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Dimedone-catalyzed Addition of Amines into Cyano Group: Facile Synthesis of Thiazol-2-yl Substituted *E*-Acrylonitriles

Zhu, Weijun[b](朱伟军) Tu, Xingchao[a](屠兴超) Feng, Hui[a](冯惠) Tu, Mansu[a](屠蔓苏)
Jiang, Bo*,[a](姜波) Wu, Feiyue[a](吴飞跃) Tu, Shujiang*,[a](屠树江)

[a] *School of Chemistry and Chemical Engineering, Laboratory of Green Synthetic Chemistry for Functional Materials, Xuzhou Normal University, Xuzhou, Jiangsu 221116, China*
[b] *School of Chemical Engineering and Technology, Xuzhou College of Industrial Technology, Xuzhou, Jiangsu 221000, China*

An efficient dimedone-catalyzed synthesis of highly functionalized thiazol-2-yl substituted *E*-acrylonitrile derivatives has been established through two-step reaction of α-thiocyanate ketones with malononitrile and amines. The α-thiocyanate ketones were subjected with malononitrile to provide thiazol-2-ylidenemalononitrile derivatives, followed with various amines in the presence of dimedone to yield the final thiazol-2-yl substituted acrylonitrile derivatives.

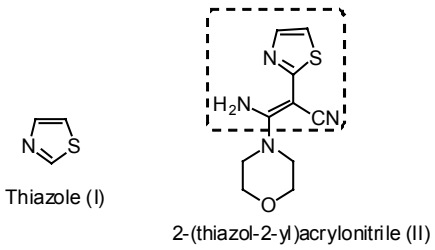
Keywords dimedone-catalyzed synthesis, *E*-acrylonitriles, addition reaction, microwave heating, heterocycles

Introduction

Organic functional group transformations (OFGTs) continue to be an area of vital concernment in the fields of organic synthesis and chemical biology.[1] The aim of OFGTs was to realize the collections of functionally and regiochemically diverse small molecules, particularly those possessing skeletons found in natural products or drug-like molecules.[2] Further chemical modifications of the natural product frameworks or drug-like molecule units such as direct functional groups transformations have allowed expansion of the research of structure-activity relationships, affording new insights into the molecular interactions. In the other hand, the OFGTs on the specific position of bioactive molecules will lead to great improvements of their biological and pharmacological activities.[3] Thus, the organic functional group transformations have been attracted much attention.[4] As one of the most important functional groups, a cyano group was usually converted into amines, imines, amides, amidines, imidates and carboxylic acids *etc.*[3] Among them, the preparation of enamines was through the addition of amines into cyano group catalyzed by metal catalyst[5a-5c] or stronger bases[5d] or *N*-trimethylsilylamines.[5e] However, to the best of our knowledge, facile transformation of cycno group to enamines catalyzed by easily available and cheap dimedone was not reported so far.

Thiazoles (I) and its derivatives exist widely in bioactive molecules because of its physiological and pharmacological activities.[6] They were also widely used in the preparation of antibiotics and antiphlogistics,[7] such as penicillin and vitamin B1. The thiazole motif is one of the significant core structures among the most extensively natural and unnatural heterocyclic compounds with remarkable medicinal activities such as anti-inflammatory,[8] antinociceptive activity,[9] and anticancer.[10] However, (*Z*)-3-amino-2-(thiazol-2-yl)-acrylonitriles (II) as important intermediates in organic synthesis were nearly neglected or not explored thoroughly so far (Scheme 1).

Scheme 1



Over the past several years, our group have developed various domino reactions that can offer easy access to useful functionalized multiple ring structures of chemical and pharmaceutical interest.[11,12] For example, a new four-component domino reaction was established as to provide an easy access to the synthesis of multi-functionalized quinazoline[11a] and tricyclo[6.2.2.0[1,6]]-dodecanes derivatives.[11b] Recently, we have also found

