Efficient Catalytic Synthesis of 3,4-Dihydropyrimidin-2-ones/thiones *via* Little Acidic Ionic Liquid Combined with Rapid Heating Ways

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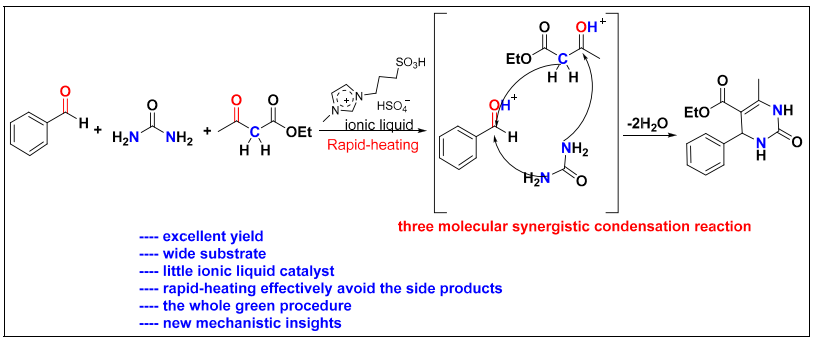
Received April 14, 2018
DOI 10.1002/jhet.3292
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



Catalytic synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones was efficiently promoted by as little as 2.5 mol% of Brønsted acidic ionic liquid $[(CH_2)_3SO_3HMIM]HSO_4$ catalyst loading via rapid heating ways. Interestingly, rapid heating effectively improved yields to avoid side products. Furthermore, the mechanism has been speculated that the reaction proceeds may be via rapidly one-step condensation rather than slowly step-by-step condensation. In addition, the catalyst can be recovered for repeated use (up to seven times), and a whole green reaction process adds to its practical applicability.

J. Heterocyclic Chem., **00,** 00 (2018).

INTRODUCTION

Dihydropyrimidinones (DHPMs) and their derivatives exhibited diverse biological and pharmacological properties such as antiviral, antitumor, anti-human immunodeficiency virus, antibacterial, anti-inflammatory, antihypertensive, calcium channel blockers, α-1-antagonists, and neuropeptide Y antagonists [1]. Besides, some drugs based on DHPM motif were developed in medicinal chemistry [2]. Therefore, the synthesis of DHPMs compounds has received extensive attention. At present, the universal strategy to synthesize DHPMs is the Biginelli reaction, which is a multicomponent condensation reaction of aldehydes with urea (or thiourea) and β-dicarbonyl compounds [3]. Usually, this kind of reaction occurred in organic solvents at a high temperature in the presence of an acid catalyst with low yields (20–50%) [4]. The main reason is that any two materials generate some side products via acid-catalyzed condition [5] such as bisureides, unsaturated carbonyl compounds, and ureide. Therefore, the synthesis of DHPMs with excellent yield to avoid the earlier side products is still a challenge.

In recent years, a number of methods have been developed to effectively accomplish the synthesis of these compounds, such as using various Brønsted acids [6], Lewis acids [7], basic catalysts [8], polymer-supported reagents [9], and nan catalysts [10]. However, many of these reported protocols suffer from various drawbacks such as the use of expensive and highly corrosive catalysts, tedious separation procedures, and prolonged reaction times. When the environmental effects are taken into account, many ionic liquids have been developed to carry out this Biginelli reaction, such as TrBuHTA [11], $BMI{\cdot}NTf_2$ [12], BIL-1 [13], MNPs-IL-HSO_4 [14], $GlyNO_3$ [15], and $[(HOCH_2CH_2)_3N]CH_3COO^-$ [16]. However, these catalytic protocols also suffer from certain drawbacks such as the harsh reaction conditions, high dosage of catalyst, narrow scope of substituents in all three components, and inevitable byproducts. Recently, Brønsted acidic ionic liquids have been developed as a kind of environment-friendly catalysts that is widely used in many organic syntheses [17] because it possesses HSO_4^- with effective catalyst. Taking the environment and economy into account, the development of efficient, whole green catalytic systems for the synthesis of Biginelli compounds is an active ongoing research area that attracted much attention in the recent years [18].

Herein, we report a high efficient and reusable protocol for synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones via Brønsted acidic ionic liquid $[(CH_2)_3SO_3HMIM]HSO_4$ in rapid heating ways (Fig. 1). Notably, rapid heating was found to effectively avoid side products in this reaction.

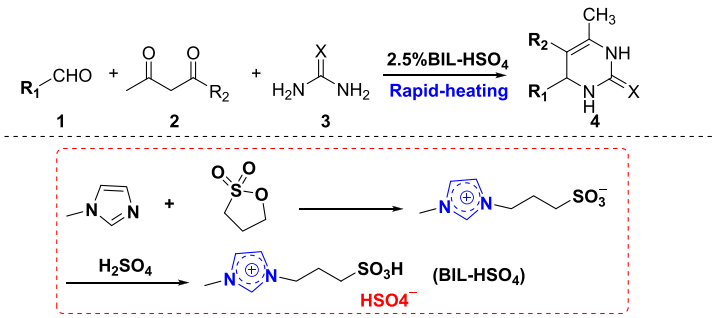


Figure 1. Rapid heating green synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones via little acidic ionic liquids (BIL-HSO_4). [Color figure can be viewed at wileyonlinelibrary.com]

Furthermore, the mechanism has been speculated that the reaction proceeds may be via rapidly one-step condensation rather than slowly step-by-step condensation. Our findings of three molecule one-step condensation pathway provide additional insights in Biginelli reactions.

