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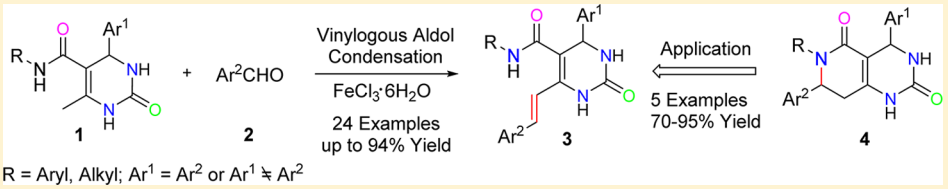
Iron-Catalyzed Vinylogous Aldol Condensation of Biginelli Products and Its Application toward Pyrido[4,3-*d*]pyrimidinones

Lianqiang Zhang, Zhiguo Zhang,* Qingfeng Liu, Tongxin Liu, and Guisheng Zhang*

Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, Henan 453007, PR China

Supporting Information



ABSTRACT: A novel iron-catalyzed vinylogous aldol condensation of Biginelli products with aryl aldehydes has been developed for the syntheses of potential bioactive (*E*)-6-arylvinyl-dihydropyrimidin-2(1*H*)-ones. These materials are valuable synthetic precursors to drug-like pyrido[4,3-*d*]pyrimidine derivatives. The amide group at the 5-position of the dihydropyrimidin-2(1*H*)-ones played an important role in the vinylogous aldol condensation reaction.

Dihydropyrimidin-2(1*H*)-ones (DHPMs) display a broad range of biological activities, such as antitumor,[1] antihypertensive,[2] anti-HIV,[3] antioxidant,[4] antimalarial,[5] antimicrobial, anti-inflammatory, antibacterial, antifungal, and anthelmintic activities.[6] To date, as the major method for the synthesis of DHPMs, the Biginelli reaction has received much attention. In the past decade, there have been nearly 500 publications concerning this reaction.[7] However, these reports have mostly focused on the improvement of the reaction catalyst.[7] Relatively, it is rare to focus on the derivatization of DHPMs, especially on the functionalization of the C-6 methyl group; in general, acetoacetates are employed in the Biginelli reaction, and, therefore, in most cases, a methyl group is introduced at the C-6 position of the pyrimidine ring.[8] To the best of our knowledge, very few reports have appeared in the literature concerning the functionalization of the C-6 methyl group, which is reported to proceed through (i) bromination and a subsequent nucleophilic replacement reaction (Scheme 1, eq 1),[9−11] or (ii) electrophilic substitution reaction in the presence of base (Scheme 1, eq 2).[12] In contrast, vinylogous aldol reaction of cyclic compounds has received much attention,[13−15] although vinylogous aldol reaction of Biginelli products has not yet been achieved to date. We present here the first report of vinylogous aldol reaction of Biginelli products, an effective and practical Lewis acid-catalyzed approach to 6-arylvinyl DHPMs **3** (Scheme 1, eq 3), and its further application to generate additional drug-like complex derivatives, including pyrido[4,3-*d*]pyrimidines **4** (Scheme 1).

In the course of our continuous research on the direct syntheses of heterocyclic compounds from readily available acyclic precursors,[16−20] we note that there is a potential vinylogous conjugated system in the Biginelli products (Schemes 1 and 2). We hypothesized that the Biginelli products **1** should form the vinylogous conjugated systems **A** in the presence of a suitable catalyst.[13−15] Then, the vinylogous enolate **A** would attack aldehyde **2** to afford the intermediates **B**, subsequently leading to the products **3** via dehydration (Scheme 2).[21−28] In our efforts to develop highly efficient methods for functional group transformations, we found that iron salts are effective, reusable, operationally simple, and environmentally benign catalysts.[29−31] As a result, we selected ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **1a** (1.0 equiv) and 5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one **1b** (1.0 equiv), respectively, to react with **2a** in the presence of $FeCl_3·6H_2O$ (10 mol %) in CH_3CN at reflux (Scheme 3). Disappointingly, after 7 h, the desired compounds **3a** and **3b** were not observed, and most of the starting materials **1a** (93%) and **1b** (95%) were recovered. Fortunately, 6-arylvinyl DHPM **3c** was isolated in 15% yield when 5-carboxamide substituted DHPM **1c**[32] was employed for the reaction, but the yield of **3c** could not be further increased by prolonging the reaction time (Table 1, entry 9) (Scheme 3). These results indicate that the amide moiety at the 5-position of DHPMs **1** is very important for this vinylogous aldol condensation reaction. We deduced that the nitrogen of the amide moiety contributed its unpaired electrons to the conjugated system **A**, which would enhance the nucleophilicity of the alkene (Scheme 2).[14,24,33−36] It is noteworthy that, according to the ^1H NMR data, the C=C double bond at the 6-position was assigned as an *E* configuration on the basis of the magnitude of the coupling constant (16.4 Hz).[37]

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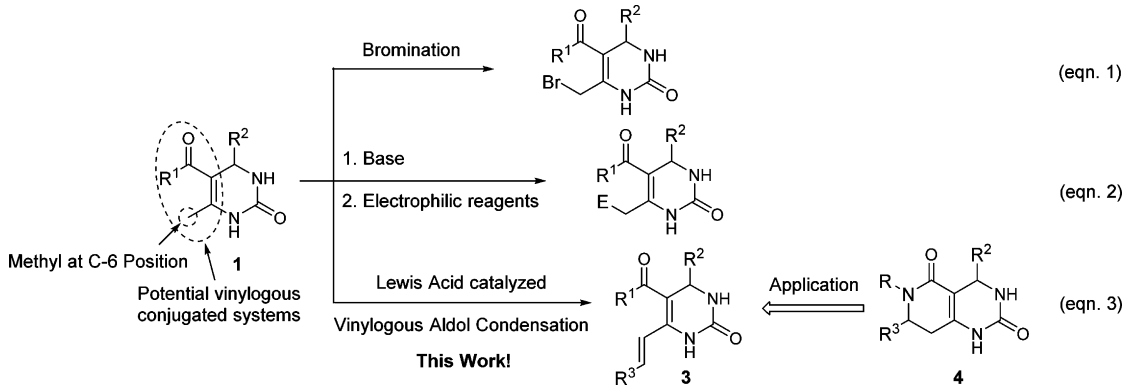
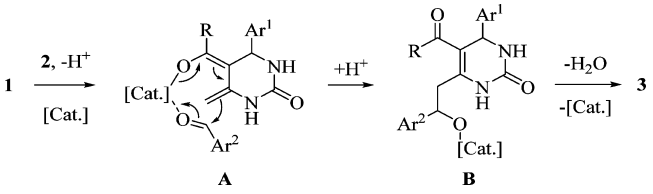
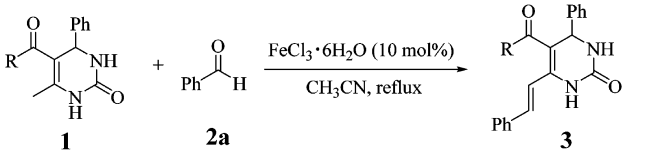
Scheme 1. Functionalization of the C-6 Methyl Position of DHPMs 1



