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Brønsted Base-Catalyzed One-Pot Three-Component Biginelli-Type Reaction: An Efficient Synthesis of 4,5,6-Triaryl-3,4-dihydropyrimidin-2(1*H*)-one and Mechanistic Study

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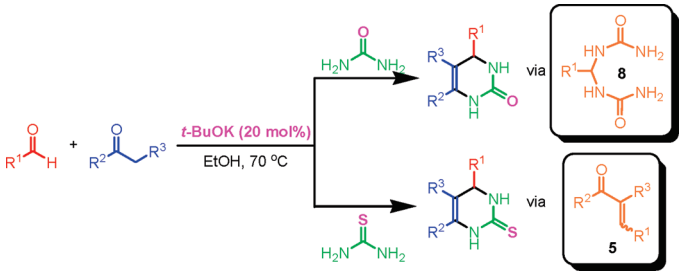

An efficient one-pot synthesis of 4,5,6-triaryl-3,4-dihydropyrimidin-2(1*H*)-ones via a three-component Biginelli-type condensation of aldehyde, 2-phenylacetophenone, and urea/thiourea in the presence of a catalytic amount of *t*-BuOK (20 mol %) is described. The reactions proceeded efficiently at 70 °C to afford the desired products in moderate to good yields. Detailed mechanistic study shows that the Biginelli-type reaction using urea and thiourea proceeds through two totally different pathways. Enone **5** and bis-urea **8** were highly suggested as respective reaction intermediates for reactions involving thiourea and urea as substrates.

Introduction

In recent decades, the utilization of multicomponent condensations[1] (MCCs) to synthesize novel, drug-like scaffold compounds has permeated in organic transformations. This is due to the fact that products can be prepared directly in a single step and diversity can be achieved simply by varying reaction substrates. Among them, the Biginelli reaction[1a,2,3] involving a multicomponent condensation of aldehyde, β-ketoester, and urea ranks as one of the most recognized and widely employed MCCs for the preparation of dihydropyrimidinones. Much effort was directed toward developing highly efficient Biginelli reaction owing to the exhibition of a wide range of biological activities[4] in dihydropyrimidinones such as antiviral, antitumor, antibacterial, and antiflammatory properties as well as calcium channel modulating activity. To date, a wide variety of Lewis acids and protic acids

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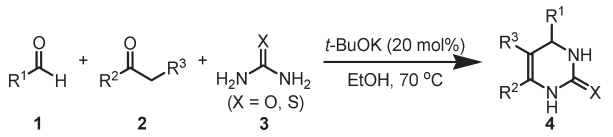
have been well-established to efficiently promote the Biginelli reaction.[5]

Recently, the use of other active methylene compounds in addition to β-ketoester in classic Biginelli reaction has emerged as one of the hot research areas in terms of the preparation of various novel dihydropyrimidinones. Just as the Biginelli reaction operates in the presence of Lewis acid or protic acid,[2,3,5] these MCC reactions for the preparation of novel dihydropyrimidinones using various active methylene compounds, such as 5,5-dimethyl-1,3-cyclohexanedione,[4b] 1,3-cyclohexanedione,[6] 1-tetralone,[6−8] acetophenone,[8] cyclopentanone,[9] aliphatic aldehydes,[10] and β-oxodithioesters,[11] were also developed to be carried out using a Lewis or protic acid such as HCl, TMSCl/NaI, $FeCl_3$, ZnI_2, $YbCl_3$, BF_3, and $SnCl_2$. More recently, a one-pot variant of Biginelli-type reaction using enaminone[12] promoted by TMSCl was also reported.