RESULTS AND DISCUSSION

Synthesis. The Biginelli reaction of benzaldehyde (**1a**) with ethyl acetoacetate (**2a**) and urea (**3a**) was chosen as a model reaction to optimize reaction conditions, and the results are summarized in Table 1. It was observed that the reaction failed to give any product without the catalyst (Table 1, entry 1). In initial studies, different catalysts were screened in ethanol as the solvent (1 mL) at 80°C (Table 1, entries 2–7). It was found that the rapid heating ways could effectively improve the yield (Table 1, entries 5–7) than slow heating ways with the same catalyst (Table 1, entries 2–4). Among them, the catalyst (BIL-HSO_4) afforded promising results in short reaction time (Table 1, entry 5). Almost no change in reactivity was observed when the loading of BIL-HSO_4 was reduced from 10 to 2.5 mol% at directly 80°C (Table 1, entries 5, 8, and 9); however, the product decreased from 98 to 81% when a catalyst load was reduced from 2.5 to 1 mol% (Table 1, entries 9 and 10). Furthermore, obvious decrease of the yield was observed when the amount of BIL-HSO_4 was reduced from 1 to 0.1 mol% (Table 1, entries 10 and 11). As a consequence, the optimal results for the Biginelli condensation reaction were observed at a molar ratio of benzaldehyde, urea, and ethyl acetoacetate of 1:1.1:1 at directly 80°C for 3 h in the presence of 2.5 mol% ionic liquid ($[(CH_2)_3SO_3HMIM]HSO_4$).

To further understand the catalytic system, the catalytic activity of ionic liquid ($[(CH_2)_3SO_3HMIM]HSO_4$) was compared with those of ionic liquids reported previously [11–16], and the results are listed in Table 2. Ionic liquid (BIL-HSO_4) is an effective catalyst for the synthesis of DHPMs with excellent yields in a relatively short time

Table 1

Optimizations of reaction conditions for the synthesis of **4a** catalyzed by ionic liquid (BIL).

Entry[a]	Catalyst (mol%)	Temperature (°C)	Time (h)	Yield (%)[d]
1[b]	—	80	24	0
2[b]	BIL-Cl (10)	80	6	41
3[b]	BIL-HSO_4 (10)	80	6	69
4[b]	$KHSO_4$ (10)	80	6	55
5[c]	BIL-HSO_4 (10)	80	3	99
6[c]	BIL-Cl (10)	80	3	92
7[c]	$KHSO_4$ (10)	80	3	95
8[c]	BIL-HSO_4 (5)	80	3	99
9[c]	BIL-HSO_4 (2.5)	80	3	98
10[c]	BIL-HSO_4 (1.0)	80	6	81
11[c]	BIL-HSO_4 (0.1)	80	6	56

[a]Reaction Conditions: Benzaldehyde (2.0 mmol), ethyl acetoacetate (2.0 mmol), and urea (2.0 mmol), ethanol (1 mL).
[b]Reaction Temperature: at directly 80°C that is using rapidly heating ways.
[c]Heating from room temperature to 80°C that is using slowly heating ways.
[d]Isolated yields.

(Table 2, entry 1). Although the reactivity of other ionic liquids is also high, their reaction systems need high catalyst loading, tedious separation procedures, and inevitable side products. Therefore, these disadvantages increased the difficulty for its practical applicability. Compared with the earlier results, the ionic liquid (BIL-HSO_4) was an effective catalyst for the Biginelli reaction.

The reusability of the catalyst (BIL-HSO_4) was investigated, and the results are described in Figure 2. The reaction mixture was concentrated under reduced pressure to remove the ethanol. Twenty milliliters of water was added to the mixture. Then the catalyst was recovered by using simple filtration technique. The filtrate containing ionic liquid was dried over vacuum to remove excess water. This catalyst was directly subjected to Biginelli reaction using the model reaction with our optimized reaction conditions. It is important to note that the recycled catalysts produced excellent yields of DHPM

Table 2

Various ionic liquids catalyzed synthesis of **4a** in the appropriate reaction condition.

Entry	IL[a]	Condition	Time (h)	Yield (%)[b]	Reference
1	BIL-HSO_4	Stirring	3	98	This work
2	TrBuHTA	Stirring	0.3	95	[11]
3	BIL-1	Stirring	1.0	80	[13]
4	MNPs-IL-HSO_4	Stirring	0.5	95	[15]
5	BMI·NTf_2	Stirring	4.0	95	[12]
6	$GlyNO_3$	MW	0.17	92	[16]
7	IL	MW	0.07	90	[14]

[a]The specific information on catalyst was shown in the corresponding papers.
[b]Isolated yields.

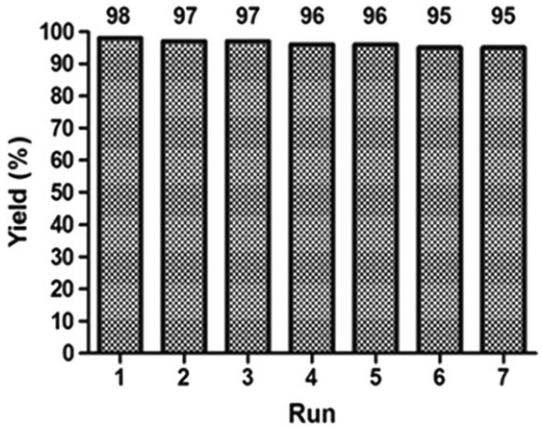


Figure 2. Reusability of ionic liquid (BIL-HSO_4) for the synthesis of compound **4a**.

(**4a**) in 95–98%, respectively (Fig. 2). It was observed that the yields were consistent without significant loss in its catalytic activity.

With these optimized conditions in hand, we extended the dihydropyrimidin-2(1*H*)-ones/thiones; the results are summarized in Table 3. To our delight, all substituted aromatic scopes of this methodology in using various aldehydes via ionic liquid ([$(CH_2)_3SO_3$HMIM]HSO_4) and rapid heating way could be converted to corresponding DHPMs and their derivatives in excellent yields of 94–98% with 1,3-dicarbonyl compounds and urea. Hetero-aromatic substituent also had been proved to be good substrates (products **4l**, **4m**, and **4w**) in excellent yields of 94–96%. Moreover, aliphatic aldehyde had been proved to be bad substrates (products **4p** and **4q**) in low yields of 32–36%. Interestingly, conjugate aliphatic aldehydes also were proved to be good substrates (products **4n** and **4o**) in high yields of 76–93%. In addition, thiourea was also successfully used to produce the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones (Table 3, entries 23–30). Under the same conditions, the yields of the products with thiourea (products **4A**–**4H**) were slightly lower than those with urea.