Scheme 2. Synthetic Hypothesis

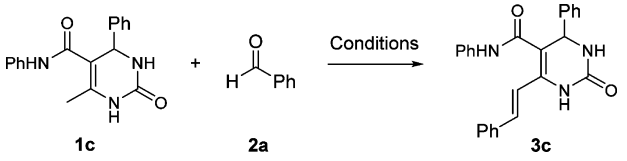


Scheme 3. Initial Attempts to Synthesize 6-Arylvinyl DHPMs 3



1a: R = OEt — 7 h, **3a**: 0% (93% **1a** was recovered)
1b: R = Me — 7 h, **3b**: 0% (95% **1b** was recovered)
1c: R = NHPh — 4 h, **3c**: 15% (80% **1c** was recovered)

Table 1. Survey of Reaction Conditions[a]



entry	cat. (equiv)	2a (equiv)	T (°C)	time (h)	yield (%)
1	$FeCl_3·6H_2O$ (0.1)	2	reflux	18	88
2[b]	$FeCl_3·6H_2O$ (0.1)	2	reflux	24	30
3[c]	$FeCl_3·6H_2O$ (0.1)	2	reflux	10	0
4[d]	$FeCl_3·6H_2O$ (0.1)	2	80	10	0
5[e]	$FeCl_3·6H_2O$ (0.1)	2	reflux	10	0
6[f]	$FeCl_3·6H_2O$ (0.1)	2	60	30	50
7[g]	$FeCl_3·6H_2O$ (0.1)	2	40	10	0
8	$FeCl_3·6H_2O$ (0.05)	2	reflux	38	80
9	$FeCl_3·6H_2O$ (0.2)	2	reflux	18	84
10[h]	$FeCl_3·6H_2O$ (0.1)	1	reflux	4	15
11[i]	$FeCl_3·6H_2O$ (0.1)	1.5	reflux	12	51
12	$FeCl_3·6H_2O$ (0.1)	3	reflux	14	88
13	$FeCl_3$ (0.1)	2	reflux	28	77
14	$Fe_2(SO_4)_3·xH_2O$ (0.1)	2	reflux	30	86
15	$FeSO_4·7H_2O$ (0.1)	2	reflux	35	82
16[j]	$Fe(NO_3)_3·9H_2O$ (0.1)	2	reflux	10	trace

[a]Unless otherwise indicated, all reactions were carried out with **1c** (0.5 mmol), **2a** (1.0 mmol), and $FeCl_3·6H_2O$ (10 mol %) in CH_3CN (3.0 mL) at reflux. [b]Reaction was performed in EtOH, and 44% **1c** was recovered. [c]Reaction was performed in CH_2Cl_2, and 95% **1c** was recovered. [d]Reaction was performed in DMSO, and 90% **1c** was recovered. [e]Reaction was performed in water, and 98% **1c** was recovered. [f]44% **1c** was recovered. [g]95% **1c** was recovered. [h]The yield of **3c** could not be increased by prolonging the reaction time, and 80% **1c** was recovered. [i]The yield of **3c** could not be increased by prolonging the reaction time, and 43% **1c** was recovered. [j]79% **1c** was recovered.

With these encouraging initial results in hand, a more detailed screening of conditions was carried out immediately by using a model compound of 5-carboxamide substituted DHPM **1c** and benzaldehyde **2a**. Some key results are summarized in Table 1. It was found that the yield of **3c** could reach 88% in the presence of $FeCl_3·6H_2O$ (10 mol %) in CH_3CN (3.0 mL) after reflux for 18 h when the ratio of **1c** and **2a** reached 1:2 (Table 1, entry 1). In EtOH, the yield of **3c** reached only 30% along with the recovered **1c** (44%) and could not be increased by prolonging the reaction time (entry 2). When the reaction was performed in CH_2Cl_2 or DMSO, the desired product **3c** was not observed, and most of the **1c** was recovered (entries 3 and 4). The efficacy of water as solvent for this reaction was also investigated, given that it is very efficient in many similar reactions.[38] However, after using water under the optimized conditions we found that the reaction of **1c** with **2a** did not afford the desired compound **3c**, and almost all of the starting material **1c** was recovered (98%). This result was observed despite the use of 10 mmol % tetrabutylammonium bromide as a phase-transfer catalyst to increase the solubility of **1c** and **2a** (entry 5). It became obvious that acetonitrile achieved the best conversion for this reaction,[39] and we considered that an iron–acetonitrile complex[40,41] might be involved in the reaction and promote the formation of the vinylogous conjugated systems. We found that temperature also had a significant influence on the transformation, because the yield of **3c** decreased significantly with decreasing temperature (entries 6 and 7). These results suggest that temperature influences the formation of the enolate of the Biginelli products, essentially affecting the formation of the vinylogous conjugated systems. In contrast, the amount of $FeCl_3·6H_2O$ had little effect on the yield of product **3c**, with different amounts of the catalyst leading to negligible changes in yield (entries 8 and 9). It was noted that the amount of **2a** had an obvious influence on the reaction. **3c** was obtained in 51% yield when 1.5 equiv of **2a** was used (43% **1c** was recovered) and the yield of **3c** was not increased by prolonging the reaction time (entry 1 vs 11). Similarly, the yield

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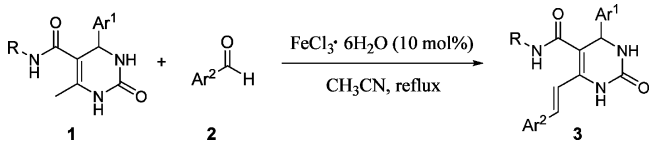
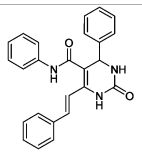
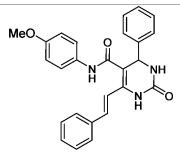
Table 2. Synthesis of 3[a]



