Note

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Synthesis of 2-Amino-5-acylthiazoles by a Tertiary Amine-Promoted One-Pot Three-component Cascade Cyclization Using Elemental Sulfur as Sulfur Source

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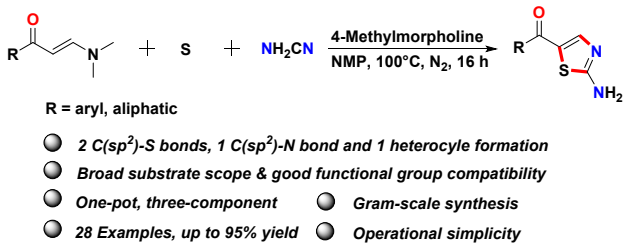


ABSTRACT: A novel one-pot three-component cascade cyclization strategy for the synthesis of 2-amino-5-acylthiazoles using enaminones, cyanamide and elemental sulfur has been developed. The reported methods have demonstrated good tolerance of various functional groups. Up to 28 2-amino-5-acylthiazole compounds bearing

diverse structural differences were successfully synthesized from easily obtained starting materials with moderate to excellent yields. Our method provides an effective way for the access of valuable and potentially bioactive 2-amino-5-acylthiazole derivatives.

Among the large family of thiazoles, 2-amino-5-acylthiazole compounds are remarkably intriguing owing to their diversified biological and pharmaceutical activities such as anticancer,[1] anti-adhesive,[2] antifungal,[3] anti-obesity[4] and antimitotic[5] activities (Fig. 1). Therefore a variety of synthetic efforts have been devoted for the construction of the 2-amino-5-acylthiazole skeleton as well as their derivatives.[6] As illustrated in Scheme 1, current existing methods mainly tackle this problem from two distinct approaches. One way is to use the classic Hantzsch reaction and its related modified methodologies, where condensation of α-haloketones with thioureas, thiocarbamoylamidine or ammonium thiocyanate is used for skeleton synthesis. These strategies have focused on the sulfuration of $C(sp^3)$-X bond and activated $C(sp^3)$-H bonds adjacent to the sp^2 carbon atom. The other method relies on the introduction of acyl and amino group onto a preexisting thiazole derivative using Friedel-Crafts acylation and the direct amination of halogen-substituted thiazoles. Recently, Roslan and co-workers developed a leaving group-free protocol for the radical coupling of 1,3-dicarbonyls and thioureas to access a wide array of 2-amino-5-acylthiazoles.[7]

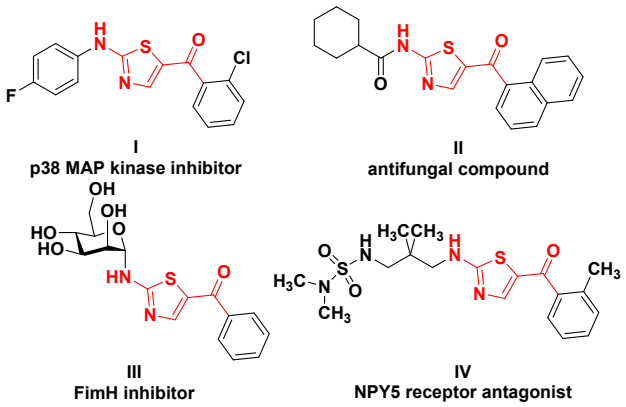
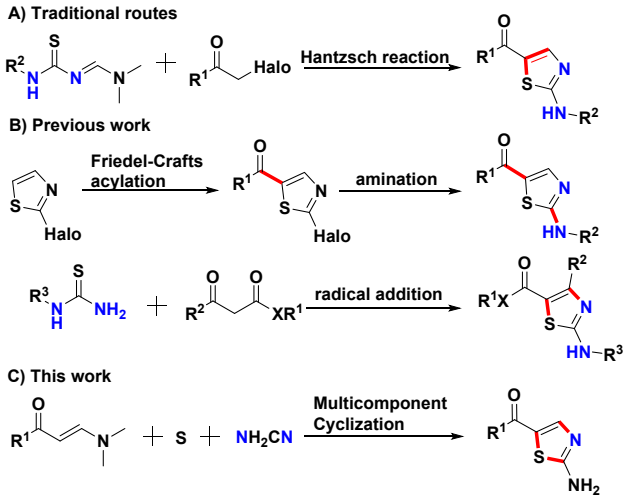


Fig. 1 Examples of biologically active 2-amino-5-acylthiazoles.

Although many elegant synthetic methods for 2-amino-5-acylthiazoles have been developed,[6,7] they are all using organosulfur as starting materials, which usually requires additional steps to prefunctionalize the starting building blocks. From the perspective of synthetic medicinal chemistry, it is highly desirable to develop an efficient method for synthesis of 2-amino-5-acylthiazole derivatives using readily available starting materials under simple and general reaction conditions. With the increasing environmental concerns, many environment-friendly approaches for the C–S bond formation using elemental sulfur have been reported.[8] To the best of our knowledge, employing elemental sulfur as the S source for the synthesis of 2-amino-5-acylthiazole moieties has not been revealed. Herein, we report a novel synthetic strategy of 2-amino-5-acylthiazoles, featuring a one-pot three-component cascade cyclization in a tertiary amine-promoted transformation of a readily available enaminone and cyanamide using elemental sulfur as sulfur source.