SCHEME 1. Brønsted Base-Mediated Biginelli-Type Reaction



However, despite extensive studies on the Biginelli-type reactions reported in the literature, to the best of our knowledge, there is no report focusing on the development of one-pot Biginelli-type reaction under basic conditions.[13] We envisioned that, if the Biginelli-type reaction can be developed under basic conditions using Brønsted bases[14] rather than Lewis acids, it will provide an important complement to classic Biginelli reaction and help deepen our understanding of Biginelli reaction. In continuation of our endeavors in developing novel and practical multicomponent reactions to synthesize useful heterocyclic compounds,[14n,15] herein, we describe a novel Brønsted base-promoted one-pot synthesis of 4,5,6-triaryl-3,4-dihydropyrimidin-2(1*H*)-one via a three-component condensation of aldehyde, 2-phenylacetophenone, and urea/thiourea. The reactions proceeded efficiently in the presence of a catalytic amount of Brønsted base (20 mol % of *t*-BuOK) to afford dihydropyrimidinones in moderate to good yields (Scheme 1). In addition, through detailed mechanistic study, enone **5** and bis-urea **8** were highly suggested as reaction intermediates for reactions involving thiourea and urea as substrates, respectively.

Results and Discussion

Initial studies were focused on the one-pot three-component condensation of 4-chlorobenzaldehyde, 2-phenylacetophenone, and thiourea at 70 °C for 12 h using different Lewis/protic acids in ethanol. The results are summarized in Table 1.

As shown in Table 1, our attempt to perform the model reaction using conventional Biginelli reaction conditions in the presence of Lewis acids such as $InCl_3$, $FeCl_3$, ceric ammonium nitrate (CAN), and I_2 did not succeed; no desired product was obtained after reacting at 70 °C for 12 h (Table 1, entries 1−4). In comparison, moderate yields of **4a**

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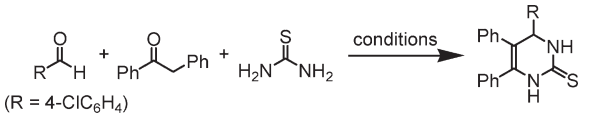
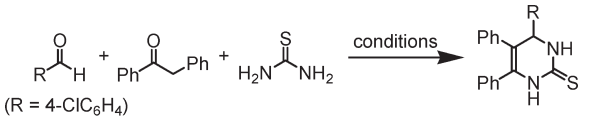
TABLE 1. Optimization of Reaction Conditions Using Different Acids[a]



entry	conditions[b]	yield (%)[c]
1	$InCl_3$ (1 equiv), EtOH, 70 °C, 12 h	0[d]
2	$FeCl_3$ (1 equiv), EtOH, 70 °C, 12 h	0
3	CAN (1 equiv), EtOH, 70 °C, 12 h	0
4	I_2 (1 equiv), EtOH, 70 °C, 12 h	0
5	HCl (1 equiv), EtOH, 70 °C, 12 h	49
6	PTSA (1 equiv), EtOH, 70 °C, 12 h	46
7	CSA (1 equiv), EtOH, 70 °C, 12 h	55 (72)[e] (59)[f]
8	CSA (1 equiv), DMF, 100 °C, 12 h	13
9	CSA (1 equiv), toluene, 100 °C, 12 h	8

[a]Unless otherwise noted, the reactions were carried out at 70 °C for 12 h using 4-chlorobenzaldehyde (1 mmol), 2-phenylacetophenone (1.1 mmol), thiourea (2 mmol), and Lewis/protic acid (1 mmol) in ethanol (5 mL). [b]CAN = ceric ammonium nitrate, PTSA = *p*-toluenesulfonic acid, CSA = D-(+)-camphor-10-sulfonic acid, DMF = *N*,*N*-dimethylformamide. [c]Isolated yield. [d]Less than 10% yield was obtained when the reaction was carried out in THF. [e]Reaction conditions: CSA (1 equiv), EtOH, 70 °C, 24 h. [f]Reaction conditions: CSA (0.2 equiv), EtOH, 70 °C, 48 h.