Because of the excellent reactivity in the presence of 2.5% BIL-HSO_4 ionic liquid under rapid heating reaction condition, it is worth exploring its catalytic mechanism for the synthesis of DHPMs. Based on the former literature studies [19], the strongly debated mechanism for the Biginelli condensation reaction mainly includes three types: the Knoevenagel mechanism, enamine mechanism, and iminium mechanism (Fig. 3). In 1973, Sweet and coworkers [5a] proposed the Knoevenagel mechanism based on their findings. However, the condensation of benzaldehyde (**1a**) and ethyl acetoacetate in our experiment generated unsaturated carbonyl compounds (**5**). Subsequently, the pure compound (**5**) was not reacted with urea at the same condition (Fig. 3b). The results indicated that the Knoevenagel mechanism was not the reaction pathway. In 1933, Folkers et al. [5b] presented the enamine mechanism. However, ethyl acetoacetate in our experiment reacted with urea to afford the ureide. The ureide was isolated and also not reacted with benzaldehyde at the same condition (Fig. 3c). The results also indicated that the enamine mechanism was not the reaction pathway. In 1997, the iminium mechanism of the Biginelli condensation reaction (Fig. 3a) was reported by Kappe [5c] based on NMR experiment. Lately, De Souza and coworkers [20] also investigated the iminium mechanism of the Biginelli reaction via NMR, electrospray ionization–tandem mass spectrometry, and density functional theory calculations.

According to the favored iminium mechanism of the Biginelli condensation reaction, the condensation of a benzaldehyde (**1a**) and urea in our experiment should not generate the imine but mainly obtain the bisureides in the presence of 2.5% BIL (Fig. 4). Subsequently, the pure bisureides were isolated and reacted with ethyl acetoacetate at the same condition. And the corresponding 3,4-dihydropyrimidin-2(1*H*)-ones (**4a**) was not obtained (Fig. 4). Interestingly, the one-pot condensation of benzaldehyde (**1a**), urea, and ethyl acetoacetate can obtain the product (**4a**) in 67% yield at slow heating 80°C

Table 3

Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones in rapid heating ways.

Entry	Compound	R_1	R_2	X	Yield (%)
1	**4a**	C_6H_5	OEt	O	98
2	**4b**	4-$CH_3C_6H_4$	OEt	O	97
3	**4c**	4-$CH_3OC_6H_4$	OEt	O	98
4	**4d**	4-ClC_6H_4	OEt	O	99
5	**4e**	4-BrC_6H_4	OEt	O	97
6	**4f**	4-OHC_6H_4	OEt	O	98
7	**4g**	4-$NO_2C_6H_4$	OEt	O	96
8	**4h**	2-FC_6H_4	OEt	O	97
9	**4i**	2-$CH_3C_6H_4$	OEt	O	96
10	**4j**	3-$NO_2C_6H_4$	OEt	O	96
11	**4k**	3-BrC_6H_4	OEt	O	97
12	**4l**	2-Thienyl	OEt	O	96
13	**4m**	2-Furan	OEt	O	94
14	**4n**	Cinnamyl	OEt	O	93
15	**4o**	$CH_3CH_2CH{=}C(CH_3)$	OEt	O	76
16	**4p**	$(CH_3)_2CH$	OEt	O	32
17	**4q**	$CH_3CH_2CH_2$	OEt	O	36
18	**4r**	C_6H_4	CH_3	O	98
19	**4s**	4-$CH_3OC_6H_4$	CH_3	O	98
20	**4t**	4-ClC_6H_4	CH_3	O	97
21	**4u**	4-$NO_2C_6H_4$	CH_3	O	96
22	**4v**	2-Thienyl	CH_3	O	95
23	**4A**	C_6H_4	OEt	S	91
24	**4B**	4-$CH_3OC_6H_4$	OEt	S	89
25	**4C**	4-BrC_6H_4	OEt	S	93
26	**4D**	4-ClC_6H_4	OEt	S	92
27	**4E**	C_6H_4	CH_3	S	90
28	**4F**	4-$CH_3OC_6H_4$	CH_3	S	91
29	**4G**	4-BrC_6H_4	CH_3	S	94
30	**4H**	4-ClC_6H_4	CH_3	S	91

[a]Rapid heating ways.
[b]Isolated yields.

(Fig. 5b). The results indicated that one-step reaction can effectively increase the yield than step-by-step reaction. Meanwhile, the product (**4a**) was obtained in excellent yield (98%) in the rapid heating one-pot way (Fig. 5a). The results indicated that rapid heating can effectively accelerate the process of increasing the yield. Based on the earlier experiment results, a plausible reaction mechanism for the synthesis of DHPMs catalyzed by Brønsted acidic ionic liquid $[(CH_2)_3SO_3HMIM]HSO_4$ is proposed in Figure 5. 3,4-Dihydropyrimidin-2(1*H*)-ones/thiones and their derivatives might be formed via one-step condensation of an aldehyde, urea, and 1,3-dicarbonyl compounds in the presence of BIL-HSO_4. The rapid heating one-pot condensation of benzaldehyde (**1a**), urea, and ethyl acetoacetate can efficiently improve the yield to avoid the side products. Therefore, the reaction proceeds via rapidly three molecular one-step condensation rather than slowly step-by-step condensation.

