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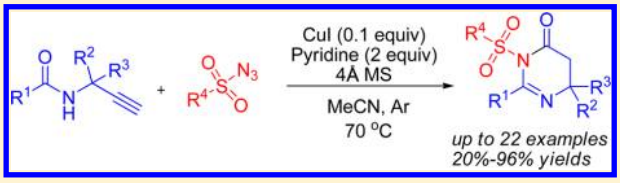
Copper-Catalyzed Cascade Preparation of Dihydropyrimidin-4-ones from *N*-(Prop-2-yn-1-yl)amides and Azides

Jinjin Wang, Jing Wang, Ping Lu,* and Yanguang Wang*

Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China

Supporting Information

ABSTRACT: Dihydropyrimidin-4-ones were efficiently synthesized from copper catalyzed reaction between *N*-(prop-2-yn-1-yl)amides and sulfonylazides under mild conditions in moderate to excellent yields (up to 96% yields). The cascade process involves the copper-catalyzed alkyne−azide cycloaddition, the formation of ketenimine intermediate, the intramolecular nucleophilic addition of ketenimine, and subsequent rearrangement.



Dihydropyrimidinones (DHPMs) are an important class of heterocycles in medicinal chemistry due to their diverse pharmacological activities.[1−4] Among these compounds, dihydropyrimidin-4-ones have attracted attention extensively in the past decade. A number of dihydropyrimidin-4-ones have been found to be non-nucleoside HIV-1 inhibitors.[5−7] Moreover, several dihydropyrimidin-4-ones, such as risperidone (Risperdal) and paliperidone (9-hydroxy-risperidone, Invega), are currently used for the treatment of schizophrenia.[8,9] Traditional methods leading to dihydropyrimidin-4-one skeleton include the condensation between β-amino amides and aldehydes,[10,11] and the reaction of amidines with methyl acrylates.[10] The three-component coupling of Meldrum's acid, aldehydes, and guanidine carbonate could afford 2-amino-dihydropyrimidin-4-ones, yet in relatively lower yields.[12,13]

In recent years, the copper-catalyzed azide−alkyne cycloaddition (CuAAC) has been developed to form ketenimines,[14,15] which shine light on the development of multicomponent approaches to a variety of principal heterocyclic compounds.[15−19] In our previous study, a number of efficient three-component[20−24] and four-component reactions[25−27] were successfully achieved by intermolecular trapping of the ketenimine intermediates generated through CuAAC mechanism. However, there are few examples presenting the intramolecular trapping of ketenimine.[28] Consequently, we were interested in integrating terminal alkyne and nucleophilic amide into one starting material molecule, such as *N*-(prop-2-yn-1-yl)amides **1**, and expected that the terminal alkyne group could react with tosyl azide to generate reactive ketenimine **A** in CuAAC conditions and the intramolcular amide could function as a trapping unit to attack central carbon of the resulting ketenimine to give heterocyclic compounds **B** and/or **B′** (Figure 1). Herein, we would like to report the results of this effort.

In our primary experiment, we selected *N*-(prop-2-yn-1-yl)amide **1a** as starting material for the model reaction with tosyl azide and obtained dihydropyrimidin-4-one **3a** in 30% isolated yield when the reaction was carried out in the presence of CuI and triethylamine in dichloromethane at 30 °C for 2.5 h

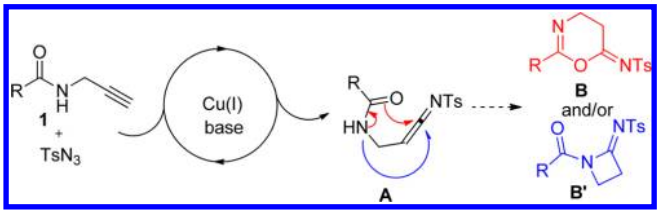


Figure 1. Our preliminary consideration.

(Table 1, entry 1). The structure of **3a** was established by single crystal analysis.[29] Encouraged by this result, we investigated the reaction conditions and the results are summarized in Table 1. After screening seven solvents, acetonitrile was found to be the optimal in comparison to other widely used solvents, such as dichloromethane (DCM), dichloroethane (DCE), tetrahydrofuran (THF), *N*,*N*-dimethylforamide (DMF), dimethyl sulfoxide (DMSO), toluene, and 1,4-dioxane (Table 1, entries 1−8). Adding the molecular sieve could prompt this transformation to increase the yield (Table 1, entry 9). When tested the catalysts, most of Cu(I) catalysts offered slightly lower yields in comparison to CuI except for Cu_2O, which did not facilitate the reaction (Table 1, entries 10−14). Additionally, pyridine (2 equiv) was found to be the optimal in comparison to other bases, such as K_2CO_3, Cs_2CO_3, and triethylamine. DABCO and DBU did not work for this transformation (Table 1, entries 15−21). Optimal reaction temperature and reaction time were found to be 70 °C and 1 h, respectively (Table 1, entry 24).