TABLE 2. Optimization of Reaction Conditions Using Various Bases[a]



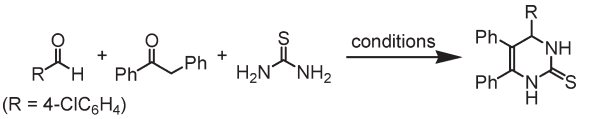
entry	conditions[b]	yield (%)[c]
1	K_2CO_3 (1 equiv), EtOH, 70 °C, 12 h	77
2	LiOH (1 equiv), EtOH, 70 °C, 12 h	84
3	NaOH (1 equiv), EtOH, 70 °C, 12 h	88
4	KOH (1 equiv), EtOH, 70 °C, 12 h	90
5	*t*-BuOK (1 equiv), EtOH, 70 °C, 12 h	95
6	pyridine (1 equiv), EtOH, 70 °C, 12 h	3
7	DABCO (1 equiv), EtOH, 70 °C, 12 h	5
8	DBU (1 equiv), EtOH, 70 °C, 12 h	41

[a]The reactions were carried out at 70 °C for 12 h using 4-chlorobenzaldehyde (1 mmol), 2-phenylacetophenone (1.1 mmol), thiourea (2 mmol), and base (1 mmol) in ethanol (5 mL). [b]DABCO = 1,4-diazabicyclo[2.2.2]-octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [c]Isolated yield.

were obtained when protic acids such as HCl, D-(+)-camphor-10-sulfonic acid (CSA), and *p*-toluenesulfonic acid (PTSA) were employed (Table 1, entries 5−7). However, operation of the reactions at higher temperature (100 °C) using CSA in solvents such as DMF or toluene led to lower yields (Table 1, entries 8 and 9).

After many trials with other additives, it was pleasing to find that the one-pot reactions proceeded efficiently in the presence of Brønsted bases such as K_2CO_3, LiOH, NaOH, KOH, and *t*-BuOK, affording the desired product **4a** in 77−95% yields after reacting at 70 °C for 12 h (Table 2, entries 1−5). In addition, yield of the desired product **4a** increases with increasing basicity. It is important to note that the best yield of 95% was obtained when *t*-BuOK was used as reaction promoter (Table 2, entry 5). Furthermore, it was found that the utilization of organic bases including pyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) resulted in poor to moderate yields of the product (Table 2, entries 6−8).

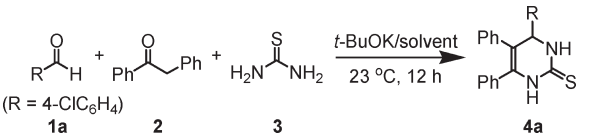
TABLE 3. Optimization of Reaction Conditions with Different Catalyst Loadings and Temperatures[a]



entry	conditions	yield (%)[b]
1	*t*-BuOK (1 equiv), EtOH, 70 °C, 12 h	95
2	*t*-BuOK (0.5 equiv), EtOH, 70 °C, 12 h	93
3	*t*-BuOK (0.2 equiv.), EtOH, 70 °C, 12 h	92
4	*t*-BuOK (0.2 equiv), EtOH, 70 °C, 8 h	90
5	*t*-BuOK (0.2 equiv), EtOH, 70 °C, 4 h	86
6	*t*-BuOK (1 equiv), EtOH, 23 °C, 12 h	86
7	*t*-BuOK (0.2 equiv), EtOH, 23 °C, 12 h	18
8	*t*-BuOK (0.2 equiv), EtOH, 23 °C, 24 h	71
9	*t*-BuOK (0.2 equiv), EtOH, 23 °C, 48 h	88

[a]The reactions were carried out at 70 or 23 °C for 4−48 h using 4-chlorobenzaldehyde (1 mmol), 2-phenylacetophenone (1.1 mmol), thiourea (2 mmol), and *t*-BuOK (0.2−1 mmol) in ethanol (5 mL). [b]Isolated yield.