In summary, we have successfully developed an efficient green procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones/thiones and their derivatives in the presence of 2.5 mol% Brønsted acidic ionic liquid $[(CH_2)_3SO_3HMIM]HSO_4$ catalyst by rapid heating way. This method not only provided excellent yields of DHPMs but also simplified post-processing for separation of the product and the catalyst with water. The catalyst can be recovered for repeated use (up to seven times). Meanwhile, the reaction can effectively improve yields to avoid by-products by rapid heating way. Mechanistic studies suggest that the reaction proceeds via rapidly three molecular one-step condensation rather than slowly step-by-step condensation. In addition, a whole green reaction process increases the possibility of its application and applicability, which is more environmental-friendly than those with metal-based catalysts. The results indicated that one-step reaction can effectively increase the yield than step-by-step reaction. Meanwhile, the product (**4a**) was obtained in excellent yield (98%) in the rapid heating one-pot way (Fig. 5a). The results indicated that rapid heating can effectively accelerate the process of increasing the yield. Based on the earlier experiment results, a plausible reaction mechanism for the synthesis of DHPMs catalyzed by Brønsted acidic ionic liquid

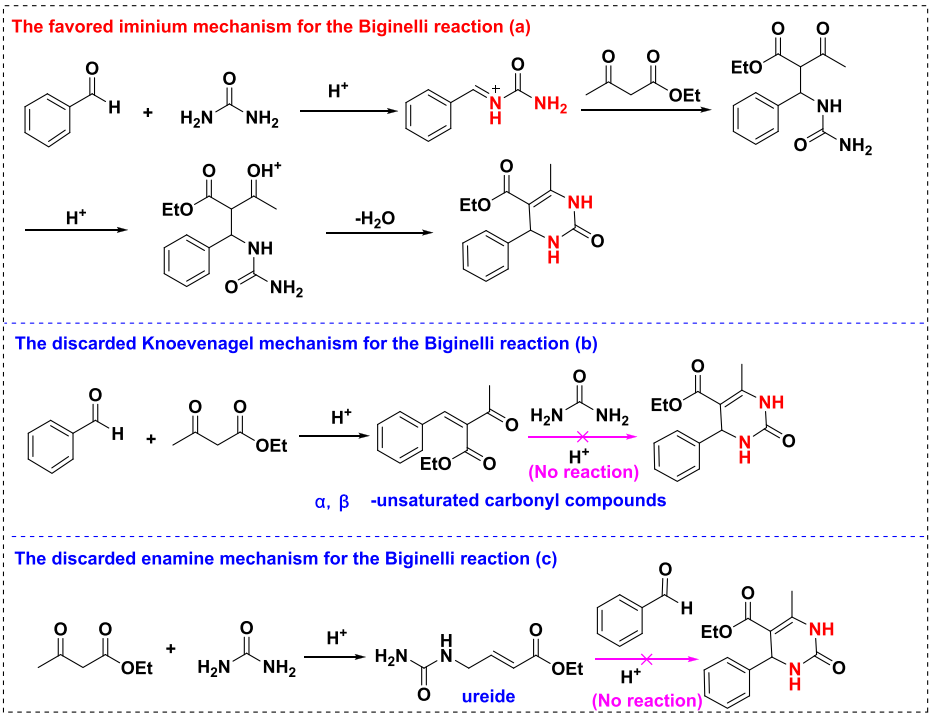


Figure 3. The mainly three types of mechanism for the Biginelli reaction. [Color figure can be viewed at wileyonlinelibrary.com]

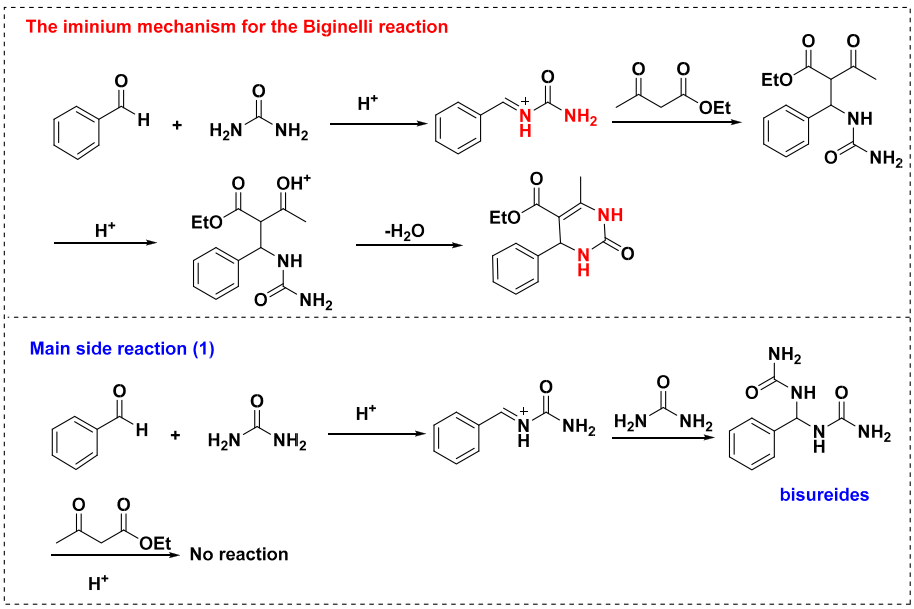


Figure 4. The favored iminium mechanism for the Biginelli reaction. [Color figure can be viewed at wileyonlinelibrary.com]

$[(CH_2)_3SO_3HMIM]HSO_4$ is proposed in Figure 5. 3,4-Dihydropyrimidin-2(1*H*)-ones/thiones and their derivatives might be formed via one-step condensation of an aldehyde, urea, and 1,3-dicarbonyl compounds in the presence of BIL-HSO_4. The rapid heating one-pot condensation of benzaldehyde (**1a**), urea, and ethyl acetoacetate can effectively improve the yield to avoid the side products. Therefore, the reaction proceeds via rapidly three molecular one-step condensation rather than slowly step-by-step condensation.