With the optimized reaction conditions in hand, we investigated the substrate scope of *N*-(prop-2-yn-1-yl)amides and sulfonylazides, respectively. As shown in Table 1, both aromatic amides (**1a**-**1h** and **1k**-**1m**) and aliphatic amides (**1j** and **1n**) worked for this cascade reaction to afford the corresponding products **3a**-**3h** and **3j**-**3n** in yields varied from 20% to 96%. Electronic effect of substituents on the phenyl ring

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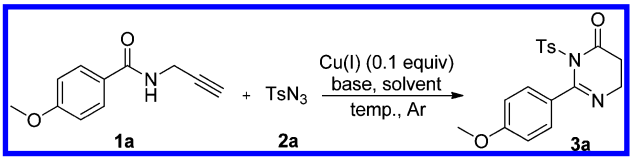
Table 1. Screening of the Reaction Conditions[a]



entry	catalyst	base/equiv	solvent	temp °C	4 Å MS[b]	time (h)[c]	yield (%)[d]
1	CuI	TEA/2	DCM	30	-	2.5	30
2	CuI	TEA/2	DCE	30	-	2.5	35
3	CuI	TEA/2	THF	30	-	2.0	12
4	CuI	TEA/2	DMF	30	-	1.3	16
5	CuI	TEA/2	DMSO	30	-	3.5	11
6	CuI	TEA/2	Toluene	30	-	2.0	13
7	CuI	TEA/2	1,4-Dioxane	30	-	1.8	6
8	CuI	TEA/2	MeCN	30	-	2.0	38
9	CuI	TEA/2	MeCN	30	+	2.0	46
10	CuCl	TEA/2	MeCN	30	+	4.0	31
11	Cu_2O	TEA/2	MeCN	30	+	72.0	0
12	CuCN	TEA/2	MeCN	30	+	5.0	27
13	CuBr	TEA/2	MeCN	30	+	4.0	37
14	CuOTf	TEA/2	MeCN	30	+	3.0	40
15	CuI	K_2CO_3/2	MeCN	30	+	1.0	45
16	CuI	DABCO/2	MeCN	30	+	7.7	0
17	CuI	DBU/2	MeCN	30	+	2.0	0
18	CuI	$CsCO_3$/2	MeCN	30	+	1.3	30
19	CuI	Pyridine/2	MeCN	30	+	3.5	47
20	CuI	Pyridine/1	MeCN	30	+	3.5	35
21	CuI	Pyridine/3	MeCN	30	+	2.0	34
22	CuI	Pyridine/2	MeCN	20	+	5.0	0
23	CuI	Pyridine/2	MeCN	50	+	2.0	52
24	CuI	Pyridine/2	MeCN	70	+	1.0	57
25	CuI	Pyridine/2	MeCN	reflux	+	0.7	54

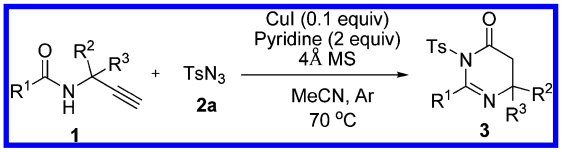
[a]Reaction conditions: **1a** (0.5 mmol); **2a** (0.5 mmol); solvent (2 mL). [b]Entries 9–25: 4 Å MS (100 mg). [c]Reaction time was determined on the basis of the disappearance of substrate by tracking with TLC. [d]Isolated yield.

of R^1 in **1** was apparent. Only substituents with moderate electron-donating property facilitated the reaction and afforded dihydropyrimidine-4-ones in good yields (Table 2, entry 3). Cinnamamide (**1i**) furnished **3i** in 50% yield. Two methyl groups attached on propargylic amine were found to be significant in increasing the yield by comparing two pairs: **1c** and **1k** (Table 2, entries 3 and 11), **1g** and **1l** (Table 2, entries 7 and 12).

As listed in Table 3, both aromatic sulfonyl azides (**2a**-**2e**) and aliphatic sulfonyl azide (**2f**) reacted with *N*-(prop-2-yn-1-yl)amides (**1a**-**1d**) in the presence of CuI to produce **3c** and **3o**–**3v** in yields varied from 30% to 81%.