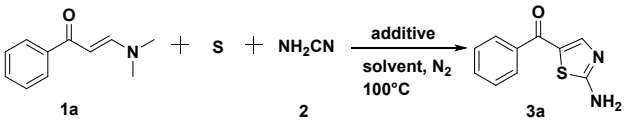
Scheme 1. Existing Strategies for 2-Amino-5-acylthiazoles Synthesis



Initially, enaminone (**1a**), cyanamide, and elemental sulfur were chosen to set up the model system for further optimization of reaction conditions, including selection of base, choice of solvent, temperature, and inert atmosphere (Table 1). No desired product was observed when *N*-methyl pyrrolidone (NMP) was used as solvent at 100 °C for 16 h in the absence of any additive (Table 1, entry 1). Interestingly, the employment of dimethylaminopyridine (DMAP) as additive led to the formation of product **3a** with good yield (Table 1, entry 2). Subsequently, different bases were screened (Table 1, entries 2-9). While K_2CO_3 cannot enable the desired cyclization (Table 1, entry 3), pyridine gave a moderate yield of **3a** (Table 1, entry 4). Among all tested bases, *N*-methylmorpholine (NMM) was shown to be the best sulfur activator, leading to the formation of product **3a** with good yield (Table 1, entry 5). In parallel entries, other aliphatic amines such as pyrrolidine, Et_3N, *N*-methylpiperidine and diisopropylethylamine (DIPEA) were less capable in promoting the reaction (Table 1, entries 6-9). Therefore, NMM was identified as base additive for this reaction and used for further optimization. The nature of solvents was found to have large impact on the reaction. The yield would dramatically decrease if other solvents than NMP

were used, including DMF, DMSO, pyridine, H_2O and toluene (Table 1, entries 10-13). In terms of the effect of reaction temperature, 100 °C was proved to be most favorable (Table 1, entries 14 and 15). No enhancement in yield was observed when the reaction was carried out with less amount of sulfur or cyanamide (Table 1, entries 16 and 17). Removing the inert nitrogen atmosphere lead to notably loss of yield, indicating that the nitrogen atmosphere was indispensable for this reaction (Table 1, entry 18). Finally, the parallel reaction using Na_2S as the alternative sulfur source gave no production of **3a** as observed with the optimal parameters shown in entry 19.

Table 1. Condition Optimization[a]



1a 2 3a

Entry	Additive	Solvent	Temp (°C)	Yield (%)
1	-	NMP	100	0
2	DMAP	NMP	100	60
3	K_2CO_3	NMP	100	0
4	pyridine	NMP	100	40
5	NMM	NMP	100	70
6	pyrrolidine	NMP	100	50
7	NEt_3	NMP	100	61
8	DIPEA	NMP	100	63
9	*N*-Methylpiperidine	NMP	100	68
10	NMM	DMF	100	63
11	NMM	DMSO	100	41
12	NMM	pyridine	100	46
13	NMM	H_2O	100	0
14	NMM	NMP	90	55
15	NMM	NMP	110	65
16[b]	NMM	NMP	100	32
17[c]	NMM	NMP	100	36
18[d]	NMM	NMP	100	35
19[e]	NMM	NMP	100	0

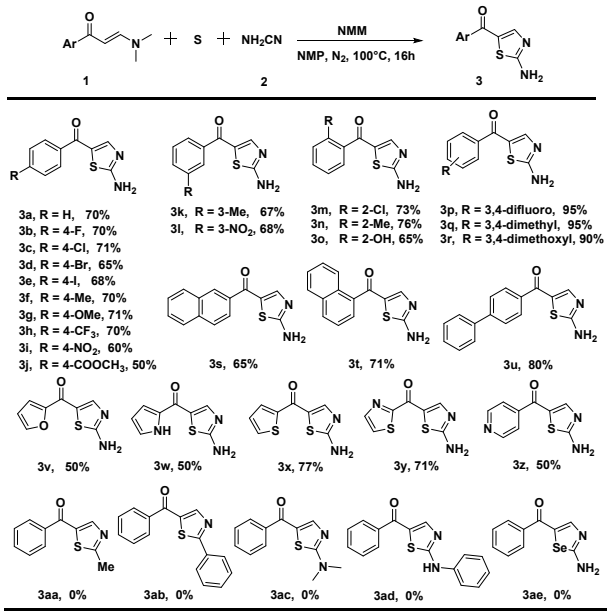
[a] Reaction conditions: **1a** (1 mmol), S (4 mmol), cyanamide solution (4 mmol) and

additive (0.2 mmol) in solvent (1 mL) for 16 h under N_2 atmosphere. [b] The amount of S is 2.0 equiv. [c] The amount of cyanamide solution is 2.0 equiv. [d] Reaction under air atmosphere. [e] Na_2S (4 mmol) used as sulfur source.