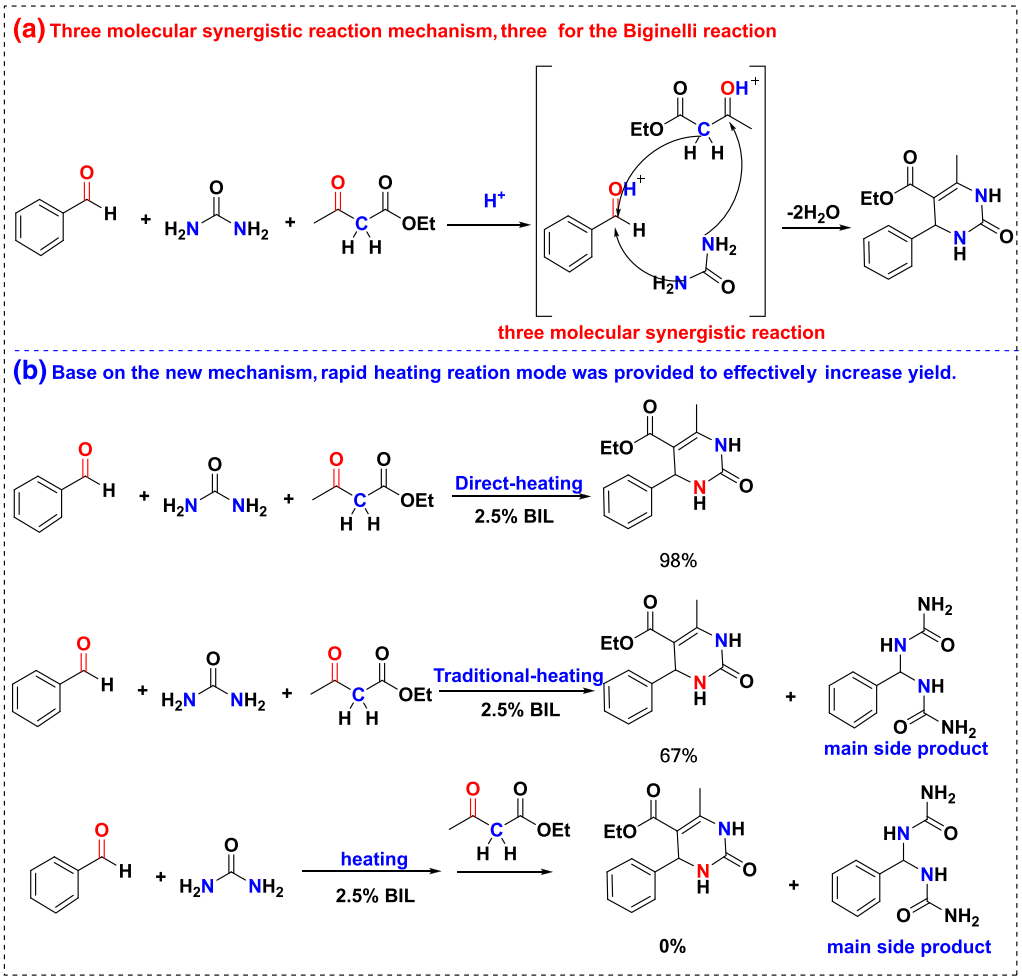


Figure 5. The proposed condensation mechanism for the Biginelli reaction. [Color figure can be viewed at wileyonlinelibrary.com]

EXPERIMENTAL

Materials and methods. In the reported literature, the information on the characterization of the products was almost retrieved. In this work, the identification of the products using ^{1}H-NMR and ^{13}C-NMR was conducted and was compared with the reported literature. Proton and carbon NMR spectra were recorded on a JEOL-ECX 500 (Tokyo, Japan). Proton chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (0.0 ppm) with the solvent resonance employed as the internal standard ($(CD_3)_2SO$, 2.49 ppm). Data are reported as follows: chemical shift multiplicity (s = singlet, d = doublet, q = quartet, and m = multiplet), coupling constant (Hz), and integration. ^{13}C chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($(CD_3)_2SO$, 40.0 ppm). All reagents were purchased from commercial suppliers and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use.

General synthetic procedure. ***Preparation of acidic ionic liquid [18].*** *N*-methylimidazole (100 mmol) and 1,3-propanesultone (100 mmol) were added to solvent-free 100-mL flask. The mixture was heated at 40°C for 24 h. The white zwitterions were washed three times with toluene to remove unreacted material and dried in a vacuum. Then, a stoichiometric amount of concentrated sulfuric acid was added dropwise to the zwitterions, and the mixture was stirred at 40°C for 2–3 days until liquefied, resulting in the formation of the ionic liquids. The ionic liquids were washed repeatedly with toluene and ether to remove unreacted material and dried under vacuum. The purity of the ionic liquids was more than 95% as characterized by NMR spectroscopy.

Data for acidic ionic liquid (BIL-HSO$_4$). ^{1}H-NMR (500 MHz, CD_3OD) δ 8.92 (s, 1H), 7.65 (s, 1H), 7.65 (d, *J* = 1.6 Hz, 1H), 7.56 (d, *J* = 1.5 Hz, 1H), 4.41 (t, *J* = 7.1 Hz, 2H), 3.93 (s, 3H), 2.82 (t, *J* = 7.1 Hz,

2H), 2.36–2.24 (m, 2H); ^{13}C-NMR (126 MHz, CD_3OD) δ 136.90 (s), 123.77 (s), 122.39 (s), 47.87 (s), 47.19 (s), 35.32 (s), 25.77 (s).

Procedure for synthesis of 3,4-dihydropyrimidin-2-ones/thiones (4a–4H). ***Rapid heating synthesis of 3,4-dihydropyrimidin-2-ones/thiones in one pot via little acidic ionic liquids (BIL-HSO$_4$).*** Aldehyde (1.0 mmol), β-ketoester (1.0 mmol), urea or thiourea (1.0 mmol), and 2.5 mol% Brønsted acidic ionic liquid were added to 1.0 mL of ethanol. The mixture was stirred directly at 80°C for 3 h. The resulting mixture was concentrated under reduced pressure to give crude product. Twenty milliliters of water was added to the crude product. The solid product was filtered and washed with *n*-hexane (5 mL × 2), which afforded pure 3,4-dihydropyrimidin-2(1*H*)-ones/thiones (4a–4H) in pure form.