Based on the investigation of reaction conditions and substrate scope, a possible mechanism is postulated as shown in Scheme 1. Terminal alkyne **1** first reacts with sulfonylazide **2a** in the presence of Cu(I) to afford ketenimine intermediate **A** *via* an expected copper-catalyzed alkyne–azide cycloaddition, following by Dimorth rearrangement. The electron-deficient central carbon of ketenimine **A** might be intramolecularly attacked by oxygen of the amide to form **B**. Theoretical calculation supported the prior formation of six-membered ring **B** instead of four-membered ring **B′** due to the ring strain. Energy difference between **B** and **B′** was calculated to be 9.25 kJ/mol when R referred to phenyl group (**1b**) (see Table S1; Calculated with Spartan'10 by density functional method at B3LYP/6-31G* level). Extension calculation for the potential energies of **B** and **B′** when R referred to 4-methoxyphenyl (**1a**),

Table 2. Substrate Scope of *N*-(Prop-2-yn-1-yl)amides[a]



entry	1(R^1/R^2/R^3)	reaction time (h)[b]	3 (yield, %)[c]
1	**1a** (4-MeOC_6H_4/H/H)	1	**3a** (57)
2	**1b** (Ph/H/H)	1	**3b** (76)
3	**1c** (4-MeC_6H_4/H/H)	1.5	**3c** (79)
4	**1d** (4-ClC_6H_4/H/H)	2.2	**3d** (53)
5	**1e** (2-ClC_6H_4/H/H)	6	**3e** (59)
6	**1f** (3-ClC_6H_4/H/H)	3	**3f** (32)
7	**1g** (4-BrC_6H_4/H/H)	4	**3g** (20)
8	**1h** (2-naphthalenyl/H/H)	2	**3h** (69)
9	**1i** (PhCH=CH/H/H)	1	**3i** (50)
10	**1j** (*c*-C_6H_{11}/H/H)	2	**3j** (21)
11	**1k** (4-MeC_6H_4/Me/Me)	4	**3k** (96)
12	**1l** (4-BrC_6H_4/Me/Me)	1	**3l** (38)
13	**1m** (4-MeC_6H_4/R^2,R^3= -$(CH_2)_5$-)	1.3	**3m** (53)
14	**1n** (Me/H/Ph)	1.3	**3n** (68)

[a]Reaction conditions: **1** (0.5 mmol); **2a** (0.5 mmol); 4 Å MS (100 mg); Acetonitrile (2 mL). [b]Reaction time was determined on the basis of the disappearance of substrate by tracking with TLC. [c]Isolated yield.

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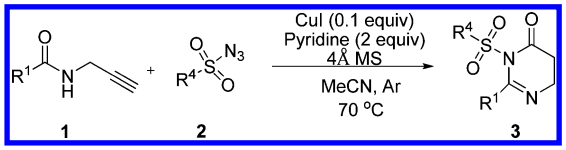
Table 3. Substrate Scope of Azides[a]

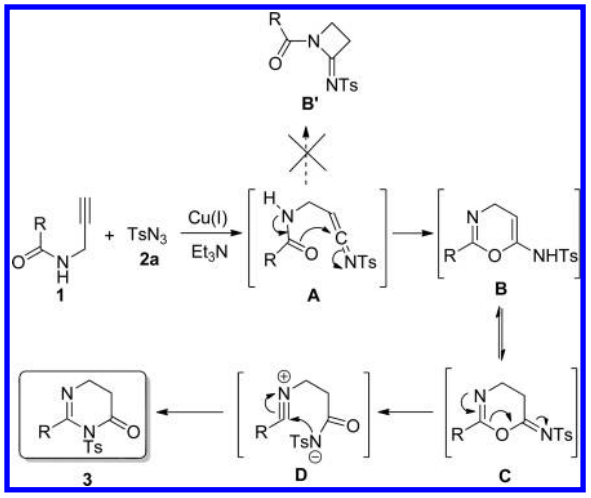


1 2 3

entry	1 (R^1)	2 (R^4)	reaction time (h)[b]	3 (yield %)[c]
1	**1c** (4-MeC_6H_4)	**2a** (4-MeC_6H_4)	1.5	**3c** (79)
2	**1b** (Ph)	**2b** (4-$MeOC_6H_4$)	1.7	**3o** (47)
3	**1c**	**2b**	1.3	**3p** (81)
4	**1a** (4-$MeOC_6H_4$)	**2c** (Ph)	2.5	**3q** (42)
5	**1c**	**2c**	1	**3r** (71)
6	**1c**	**2d** (2-naphthalenyl)	2	**3s** (49)
7	**1c**	**2e** (4-ClC_6H_4)	3	**3t** (37)
8	**1d** (4-ClC_6H_4)	**2e**	2	**3u** (30)
9	**1c**	**2f** (Me)	1.5	**3v** (42)

[a]Reaction conditions: **1** (0.5 mmol); **2a** (0.5 mmol); 4 Å MS (100 mg); Acetonitrile (2 mL). [b]Reaction time was determined on the basis of the disappearance of substrate by tracking with TLC. [c]Isolated yield.