With the optimal conditions in hand, we then explored the scope of this cascade cyclization reaction first with respect to enaminones (**1**) as shown in Scheme 2. Pleasingly, both electron-donating (Me, OMe) and electron-withdrawing (F, Cl, Br, I, CF_3, NO_2) groups are well tolerated on the aryl ring, giving the corresponding products in moderate to good yields (**3a-3o**). These results revealed that the electronic effect and position of the substituent on the aryl-enaminone had little impact on the yield of the desired product. Additionally, more sterically hindered naphthyl group was also found to be compatible with the reaction condition, and the respective products **3s** and **3t** could be obtained in good yield. Notably, for the dimethyl-, dimethoxyl- and difluoro-substituted benzene ring, the desired products could be isolated in excellent yields over 90% (**3p-3r**). The diversity of the functional groups (methyl, methoxyl, halogen, nitro, ester and trifluoromethyl) on substituted phenyl moiety further demonstrated the broad substrate scope of this method. Furthermore, enaminones bearing heterocycles, including furanyl (**3v**), pyrrolyl (**3w**) and thienyl (**3x**) moieties, were also able to give the desired products in good yields. Unfortunately, the reaction employing nitriles (such as acetonitrile or benzonitrile) or substituted cyanamides (such as dimethylcyanamide or *N*-phenylcyanamide) instead of cyanamide did not produce the target products (**3aa**, **3ab, 3ac and 3ad**). Expanding the scope from elemental sulfur to elemental selenium, no desired product (**3ae**) was

obtained.

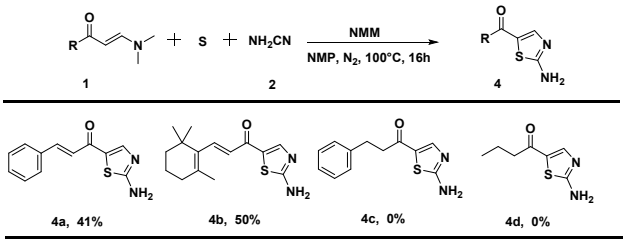
Scheme 2. Substrate Scope, with Respect to the Aryl-enaminones [a]



[a] Reaction conditions: **1** (1 mmol), S (4 mmol), cyanamide solution (4 mmol) and NMM (0.2 mmol) in NMP (1 mL) for 16 h under N_2 atmosphere.

We further inspected the scope of the reaction by using alkenyl- and alkyl-enaminones (**1**) instead of aryl-enaminones under the optimal conditions (Scheme 3). Although enaminones bearing styryl (**4a**) and terpenoid (**4b**) structures were found to have good reactivities and produce the corresponding products, their yields were comparably lower than that of aryl-enaminones, indicating the importance of aromatic structure in this method. When the phenethyl-enaminone and n-propyl-enaminone were used as substrates, the reaction did not proceed to produce the desired products (**4c** and **4d**).

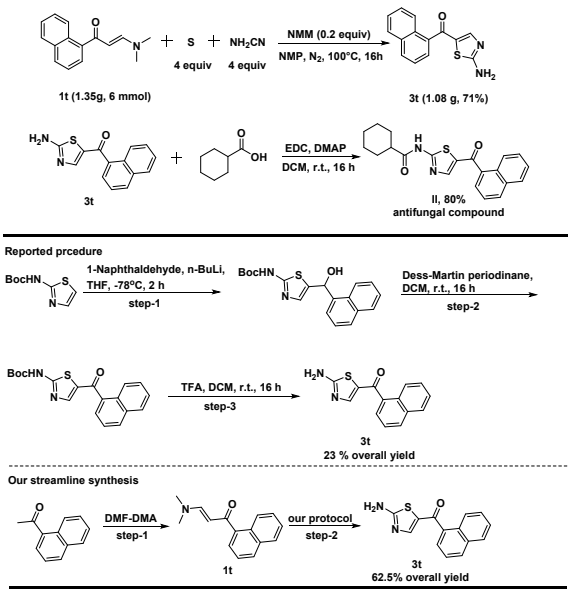
Scheme 3. Substrate Scope, with Respect to the Alkenyl- and Alkyl-enaminones[a]



[a] Reaction conditions: **1** (1 mmol), S (4 mmol), cyanamide solution (4 mmol) and NMM (0.2 mmol) in NMP (1 mL) for 16 h under N_2 atmosphere.

To demonstrate the synthetic utility of this cyclization approach for 2-amino-5-acylthiazoles, a gram-scale synthesis was performed. As shown in Scheme 4, the cyclization could be easily scaled up to gram scale and afford 1.08 g of **3t** in 71% yield on a 6 mmol scale. Further, we were interested in employing the developed method to synthesize a 2-amino-5-acylthiazole-based antifungal compound **II**. Upon a further *N*-acylation of **3t** with cyclohexanecarboxylic acid, product antifungal compound **II** was obtained in 80% yield. As shown in Scheme 4, the synthesis of 2-amino-5-naphthoylthiazole (**3t**) was simplified from three steps to one single operation with a satisfactory yield (71%). Such a synthesis is far superior to the reported protocol (3 steps with 23% overall yield),[3] since less steps (2 steps) and less-environmentally benign reagents are employed to afford much higher overall product yield (62.5% overall yield).