TABLE 4. Optimization of Reaction Conditions Using Various Solvents[a]



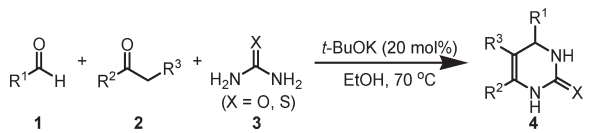
entry	solvent	yield (%)[b]
1	EtOH	86
2	MeOH	82
3	*i*-PrOH	85
4	THF	23
5	CH_2Cl_2	13
6	CH_3CN	56
7	*n*-hexane	8
8	toluene	15

[a]The reactions were carried out at 23 °C for 12 h using 4-chlorobenzaldehyde (1 mmol), 2-phenylacetophenone (1.1 mmol), thiourea (2 mmol), and *t*-BuOK (1 mmol) in organic solvent (5 mL). [b]Isolated yield.

Under the same reaction conditions, it was gratifying to observe that similar high yields were obtained when the amount of *t*-BuOK was decreased to 0.5 or 0.2 equiv (93 and 92% yields, Table 3, entries 2 and 3). It indicates that the reaction can also proceed well in a catalytic manner (20 mol % of *t*-BuOK). When the reaction times were reduced to 8 or 4 h, relatively low yields of 90 or 86% were obtained, respectively (Table 3, entries 4 and 5 versus entry 1). Moreover, it was noteworthy that the reaction also worked well at 23 °C after reacting for 12 h using 1 equiv of *t*-BuOK or 48 h using 0.2 equiv of *t*-BuOK (86 and 88% yields, Table 3, entries 6−9).

Different organic solvents were also screened to see their efficiency in the reaction. As shown in Table 4, it seems that the reaction proceeds better in protic solvent than in aprotic solvent. Good yields were obtained when the reactions were operated in protic solvents such as EtOH, MeOH, and

TABLE 5. Substrate Scope Studies[a]



entry	R^1	R^2	R^3	X	time (h)	yield (%)[b]
1	4-ClC_6H_4	Ph	Ph	S	12	92
2	4-ClC_6H_4	Ph	Ph	O	9	90
3	2-ClC_6H_4	Ph	Ph	S	9	85
4	2-ClC_6H_4	Ph	Ph	O	12	84
5	4-CNC_6H_4	Ph	Ph	S	12	85
6	4-CNC_6H_4	Ph	Ph	O	12	80
7	Ph	Ph	Ph	S	12	87
8	Ph	Ph	Ph	O	12	91
9	4-MeC_6H_4	Ph	Ph	S	12	79
10	4-MeC_6H_4	Ph	Ph	O	12	78
11	4-$OMeC_6H_4$	Ph	Ph	S	18	78
12	4-$OMeC_6H_4$	Ph	Ph	O	24	68
13	3,4-$O_2CH_2C_6H_3$	Ph	Ph	S	18	85
14	3,4-$O_2CH_2C_6H_3$	Ph	Ph	O	24	73
15	1-naphthyl	Ph	Ph	S	12	89
16	1-naphthyl	Ph	Ph	O	12	80
17	2-pyridyl	Ph	Ph	S	18	85
18	2-pyridyl	Ph	Ph	O	24	65
19	2-thienyl	Ph	Ph	S	18	72
20	2-thienyl	Ph	Ph	O	48	67
21	2-furyl	Ph	Ph	S	18	73
22	2-furyl	Ph	Ph	O	18	64
23	4-ClC_6H_4	4-ClC_6H_4	4-BrC_6H_4	S	12	96
24	4-ClC_6H_4	4-ClC_6H_4	4-BrC_6H_4	O	12	90
25	4-ClC_6H_4	Ph	4-BrC_6H_4	S	12	78
26	4-ClC_6H_4	Ph	4-BrC_6H_4	O	12	82
27	4-ClC_6H_4	4-MeC_6H_4	4-BrC_6H_4	S	12	94
28	4-ClC_6H_4	4-MeC_6H_4	4-BrC_6H_4	O	24	91
29	4-ClC_6H_4	4-MeC_6H_4	Ph	S	24	92
30	4-ClC_6H_4	4-MeC_6H_4	Ph	O	24	89
31	4-ClC_6H_4	4-ClC_6H_4	Ph	S	24	83
32	4-ClC_6H_4	4-ClC_6H_4	Ph	O	24	87
33	4-ClC_6H_4	4-$OMeC_6H_4$	Ph	S	24	98
34	4-ClC_6H_4	4-$OMeC_6H_4$	Ph	O	24	97
35	$PhCH_2CH_2$	Ph	Ph	S	24	5