Scheme 1. Proposed Mechanism for the Formation of 3



4-methylphenyl (**1c**), or 4-chlorophenyl (**1d**) further supported that the formation of **B** was prior to the formation of **B′**. **B** is unstable with an imidic anhydride substructure, which undergoes a ring-opening to form intermediate **C**. As a result, the thermodynamically stable product **3** is constructed *via* an intramolecular nucleophilic addition. Also, this could be explained by the calculated result. The energy difference between **B** and **3b** (R = Ph) was calculated to be 27.98 kJ/mol and **3b** is more stable. Similar results were observed for the cases where R is 4-methoxyphenyl (**3a**), 4-methylphenyl (**3c**), or 4-chlorophenyl (**3d**) (see Table S1).

In conclusion, we developed an efficient method for the preparation of dihydropyrimidin-4-ones from *N*-(prop-2-yn-1-yl)amides and sulfonyl azides. The cascade reaction underwent copper-catalyzed alkyne−azide cycloaddition, formation and intramolecular nucleophilic addition of ketenimine, and subsequent rearrangement in a single step. Moreover, the starting materials, propargylamides, could be easily prepared from propargylic alcohols via Ritter reaction[30] or from propargylamines via aminolysis of acid chlorides,[31] while sulfonylazides could be obtained from sulfonylchlorides and sodium azide.[32] With the diverse pharmacological activities of dihydropyrimidinones, our method shall find its applications in medicinal chemistry.

EXPERIMENTAL SECTION

General Considerations. Infrared spectra were obtained on a FTIR spectrometer. ^{1}H NMR spectra were recorded on 500 or 400 MHz spectrometer, referred to the internal solvent signals (0 for TMS in $CDCl_3$ or 2.5 for the residue of DMSO). The following abbreviations were used to describe peak patterns where appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants were reported in Hertz (Hz). ^{13}C NMR were recorded on 125 or 100 MHz spectrometer, referred to the internal solvent signals (77.27 for $CDCl_3$ or 40.0 for DMSO-d_6). High resolution mass spectra (HRMS) were performed on an electron ionization time-of-flight (EI-TOF) mass spectrometer. Melting points were measured with micromelting point apparatus.

General Procedure for the Synthesis of Dihydropyrimidin-4-ones 3. To a solution of N-(prop-2-yn-1-yl)amides (0.5 mmol), sulfonyl azide (0.6 mmol), 4 Å MS (100 mg), and CuI (0.05 mmol) in MeCN (1.5 mL) protected by argon was added a solution of pyridine (1 mmol) in MeCN (0.5 mL) via syringe, and the mixture was reacted at 70 °C (oil bath) for a certain period of time which was determined by TLC. After filtrated, the reaction mixture was then diluted with CH_2Cl_2 (10 mL), washed with dilute hydrochloric acid, water, and brine, dried over anhydrous Na_2SO_4, and evaporated in vacuum. The residue was subject to silica gel column chromatography with EA/Pet (1:3, v/v) as eluent to give products **3**.

2-(4-Methoxyphenyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3a). Unknown compound, a white powder (103 mg, 0.29 mmol, 57%); mp 161.8−162.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.5 Hz 2H), 7.32 (d, J = 8.5 Hz, 2H), 6.91 (d, J_1 = 9.0 Hz, 2H), 3.86 (s, 3H), 3.68 (t, J = 6.0 Hz, 2H), 2.52 (t, J = 6.0 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 161.9, 154.3, 145.9, 136.3, 129.6, 129.3, 126.7, 113.9, 55.6, 43.5, 34.4, 22.0; IR (KBr) ν 2991, 2859, 1734, 1637, 1606, 1511, 1361, 1259, 1184, 1147, 1102, 823, 685 cm^{-1}; HRMS (EI-TOF) calcd for $C_{18}H_{18}N_2O_4S$ (M^+), 358.0987; found, 358.0985.