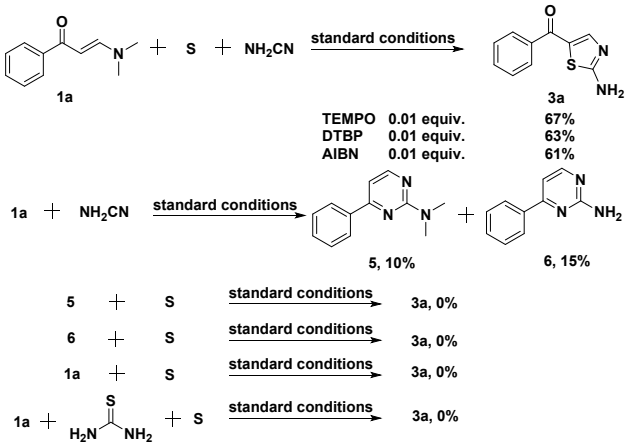
Scheme 4. Applications



In order to elucidate the reaction mechanism, several control experiments were carried out (Scheme 5). To determine whether the cyclization reaction was initiated by free radicals, the radical initiator 2,2,6,6-tetramethylpiperidinooxy (TEMPO, 0.01 equiv) or di-tert-butyl peroxide (DTBP, 0.01 equiv) or 2,2'-azobis(2-methylpropionitrile) (AIBN, 0.01 equiv) were used in the reactions. As a result, it is found that none of the selected radical initiators could promote this cyclization reaction, therefore suggesting that the radical process might not be involved in this reaction mechanism. When the reactions were carried out in the absence of S under the standard reaction conditions, compound **5** and **6** were obtained. Subsequently, **5** and **6** were used as the substrate to react with S, respectively. As a result, the desired product **3a** was not isolated. These observations indicated that **5** and **6** are the off-cycle by-products instead of an intermediate. Next, we blended the **1a** and S under the standard conditions, and the product **3a** was not afforded as well. Similarly, the reaction of **1a** and thiourea in the presence of S as an oxidant under the standard conditions did not afforded the target product **3a**, suggesting that thiourea

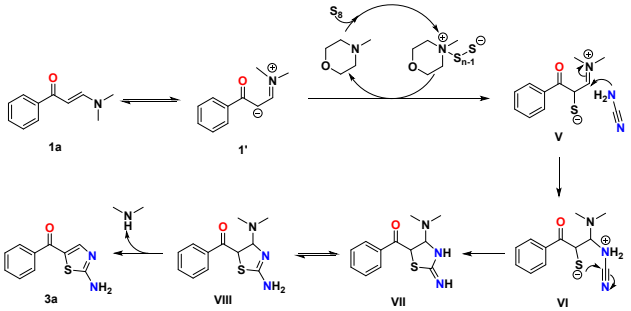
might not be involved in this transformation

Scheme 5. Control Experiments



According to the above-mentioned experimental observations and previous reports,[9] we suggest a possible reaction pathway (Scheme 6). Firstly, the elemental sulfur incorporates the nucleophilic NMM to form the active 4-methylmorpholine N-S species, which mediates the transfer of the sulfur atom to enaminone and provides intermediate **V** via the enaminone's isomeric version **1'**. Next, intermediate **V** is attacked by cyanamide and leads to the formation of **VI**, which undergoes an intramolecular nucleophilic addition to afford intermediate **VII**. Subsequently, tautomerization of intermediate **VII** afforded the intermediate **VIII**. Finally, the intermediate **VIII** can be converted to the desired product **3a** via the release of dimethylamine.

Scheme 6. Possible Reaction Mechanism



In conclusion, a novel one-pot three-component strategy to construct 2-amino-5-acylthiazoles from easily available enaminones, cyanamide, and elemental sulfur was developed, giving products in moderate to excellent yields. The easiness of the availability of the starting materials, excellent functional group tolerance, mild reaction conditions, and the capacity of gram-scale synthesis, all make this reaction a practical synthetic method in medicinal chemistry. Further development and applications of this cascade of direct construction of two C-S bonds and a C(sp^2)-N bond, and elemental sulfur are ongoing in our laboratory and the related results will be reported in due course.

EXPERIMENTAL SECTION

General Information.

Enaminones **1** used in the experiments were synthesized in the lab following literature process.[10] Other chemicals and solvents used in the experiments were acquired from commercial sources and used directly without further treatment. Column chromatography was performed using silica gel, SiO_2 (200-300 mesh). ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded on Bruker-AV (600 or 500 and 151 or 126 MHz, respectively) instrument internally referenced to tetramethylsilane (TMS) or chloroform signals. High-resolution mass spectra (HRMS) were recorded using Agilent 6545 LC/Q-TOF. The melting points of solid samples were tested in an X-4 apparatus without correcting the temperature.

General procedure for 2-amino-5-acylthiazoles synthesis

Enaminones (1 mmol), 50 wt% aqueous cyanamide solution (340 mg, 4 mmol), sulfur

powder (128 mg, 4 mmol), NMM (20 mg, 0.2 mmol) and NMP (1 mL) were added to an oven-dried reaction vessel (20 mL). The reaction vessel was evacuated and back filled with nitrogen gas three times. The reaction vessel was placed in an oil bath. The mixture was stirred at 100℃ for 16 h under N_2 atmosphere. After the reaction was completed (TLC), the mixture was cooled to room temperature and then water was added and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, dried under reduced pressure and finally purified by silica gel column chromatography on silica gel with petroleum ether/ethyl acetate (PE/EA = 1:1-4:1, v/v) as the eluent to afford the desired product.