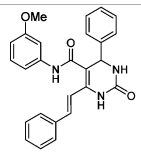
1 2 3



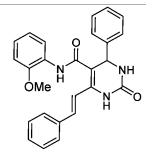
3c: 18 h, 88%



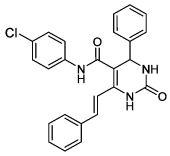
3d: 15 h, 85%



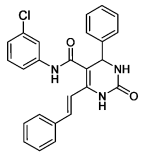
3e: 17 h, 79%



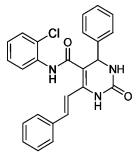
3f: 10 h, 88%[b]



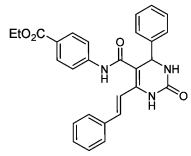
3g: 35 h, 87%



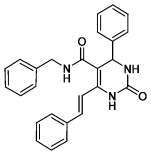
3h: 13 h, 77%



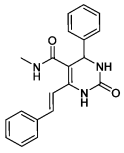
3i: 13 h, 94%[b]



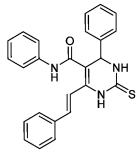
3j: 32 h, 75%



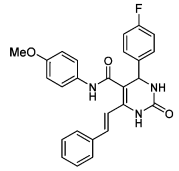
3k: 14 h, 80%



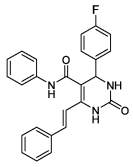
3l: 8 h, 35%[c]



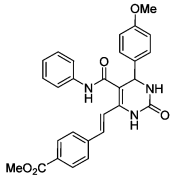
3m: 30 h, 81%[d]



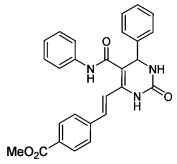
3n: 9.0 h, 87%



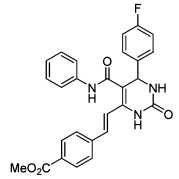
3o: 12 h, 84%



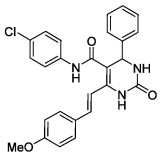
3p: 24 h, 85%



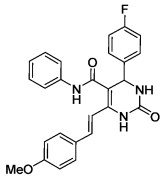
3q: 16 h, 73%



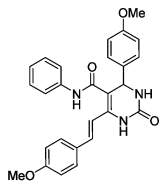
3r: 53 h, 87%



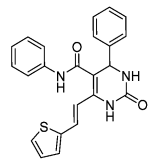
3s: 48 h, 91%



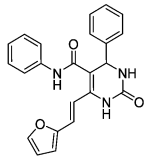
3t: 12 h, 85%



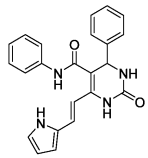
3u: 4 h, 73%[b]



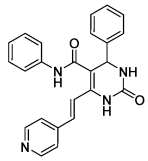
3v: 7 h, 45%[e]



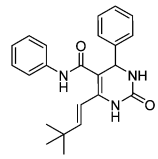
3w: 5 h, 11%[f]



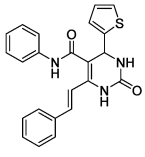
3x: 5 h, 0%[g]



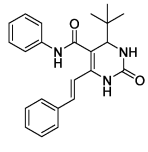
3y: 5 h, 0%[h]



3z: 5 h, 0%[h]



3aa: 5 h, 32%[i]



3ab: 5 h, 0%[j]

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Table 2. continued

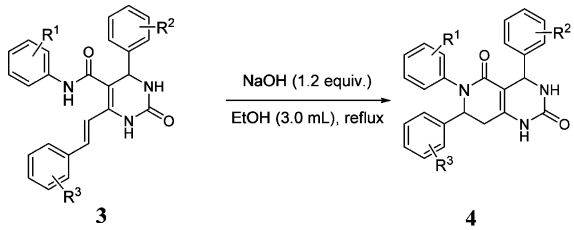
[a]Unless otherwise indicated, all reactions were carried out with **1** (0.5 mmol), **2** (1.0 mmol), and $FeCl_3·6H_2O$ (10 mol %) in CH_3CN (3.0 mL). [b]3.0 equiv of **2** was used. [c]Unidentified complex mixture was observed. [d]10 mol % $Fe_2(SO_4)_3·xH_2O$ was used, and the yield was based on the conversion of **1m**, and 42% substrate **1m** was recovered. [e]50 mol % $Fe_2(SO_4)_3·xH_2O$ was used, and some unidentified complex mixture was obtained. [f]56% substrate **1** was recovered, and the yield of **3w** could not be increased by prolonging the reaction time. [g]93% substrate **1** was recovered. [h]95% substrate **1** was recovered. [I]56% substrate **1** was recovered, and the yield of **3aa** would decrease by prolonging the reaction time. [j]87% substrate **1** was recovered.

of **3c** did not improve when the amount of **2a** was increased from 2.0 to 3.0 equiv, although an increased amount of **2a** appeared beneficial for the conversion (entry 1 vs 12). The effectiveness of other iron salts such as anhydrous $FeCl_3$, $Fe_2(SO_4)_3·xH_2O$, $FeSO_4·7H_2O$, and $Fe(NO_3)_3·9H_2O$ varied between slightly less effective and near ineffective (entries 13−16).

Using the optimized reaction conditions (Table 1, entry 1), the scope of this protocol was investigated (Table 2). First, the reactions of benzaldehyde **2a** with a series of DHPMs **1d−1j** bearing different substituents [such as an electron-donating group (OMe) or an electron-withdrawing group (Cl, CO_2Et) at *ortho*-, *meta*-, or *para*-position] on the benzene ring of *N*-aryl group at the 5-position were performed. As expected, these reactions worked well and gave the target products **3d−3j** in good to excellent yields (75−94%) regardless of the electronic nature and the position of the diverse substituents. The variation in yields of the products **3g**, **3h**, **3i**, and **3d**, **3e**, **3f** is likely the result of the electronic effect of the substituent on the aryl ring, which affects the electron density of the amide nitrogen atom, and thereby affects the formation of the vinylogous conjugated systems. In addition, the reactions of **2a** with *N*-aliphatic substituted DHPMs **1k** and **1l** resulted in the yields of **3k** and **3l** of 80 and 35%, respectively. When 4-phenyl-3,4-dihydropyrimidin-2(1*H*)-thione **1m** was employed for the condensation, **3m** was obtained in 81% yield based on the conversion of **1m** after 30 h in the presence of 10 mol % $Fe_2(SO_4)_3·xH_2O$, while 42% substrate **1m** was recovered. The yield of **3m** was not improved by increasing the amount of $Fe_2(SO_4)_3·xH_2O$. Next, to enlarge the available drug-like library of the diverse **3** for bioactive screening, several DHPMs **1** and aldehydes **2** (commonly different from the aldehydes being used in the preparation of Biginelli products **1**) were selected randomly to prepare **3n−3u**. These products, featuring a variety of substituents with different electronic properties, were smoothly prepared in good to excellent yields (73−91%) under the optimized conditions. Subsequently, the condensations of **1c** with heterocyclic aldehydes and aliphatic aldehyde were investigated. The reaction of 2-furaldehyde with **1c** gave **3w** in 11% yield, while 2-thienaldehyde reacted with **1c** to give **3v** in 45% yield along with some unidentified complex mixture by using 0.5 equiv of $Fe_2(SO_4)_3·xH_2O$. However, when 2-pyrrolaldehyde, 4-pyridylaldehyde, and pivaldehyde were subjected to the optimized reaction conditions, the desired products **3x−3z** were not obtained, and most of the starting materials were recovered. In further experiments, the thiophene-substituted Biginelli product **1aa** gave the desired product **3aa** in 32% yield, while no reaction occurred using 4-*t*-butyl-substituted DHPM **1ab**.