2-Phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3b). Unknown compound, a light yellow powder (125 mg, 0.38 mmol, 76%); mp 163.0−164.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2H), 7.62−7.56 (m, 2H), 7.48 (m, 1H), 7.40 (m, 2H), 7.32 (d, J = 8.0 Hz, 2H), 3.74 (t, J = 6.5 Hz, 2H), 2.55 (t, J = 6.5 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 154.7, 146.0, 136.4, 136.1, 131.0, 129.6, 129.6, 128.6, 127.6, 43.6, 34.2, 22.0; IR (KBr) ν 2959, 1736, 1640, 1449, 1370, 1282, 1252, 1191, 1169, 1151, 1102, 1084, 1002, 809, 771, 699, 686, 671 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{16}N_2O_3S$ (M^+), 328.0882; found, 328.0878.

2-(*p*-Tolyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3c). Unknown compound, a white powder (136 mg, 0.40 mmol, 79%); mp 176.0−177.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 3.70 (t, J = 6.3 Hz, 2H), 2.52 (t, J = 6.3 Hz, 2H), 2.45 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 154.6, 145.9, 141.4, 136.2, 133.7, 129.6, 129.3, 127.5, 43.5, 34.2, 22.0, 21.8; IR (KBr) ν 2916, 1744, 1634, 1361, 1279, 1185, 1106, 811, 685 cm^{-1}; HRMS (EI-TOF) calcd for $C_{18}H_{18}N_2O_3S$ (M^+), 342.1038; found, 342.1042.

2-(4-Chlorophenyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3d). Unknown compound, a white powder (96 mg, 0.26 mmol, 53%); mp 171.5−172.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2H), 7.59−7.54 (m, 2H), 7.41−7.36 (m, 2H), 7.33 (d, J = 8.2 Hz, 2H), 3.72 (t, J = 6.4 Hz, 2H), 2.53(t, J = 6.4 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 153.7, 146.2, 137.1, 136.0, 134.9, 129.7, 129.5, 129.0, 128.8, 43.6, 34.1, 22.0; IR (KBr) ν 2971, 1730, 1637, 1595, 1371, 1277, 1185, 1168, 1152, 1088, 1003, 822, 690 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{15}ClN_2O_3S$ (M^+), 362.0492; found, 362.0489.

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2-(2-Chlorophenyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3e). Unknown compound, a white powder (107 mg, 0.29 mmol, 59%); mp 115.0−116.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57−7.54 (m, 1H), 7.50 (d, J = 8.3 Hz, 2H), 7.39−7.36 (m, 2H), 7.18 (d, J = 7.2 Hz, 2H), 3.86 (t, J = 5.5, 2H), 2.67 (t, J = 5.5, 2H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 151.6, 145.8, 134.9, 134.3, 132.5, 131.9, 131.0, 129.3, 129.2, 129.1, 127.0, 43.8, 34.1, 22.0; IR (KBr) ν 3282, 2925, 1732, 1599, 1546, 1438, 1370, 1281, 1224, 1142, 1084, 938, 811, 751, 683 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{15}ClN_2O_3S$ (M^+), 362.0492; found, 362.0492.

2-(3-Chlorophenyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3f). Unknown compound, a white powder (59 mg, 0.16 mmol, 32%); mp 184.2−185.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 7.7 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.37−7.33 (m, 3H), 3.77 (t, J = 6.5 Hz, 2H), 2.57 (t, J = 6.4 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 153.5, 146.2, 138.0, 135.8, 134.5, 131.0, 130.0, 129.8, 129.5, 127.6, 126.0, 43.7, 34.2, 22.0; IR (KBr) ν 3073, 2965, 2906, 2854, 1723, 1633, 1593, 1414, 1359, 1263, 1174, 1112, 1007, 813, 791, 733, 677 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{15}ClN_2O_3S$ (M^+), 362.0492; found, 362.0499.

2-(4-Bromophenyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3g). Unknown compound, a white powder (40 mg, 0.10 mmol, 20%); mp 180.0−181.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 3.71 (t, J = 6.3 Hz, 2H), 2.53 (t, J = 6.3 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 153.9, 146.2, 136.0, 135.4, 131.8, 129.7, 129.5, 129.2, 125.5, 43.6, 34.1, 22.0; HRMS (EI-TOF) calcd for $C_{17}H_{15}BrN_2O_3S$ (M^+), 405.9987; found, 405.9994.