2-Amino-5-benzoylthiazole (3a) Yellow solid, yield 142.8 mg (70%); mp 181-182 ℃; ^{1}H NMR (600 MHz, $CDCl_3$) 7.79 (d, J = 7.0 Hz, 2H), 7.64 (s, 1H), 7.58 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 5.71 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 187.0, 173.4, 149.2, 138.1, 132.1, 130.7, 128.7, 128.6. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_9N_2OS$: 205.0429. Found: 205.0432.

2-Amino-5-(4-fluorobenzoyl)thiazole (3b) Yellow solid, yield 155.4 mg (70%); mp 212-214 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.24 (s, 2H), 7.82 (dd, J = 8.7, 5.6 Hz, 2H), 7.66 (s, 1H), 7.34 (t, J = 8.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 184.4, 175.2, 164.5 (C_6H_5F) (d, $J_{c\text{-}F}$ = 249.4 Hz), 151.6, 135.2 (d, $J_{c\text{-}F}$ = 3.0 Hz), 131.4 (d, $J_{c\text{-}F}$ = 9.0 Hz), 127.1, 116.1 (d, $J_{c\text{-}F}$ = 21.7 Hz). HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_8FN_2OS$: 223.0335. Found: 223.0337.

2-Amino-5-(4-chlorobenzoyl)thiazole (3c)[11] Yellow solid, yield 169 mg (71%); mp

228-230 ℃; ^{1}H NMR (600 MHz, DMSO-d_6): 8.27 (s, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.67 (s, 1H), 7.58 (d, J = 8.5 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 184.5, 175.4, 151.9, 137.3, 136.9, 130.6, 129.1, 127.1. HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{10}H_8ClN_2OS$: 239.0040. Found: 239.0043.

2-Amino-5-(4-bromobenzoyl)thiazole (3d)[11] Yellow solid, yield 183 mg (65%); mp 254-256 ℃; ^{1}H NMR (600 MHz, DMSO-d_6): 8.27 (s, 2H), 7.72 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 7.5 Hz, 2H), 7.67 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 184.6, 175.4, 151.9, 137.7, 132.1, 130.8, 127.0, 125.8. HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{10}H_8BrN_2OS$: 282.9534. Found: 282.9533.

2-Amino-5-(4-iodobenzoyl)thiazole (3e) Yellow solid, yield 224.4 mg (68%); mp 253-255 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.25 (s, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.66 (s, 1H), 7.51 (d, J = 8.4 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 184.9, 175.4, 151.8, 138.0, 137.9, 130.6, 127.0, 99.9. HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{10}H_8IN_2OS$: 330.9396. Found: 330.9399.

2-Amino-5-(4-methylbenzoyl)thiazole (3f)[11] Yellow solid, yield 152.6 mg (70%); mp 215-217 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.16 (s, 2H), 7.64 (d, J = 8.1 Hz, 2H), 7.63 (s, 1H), 7.33 (d, J = 8.1 Hz, 2H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 185.6, 175.0, 151.0, 142.3, 136.0, 129.6, 128.8, 127.5, 21.5. HRMS (ESI) m/z [M+H]$^+$: Calcd for $C_{11}H_{11}N_2OS$: 219.0586. Found: 219.0582.

2-Amino-5-(4-methoxybenzoyl)thiazole (3g) Yellow solid, yield 166 mg (71%); mp 214-216 ℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.11 (s, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.64 (s, 1H), 7.05 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz,

DMSO-d_6) δ 184.6, 174.7, 162.6, 150.3, 131.1, 130.9, 127.6, 114.3, 55.9. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{11}N_2O_2S$: 235.0535. Found: 235.0538.

2-Amino-5-(4-trifluoromethylbenzoyl)thiazole (3h) Yellow solid, yield 190.4 mg (70%); mp 232-234℃; ^{1}H NMR (600 MHz, DMSO-d_6): 8.35 (s, 2H), 7.93 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 7.69 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 184.6, 175.7, 152.7, 142.3, 131.7 ($C_6H_5CF_3$) (q, $J_{c\text{-}F}$ = 31.8 Hz) , 129.5, 126.9, 126.0 (q, $J_{c\text{-}F}$ = 3.0 Hz), 124.4 (CF_3) (q, $J_{c\text{-}F}$ = 271.8 Hz). HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_8F_3N_2OS$: 273.0303. Found: 273.0305.

2-Amino-5-(4-nitrobenzoyl)thiazole (3i) Yellow solid, yield 149 mg (60%); mp 254-256℃; ^{1}H NMR (600 MHz, DMSO-d_6): 8.40 (s, 2H), 8.33 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.2 Hz, 2H), 7.69 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 184.0, 175.9, 153.1, 149.4, 144.1, 130.0, 126.8, 124.2. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_8N_3O_3S$: 250.0280. Found: 250.0283.

Methyl 4-(2-aminothiazole-5-carbonyl)benzoate (3j) Yellow solid, yield 131 mg (50%); mp 234-235℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.33 (s, 2H), 8.08 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.67 (s, 1H), 3.90 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 185.0, 175.6, 166.2, 152.4, 142.6, 132.4, 129.9, 129.0, 127.0, 52.9. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{11}N_2O_3S$: 263.0484. Found: 263.0486.

