlorobenzylidene)-4-(2,4-dichlorophenyl)-1,3,4,5,6,7-hexahydro-2H-cyclopenta[d]pyrimidin-2-one (**4j**, $C_{20}H_{14}Cl_4N_2O$)

White solid, yield 83%; m.p.: 251-254 °C; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 9.19$ (brs, 1H), 7.33–7.68 (m, 6H), 7.25 (s, 1H), 6.74 (brs, 1H), 5.6 (s, 1H), 2.62–2.83

(m, 2H), 2.37–2.46 (m, 1H), 1.91–2.04 (m, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 153.6, 142.6, 139.8, 136.9, 134.9, 133.7, 133.3, 132.3, 131.7, 131.1, 130.6, 129.3, 129.2, 128.8, 128.4, 127.6, 113.0, 54.5, 28.4, 28.3$ ppm; MS (EI): $m/z = 442, 440, 438$ (M^+).

7-[4-(Benzyloxy)benzylidene]-4-[4-(benzyloxy)phenyl]-1,3,4,5,6,7-hexahydro-2H-cyclopenta[d]pyrimidin-2-one (**4k**, $C_{34}H_{30}N_2O_3$)

Yellow solid, yield 90%; m.p.: 201–204 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.68$ (brs, 1H), 6.95–7.45 (m, 19H), 6.56 (s, 1H), 5.03–5.13 (m, 5H), 2.67–2.78 (m, 2H), 1.95–2.04 (m, 1H), 1.78–1.90 (m, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 165.2, 158.2, 153.7, 143.1, 143.0, 137.6, 137.4, 136.2, 136.1, 131.1, 131.0, 129.6, 128.9, 128.8, 128.3, 128.2, 128.1, 118.1, 116.6, 115.4, 115.3, 69.7, 69.6, 57.3, 28.7, 28.8$ ppm; MS (ESI): $m/z = 537$ ($[M + Na]^+$).

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