We reasoned that an important application of vinylogous reaction products **3** could be the conversion via an intramolecular addition reaction to give pyrido[4,3-*d*]pyrimidine derivatives **4**, which possess various remarkable biological activities including fungicidal, antiviral, anti-inflammatory, antitumor, and antimicrobial properties,[42] while some compounds have also been discovered as EGFr-TK inhibitors[43] or DHFR inhibitors.[44] Commonly, compounds **4** can be obtained by intramolecular cyclization of the side chain of pyridines or pyrimidines.[45−47] However, sometimes this requires a multistep process, relatively strict reaction conditions, and/or long reaction time. Thus, we became interested in developing a more facile and flexible synthetic approach to a wide range of structurally different pyrido[4,3-*d*]pyrimidinones **4**. Some compounds **3** were randomly selected as substrates to prepare compounds **4**. As a result, we found that pyrido[4,3-*d*]pyrimidines **4a−4e** could be successfully produced in good to excellent yields via intramolecular cyclocondensation of corresponding **3** in the presence of NaOH in EtOH at reflux. Compared with known procedures, the present methodology allows ready access to multisubstituted pyrido[4,3-*d*]-pyrimidines **4** via two reactions and is much more concise and practical (Scheme 4).

Scheme 4. Synthesis of Pyrido[4,3-*d*]pyrimidine-2,5-diones 4



3 **4**

3c: R^1 = H; R^2 = H; R^3 = H.	**4a**: 8.0 h, 83%
3e: R^1 = 3-OMe; R^2 = H; R^3 = H.	**4b**: 2.5 h, 70%
3h: R^1 = 3-Cl; R^2 = H; R^3 = H.	**4c**: 2.0 h, 80%
3u: R^1 = H; R^2 = 4-OMe; R^3 = 4-OMe.	**4d**: 15 h, 95%
3q: R^1 = H; R^2 = H; R^3 = CO_2Me.	**4e**: 0.5 h, 82% (R^3 = CO_2Et)

In summary, we developed an iron-catalyzed intermolecular vinylogous aldol condensation of DHPMs **1** and aldehydes **2** for the synthesis of useful 6-arylvinyl DHPMs **3** in good to excellent yields. It is noteworthy that the amide group at the 5-position of the DHPMs played an important role in the vinylogous aldol condensation reaction. Advantages of the present method include the variety of cheap and readily available reactants, a wide range of substrates with dense or flexible substitution patterns, and the important synthetic potential of the products. As one of the important applications of 6-arylvinyl DHPMs **3**, multisubstituted pyrido[4,3-*d*]-pyrimidines **4** were easily prepared in good yields via intramolecular addition.

EXPERIMENTAL SECTION

General Information. All reagents were purchased from commercial sources and used without further treatment. All reactions were carried out under air atmosphere. ^1H NMR and $^{13}C\{^1H\}$ NMR

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spectra were recorded on a 400 MHz NMR spectrometer (^{1}H: 400 MHz, ^{13}C{^{1}H}: 100 MHz at 25 °C) and TMS as internal standard. Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). All high-resolution mass spectra (HRMS) were measured on a mass spectrometer by using electrospray ionization (ESI), and the purity of all samples used for HRMS (>95%) were confirmed by ^{1}H and ^{13}C{^{1}H} NMR spectroscopic analysis. Melting points were measured on a melting point apparatus equipped with a thermometer and were uncorrected. All reactions were monitored by TLC with GF254 silica gel coated plates. Flash chromatography was carried out on SiO_2 (silica gel 200−300 mesh).

Typical Experimental Procedure for the Synthesis of 3 (3c as an Example). To a round-bottom flask (25 mL) equipped with a spherical condenser (40 cm length) were added 6-methyl-2-oxo-*N*,4-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide **1c** (153.5 mg, 0.5 mmol), benzaldehyde **2a** (106.0 mg, 1.00 mmol), $FeCl_3·6H_2O$ (13.5 mg, 0.05 mmol), CH_3CN (3.0 mL). Then the mixture was well stirred under reflux for 18 h (the whole process was closely monitored by TLC). After the mixture cooled off, water was added (3.0 mL), the mixture was filtered, and then the filter cake was purified by a short flash silica gel column chromatography (eluent: dichloromethane/methanol = 80/1) to give (*E*)-2-oxo-*N*,4-diphenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide **3c** as white solid (173.8 mg, 88%): mp 221−223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.84 (s, 1H), 7.76 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.45−7.25 (m, 13H), 7.22 (d, J = 16.8 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 5.51 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 164.88, 152.84, 143.62, 139.06, 136.29, 136.19, 131.50, 128.94, 128.61, 127.58, 126.70, 126.41, 123.48, 119.93, 119.35, 110.03, 106.61, 55.75; HRMS (ESI), m/z calcd. for $C_{25}H_{21}N_3O_2$ ([M + H]$^+$) 396.1707, found 396.1704.

Typical Experimental Procedure for the Synthesis of 4 (4a as an Example). To a round-bottom flask (25 mL) equipped with a spherical condenser (40 cm length) were added (*E*)-2-oxo-*N*,4-diphenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide **3c** (197.5 mg, 0.5 mmol), NaOH (24.0 mg, 0.6 mmol), EtOH (3.0 mL). Then the mixture was well stirred under reflux for 8 h (the whole process was closely monitored by TLC). After cooling off, the mixture was treated with saturated aqueous NH_4Cl solution (30 mL), and the aqueous phase was extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with brine (3.0 mL) and dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by a short flash silica gel column chromatography (eluent: dichloromethane/methanol = 100/1) to give 4,6,7-triphenyl-3,4,7,8-tetrahydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione **4a** as white solid (163.9 mg, 83%): mp 302−304 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 7.74 (s, 1H), 7.40−7.14 (m, 12H), 7.10 (d, J = 7.6 Hz, 2H), 7.03 (t, J = 7.2 Hz, 1H), 5.33 (t, J = 5.2 Hz, 1H), 5.22 (s, 1H), 3.28 (dd, J_1 = 16.4 Hz, J_2 = 5.6 Hz, 1H), 2.72 (dd, J_1 = 16.4 Hz, J_2 = 4.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 163.73, 152.11, 144.94, 143.45, 141.84, 141.06, 128.52, 128.37, 128.09, 127.47, 127.19, 126.85, 126.67, 126.54, 125.25, 100.94, 59.91, 53.33, 33.33; HRMS (ESI), m/z calcd. for $C_{25}H_{21}N_3O_2$ ([M + H]$^+$) 396.1707, found 396.1706.