[a]The reactions were carried out at 70 °C for a specific time using aldehyde (1 mmol), ketone (1.1 mmol), urea or thiourea (2 mmol), *t*-BuOK (0.2 mmol), and ethanol (5 mL). [b]Isolated yield.

i-PrOH (Table 4, entries 1−3). However, only moderate to poor yields (Table 4, entries 4−8) were observed when the reactions were carried out in THF, CH_2Cl_2, CH_3CN, *n*-hexane, and toluene (1 equiv of *t*-BuOK, 23 °C, 12 h).

Thus, considering the overall effects of reaction time, temperature, solvent, and catalyst loading, ensuing studies on the exploration of substrate scopes were performed at 70 °C using a catalytic amount of *t*-BuOK (20 mol %) in ethanol. It should be noted that, based on the relative acidity of *t*-BuOH and EtOH, a metathesis reaction (double decomposition reaction) between *t*-BuOK and EtOH may take place to generate *t*-BuOH and EtOK. Therefore, what really works in the reaction could be EtOK rather than *t*-BuOK. However, in view of the lower price and ready availability of *t*-BuOK as compared to EtOK, *t*-BuOK was chosen as the catalyst in subsequent reactions.

With the optimized reaction conditions in hand, we continued to apply the approach to various aldehydes, substituted 2-phenylacetophenones, and urea/thiourea. As shown in Table 5, the Brønsted base-mediated one-pot condensation of aldehyde, substituted 2-phenylacetophenone, and urea/thiourea proceeded efficiently to furnish the corresponding 4,5,6-triaryl-3,4-dihydropyrimidin-2(1*H*)-ones in moderate to good yields. It is noteworthy that the methodology worked well even for heterocyclic aldehydes such as 2-pyridinecarbaldehyde, 2-thiophenecarbaldehyde, and 2-furanecarbaldehyde (Table 5, entries 17−22). Good to excellent yields were also achieved for various substituted 2-phenylacetophenones (Table 5, entries 23−34). However, poor yield (5%) was obtained when the reaction was applied to aliphatic aldehyde such as hydrocinnamaldehyde due to the ease of aldol-type self-condensation of the aldehyde under strong basic conditions (Table 5, entry 35). In addition, we also investigated the reaction using phenyl acetone as substrate. However, the reaction involving 4-chlorobenzaldehyde, phenyl acetone, and urea proceeded sluggishly under above optimized reaction conditions to afford the desired product only in 18% yield.

It is interesting to know that such a kind of three-component condensation can proceed well under basic conditions. To the best of our knowledge, this is the first Brønsted base-mediated *one-pot* Biginelli-type reaction for the synthesis of dihydropyrimidinones. Compared to other commonly employed methods for the preparation of dihydropyrimidinones using Lewis acids or protic acids,[2,3,5] the methodology presented herein also provided a novel, convenient, efficient, and cheap access to a wide variety of dihydropyrimidinones in a one-pot manner.

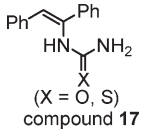
In a previous report, Kappe proposed that Lewis acid or protic acid-mediated Biginelli reaction proceeded via the formation of an iminium ion (formed by acid-catalyzed condensation of aldehyde with urea) as a key intermediate rather than the carbenium ion intermediate (derived from the acid-catalyzed aldol reaction of aldehyde and ethyl acetoacetate).[16] Considering the basic conditions involved in the current methodology using *t*-BuOK, we envisaged that the reaction may have proceeded in a different way.