2-Amino-5-(3-methylbenzoyl)thiazole (3k) Yellow solid, yield 146.06 mg (67%); mp 223-225℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.19 (s, 2H), 7.61 (s, 1H), 7.51-7.53 (m, 2H), 7.38-7.42 (m, 2 H), 2.39 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 186.0, 175.1, 151.4, 138.8, 138.5, 132.8, 129.1, 128.9, 127.4, 125.9, 21.4. HRMS (ESI) m/z

$[M+H]^+$: Calcd for $C_{11}H_{11}N_2OS$: 219.0586. Found: 219.0582.

2-Amino-5-(3-nitrobenzoyl)thiazole (3l) Yellow solid, yield 169 mg (68%); mp 220-222℃; ^1H NMR (600 MHz, DMSO-d_6) 8.41-8.44 (m, 2H), 8.38 (s, 2H), 8.16-8.17 (m, 1H), 7.81 (t, J = 7.9 Hz, 1H), 7.77 (s, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 183.4, 175.9, 153.1, 148.2, 139.8, 134.9, 130.9, 126.6, 126.4, 123.3. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_8N_3O_3S$: 250.0280. Found: 250.0278.

2-Amino-5-(2-chlorobenzoyl)thiazole (3m) Yellow solid, yield 173.7 mg (73%); mp184-186 ℃; ^1H NMR (600 MHz, DMSO-d_6) 8.37 (s, 2H), 7.56 (d, J = 8.0 Hz, 1H), 7.49-7.53 (m, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.28 (s, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 184.3, 176.1, 153.3, 138.6, 131.8, 130.4, 130.2, 129.4, 127.6, 127.0. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_8ClN_2OS$: 239.0040. Found: 239.0043.

2-Amino-5-(2-methylbenzoyl)thiazole (3n) Yellow solid, yield 165.7 mg (76%); mp 207-209℃; ^1H NMR (600 MHz, DMSO-d_6) 8.25 (s, 2H), 7.37-7.41 (m, 2H), 7.25-7.32 (m, 3H), 2.26 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 188.1, 175.7, 152.2, 139.1, 135.6, 131.2, 130.2, 128.2, 127.9, 125.9, 19.5. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{11}H_{11}N_2OS$: 219.0586. Found: 219.0582.

2-Amino-5-(2-hydroxybenzoyl)thiazole (3o) Yellow solid, yield 143 mg (65%); mp 208-210℃; ^1H NMR (600 MHz, DMSO-d_6) 10.31 (s, 1H), 8.20 (s, 2H), 7.53 (s, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.90 (t, J = 7.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 186.6, 175.3, 156.8, 151.8, 132.9, 129.9, 127.5, 125.1, 119.4, 117.2. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_9N_2O_2S$: 221.0379. Found: 221.0381.

2-Amino-5-(3,4-difluorobenzoyl)thiazole (3p) Yellow solid, yield 228 mg (95%); mp 232-235℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.30 (s, 2H), 7.77-7.80 (m, 1H), 7.72 (s, 1H), 7.62-7.64 (m, 1H), 7.55-7.60 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 183.2, 175.5, 152.1 (C_6H_5F) (dd, $J_{c\text{-}F}$= 252.2, 13.59 Hz), 149.7 (C_6H_5F) (dd, $J_{c\text{-}F}$ = 247.8, 12.8 Hz), 136.0, 126.2 (dd, $J_{c\text{-}F}$ = 7.3, 3.2 Hz), 118.2 (dd, $J_{c\text{-}F}$ = 25.9, 17.9 Hz). HRMS (ESI) m/z [M+H]$^{+}$: Calcd for $C_{10}H_7F_2N_2OS$: 241.0241. Found: 241.0244.

2-Amino-5-(3,4-dimethylbenzoyl)thiazole (3q) Yellow solid, yield 220.4 mg (95%); mp 239-241℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.14 (s, 2H), 7.63 (s, 1H), 7.51 (s, 1H), 7.47 (dd, J = 7.7, 1.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 2.29 (s, 6H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 185.7, 174.9, 150.9, 141.1, 137.1, 136.4, 130.0, 129.7, 127.6, 126.4, 19.9, 19.8. HRMS (ESI) m/z [M+H]$^{+}$: Calcd for $C_{12}H_{13}N_2OS$: 233.0743. Found: 233.0742.

2-Amino-5-(3,4-dimethoxybenzoyl)thiazole (3r) Yellow solid, yield 237.6 mg (90%); mp 194-196℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.10 (s, 2H), 7.69 (s, 1H), 7.41 (dd, J = 8.3, 2.0 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 184.6, 174.7, 152.4, 150.4, 149.0, 131.1, 127.6, 122.7, 111.7, 111.4, 56.1, 56.0. HRMS (ESI) m/z [M+H]$^{+}$: Calcd for $C_{12}H_{13}N_2O_3S$: 265.0641. Found: 265.0638.

2-Amino-5-(2-naphthoyl)thiazole (3s) Yellow solid, yield 165 mg (65%); mp 230-233℃; ^{1}H NMR (600 MHz, DMSO-d_6) 8.41 (s, 1H), 8.24 (s, 2H), 8.14 (d, J = 8.0 Hz, 1H), 8.00-8.05 (m, 2H), 7.77-7.80 (m, 2H), 7.61-7.66 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 185.7, 175.2, 151.7, 135.9, 134.8, 132.6, 129.8, 129.4, 128.8,

128.4, 128.1, 127.5, 127.3, 125.3. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{11}N_2OS$: 255.0586. Found: 255.0584.