Slow heating synthesis of 3,4-dihydropyrimidin-2-ones/thiones in one pot via little acidic ionic liquids (BIL-HSO$_4$). Aldehyde (1.0 mmol), β-ketoester (1.0 mmol), urea or thiourea (1.0 mmol), and 2.5 mol% Brønsted acidic ionic liquid were added to 1.0 mL of ethanol. The mixture was heated to 80°C for 6 h. The resulting mixture was concentrated under reduced pressure to give crude product. Twenty milliliters of water was added to the crude product. The solid product was filtered and washed with *n*-hexane (5 mL × 2), which afforded crude 3,4-dihydropyrimidin-2(1*H*)-ones/thiones containing main side product of bisureides.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-pyrimidin-2(1H)-one (4a) [21]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.16 (s, 1H), 7.70 (s, 1H), 7.35–7.28 (m, 2H), 7.26–7.19 (m, 3H), 5.14 (d, *J* = 3.3 Hz, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 2.24 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.40 (s), 152.19 (s), 148.39 (s), 144.93 (s), 128.44 (s), 127.31 (s), 126.30 (s), 99.35 (s), 59.23 (s), 54.04 (s), 17.83 (s), 14.13 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (4b) [6e]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.67 (s, 1H), 7.10 (s, 4H), 5.09 (d, *J* = 3.3 Hz, 1H), 3.96 (q, *J* = 7.0 Hz, 2H), 2.25 (s, 3H), 2.22 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.89 (s), 152.70 (s), 148.69 (s), 142.49 (s), 136.90 (s), 129.42 (s), 126.68 (s), 99.93 (s), 59.69 (s), 54.15 (s), 21.18 (s), 18.29 (s), 14.63 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4c) [21]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.11 (s, 1H), 7.63 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.08 (d, *J* = 3.3 Hz, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.71 (s, 3H), 2.23 (s, 3H), 1.09 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.43 (s), 158.50 (s), 152.19 (s), 148.04 (s), 137.12 (s), 127.44 (s), 113.76 (s), 99.64 (s), 59.19 (s), 55.12 (s), 53.39 (s), 17.80 (s), 14.16 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4d) [6e]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.23 (s, 1H), 7.76 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 5.13 (d, *J* = 3.3 Hz, 1H), 3.97 (q, *J* = 6.9 Hz, 2H), 2.24 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.29 (s), 152.02 (s), 148.82 (s), 143.88 (s), 131.87 (s), 128.49 (s), 128.27 (s), 98.90 (s), 59.35 (s), 53.50 (s), 17.89 (s), 14.16 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-bromophenyl)-3,4-dihydropyrimidin-2(1H)-one (4e) [6e]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.23 (s, 1H), 7.75 (d, *J* = 2.1 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 2H), 5.11 (d, *J* = 3.3 Hz, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 2.23 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.28 (s), 152.00 (s), 148.83 (s), 144.28 (s), 131.41 (s), 128.63 (s), 120.39 (s), 98.83 (s), 59.35 (s), 53.56 (s), 17.89 (s), 14.16 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (4f) [21]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.31 (s, 1H), 9.09 (s, 1H), 7.60 (s, 1H), 7.01 (d, *J* = 7.7 Hz, 2H), 6.67 (d, *J* = 7.5 Hz, 2H), 5.02 (d, *J* = 3.0 Hz, 1H), 3.96 (q, *J* = 7.1 Hz, 2H), 2.22 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.51 (s), 156.62 (s), 152.26 (s), 147.86 (s), 135.53 (s), 127.49 (s), 115.07 (s), 99.81 (s), 59.19 (s), 53.51 (s), 39.60 (s), 17.83 (s), 14.20 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4g) [21]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.21 (d, *J* = 8.2 Hz, 2H), 7.88 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 5.27 (d, *J* = 3.3 Hz, 1H), 3.98 (q, *J* = 7.0 Hz, 2H), 2.26 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.14 (s), 152.08 (s), 151.84 (s), 149.48 (s), 146.80 (s), 127.75 (s), 123.92 (s), 98.27 (s), 59.48 (s), 53.77 (s), 17.97 (s), 14.14 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-fluorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4h) [22]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H), 7.66 (s, 1H), 7.32–7.22 (m, 2H), 7.18–7.08 (m, 2H), 5.44 (d, *J* = 2.9 Hz, 1H), 3.91 (q, *J* = 7.1 Hz, 2H), 2.26 (s, 3H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.53 (s), 158.91 (s), 152.07 (s), 149.47 (s), 132.21 (d, *J* = 13.8 Hz), 129.88 (d, *J* = 8.3 Hz), 129.39 (s), 125.02 (s), 115.95 (d, *J* = 147.42 Hz), 98.01 (s), 59.61 (s), 49.18 (s), 18.25 (s), 14.41 (s).

5-Ethoxycarbonyl-6-methyl-4-(2-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one (4i) [23]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.12 (s, 1H), 7.59 (s, 1H), 7.17–7.03 (m, 4H), 5.37 (d, *J* = 2.7 Hz, 1H), 3.93–3.78 (m, 2H), 2.38 (s, 3H), 2.26 (s, 3H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.78 (s), 152.08 (s), 148.96 (s), 143.79 (s), 135.19 (s), 130.62 (s), 127.69 (s), 127.05 (s), 99.70 (s), 59.60 (s), 50.96 (s), 19.18 (s), 18.22 (s), 14.46 (s).

5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (4j) [24]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.36 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 8.05 (s, 1H), 7.89 (s, 1H), 7.65 (dt, *J* = 15.6, 4.5 Hz, 2H), 5.27 (d, *J* = 3.3 Hz, 1H), 4.02–3.88 (m, 2H), 2.24 (s,

3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.59 (s), 152.32 (s), 149.99 (s), 148.26 (s), 147.52 (s), 133.54 (s), 130.79 (s), 122.92 (s), 121.54 (s), 98.83 (s), 59.94 (s), 54.06 (s), 18.40 (s), 14.55 (s).