To probe the mechanism of this Brønsted base-mediated one-pot reaction, 3-(4-chlorophenyl)-1,2-diphenylprop-2-en-1-one (*E*)-**5** (derived from the condensation of 4-chlorobenzaldehyde and 2-phenylacetophenone)[17,18] was preformed and subsequently subjected to *t*-BuOK or CSA-mediated condensation with both urea and thiourea (Table 6). It was gratifying to observe that the reaction of compound **5** with thiourea proceeded efficiently at 70 °C in the presence of *t*-BuOK to generate the desired product **4a** in 96% yield

(16) For a detailed mechanism study on Biginelli reaction by Kappe's group, see: (a) Kappe, C. O. *J. Org. Chem.* **1997**, *62*, 7201. For a recent mechanistic study using mass spectrometry analysis, see: (b) De Souza, R. O. M. A.; da Penha, E. T.; Milagre, H. M. S.; Garden, S. J.; Esteves, P. M.; Eberlin, M. N.; Antunes, O. A. C. *Chem.—Eur. J.* **2009**, *15*, 9799.

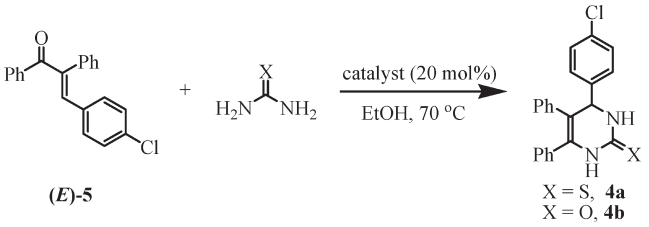
(17) For the preparation of intermediate **5**, see: (a) Mittal, S.; Durani, S.; Kapil, R. S. *J. Med. Chem.* **1985**, *28*, 492. (b) Duke, P. J.; Boykin, D. W. *J. Org. Chem.* **1972**, *37*, 1436.

(18) Compound **17** which derived from the condensation of 2-phenyl acetophenone and thiourea/urea also might be an intermediate of the reaction. However, we failed to preprepare it (reaction conditions: 1 equiv of 2-phenylacetophenone, 2 equiv of thiourea, 0.2 equiv of PTSA (or 1 equiv of KOH) in refluxing toluene or ethanol for 12 h).



compound **17**

TABLE 6. Mechanistic Study Using Enone 5[a]



entry	catalyst	X	time (h)	yield (%)[b]
1	*t*-BuOK	S	6	96
2	*t*-BuOK	O	12	15
3	CSA	S	12	0
4	CSA	O	12	0

[a]The reactions were carried out at 70 °C for a specific time using enone **5** (1 mmol), urea or thiourea (2 mmol), *t*-BuOK or CSA (0.2 mmol), and ethanol (5 mL). [b]Isolated yield.

within 6 h (Table 6, entry 1), and such a type of reaction is well-documented in previous reports,[19] whereas, under the same conditions, it is important to note that the reaction of enone **5** with urea proceeded sluggishly to give the target product **4b** in only 15% yield (Table 6, entry 2). In addition, no reaction took place when CSA (20 mol %) was used. At this stage, we think that the reaction using thiourea might proceed via the formation of enone **5** as a key intermediate, whereas the reaction using urea might proceed via a different mechanism since very low yield was obtained.

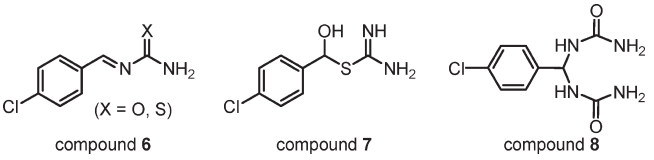
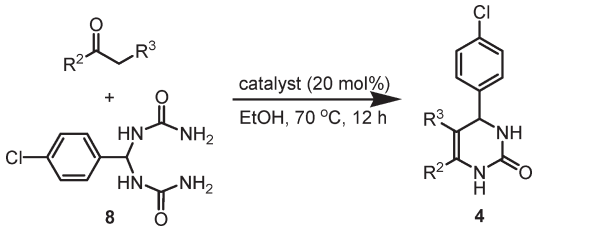


FIGURE 1. Possible reaction intermediates.