2-Amino-5-naphthoylthiazole (3t)[3] Yellow solid, yield 180.3 mg (71%); mp 188-190℃; ^1H NMR (600 MHz, DMSO-d_6) 8.31 (s, 2H), 8.09 (d, J = 8.3 Hz, 1H), 8.00 (dd, J = 21.1, 7.9 Hz, 2H), 7.71 (dd, J = 7.0, 1.1 Hz, 1H), 7.55-7.61 (m, 3H), 7.36 (s, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 187.2, 175.8, 152.6, 136.6, 133.8, 130.9, 130.3, 128.9, 128.8, 127.5, 126.9, 126.8, 125.5, 125.4. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{14}H_{11}N_2OS$: 255.0586. Found: 255.0584.

([1,1'-Biphenyl]-4-yl)-[2-aminothiazol-5-yl]methanone (3u) Yellow solid, yield 224 mg (80%); mp 250-252℃; ^1H NMR (600 MHz, DMSO-d_6) 8.23 (s, 2H), 7.81-7.85 (m, 4H), 7.75 (d, J = 7.2 Hz, 2H), 7.72 (s, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.43 (t, J = 7.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 185.3, 175.2, 151.4, 143.7, 139.6, 137.5, 129.6, 129.5, 128.7, 127.4, 127.4, 127.3. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{16}H_{13}N_2OS$: 281.0743. Found: 281.0740.

(2-Amino-5-thiazolyl)-2-furanyl-methanone (3v) Yellow solid, yield 97 mg (50%); mp 259-261 ℃; ^1H NMR (600 MHz, DMSO-d_6) 8.20 (s, 3H), 7.99 (s, 1H), 7.34-7.35 (m, 1H), 6.72-6.73 (m, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 174.9, 171.4, 152.1, 150.0, 147.3, 126.3, 117.4, 112.8. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_8H_7N_2O_2S$: 195.0222. Found: 195.0223.

(2-Amino-5-thiazolyl)-1H-pyrrol-2-yl-methanone (3w) Yellow solid, yield 96.5 mg (50%); mp 277-279℃; ^1H NMR (600 MHz, DMSO-d_6) 11.77 (s, 1H), 7.94 (s, 1H), 7.91 (s, 2H), 7.03-7.04 (m, 1H), 7.07-7.08 (m, 1H), 6.21-6.22 (m, 1H). $^{13}C\{^1H\}$ NMR

(151 MHz, DMSO-d_6) δ 174.06, 173.6, 147.1, 130.5, 127.0, 125.0, 115.5, 110.4. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_8H_8N_3OS$: 194.0382. Found: 194.0375.

(2-Amino-5-thiazolyl)-2-thienyl-methanone (3x) Yellow solid, yield 161 mg (77%); mp 183-185℃; ^1H NMR (600 MHz, $CDCl_3$) 7.94 (s, 1H), 7.80 (dd, J = 3.8, 1.1 Hz, 1H), 7.66 (dd, J = 4.9, 1.1 Hz, 1H), 7.17 (dd, J = 4.9, 3.8 Hz, 1H), 5.61 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 177.4, 172.9, 147.3, 142.5, 132.6, 131.8, 130.2, 127.9. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_8H_7N_2OS_2$: 210.9994. Found: 210.9996.

(2-Amino-5-thiazolyl)-2-thiazolyl-methanone (3y) Yellow solid, yield 150 mg (71%); mp 264-266℃; ^1H NMR (600 MHz, DMSO-d_6) 8.68 (s, 1H), 8.43 (s, 2H), 8.16 (d, J = 2.5 Hz, 1H), 8.15 (s, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 176.6, 173.4, 167.7, 154.0, 145.3, 127.2. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_7H_6N_3OS_2$: 211.9948. Found: 211.9951.

(2-Amino-5-thiazolyl)-4-pyridinyl-methanone (3z) Yellow solid, yield 102.5 mg (50%); mp 254-256℃; ^1H NMR (600 MHz, DMSO-d_6) 8.75 (dd, J = 4.4, 1.6 Hz, 2H), 8.40 (s, 2H), 7.70 (s, 1H), 7.63 (dd, J = 4.3, 1.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 184.3, 176.0, 153.2, 150.8, 145.3, 126.5, 122.4. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_9H_8N_3OS$: 206.0382. Found: 206.0386.

1-(2-Amino-5-thiazolyl)-3-(phenyl)-(2E)-propen-1-one (4a) Yellow solid, yield 94.3 mg (41%); mp 217-219℃; ^1H NMR (600 MHz, DMSO-d_6) 8.38 (s, 1H), 8.18 (s, 2H), 7.82-7.84 (m, 2H), 7.70 (d, J = 15.6 Hz, 1H), 7.55 (d, J = 15.6 Hz, 1H), 7.42-7.44 (m, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 180.0, 175.3, 150.4, 140.7, 135.29, 130.6, 130.0, 129.3, 129.1, 122.6. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{10}N_2OS$:

231.0586. Found: 231.0594.

1-(2-Amino-5-thiazolyl)-3-(2,6,6-trimethyl-2-cyclohexen-1-yl)-(2E)-propen-1-one

(4b) Yellow solid, yield 138 mg (50%); mp 190-192℃; ^{1}H NMR (600 MHz, $CDCl_3$) 7.77 (s, 1H), 7.51 (d, J = 15.7 Hz, 1H), 6.66 (d, J = 15.7 Hz, 1H), 5.65 (s, 2H), 2.10 (t, J = 6.3 Hz, 2H), 1.82 (s, 3H), 1.62-1.66 (m, 2H), 1.49-1.51 (m, 2H), 1.10 (s, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 181.3, 173.1, 145.5, 142.6, 136.6, 136.5, 132.9, 125.1, 39.8, 34.2, 33.7, 28.9, 21.9, 18.9. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{15}H_{21}N_2OS$: 277.1369. Found: 277.1367.