* E-mail: jiangchem@xznu.edu.cn (B. Jiang); laotu@xznu.edu.cn (S-J. Tu); Fax: 86(516) 83500065
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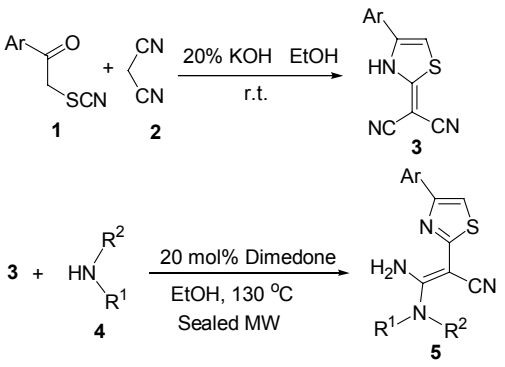
that the domino reaction of Meldrum's acid, aromatic aldehydes and electron-rich heteroaryl-amines in aqueous phase under microwave (MW) irradiation led to the multifunctionalized spiro{[1,3]dioxanes-pyridine}-4,6-dione with high chemo-, regio- and stereoselectivity and good yields.[11c]

As a part of our continuing interest in the development of new domino reaction and new organocatalysts[11] in heterocyclic compounds, in this paper, we would like to report a new route to a set of thiazol-2-yl substituted *E*-acrylonitrile derivatives that are of chemical and biomedical importance using readily available *α*-thiocyanate ketones, malononitrile and amines as starting materials. This reaction was achieved through two-step strategy which was shown in Scheme 2. Interestingly, during second-step reaction process dimedone as a new and efficient catalyst provided a series of thiazol-2-yl substituted *E*-acrylonitrile derivatives **5** with good yields.

Scheme 2

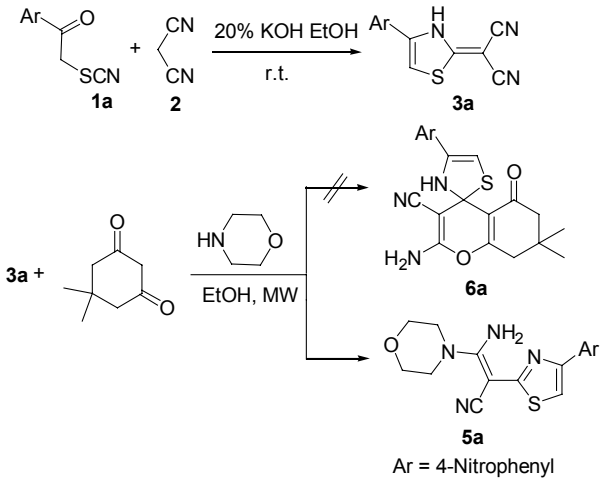


Results and Discussion

The *α*-thiocyanate ketones, possessing four high reactivity centers including two electrophilic centers and two nucleophilic centers, have proven to be important building blocks for the construction of important heterocyclic frameworks.[12] Our strategy of synthesizing the highly multifunctionalized thiazol-2-yl substituted *E*-acrylonitrile was through the reaction of a preformed thiazol-2-ylidenemalononitriles with an amine. The preparation of thiazol-2-ylidenemalononitriles was commonly achieved in the presence of potassium hydroxide at room temperature for 2 h.[12b] We then started this synthesis by conducting the reaction of thiazol-2-ylidenemalononitriles (**3a**) with dimedone in the presence of morpholine in EtOH. The expected compound **6a** was not obtained (Scheme 3). All of the analytical data showed that morpholine unit was introduced in the final product, and dimedone did not take part in this reaction. Thus a new thiazol-2-yl substituted *E*-acrylonitrile **5a** was produced and its structure was further confirmed by single crystal X-ray (Figure 1).[13]

Encouraged by the above interesting results, we devoted our efforts to the study of the reaction of **3a** with morpholine **4a** as a model reaction to optimize the reaction conditions. Experiments were carried out in various bases such as K_2CO_3, Et_3N, and DMAP. The incomplete reactions were observed using these bases. Next, the similar reaction was conducted in the presence of 1.0 equiv. of different cyclic-1,3-dicarbonyls with high reactivity, such as tetronic acid, Meldrum's acid, 1,3-cyclo-hexanedione, and dimedone. As shown in Table 1, the use of dimedone allowed the direct conversion of thiazol-2-ylidenemalononitriles **3a** into the corresponding thiazol-2-yl substituted acrylonitrile **5a** in a yield of 52% at 90 ℃ for 25 min under microwave irradiation condition (Table 1, Entry 4). Other cyclic-1,3-dicarbonyls gave much lower yields of 40%—47% (Table 1, Entries 1—3). Subsequently, the reaction was performed in EtOH and repeated many times at different temperatures in a sealed vessel under microwave irra-

Scheme 3



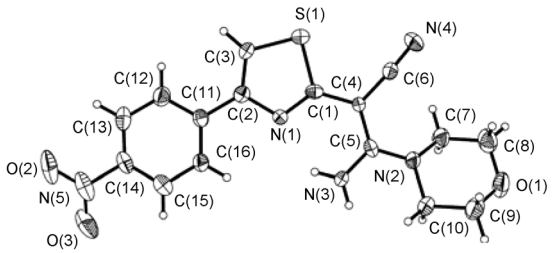


Figure 1 X-ray crystallography structure of compound **5a**.