2-(Naphthalen-2-yl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3h). Unknown compound, a white powder (130 mg, 0.34 mmol, 69%); mp 162.5−163.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90−7.86 (m, 3H), 7.83 (d, J = 8.3 Hz, 2H), 7.76 (dd, J_1 = 8.6, J_2 = 1.6 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.57−7.48 (m, 2H), 7.3 (d, J = 8.0 Hz, 2H), 3.81 (t, J = 6.4 Hz, 2H), 2.61 (t, J = 6.4 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 154.8, 145.9, 136.2, 134.6, 133.7, 132.5, 129.6, 128.9, 128.7, 128.1, 127.6, 126.9, 124.7, 43.8, 34.5, 22.0; IR (KBr) ν 3057, 2922, 2862, 1741, 1637, 1358, 1280, 1145, 1182, 1096, 1000, 814, 665 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{18}N_2O_3S$ (M^+), 378.1038; found, 378.1039.

(*E*)-2-Styryl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3i). Unknown compound, a white powder (88 mg, 0.25 mmol, 50%); mp 117.1−118.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.3 Hz, 2H), 7.51−7.45 (m, 3H), 7.41−7.35 (m, 5H), 6.88 (d, J = 15.7 Hz, 1H), 3.67 (t, J = 6.4 Hz, 2H), 2.51 (t, J = 6.4 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 151.5, 146.0, 137.3, 136.5, 135.5, 129.9, 129.7, 129.1, 129.1, 127.9, 122.1, 43.0, 33.8, 22.0; IR (KBr) ν 3315, 2847, 1739, 1636, 1607, 1535, 1362, 1175, 1086, 758, 667 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{18}N_2O_3S$ (M^+), 354.1038; found, 354.1035.

2-Cyclohexyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3j). Unknown compound, a yellow powder (35 mg, 0.10 mmol, 21%); mp 115.9−117.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 3.55 (t, J = 6.2 Hz, 2H), 3.03 (t, J = 10.9 Hz, 1H), 2.46 (s, 3H), 2.40 (t, J = 6.2 Hz, 2H), 1.83 (d, J = 12.1 Hz, 2H), 1.74 (d, J = 12.4 Hz, 2H), 1.68 (d, J = 11.2 Hz, 1H), 1.37−1.15 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 160.2, 145.7, 136.6, 129.8, 128.8, 44.2, 42.5, 31.6, 26.2, 26.1, 21.9; IR (KBr) ν 3354, 3067, 2923, 2855, 1745, 1645, 1581, 1542, 1365, 1175, 1081, 852, 665 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{22}N_2O_3S$ (M^+), 334.1351; found, 334.1357.

6,6-Dimethyl-2-(*p*-tolyl)-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3k). Unknown compound, a white powder (179 mg, 0.48 mmol, 96%); mp 130.1−132.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 2.47 (s, 2H), 2.45 (s, 3H), 2.39 (s, 3H), 1.31 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 150.7, 145.9, 140.7, 135.8, 134.4, 131.1, 129.4, 129.1, 127.4, 54.2, 45.6, 27.5, 22.0, 21.7; IR (KBr) ν 2975, 2927, 1727, 1624, 1366, 1274, 1233, 1168, 1084, 814, 696, 668 cm^{-1}; HRMS (EI-TOF) calcd for $C_{20}H_{22}N_2O_3S$ (M^+), 370.1351; found, 370.1357.

2-(4-Bromophenyl)-6,6-dimethyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3l). Unknown compound, a white powder (84 mg, 0.19 mmol, 38%); mp 143.5−144.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.2 Hz, 2H), 2.47 (s, 2H), 2.46 (s, 3H), 1.31 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 150.0, 146.2, 136.1, 135.6, 131.7, 130.1, 129.5, 129.1, 124.9, 54.5, 45.5, 27.5, 22.0; IR (KBr) ν 2969, 2929, 1728, 1636, 1591, 1360, 1273, 1175, 1083, 1010, 815, 667 cm^{-1}; HRMS (EI-TOF) calcd for $C_{19}H_{19}BrN_2O_3S$ (M^+), 434.0300; found, 434.0305.

2-(*p*-Tolyl)-3-tosyl-1,3-diazaspiro[5.5]undec-1-en-4-one (3m). Unknown compound, a white powder (108 mg, 0.26 mmol, 53%); mp 141.6−142.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 7.9 Hz, 2H), 2.45 (s, 3H), 2.44 (s, 2H), 2.39 (s, 3H), 1.83−1.72 (m, 4H), 1.62 (s, 1H), 1.51 (m, 2H), 1.45−1.30 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 145.0, 145.8, 140.7, 135.8, 134.6, 130.1, 129.3, 129.1, 127.5, 56.4, 44.7, 36.4, 25.8, 22.2, 22.0, 21.7; IR (KBr) ν 2928, 2855, 1738, 1637, 1372, 1297, 1172, 1082, 677, 665 cm^{-1}; HRMS (EI-TOF) calcd for $C_{23}H_{26}N_2O_3S$ (M^+), 410.1664; found, 410.1664.