(*E*)-2-Oxo-*N*,4-diphenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3c). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (173.8 mg, 88%): mp 221−223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.84 (s, 1H), 7.76 (s, 1H), 7.58 (d, J = 8.0 Hz, 2H), 7.43−7.26 (m, 13H), 7.22 (d, J = 16.8 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 5.51 (d, J = 2.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 164.9, 152.8, 143.6, 139.1, 136.3, 136.2, 131.5, 128.9, 128.6, 127.6, 126.7, 126.4, 123.5, 119.9, 119.4, 110.0, 106.6, 55.8; HRMS (ESI), m/z calcd. for $C_{25}H_{21}N_3O_2$ ([M + H]$^+$) 396.1707, found 396.1704.

(*E*)-*N*-(4-Methoxyphenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3d). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (180.6 mg, 85%): mp 242−244 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.88 (s, 1H), 8.77 (s, 1H), 7.71 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.42−7.24 (m, 11H), 7.21 (d, J = 16.4 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 5.48 (s, 1H), 3.71 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 164.4, 155.5, 152.9, 143.6, 136.3, 135.8, 132.1, 131.2, 128.9, 128.5, 128.4, 127.5, 126.6, 126.4, 121.5, 119.4, 113.7, 110.2, 55.7, 55.2; HRMS (ESI), m/z calcd. for $C_{26}H_{23}N_3O_3$ ([M + Na]$^+$) 448.1634, found 448.1631.

(*E*)-*N*-(3-Methoxyphenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3e). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 100/1) as a white solid (167.8 mg, 79%): mp 212−214 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.82 (s, 1H), 7.75 (s, 1H), 7.42−7.38 (m, 3H), 7.37−7.26 (m, 9H), 7.20−7.15 (m, 3H), 6.63 (dd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 1H), 5.47 (d, J = 2.4 Hz, 1H), 3.70 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 164.9, 159.4, 152.8, 143.6, 140.2, 136.9, 136.3, 131.6, 129.4, 129.3, 128.9, 128.6, 127.6, 126.7, 126.4, 119.3, 112.2, 110.0, 108.8, 105.7, 55.7, 55.0; HRMS (ESI), m/z calcd. for $C_{26}H_{23}N_3O_3$ ([M + H]$^+$) 426.1812, found 426.1822.

(*E*)-*N*-(2-Methoxyphenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3f). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 100/1) as a yellow solid (187.3 mg, 88%): mp 234−236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.77 (s, 1H), 7.74 (d, J = 7.2 Hz, 2H), 7.51−7.31 (m, 12H), 7.07 (t, J = 7.6 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.88 (t, J = 7.2 Hz, 1H), 5.39 (s, 1H), 3.60 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 164.9, 153.2, 150.7, 143.9, 138.3, 136.7, 133.0, 129.3, 129.1, 128.2, 127.5, 127.4, 127.1, 125.3, 123.0, 120.7, 120.0, 111.5, 109.2, 56.0, 55.9; HRMS (ESI), m/z calcd. for $C_{26}H_{23}N_3O_3$ ([M + H]$^+$) 426.1812, found 426.1810.

(*E*)-*N*-(4-Chlorophenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3g). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (186.6 mg, 87%): mp 252−254 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.86 (s, 1H), 7.78 (s, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.42−7.26 (m, 13H), 7.19 (d, J = 16.8 Hz, 1H), 5.48 (d, J = 2.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 165.6, 153.4, 143.5, 138.0, 136.8, 136.3, 132.4, 129.4, 129.3, 129.1, 129.0, 128.3, 128.0, 127.2, 126.9, 122.1, 119.4, 110.0, 56.2; HRMS (ESI), m/z calcd. for $C_{25}H_{20}ClN_3O_2$ ([M + H]$^+$) 430.1317, found 430.1316.

(*E*)-*N*-(3-Chlorophenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3h). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (165.2 mg, 77%): mp 225−227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 8.89 (s, 1H), 7.80 (s, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.45−7.36 (m, 6H), 7.34−7.27 (m, 6H), 7.22 (d, J = 16.4 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 5.52 (d, J = 2.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 165.6, 153.2, 144.0, 141.0, 137.4, 136.7, 133.4, 132.5, 130.7, 129.4, 129.1, 128.1, 127.2, 126.9, 123.6, 119.7, 118.6, 109.9, 107.1, 56.1; HRMS (ESI), m/z calcd. for $C_{25}H_{20}ClN_3O_2$ ([M + H]$^+$) 430.1317, found 430.1314.

(*E*)-*N*-(2-Chlorophenyl)-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3i). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 100/1) as a white solid (201.6 mg, 94%): mp 225−227 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.87 (s, 1H), 7.76 (s, 1H), 7.48−7.39 (m, 12H), 7.30 (t, J = 7.2 Hz, 3H), 7.20 (t, J = 7.6 Hz, 1H), 5.46 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 165.5, 153.2, 143.9, 137.7, 136.7, 135.5, 132.5, 129.9, 129.3, 129.1, 129.0, 128.7, 128.1, 127.9, 127.6, 127.4, 127.3, 127.1, 120.0, 109.3, 56.1; HRMS (ESI), m/z calcd. for $C_{25}H_{20}ClN_3O_2$ ([M + H]$^+$) 430.1317, found 430.1304.

(*E*)-Ethyl 4-(2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamido)benzoate (3j). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (175.1 mg, 75%): mp 211−213 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.90 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.80 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.42−7.26 (m, 11H), 7.21 (d, J = 16.4 Hz, 1H), 5.51 (d, J = 2.4 Hz, 1H), 4.28 (q, J = 7.2 Hz,

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2H), 1.30 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.4, 165.3, 152.8, 143.6, 143.5, 137.3, 136.2, 132.1, 130.1, 129.0, 128.7, 127.6, 126.8, 126.4, 124.3, 119.2, 119.1, 109.3, 60.4, 55.6, 14.2; One carbon was not observed; HRMS (ESI), m/z calcd. for $C_{28}H_{25}N_3O_4$ ([M + Na]$^+$) 490.1737, found 490.1710.