Table 1 Catalyst optimization for the synthesis of **5a** under MW

Entry	Catalyst	*T*/℃	Time/min	Yield[a]/%
1	Tetronic acid	1.0	90	43
2	Meldrum's acid	1.0	90	40
3	1,3-Cyclohexanedione	1.0	90	47
4	Dimedone	1.0	90	52
5	Dimedone	0.6	130	76
6	Dimedone	0.4	130	76
7	Dimedone	0.2	130	78
8	Dimedone	0.1	130	65

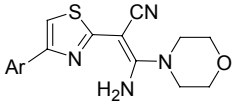
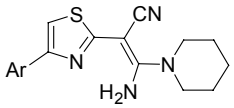
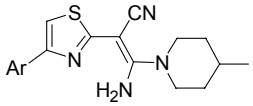
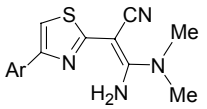
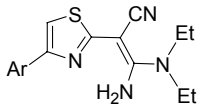
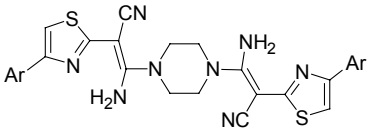
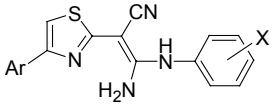
[a] Isolated yield.

diation for 25 min. The yield of product **5a** was increased from 52% to 78% as the temperature varied from 90 to 130 ℃. When 0.2 equiv. of dimedone was employed as a promoter in this reaction, the yield of product **5a** was slightly raised to 78% at 130 ℃ (Table 1, Entry 7).

With this result in hand, we went on to study the scope of the methodology. Using the optimized reaction conditions, a variety of structurally diverse thiazol-2-ylidenemalononitriles were investigated, and a series of new thiazol-2-yl substituted *E*-acrylonitriles were synthesized in good yields. As shown in Table 2, at the beginning, we made a search for the thiazol-2-ylidenemalononitriles scope, morpholine **4a** was used as model substrate (Table 2), and the results indicated that substrates **3** bearing either electron donating or electron withdrawing functional groups such as nitro, chloro, or methoxyl were able to affect the synthesis of compound **5**.

To further expand the scope of amine substrates, different substrates **3** were subjected to examine various amines including secondary amines **4b**—**4f** (piperidine **4b**, 4-methylpiperidine **4c**, dimethylamine **4d**, diethylamine **4e**, piperazine **4f**) and aromatic amines **4g**—**4i**

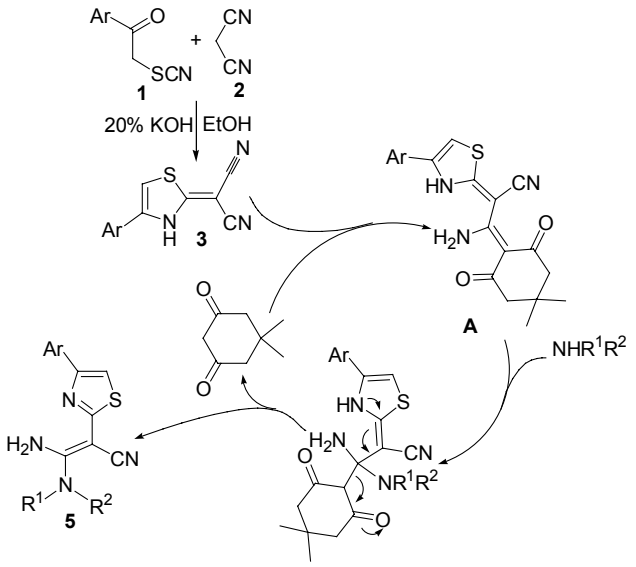
Table 2 Synthesis of compounds **5** under microwave irradiation