Compound **6**, which is derived from the reaction of 4-chlorobenzaldehyde with urea/thiourea, might be an intermediate which accounts for the mechanism of the reaction (Figure 1).[16,18] However, our attempt to synthesize intermediate **6** failed (currently, there is no report on the successful synthesis of compound **6** using aldehyde and urea/thiourea as substrates). Only compound **7** was obtained when 4-chlorobenzaldehyde (1 equiv), thiourea (2 equiv), and PTSA (0.2 equiv) were condensed in refluxing toluene for 24 h.[20,21] In comparison, bis-urea **8** was easily obtained when urea was reacted under the above reaction conditions.[16,21] When compound **7** was condensed with 2-phenylacetophenone (20 mol % of *t*-BuOK or CSA, 70 °C, 12 h), no desired product **4a** was obtained. Therefore, we conclude that the Biginelli-type reaction using thiourea as substrate may proceed via enone **5** rather than intermediate **6** or **7**.

It was interesting to find that the condensation of bis-urea compound **8** (1 mmol) with 2-phenylacetophenone (1.1 mmol)

TABLE 7. Mechanistic Study Using Bis-urea 8[a]



entry	catalyst	R^2	R^3	yield (%)[b]
1	CSA	Ph	Ph	0
2	*t*-BuOK	Ph	Ph	98
3	*t*-BuOK	4-ClC_6H_4	4-BrC_6H_4	89
4	*t*-BuOK	Ph	4-BrC_6H_4	93
5	*t*-BuOK	4-MeC_6H_4	4-BrC_6H_4	87
6	*t*-BuOK	4-MeC_6H_4	Ph	87
7	*t*-BuOK	4-ClC_6H_4	Ph	81

[a]The reactions were carried out at 70 °C for 12 h using bis-urea **8** (1 mmol), substituted 2-phenylacetophenone (1.1 mmol), *t*-BuOK or CSA (0.2 mmol), and ethanol (5 mL). [b]Isolated yield.

occurred efficiently using *t*-BuOK (20 mol %) in ethanol, generating the desired product **4b** in 98% yield after reacting at 70 °C for 12 h (Table 7, entry 2). Good to excellent yields were also afforded using other substituted 2-phenylacetophenones (Table 7, entries 3−7). Moreover, no desired product **4b** was obtained when CSA (20 mol %) was employed under the same conditions (Table 7, entry 1). Thus, we hypothesize that bis-urea compound **8** may be the key intermediate involved in the Biginelli-type reaction using urea as substrate.

It was the first observation that the Biginelli-type reaction using urea and thiourea proceeds through two totally different pathways. According to these observations, two plausible reaction mechanisms were proposed for the Brønsted base-mediated Biginelli-type reaction using urea and thiourea.

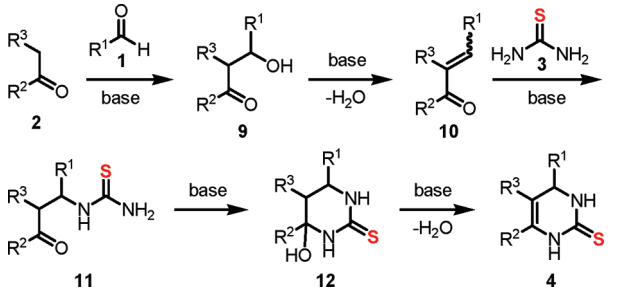


FIGURE 2. Proposed reaction mechanism using thiourea as substrate.