5-Ethoxycarbonyl-6-methyl-4-(3-bromophenyl)-3,4-dihydropyrimidin-2(1H)-one (4k) [25]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.26 (s, 1H), 7.78 (s, 1H), 7.44 (d, J = 7.0 Hz, 1H), 7.38 (s, 1H), 7.29 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 5.13 (s, 1H), 4.10–3.80 (m, 2H), 2.25 (s, 3H), 1.09 (t, J = 6.2 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.69 (s), 152.44 (s), 149.48 (s), 148.02 (s), 131.34 (s), 130.67 (s), 129.71 (s), 125.80 (s), 122.06 (s), 99.15 (s), 59.84 (s), 54.14 (s), 18.36 (s), 14.58 (s).

5-Ethoxycarbonyl-6-methyl-4-(2-thienyl)-3,4-dihydro-pyrimidin-2(1H)-one (4l) [26]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.28 (s, 1H), 7.87 (s, 1H), 7.32 (dd, J = 5.0, 1.3 Hz, 1H), 6.91 (dd, J = 5.0, 3.5 Hz, 1H), 6.86 (d, J = 3.4 Hz, 1H), 5.38 (d, J = 3.6 Hz, 1H), 4.03 (q, J = 7.1 Hz, 2H), 2.19 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.10 (s), 152.32 (s), 148.87 (s), 148.74 (s), 126.75 (s), 124.71 (s), 123.59 (s), 99.86 (s), 59.44 (s), 49.43 (s), 17.77 (s), 14.24 (s).

5-Ethoxycarbonyl-6-methyl-4-(2-furyl)-3,4-dihydro-pyrimidin-2(1H)-one (4m) [24]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.24 (s, 1H), 7.75 (s, 1H), 7.54 (dd, J = 1.8, 0.9 Hz, 1H), 6.34 (dd, J = 3.2, 1.8 Hz, 1H), 6.08 (d, J = 3.2 Hz, 1H), 5.19 (d, J = 3.5 Hz, 1H), 4.05–3.97 (m, 2H), 2.22 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.08 (s), 156.01 (s), 152.47 (s), 149.40 (s), 142.20 (s), 110.40 (s), 105.33 (s), 96.83 (s), 59.29 (s), 47.80 (s), 39.60 (s), 17.79 (s), 14.22 (s).

5-Ethoxycarbonyl-6-methyl-4-(2-cinnamenyl)-3,4-dihydro-pyrimidin-2(1H)-one (4n) [27]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.13 (s, 1H), 7.53 (s, 1H), 7.37 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 6.32 (d, J = 15.8 Hz, 1H), 6.16 (dd, J = 15.8, 6.1 Hz, 1H), 4.69 (d, J = 9.2 Hz, 1H), 4.15–3.95 (m, 2H), 2.16 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.72 (s), 153.12 (s), 149.11 (s), 136.74 (s), 130.47 (s), 129.22 (s), 128.63 (s), 128.13 (s), 126.88 (s), 98.26 (s), 59.76 (s), 52.42 (s), 18.31 (s), 14.80 (s).

5-Acetyl-6-methyl-4-(2-pent-2-en-2-yl)-3,4-dihydro-pyrimidin-2(1H)-one (4o). ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.92 (s, 1H), 7.28 (s, 1H), 5.17 (t, J = 7.0 Hz, 1H), 4.48 (d, J = 3.1 Hz, 1H), 4.10–3.87 (m, 2H), 2.14 (s, 3H), 1.98–1.83 (m, 2H), 1.46 (s, 3H), 1.12 (t, J = 6.9 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.58 (s), 152.56 (s), 148.18 (s), 135.38 (s), 127.22 (s), 97.50 (s), 59.03 (s), 57.68 (s), 20.49 (s), 17.69 (s), 14.18 (d, J = 15.8 Hz), 11.31 (s).

5-Acetyl-6-methyl-4-isopropyl-3,4-dihydropyrimidin-2(1H)-one (4p) [28]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.86 (s, 1H), 7.26 (s, 1H), 4.11–3.97 (m, 2H), 3.93 (t, J = 3.7 Hz, 1H), 2.16 (s, 3H), 1.70–1.61 (m, 1H), 1.17 (t, J = 7.1 Hz, 3H), 0.80 (d, J = 6.9 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.90 (s), 153.24 (s), 148.61 (s), 98.23 (s), 59.16 (s), 55.61 (s), 34.70 (s), 18.62 (s), 17.84 (s), 16.07 (s), 14.32 (s).

5-Acetyl-6-methyl-4-propyl-3,4-dihydropyrimidin-2(1H)-one (4q) [6e]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 8.90 (s, 1H), 7.29 (s, 1H), 4.10–3.95 (m, 3H), 2.12 (s, 3H), 1.45–1.18 (m, 4H), 1.15 (t, J = 7.1 Hz, 3H), 0.81 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 165.98 (s), 153.33 (s), 148.82 (s), 99.94 (s), 59.58 (s), 50.32 (s), 18.23 (s), 17.54 (s), 14.76 (s), 14.29 (s).

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (4r) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.17 (s, 1H), 7.81 (s, 1H), 7.34–7.28 (m, 2H), 7.24 (d, J = 6.4 Hz, 3H), 5.25 (d, J = 3.5 Hz, 1H), 2.28 (s, 3H), 2.09 (s, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 194.37 (s), 152.23 (s), 148.23 (s), 144.34 (s), 128.62 (s), 127.44 (s), 126.52 (s), 109.68 (s), 53.91 (s), 39.60 (s), 30.42 (s), 19.01 (s).

5-Acetyl-6-methyl-4-(4-methoxylphenyl)-3,4-dihydro-pyrimidin-2(1H)-one (4s) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.14 (s, 1H), 7.75 (s, 1H), 7.15 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.19 (d, J = 3.4 Hz, 1H), 3.71 (s, 3H), 2.27 (s, 3H), 2.06 (s, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 194.46 (s), 158.60 (s), 152.19 (s), 147.88 (s), 136.47 (s), 127.74 (s), 113.95 (s), 109.70 (s), 55.16 (s), 53.42 (s), 30.26 (s), 18.94 (s).