(*E*)-*N*-Benzyl-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3k). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 60/1) as a white solid (163.6 mg, 80%): mp 228−230 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.60 (s, 1H), 7.66 (s, 1H), 7.36−7.24 (m, 14H), 7.20 (d, J = 16.8 Hz, 1H), 7.14−7.12 (m, 2H), 5.37 (d, J = 2.8 Hz, 1H), 4.39 (dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1H), 4.20 (dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 166.0, 152.9, 143.5, 139.6, 136.4, 135.1, 130.8, 128.9, 128.6, 128.5, 128.3, 127.6, 127.4, 126.74, 126.69, 119.4, 110.1, 55.7, 42.4; One carbon was not observed; HRMS (ESI), m/z calcd. for $C_{26}H_{23}N_3O_2$ ([M + Na]$^+$) 432.1682, found 432.1648.

(*E*)-*N*-Methyl-2-oxo-4-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3l). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 40/1) as a yellow solid (58.3 mg, 35%): mp 250−252 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 7.96 (s, 1H), 7.68 (s, 1H), 7.45−7.26 (m, 12H), 5.32 (d, J = 2.4 Hz, 1H), 2.60 (d, J = 4.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 166.4, 153.0, 143.6, 136.5, 135.6, 130.9, 128.9, 128.5, 128.4, 127.5, 126.8, 126.4, 119.7, 109.8, 55.3, 26.1; HRMS (ESI), m/z calcd. for $C_{20}H_{19}N_3O_2$ ([M + Na]$^+$) 356.1369, found 356.1368.

(*E*)-*N*,4-Diphenyl-6-styryl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3m). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 500/1) as a yellow solid (96.6 mg, 47%): mp 237−239 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.20 (s, 1H), 9.98 (s, 1H), 9.69 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.50−7.27 (m, 13H), 7.17 (d, J = 16.4 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 5.50 (d, J = 2.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 174.9, 164.6, 142.4, 138.9, 136.2, 134.0, 132.7, 129.0, 128.8, 128.7, 127.9, 126.8, 126.5, 123.7, 120.0, 118.4, 111.0, 55.7; One carbon was not observed; HRMS (ESI), m/z calcd. for $C_{25}H_{21}N_3OS$ ([M + Na]$^+$) 434.1298, found 434.1286.

(*E*)-4-(4-Fluorophenyl)-*N*-(4-methoxyphenyl)-2-oxo-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3n). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (192.7 mg, 87%): mp 248−250 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 8.85 (s, 1H), 7.77 (s, 1H), 7.47 (d, J = 8.8 Hz, 2H), 7.43−7.35 (m, 7H), 7.29 (t, J = 7.2 Hz, 1H), 7.23−7.17 (m, 3H), 6.86 (d, J = 8.8 Hz, 2H), 5.49 (s, 1H), 3.70 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 164.4, 161.6 (d, J = 241.3 Hz), 155.5, 152.8, 139.9 (d, J = 2.5 Hz), 136.3, 136.0, 132.1, 131.5, 129.0, 128.6, 128.5, 126.7, 121.6, 119.4, 115.4 (d, J = 21.1 Hz), 113.8, 110.1, 55.2, 55.1; HRMS (ESI), m/z calcd. for $C_{26}H_{22}FN_3O_3$ ([M + Na]$^+$) 466.1537, found 466.1524.

(*E*)-4-(4-Fluorophenyl)-2-oxo-*N*-phenyl-6-styryl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3o). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (173.4 mg, 84%): mp 238−240 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 8.85 (s, 1H), 7.75 (s, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.44−7.26 (m, 10H), 7.20 (dd, J_1 = 17.2 Hz, J_2 = 8.8 Hz, 3H), 7.04 (t, J = 7.2 Hz, 1H), 5.52 (d, J = 1.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.3, 162.0 (d, J = 242.3 Hz), 153.2, 140.3 (d, J = 2.3 Hz), 139.5, 136.8, 136.7, 132.2, 129.4, 129.0, 128.9, 127.2, 124.0, 120.5, 119.8, 115.8 (d, J = 21.4 Hz), 110.3, 55.6; HRMS (ESI), m/z calcd. for $C_{25}H_{20}FN_3O_2$ ([M + H]$^+$) 414.1612, found 414.1618.

(*E*)-Methyl 4-(2-(6-(4-methoxyphenyl)-2-oxo-5-(phenylcarbamoyl)-1,2,3,6-tetrahydropyrimidin-4-yl)vinyl)benzoate (3p). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (205.3 mg, 85%): mp 269−271 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.88 (s, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.76 (s, 1H), 7.56 (dd, J_1 = 12.0 Hz, J_2 = 8.4 Hz, 4H), 7.44 (d, J = 16.4 Hz, 1H), 7.36 (d, J = 16.8 Hz, 1H), 7.30−7.23 (m, 4H), 7.04 (t, J = 7.2 Hz, 1H), 6.91 (d, J = 8.4 Hz, 2H), 5.50 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.9, 164.7, 158.8, 152.7, 141.0, 139.0, 135.8, 135.6, 130.1, 129.9, 129.1, 128.6, 127.7, 126.9, 123.6, 122.0, 120.0, 114.0, 111.5, 55.3, 55.1, 52.2; HRMS (ESI), m/z calcd. for $C_{28}H_{25}N_3O_5$ ([M + Na]$^+$) 506.1686, found 506.1664.

(*E*)-Methyl 4-(2-(2-oxo-6-phenyl-5-(phenylcarbamoyl)-1,2,3,6-tetrahydropyrimidin-4-yl)vinyl)benzoate (3q). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (165.3 mg, 73%): mp 270−272 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 8.87 (s, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.79 (s, 1H), 7.56 (t, J = 8.0 Hz, 4H), 7.45 (d, J = 16.8 Hz, 1H), 7.37−7.27 (m, 8H), 7.05 (t, J = 7.2 Hz, 1H), 5.55 (d, J = 2.0 Hz, 1H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.8, 164.6, 152.7, 143.4, 140.9, 138.9, 135.9, 130.2, 129.8, 129.1, 128.6, 127.6, 126.8, 126.4, 123.5, 121.9, 120.0, 111.1, 55.8, 52.1; HRMS (ESI), m/z calcd. for $C_{27}H_{23}N_3O_4$ ([M + H]$^+$) 454.1761, found 454.1747.