As shown in Figure 2, the reaction using thiourea is initiated via a Brønsted base-mediated aldol condensation of aldehyde **1** with 2-phenylacetophenone (**2**), followed by elimination of the resulting hydroxyl group to give enone **10**. Subsequent base-catalyzed aza-Michael addition of thiourea to enone **10** leads to the formation of Michael adduct **11**. Finally, 1,2-addition of amino group (NH_2) to the carbonyl group followed by in situ elimination of the hydroxyl group affords the desired product **4**.

As for the reaction using urea as substrate, the reaction is proposed to initiate via the formation of an equilibrium mixture of intermediates **13** and **14** (Figure 3). When compound **2** is

(19) For examples, see: (a) Simon, D.; Lafont, O.; Farnoux, C. C.; Miocque, M. *J. Heterocycl. Chem.* **1985**, *22*, 1551. (b) Campbell, M. M.; Jigajinni, V. B.; Wightman, R. H. *Tetrahedron Lett.* **1979**, *26*, 2455.
(20) Taylor, J. *J. Chem. Soc.* **1922**, *115*, 2267.
(21) See Supporting Information for detailed experimental procedures.

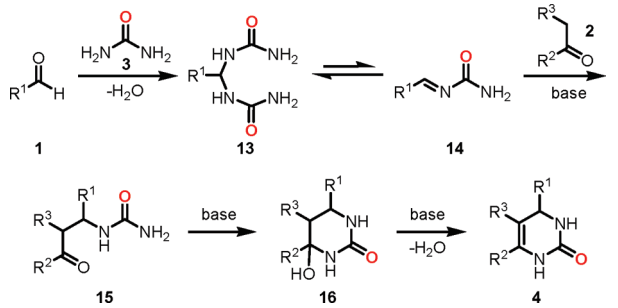


FIGURE 3. Proposed reaction mechanism using urea as substrate.

present, it reacts with either intermediate **13** or **14** to generate compound **15**. Compound **15** further cyclizes under base catalysis and finally affords the desired product **4** upon elimination of the hydroxyl group.

In the case of the CSA-mediated Biginelli-type reaction (Table 1, entry 7), because it cannot proceed via the aforementioned possible intermediates **5** and **8** (Table 6, entries 3 and 4 and Table 7, entry 6), we hypothesize that the reaction may have occurred through the formation of intermediate **17**.[18] However, our attempt to synthesize the intermediate **17** proved futile.

Conclusion

In conclusion, we have described a novel Brønsted base-mediated one-pot procedure for the preparation of a wide variety of novel 4,5,6-triaryl-3,4-dihydropyrimidin-2(1*H*)-ones via a three-component condensation of aldehyde, 2-phenylacetophenone, and urea/thiourea. The method is simple, convenient, efficient, and is expected to be a useful synthetic protocol for the synthesis of a wide range of novel drug-like dihydropyrimidinones. In addition, enone **5** and bis-urea **8** were highly suggested as reaction intermediates for reactions involving thiourea and urea as substrates, respectively. Application of the methodology to other active methylene compounds, development of an asymmetric version of this reaction, and the use of bis-urea compound as substrate for the synthesis of various dihydropyrimidinones are currently in progress.

Experimental Section

General Procedure for the Three-Component Condensation of Aldehyde, 2-Phenylacetophenone, and Urea/Thiourea: To a mixture of aldehyde **1** (1 mmol), substituted 2-phenylacetophenone **2** (1.1 mmol), and urea or thiourea **3** (2 mmol) was added absolute ethanol (5 mL), and it was stirred at room temperature for 5 min. Then *t*-BuOK (0.2 mmol) was added, and the reaction mixture was stirred vigorously at 70 °C for a certain time, as shown in Table 5. After the completion of the reaction, solvent was removed under vacuum. The residue was purified by silica gel column chromatography using CH_2Cl_2 and MeOH as eluant to afford the desired product of 4,5,6-triaryl-3,4-dihydropyrimidin-2(1*H*)-one.

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Supporting Information Available: General experimental procedures and spectral data for all reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.