Entry	Product		Ar'	Amine	Time/min	Yield/%
1		**5a**	4-Nitrophenyl	Morpholine	25	78
2		**5b**	3-Nitrophenyl	Morpholine	25	75
3		**5c**	3-Chlorophenyl	Morpholine	30	73
4	**5a**—**5e**	**5d**	Phenyl	Morpholine	35	74
5		**5e**	4-Methoxyphenyl	Morpholine	35	76
6		**5f**	4-Nitrophenyl	Piperidine	35	72
7		**5g**	3-Nitrophenyl	Piperidine	35	70
8		**5h**	3-Chlorophenyl	Piperidine	40	69
9	**5f**—**5j**	**5i**	Phenyl	Piperidine	40	70
10		**5j**	4-Methoxyphenyl	Piperidine	40	65
11	 **5k**	**5k**	4-Nitrophenyl	4-Methylpiperidine	35	67
12		**5l**	4-Nitrophenyl	Dimethylamine	30	74
13		**5m**	3-Nitrophenyl	Dimethylamine	30	72
14		**5n**	Phenyl	Dimethylamine	32	69
15	**5l**—**5o**	**5o**	4-Methoxyphenyl	Dimethylamine	35	71
16		**5p**	4-Nitrophenyl	Diethylamine	35	72
17	**5p**—**5q**	**5q**	4-Methoxyphenyl	Diethylamine	35	68
18		**5r**	3-Nitrophenyl	Piperazine	30	69
19		**5s**	3-Chlorophenyl	Piperazine	33	67
20	**5r**—**5t**	**5t**	4-Methoxyphenyl	Piperazine	35	71
21		**5u**	3-Nitrophenyl	4-Chlorobenzenamine	27	75
22		**5v**	3-Nitrophenyl	4-Bromobenzenamine	28	71
23	**5u**—**5w**	**5w**	Phenyl	4-Methlybenzenamine	30	74

(4-chlorobenzenamine **4g**, 4-bromobenzenamine **4h**, 4-methoxybenzenamine **4i**). In all these cases, the reactions proceeded smoothly to give the corresponding thiazol-2-yl substituted *E*-acrylonitriles in good yields of 67%—76% (Table 2, Entries 6—23). Indeed, the protocol provides a straightforward pathway to construct highly functionalized thiazol-2-yl substituted *E*-crylonitrile. The structures of products **5** were deduced from their IR, ^{1}H NMR, ^{13}C NMR and HRMS.

A reasonable mechanism for formation of **5** was proposed in Scheme 4. The formation of **5** is expected to proceed via initial condensation of *α*-thiocyanate ketones **1** and malononitrile **2** to afford 2-(4-aryl-3*H*-thiazol-2-ylidene)-malononitrile (**3**). And then the nucleophilic addition between dimedone and cyano group of substrate **3** occurred, providing intermediate **A** which underwent nucleophilic addition with amine and subsequent isomerization to afford the products **5**.

Scheme 4 The reasonable mechanism for the formations of thiazol-2-yl substituted E-acrylonitriles **5**



Conclusions

In summary, a new dimedone-mediated addition of amines to cyano group has been established to afford a series of thiazol-2-yl substituted *E*-acrylonitriles that serve as versatile building block. The reactions showed high chemoselectivity and a broad scope of substrates which can employ a wide range of common commercial starting materials. A new mechanism has been proposed to explain the reaction process.

Experimental

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^{1}H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 (100 MHz, ^{13}C NMR) with chemical shift (δ) relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-QII HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the synthesis of compounds 5

Preparation of compounds 3 *α*-Thiocyanate ketones and malononitrile in an ethanolic aqueous solution of 20% potassium hydroxide at room temperature for 2 h produced a sole product **3**.

Preparation of compounds 5 Typically, in a 10-mL Biotage microwave vial, the thiazol-2-ylidene-malononitriles 3 (1 mmol), morpholine (1 mmol), dimedone (0.2 equiv.) and EtOH (2 mL) were capped and pre-stirred for 20 s. The mixture was subjected to microwave irradiation at 130 ℃ for a given time. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature, filtered to give the crude product, which was further purified by recrystallization from acetone to give the corresponding products **5** with good yields.