5-Acetyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydro-pyrimidin-2(1H)-one (4t) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.23 (s, 1H), 7.86 (s, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 5.24 (d, J = 3.5 Hz, 1H), 2.27 (s, 3H), 2.11 (s, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 194.18 (s), 152.10 (s), 148.52 (s), 143.27 (s), 131.89 (s), 128.45 (d, J = 19.9 Hz), 109.58 (s), 53.14 (s), 30.48 (s), 19.04 (s).

5-Acetyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydro-pyrimidin-2(1H)-one (4u) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.22 (s, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 5.25 (d, J = 3.5 Hz, 1H), 2.28 (s, 3H), 2.11 (s, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 194.18 (s), 152.13 (s), 148.54 (s), 143.28 (s), 131.91 (s), 128.55 (s), 128.39 (s), 109.59 (s), 53.15 (s), 30.51 (s), 19.06 (s).

5-Acetyl-6-methyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1H)-one (4v) [30]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 9.31 (s, 1H), 7.96 (s, 1H), 7.34 (dd, J = 5.0, 1.4 Hz, 1H), 6.93 (dd, J = 5.0, 3.5 Hz, 1H), 6.90 (d, J = 3.4 Hz, 1H), 5.50 (d, J = 3.6 Hz, 1H), 2.25 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 193.92 (s), 152.35 (s), 148.74 (s), 148.33 (s), 126.83 (s), 124.99 (s), 124.04 (s), 110.59 (s), 49.38 (s), 30.28 (s), 18.97 (s).

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydro-pyrimidin-2(1H)-thione (4A) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.64 (s, 1H), 7.34 (t, J = 7.6 Hz, 2H), 7.27 (d, J = 7.3 Hz, 1H), 7.21 (d, J = 7.3 Hz, 2H), 5.16 (d, J = 3.7 Hz, 1H), 4.00 (q, J = 7.0 Hz, 2H), 2.28 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz,

DMSO-d_6) δ 174.76 (s), 165.66 (s), 145.57 (s), 144.03 (s), 129.10 (s), 128.22 (s), 126.92 (s), 101.24 (s), 60.13 (s), 54.57 (s), 17.70 (s), 14.55 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-methoxylphenyl)-3,4-dihydropyrimidin-2(1H)-thione (4B) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.27 (s, 1H), 9.57 (s, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.10 (d, *J* = 3.6 Hz, 1H), 3.99 (q, *J* = 7.0 Hz, 2H), 3.71 (s, 3H), 2.27 (s, 3H), 1.10 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 174.09 (s), 165.22 (s), 158.80 (s), 144.80 (s), 135.77 (s), 127.67 (s), 113.95 (s), 101.03 (s), 59.61 (s), 55.17 (s), 53.51 (s), 17.20 (s), 14.11 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-bromophenyl)-3,4-dihydropyrimidin-2(1H)-thione (4C) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.64 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 5.12 (d, *J* = 3.7 Hz, 1H), 3.97 (q, *J* = 7.0 Hz, 2H), 2.26 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 174.75 (s), 165.51 (s), 145.94 (s), 143.31 (s), 132.07 (s), 129.20 (s), 121.36 (s), 100.73 (s), 60.21 (s), 54.04 (s), 17.72 (s), 14.55 (s).

5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-thione (4D) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.64 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 5.13 (d, *J* = 3.0 Hz, 1H), 4.00–3.95 (m, 2H), 2.26 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 174.77 (s), 165.52 (s), 145.92 (s), 142.91 (s), 132.79 (s), 129.14 (s), 128.85 (s), 100.82 (s), 60.20 (s), 53.98 (s), 17.72 (s), 14.55 (s).

5-Acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (4E) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.26 (s, 1H), 9.74 (s, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 7.22 (dd, *J* = 8.1, 1.2 Hz, 2H), 5.29 (d, *J* = 3.9 Hz, 1H), 2.32 (s, 3H), 2.15 (s, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 194.84 (s), 174.16 (s), 144.61 (s), 142.98 (s), 128.70 (s), 127.76 (s), 126.62 (s), 110.55 (s), 53.86 (s), 30.49 (s), 18.32 (s).

5-Acetyl-6-methyl-4-(4-methoxylphenyl)-3,4-dihydro-pyrimidin-2(1H)-thione (4F) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.22 (s, 1H), 9.68 (s, 1H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.22 (d, *J* = 3.8 Hz, 1H), 3.71 (s, 3H), 2.31 (s, 3H), 2.11 (s, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 194.95 (s), 173.90 (s), 158.85 (s), 144.29 (s), 135.15 (s), 127.92 (s), 114.06 (s), 110.53 (s), 55.18 (s), 53.40 (s), 39.60 (s), 30.32 (s), 18.24 (s).

5-Acetyl-6-methyl-4-(4-bromophenyl)-3,4-dihydro-pyrimidin-2(1H)-thione (4G) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.77 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 5.26 (d, *J* = 3.9 Hz, 1H), 2.32 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 194.72 (s), 174.30 (s), 144.99 (s), 142.29 (s), 131.61 (s), 128.83 (s), 120.90 (s), 110.37 (s), 53.19 (s), 39.60 (s), 30.59 (s), 18.39 (s).

5-Acetyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydro-pyrimidin-2(1H)-thione (4H) [29]. ^{1}H-NMR (500 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.78 (s, 1H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 5.28 (d, *J* = 3.9 Hz, 1H), 2.32 (s, 3H), 2.17 (s, 3H); ^{13}C-NMR (126 MHz, DMSO-d_6) δ 194.77 (s), 174.30 (s), 145.06 (s), 141.91 (s), 132.36 (s), 128.73 (s), 128.52 (s), 110.43 (s), 53.12 (s), 30.65 (s), 18.43 (s).

Acknowledgments. We gratefully acknowledge the financial supports of this work by the National Key Research and Development Program of China (no. 2017YFD0200506), the National Natural Science Foundation of China (No.21807037), the Provincial Major Project of Education Department in Anhui (no. KJ2018A0386), the Provincial Major Project of Excellent Youth Talent Support Program in Anhui (no. gxyqZD2018092), and the Provincial Undergraduate Training Programs for Innovation (no. 201710373055).

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SUPPORTING INFORMATION

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