(*E*)-Methyl 4-(2-(6-(4-fluorophenyl)-2-oxo-5-(phenylcarbamoyl)-1,2,3,6-tetrahydropyrimidin-4-yl)vinyl)benzoate (3r). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (204.8 mg, 87%): mp 283−285 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.91 (s, 1H), 7.94 (d, J = 7.6 Hz, 2H), 7.81 (s, 1H), 7.55 (s??, 4H), 7.44 (d, J = 16.4 Hz, 1H), 7.37−7.26 (m, 5H), 7.19 (t, J = 8.4 Hz, 2H), 7.04 (d, J = 6.8 Hz, 1H), 5.53 (s, 1H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.9, 164.6, 152.6, 140.9, 139.7, 138.9, 136.1, 130.4, 129.9, 129.1, 128.7, 128.5 (d, J = 8.4 Hz), 126.9, 123.6, 121.9, 120.1, 115.4 (d, J = 21.2 Hz), 110.9, 55.2, 52.2; One carbon was not observed; HRMS (ESI), m/z calcd. for $C_{27}H_{22}FN_3O_4$ ([M + H]$^+$) 472.1667, found 472.1665.

(*E*)-*N*-(4-Chlorophenyl)-6-(4-methoxystyryl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3s). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (208.8 mg, 91%): mp 236−238 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.07 (s, 1H), 8.76 (s, 1H), 7.72 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.36−7.26 (m, 10H), 7.07 (d, J = 16.4 Hz, 1H), 6.94 (d, J = 8.0 Hz, 2H), 5.47 (s, 1H), 3.76 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.6, 160.2, 153.3, 144.2, 138.6, 137.5, 132.0, 129.3, 129.0, 128.9, 128.6, 128.0, 127.4, 126.8, 121.8, 117.4, 114.9, 109.1, 56.0, 55.7; HRMS (ESI), m/z calcd. for $C_{26}H_{22}ClN_3O_3$ ([M + H]$^+$) 460.1422, found 460.1422.

(*E*)-4-(4-Fluorophenyl)-6-(4-methoxystyryl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3t). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (188.3 mg, 85%): mp 248−250 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.00 (s, 1H), 8.82 (s, 1H), 7.77 (s, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.37−7.34 (m, 4H), 7.28 (dd, J_1 = 14.8 Hz, J_2 = 7.6 Hz, 3H), 7.19 (t, J = 8.8 Hz, 2H), 7.09−7.02 (m, 2H), 6.94 (d, J = 8.4 Hz, 2H), 5.48 (d, J = 2.8 Hz, 1H), 3.74 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.0, 161.5 (d, J = 241.8 Hz), 159.7, 152.7, 140.0 (d, J = 2.8 Hz), 139.1, 136.7, 131.4, 128.8, 128.6, 128.5 (d, J = 8.3 Hz), 128.2, 123.5, 119.9, 116.9, 115.3 (d, J = 21.5 Hz), 114.5, 108.8, 55.2, 55.0; HRMS (ESI), m/z calcd. for $C_{26}H_{22}FN_3O_3$ ([M + H]$^+$) 444.1718, found 444.1715.

(*E*)-4-(4-Methoxyphenyl)-6-(4-methoxystyryl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3u). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 60/1) as a white solid (166.1 mg, 73%): mp 240−242 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.74 (s, 1H), 7.67 (s, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.37−7.24 (m, 7H), 7.10 (d, J = 16.4 Hz, 1H), 7.03 (t, J = 7.2 Hz, 1H), 6.92 (dd, J_1 = 14.4 Hz, J_2 = 8.4 Hz, 4H), 5.45 (s, 1H), 3.75 (s, 3H), 3.71 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 165.1, 159.6, 158.7, 152.8, 139.2, 136.4, 135.9, 131.1, 128.9, 128.6, 128.1, 127.7, 123.4, 119.9, 117.1, 114.4, 113.9, 109.3, 55.2, 55.14, 55.08; HRMS (ESI), m/z calcd. for $C_{27}H_{25}N_3O_4$ ([M + Na]$^+$) 478.1737, found 478.1731.

(*E*)-2-Oxo-*N*,4-diphenyl-6-(2-(thiophen-2-yl)vinyl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3v). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 100/1) as a white solid (90.2 mg, 45%): mp 236−238 °C; ^1H NMR

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(400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.80 (s, 1H), 7.75 (s, 1H), 7.57 (dd, J_1 = 12.4 Hz, J_2 = 3.6 Hz, 3H), 7.50 (d, J = 4.8 Hz, 1H), 7.37−7.26 (m, 7H), 7.13 (d, J = 3.2 Hz, 1H), 7.07−7.04 (m, 2H), 7.01 (d, J = 16.0 Hz, 1H), 5.48 (d, J = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 164.8, 152.8, 143.6, 141.5, 139.0, 136.0, 128.62, 128.60, 128.3, 128.2, 127.6, 126.9, 126.4, 125.1, 123.5, 119.9, 118.4, 109.8, 55.7; HRMS (ESI), m/z calcd. for $C_{23}H_{19}N_3O_2S$ ($[M + H]^+$) 402.1271, found 402.1272.

(*E*)-6-(2-(Furan-2-yl)vinyl)-2-oxo-*N*,4-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3w). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 100/1) as a white solid (21.3 mg, 11%): mp 173−175 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.80 (s, 1H), 7.72 (s, 1H), 7.67 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.34−7.21 (m, 8H), 7.04 (t, J = 8.0 Hz, 2H), 6.52 (d, J = 2.0 Hz, 2H), 5.47 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 164.9, 152.8, 151.8, 144.1, 143.6, 139.1, 135.8, 128.60, 128.58, 127.6, 126.4, 123.5, 119.8, 119.4, 117.0, 112.3, 111.4, 110.2, 55.8; HRMS (ESI), m/z calcd. for $C_{23}H_{19}N_3O_3$ ($[M + H]^+$) 386.1499, found 386.1494.

(*E*)-2-Oxo-*N*-phenyl-6-styryl-4-(thiophen-2-yl)-1,2,3,4-tetrahydropyrimidine-5-carboxamide (3aa). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 60/1) as a white solid (64.2 mg, 32%): mp 240−242 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 8.96 (s, 1H), 7.96 (s, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.43−7.35 (m, 6H), 7.29 (dd, J_1 = 16.0 Hz, J_2 = 6.8 Hz, 4H), 7.05 (t, J = 7.2 Hz, 1H), 6.97−6.95 (m, 2H), 5.77 (d, J = 2.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 164.5, 152.7, 147.8, 139.1, 137.1, 136.2, 132.1, 128.9, 128.6, 126.8, 125.4, 123.9, 123.5, 120.0, 119.4, 109.4, 51.2; Two carbons were not observed; HRMS (ESI), m/z calcd. for $C_{23}H_{19}N_3O_2S$ ($[M + Na]^+$) 424.1090, found 424.1093.