(*E*)-3-Amino-3-morpholin-4-yl-2-[4-(4-nitrophenyl)-thiazol-2-yl]-acrylonitrile (5a) Yellow solid, m.p. 294—295 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.30 (d, J=8.8 Hz, 2H, ArH), 8.14 (d, J=8.8 Hz, 2H, ArH), 8.02 (s, 1H, =CH), 3.70—3.68 (m, 4H, CH_2), 3.51—3.49 (m, 4H, CH_2); IR (KBr) v: 3319, 3108, 2956, 2178, 1644, 1598, 1528, 1513, 1453, 1378, 1340, 1271, 1204, 1149, 1117, 1066, 1023, 967, 854, 838, 741, 618 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_5O_3S$ [M−H]$^-$ 356.0812, found 356.0795.

(*E*)-3-Amino-3-morpholin-4-yl-2-[4-(3-nitrophenyl)-thiazol-2-yl]-acrylonitrile (5b) Yellow solid, m.p. 214—216 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.63 (s, 1H, ArH), 8.32 (d, J=8.0 Hz, 1H, ArH), 8.19—8.16 (m, 1H, ArH), 7.94 (s, 1H, =CH), 7.72 (t, J=8.0 Hz, 1H, ArH), 3.71—3.69 (m, 4H, CH_2), 3.51—3.49 (m, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.0, 163.0, 150.0, 148.3, 135.5, 131.9, 130.3, 122.3, 122.1, 120.0, 109.7, 65.9, 60.1, 48.6; IR (KBr) v: 3371, 3109, 2960, 2174, 1635, 1537, 1528, 1450, 1376, 1351, 1264, 1200, 1136, 1117, 1063, 1024, 975, 897, 719, 596 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}N_5O_3S$ [M − H]$^-$ 356.0812, found 356.0804.

(*E*)-3-Amino-2-[4-(3-chlorophenyl)-thiazol-2-yl]-3-morpholin-4-yl-acrylonitrile (5c) Yellow solid, m.p. 207—208 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.87 (s, 1H, ArH), 7.79 (d, J=7.6 Hz, 1H, ArH), 7.74 (s, 1H, =CH), 7.42 (t, J=7.6 Hz, 1H, ArH), 7.34 (d, J=8.0 Hz, 1H, ArH), 3.64—3.63 (m, 4H, CH_2), 3.44 (s, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.7, 163.1, 150.8, 136.0, 133.6, 130.6, 127.5, 125.4, 124.3, 122.2, 112.7, 108.6, 65.9, 60.1, 48.5; IR (KBr) v: 3329, 3109, 2855, 2176, 1639, 1598, 1541, 1494, 1447, 1404, 1379,

1318, 1257, 1177, 1150, 1118, 1064, 1026, 975, 908, 871, 787, 742, 720, 591 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}ClN_4OS$ $[M-H]^-$ 345.0571, found 345.0580.

(*E*)-3-Amino-3-morpholin-4-yl-2-(4-phenylthiazol-2-yl)-acrylonitrile (5d) Yellow solid, m.p. 205—206 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.86 (d, J=7.6 Hz, 2H, ArH), 7.64 (s, 1H, =CH), 7.44 (t, J=7.6 Hz, 2H, ArH), 7.34 (t, J=7.2 Hz, 1H, ArH), 3.69 (t, J=4.4 Hz, 4H, CH_2), 3.49 (t, J=4.8 Hz, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.5, 163.2, 152.4, 134.0, 128.7, 127.8, 125.7, 122.2, 107.1, 65.9, 60.3, 48.6; IR (KBr) v: 3339, 2966, 2175, 1636, 1520, 1499, 1444, 1377, 1337, 1242, 1148, 1117, 1061, 1019, 971, 895, 835, 721, 690 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}N_4OS$ $[M-H]^-$ 311.0961, found 311.0954.

(*E*)-3-Amino-2-[4-(4-methoxyphenyl)-thiazol-2-yl]-3-morpholin-4-yl-acrylonitrile (5e) Yellow solid, m.p. 238—239 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.79 (d, J=8.8 Hz, 2H, ArH), 7.46 (s, 1H, =CH), 6.99 (d, J=8.4 Hz, 2H, ArH), 3.79 (s, 3H, OCH_3), 3.69 (t, J=4.0 Hz, 4H, CH_2), 3.48 (t, J=4.0 Hz, 4H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.2, 163.2, 159.0, 152.3, 127.1, 126.9, 122.2, 114.1, 105.1, 65.9, 60.3, 55.2, 48.6; IR (KBr) v: 3312, 3146, 3111, 2960, 2184, 1649, 1610, 1537, 1525, 1506, 1457, 1377, 1361, 1322, 1304, 1244, 1177, 1121, 1031, 971, 841, 617 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}N_4O_2S$ $C_{17}H_{18}N_4O_2S$ $[M-H]^-$ 341.1066, found 341.1055.