2-Methyl-6-phenyl-3-tosyl-5,6-dihydropyrimidin-4(3*H*)-one (3n). Unknown compound, a white powder (117 mg, 0.34 mmol, 68%); mp 167.0−168.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.39−7.33 (m, 6H), 7.32−728 (m, 1H), 4.74−4.60 (m, 1H), 2.77 (dd, J_1 = 17.3, J_2 = 3.8 Hz, 1H), 2.60 (d, J = 1.7 Hz, 3H), 2.53−2.48 (m, 1H), 2.46 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 151.0, 145.9, 140.4, 136.1, 129.8, 129.2, 129.1, 128.0, 126.7, 56.4, 40.8, 24.5, 22.0; IR (KBr) ν 3067, 2992, 1737, 1667, 1597, 1362, 1204, 1170, 1087, 1031, 938, 841, 750, 702, 679 cm^{-1}; HRMS (EI-TOF) calcd for $C_{18}H_{18}N_2O_3S$ (M^+), 342.1038; found, 342.1033.

3-((4-Methoxyphenyl)sulfonyl)-2-phenyl-5,6-dihydropyrimidin-4(3*H*)-one (3o). Unknown compound, a white powder (81 mg, 0.23 mmol, 47%); mp 169.0−171.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 9.0 Hz, 2H), 7.59 (d, J = 7.2 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.40 (t, J = 7.5 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 3.89 (s, 3H), 3.73 (t, J = 6.3 Hz, 2H), 2.55 (t, J = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 164.5, 154.7, 136.5, 132.0, 130.9, 130.3, 128.5, 127.6, 114.1, 56.0, 43.6, 34.2; IR (KBr) ν 2971, 1728, 1635, 1595, 1450, 1360, 1281, 1269, 1198, 1163, 1087, 1019, 840, 777, 698, 683 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{16}N_2O_4S$ (M^+), 344.0831; found, 344.0827.

3-((4-Methoxyphenyl)sulfonyl)-2-(*p*-tolyl)-5,6-dihydropyrimidin-4(3*H*)-one (3p). Unknown compound, a yellow powder (145 mg, 0.40 mmol, 81%); mp 163.9−164.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 7.3 Hz, 2H), 7.21 (d, J = 7.3 Hz, 2H), 6.97 (d, J = 8.5 Hz, 2H), 3.89 (s, 3H), 3.70 (s, 2H), 2.53 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 164.5, 154.7, 141.3, 133.8, 132.0, 130.4, 129.2, 127.5, 114.1, 56.0, 43.5, 34.3, 21.7; IR (KBr) ν 2961, 2845, 1741, 1630, 1593, 1499, 1359, 1271, 1188, 1059, 1086, 1010, 838, 825, 686 cm^{-1}; HRMS (EI-TOF) calcd for $C_{18}H_{18}N_2O_4S$ (M^+), 358.0987; found, 358.0998.

2-(4-Methoxyphenyl)-3-(phenylsulfonyl)-5,6-dihydropyrimidin-4(3*H*)-one (3q). Unknown compound, a white powder (72 mg, 0.21 mmol, 42%); mp 151.1−152.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (dd, J_1 = 8.4, J_2 = 1.0 Hz, 2H), 7.66 (t, J = 7.5 Hz, 1H), 7.58−7.56 (m, 1H), 7.53 (m, 3H), 6.93−6.87 (m, 2H), 3.85 (s, 3H), 3.69 (t, J = 6.4 Hz, 2H), 2.53 (t, J = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 161.9, 154.9, 139.3, 134.6, 129.4, 129.3, 129.0, 128.8, 113.9, 55.6, 43.5, 34.4; IR (KBr) ν 2972, 1736, 1634, 1611, 1514, 1362, 1267, 1173, 1082, 1021, 826, 724, 688 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{16}N_2O_4S$ (M^+), 344.0831; found, 344.0836.