4,6,7-Triphenyl-3,4,7,8-tetrahydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (4a). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (163.9 mg, 83%): mp 302−304 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 7.74 (s, 1H), 7.35−7.16 (m, 12H), 7.10 (d, J = 7.6 Hz, 2H), 7.03 (t, J = 7.2 Hz, 1H), 5.33 (t, J = 5.2 Hz, 1H), 5.22 (s, 1H), 3.28 (dd, J_1 = 16.4 Hz, J_2 = 5.6 Hz, 1H), 2.72 (dd, J_1 = 16.4 Hz, J_2 = 4.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 163.7, 152.1, 144.9, 143.5, 141.8, 141.1, 128.5, 128.4, 128.1, 127.5, 127.2, 126.9, 126.7, 126.5, 125.3, 100.9, 59.9, 53.3, 33.3; HRMS (ESI), m/z calcd. for $C_{25}H_{21}N_3O_2$ ($[M + H]^+$) 396.1707, found 396.1714.

6-(3-Methoxyphenyl)-4,7-diphenyl-3,4,7,8-tetrahydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (4b). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 100/1) as a white solid (148.7 mg, 70%): mp 303−305 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.24 (s, 1H), 7.70 (s, 1H), 7.34−7.21 (m, 10H), 7.07 (t, J = 8.0 Hz, 1H), 6.69−6.66 (m, 2H), 6.61 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 5.31 (t, J = 6.0 Hz, 1H), 5.20 (d, J = 3.2 Hz, 1H), 3.61 (s, 3H), 3.25 (dd, J_1 = 16.8 Hz, J_2 = 6.8 Hz, 1H), 2.70 (dd, J_1 = 16.8 Hz, J_2 = 5.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 163.7, 159.0, 152.1, 144.9, 143.5, 142.9, 141.1, 128.7, 128.5, 128.3, 127.5, 127.2, 126.8, 126.5, 119.2, 113.0, 110.5, 100.9, 59.9, 55.0, 53.3, 33.3; HRMS (ESI), m/z calcd. for $C_{26}H_{23}N_3O_3$ ($[M + H]^+$) 426.1812, found 426.1816.

6-(3-Chlorophenyl)-4,7-diphenyl-3,4,7,8-tetrahydropyrido-[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (4c). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 100/1) as a white solid (171.6 mg, 80%): mp 273−275 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 7.75 (s, 1H), 7.34−7.19 (m, 12H), 7.07 (dd, J_1 = 16.0 Hz, J_2 = 8.0 Hz, 2H), 5.38 (t, J = 4.4 Hz, 1H), 5.21(s, 1H), 3.24 (dd, J_1 = 16.8 Hz, J_2 = 5.2 Hz, 1H), 2.75 (dd, J_1 = 16.8 Hz, J_2 = 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 163.7, 151.9, 144.8, 144.0, 143.1, 140.6, 132.2, 129.6, 128.6, 128.4, 127.6, 127.2, 126.9, 126.7, 126.5, 125.2, 125.1, 100.6, 59.6, 53.3, 33.3; HRMS (ESI), m/z calcd. for $C_{25}H_{20}ClN_3O_2$ ($[M + H]^+$) 430.1317, found 430.1328.

4,7-Bis(4-methoxyphenyl)-6-phenyl-3,4,7,8-tetrahydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,6*H*)-dione (4d). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 80/1) as a white solid (216.2 mg, 95%): mp 278−280 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 7.65 (s, 1H), 7.25−7.16 (m, 6H), 7.08−7.03 (m, 3H), 6.87 (dd, J_1 = 12.8 Hz, J_2 = 8.4 Hz, 4H), 5.24 (br, 1H), 5.15 (s, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.19 (dd, J_1 = 16.4 Hz, J_2 = 4.8 Hz, 1H), 2.68 (dd, J_1 = 16.0 Hz, J_2 = 2.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 163.8, 158.4, 152.1, 143.2, 141.9, 137.2, 132.8, 128.0, 127.6, 126.7, 125.2, 113.8, 113.6, 101.2, 59.4, 55.1, 55.0, 52.7, 33.5; HRMS (ESI), m/z calcd. for $C_{27}H_{25}N_3O_4$ ($[M + Na]^+$) 478.1737, found 478.1734.

Ethyl 4-(2,5-dioxo-4,6-diphenyl-1,2,3,4,5,6,7,8-octahydropyrido[4,3-*d*]pyrimidin-7-yl)benzoate (4e). The product was isolated by flash chromatography (eluent: dichloromethane/methanol = 60/1) as a white solid (191.5 mg, 82%): mp 265−267 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.22 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.58−7.52 (m, 3H), 7.43 (t, J = 8.0 Hz, 2H), 7.13 (dd, J_1 = 17.6 Hz, J_2 = 7.2 Hz, 2H), 7.01 (t, J = 8.0 Hz, 4H), 6.53 (d, J = 7.6 Hz, 2H), 5.44 (br, 1H), 5.02 (s, 1H), 4.35 (q, J = 7.2 Hz, 2H), 3.38 (dd, J_1 = 14.4 Hz, J_2 = 3.2 Hz, 1H), 3.13 (dd, J_1 = 14.4 Hz, J_2 = 3.2 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 166.3, 165.7, 152.2, 151.3, 142.5, 140.1, 137.1, 129.8, 129.0, 128.9, 128.5, 127.8, 127.2, 126.6, 123.5, 121.4, 103.3, 60.6, 56.5, 52.9, 32.2, 14.3; HRMS (ESI), m/z calcd. for $C_{28}H_{25}N_3O_4$ ($[M + Na]^+$) 490.1737, found 490.1761.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental methods and ^1H NMR and $^{13}C\{^1H\}$ NMR spectra of compounds **3** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*Fax: (+86) 373-3325250. E-mail: zhangzg@htu.edu.cn.

*E-mail: zgs6668@yahoo.com.

Notes

The authors declare no competing financial interest.

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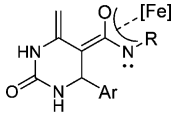
(36) In Biginelli products **1**, the methyl at 6-position is weakly acidic in the absence of a base.[12] Compound **1** (with the acylamino at 5-position) forms the vinylogous conjugated systems **A** with the iron salts.[33−35] The orientation of bonds facilitates the delocalization of electrons within the vinylogous conjugated systems **A**, making the methyl substituent more acidic. This delocalization of electrons provides a partial double bond character to the methyl substituent, thereby creating the stage for the initiation of the reaction.[22]



A

(37) For details, please see the Supporting Information.
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