Scale-up synthesis of 2-amino-5-naphthoylthiazole (3t)

1t (1.35 g, 6 mmol), 50 wt% aqueous cyanamide solution (2.0 g, 24 mmol), sulfur powder (0.77 g, 24 mmol), NMM (0.12 g, 1.2 mmol) and NMP (6 mL) were added to an oven-dried reaction vessel (20 mL). The reaction vessel was evacuated and back filled with nitrogen gas three times. The reaction vessel was placed in an oil bath. The mixture was stirred at 100℃ for 16 h under N_2 atmosphere. After the reaction was completed (TLC), the mixture was cooled to room temperature and then water was added and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, dried under reduced pressure. The resulting mixture was purified by silica gel column chromatography on silica gel with petroleum ether/ethyl acetate (PE/EA = 1:1- 4:1, v/v) as the eluent to afford **3t** in the yield of 71% (1.08 g).

Synthesis of compound 5 and 6

Enaminone **1a** (175 mg, 1 mmol), 50 wt% aqueous cyanamide solution (340 mg, 4

mmol), NMM (20 mg, 0.2 mmol) and NMP (1 mL) were added to an oven-dried reaction vessel (20 mL). The reaction vessel was evacuated and back filled with nitrogen gas three times. The reaction vessel was placed in an oil bath. The mixture was stirred at 100℃ for 16 h under N_2 atmosphere. After the reaction was completed (TLC), the mixture was cooled to room temperature and then water was added and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered, dried under reduced pressure and finally purified by silica gel column chromatography on silica gel with petroleum ether/ethyl acetate (PE/EA = 1:1- 4:1, v/v) as the eluent to afford the desired product.

2-Dimethylamino-4-phenylpyrimidine (5)[12] Yellow oil, yield 20 mg (10%); ^{1}H NMR (500 MHz, $CDCl_3$) 8.37 (d, *J* = 5.1 Hz, 1H), 8.06-8.08 (m, 2H). 7.46-7.47 (m, 3H), 6.91 (d, *J* = 5.1 Hz, 1H), 3.27 (s, 6H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 164.1, 162.5, 158.2, 137.9, 130.4, 128.6, 127.0, 104.7, 37.1. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{12}H_{13}N_3$: 200.1181. Found: 200.1182.

4-Phenylpyrimidin-2-amine (6)[13] White solid, yield 26 mg (15%); mp 159-161℃; ^{1}H NMR (500 MHz, $CDCl_3$) 8.35 (d, *J* = 5.2 Hz, 1H), 7.98-8.00 (m, 2H). 7.47-7.48 (m, 3H), 7.04 (d, *J* = 5.2 Hz, 1H), 5.25 (s, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.5, 163.3, 158.8, 137.3, 130.6, 128.8, 127.1, 107.8. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{10}H_9N_3$: 172.0868. Found: 172.0870.

Synthesis of *N*-[5-(1-naphthoyl)thiazol-2-yl]cyclohexanecarboxamide (II)[3]

To a solution of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (714 mg, 3.7 mmol), 4-dimethylaminopyridine (20 mg, 0.16 mmol) and

cyclohexanecarboxylic acid (512 mg, 4 mmol) in dry dichloromethane (20 mL) were added **3t** (254 mg, 1 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 14 h. The mixture was diluted with water, Na_2SO_4, filtered, and concentrated. The resulting mixture was purified by silica gel column chromatography on silica gel with petroleum ether/ethyl acetate (PE/EA = 1:1- 4:1, v/v) as the eluent to afford **II**.

White solid, yield 291 mg (80%); mp 231-232℃; ^{1}H NMR (600 MHz, DMSO-d_6) 12.638 (s, 1H), 8.15-8.17 (m, 1H), 8.03-8.06 (m, 2H), 7.84 (s, 1H), 7.82 (d, J = 7.0 Hz, 2H), 7.57-7.65 (m, 3H), 2.53-2.58 (m, 1H), 1.85 (d, J = 12.2 Hz, 2H), 1.74-1.76 (m, 2H), 1.63-1.65 (m, 1H), 1.40-1.46 (m, 2H), 1.19-1.29 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 189.3, 175.7, 164.7, 148.4, 136.0, 133.8, 133.3, 131.7, 130.1, 129.0, 127.8, 127.6, 127.1, 125.4, 125.3, 43.9, 29.1, 25.7, 25.5. HRMS (ESI) m/z $[M+H]^+$: Calcd for $C_{21}H_{20}N_2O_2S$: 365.1317. Found: 365.1317.

ASSOCIATED CONTENT

Supporting Information

NMR spectra of the products. The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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