3-(Phenylsulfonyl)-2-(*p*-tolyl)-5,6-dihydropyrimidin-4(3*H*)-one (3r). Unknown compound, a white powder (117 mg, 0.36 mmol, 71%); mp 152.6−154.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, J = 7.8 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.54−7.48 (m, 4H), 7.20 (d, J = 8.0 Hz, 2H), 3.71 (t, J = 6.4 Hz, 2H), 2.53 (t, J = 6.4 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 154.5, 141.4, 139.2, 134.6, 133.6, 129.4, 129.2, 128.9, 127.5, 43.5, 34.2, 21.7; IR (KBr) ν 3328, 3068, 2920, 1738, 1635, 1561, 1365, 1281, 1172, 1146, 1085,

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1006, 811, 724, 685 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{16}N_2O_3S$ (M^+), 328.0882; found, 328.0886.

3-(Naphthalen-2-ylsulfonyl)-2-(*p*-tolyl)-5,6-dihydropyrimidin-4(3*H*)-one (3s). Unknown compound, a white powder (92 mg, 0.24 mmol, 49%); mp 175.0−176.2 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.96 (m, 4H), 7.69 (m, 1H), 7.63 (m, 1H), 7.50 (d, J = 7.8 Hz, 2H), 7.18 (d, J = 7.7 Hz, 2H), 3.73 (t, J = 6.1 Hz, 2H), 2.53 (t, J = 6.1 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 154.6, 141.4, 135.9, 135.8, 133.6, 132.0, 131.8, 130.0, 130.0, 129.3, 128.2, 128.0, 127.7, 123.5, 43.6, 34.3, 21.8; IR (KBr) ν 3337, 3053, 2917, 1729, 1646, 1373, 1349, 1284, 1199, 1176, 1150, 1102, 1071, 1008, 817, 758, 689 cm^{-1}; HRMS (EI-TOF) calcd for $C_{21}H_{18}N_2O_3S$ (M^+), 378.1038; found, 378.1040.

3-((4-Chlorophenyl)sulfonyl)-2-(*p*-tolyl)-5,6-dihydropyrimidin-4(3*H*)-one (3t). Unknown compound, a white powder (68 mg, 0.19 mmol, 37%); mp 164.3−165.9 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 7.9 Hz, 2H), 3.73 (t, J = 6.2 Hz, 2H), 2.56 (t, J = 6.3 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 154.2, 141.6, 141.4, 137.5, 133.5, 131.1, 129.3, 129.3, 127.5, 43.6, 34.3, 21.8; IR (KBr) ν 3107, 2917, 1736, 1640, 1578, 1362, 1281, 1171, 1090, 1009, 816, 755, 668 cm^{-1}; HRMS (EI-TOF) calcd for $C_{17}H_{15}ClN_2O_3S$ (M^+), 362.0492; found, 362.0488.

2-(4-Chlorophenyl)-3-((4-chlorophenyl)sulfonyl)-5,6-dihydropyrimidin-4(3*H*)-one (3u). Unknown compound, a yellow powder (57 mg, 0.15 mmol, 30%); mp 157.3−159.2 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.95−7.91 (m, 2H), 7.55−7.50 (m, 4H), 7.41−7.37 (m, 2H), 3.75 (t, J = 6.4 Hz, 2H), 2.57 (t, J = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 153.4, 141.7, 137.3, 134.8, 131.0, 129.5, 129.0, 43.7, 34.1; IR (KBr) ν 3103, 2970, 2921, 2858, 1736, 1641, 1578, 1489, 1364, 1280, 1181, 1153, 1095, 1013, 879, 821, 679 cm^{-1}; HRMS (EI-TOF) calcd for $C_{16}H_{12}Cl_2N_2O_3S$ (M^+), 381.9946; found, 381.9940.

3-(Methylsulfonyl)-2-(*p*-tolyl)-5,6-dihydropyrimidin-4(3*H*)-one (3v). Unknown compound, a yellow powder (56 mg, 0.21 mmol, 42%); mp 124.4−126.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 3.82 (t, J = 6.3 Hz, 2H), 3.46 (s, 3H), 2.68 (t, J = 6.4 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 153.6, 141.3, 133.6, 129.5, 126.9, 44.4, 43.6, 34.2, 21.7; IR (KBr) ν 3308 (m), 3203, 1739, 1635, 1538, 1411, 1185, 1168, 1139, 1102, 1008, 820), 759 cm^{-1}; HRMS (EI-TOF) calcd for $C_{12}H_{14}N_2O_3S$ (M^+), 266.0725; found, 266.0727.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds and crystallographic information (CIF file) for compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pinglu@zju.edu.cn; orgwyg@zju.edu.cn

Notes

The authors declare no competing financial interest.

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(29) For ORTEPs of compound **3a**, please see the Supporting Information. CCDC 943090 (**3a**) contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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