(*E*)-3-Amino-2-[4-(4-nitrophenyl)-thiazol-2-yl]-3-piperidin-1-yl-acrylonitrile (5f) Yellow solid, m.p. 288—290 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.29 (d, J=9.2 Hz, 2H, ArH), 8.12 (d, J=8.8 Hz, 2H, ArH), 7.98 (s, 1H, =CH), 3.46 (s, 4H, CH_2), 1.62 (s, 6H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.6, 162.9, 150.3, 146.4, 140.0, 126.6, 124.1, 112.7, 111.3, 59.8, 49.3, 25.5, 23.7; IR (KBr) v: 3309, 3137, 3109, 2938, 2176, 1643, 1598, 1531, 1496, 1453, 1410, 1383, 1340, 1282, 1259, 1201, 1123, 1063, 962, 852, 737, 657, 618 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}N_5O_2S$ $[M-H]^-$ 354.1019, found 354.1017.

(*E*)-3-Amino-2-[4-(3-nitrophenyl)-thiazol-2-yl]-3-piperidin-1-yl-acrylonitrile (5g) Yellow solid, m.p. 230—231 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.63 (s, 1H, ArH), 8.31 (d, J=8.0 Hz, 1H, ArH), 8.19—8.16 (m, 1H, ArH), 7.91 (s, 1H, =CH), 7.73 (t, J=8.0 Hz, 1H, ArH), 3.46 (s, 4H, CH_2), 1.62 (s, 6H, CH_2); IR (KBr) v: 3318, 2945, 2175, 1644, 1539, 1513, 1455, 1437, 1380, 1344, 1300, 1216, 1160, 1120, 1104, 1031, 971, 917, 736, 619 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}N_5O_2S$ $[M-H]^-$ 354.1019, found 354.1019.

(*E*)-3-Amino-2-[4-(3-chlorophenyl)-thiazol-2-yl]-3-piperidin-1-yl-acrylonitrile (5h) Yellow solid, m.p. 195—196 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.90 (s, 1H, ArH), 7.82 (d, J=7.6 Hz, 1H, ArH), 7.74 (s, 1H, =CH), 7.46 (t, J=8.0 Hz, 1H, ArH), 7.38 (d, J=7.6 Hz, 1H, ArH), 3.45 (s, 4H, CH_2), 1.62 (s, 6H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.1, 163.0, 150.7, 136.0, 133.6, 130.6, 127.5, 125.4, 124.3, 122.4, 108.2, 59.7, 49.2, 25.5, 23.7; IR (KBr) v: 3333, 3147, 2932, 2178, 1643, 1596, 1548, 1491, 1452, 1407, 1390, 1360, 1314, 1255, 1214, 1159, 1126, 1060, 968, 906, 776, 740, 709 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}ClN_4S$ $[M-H]^-$ 343.0777, found 343.0770.

(*E*)-3-Amino-2-(4-phenylthiazol-2-yl)-3-piperidin-1-yl-acrylonitrile (5i) Yellow solid, m.p. 200—201 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.85 (d, J=7.2 Hz, 2H, ArH), 7.61 (s, 1H, =CH), 7.43 (t, J=7.6 Hz, 2H, ArH), 7.33 (t, J=7.2 Hz, 1H, ArH), 3.45 (s, 4H, CH_2), 1.62 (s, 6H, CH_2); IR (KBr) v: 3311, 3146, 3119, 2935, 2855, 2181, 1644, 1598, 1544, 1503, 1470, 1435, 1391, 1362, 1328, 1262, 1214, 1177, 1125, 1105, 965, 709, 599 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}N_4S$ $[M-H]^-$ 309.1168, found 309.1168.

(*E*)-3-Amino-2-[4-(4-methoxyphenyl)-thiazol-2-yl]-3-piperidin-1-yl-acrylonitrile (5j) Yellow solid, m.p. 200—202 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.77 (d, J=8.8 Hz, 2H, ArH), 7.43 (s, 1H, =CH), 6.99 (d, J=8.4 Hz, 2H, ArH), 3.79 (s, 3H, OCH_3), 3.44 (s, 4H, CH_2), 1.61 (s, 6H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 168.7, 163.1, 159.0, 152.1, 127.0, 122.4, 114.1, 104.7, 59.9, 55.2, 49.2, 25.5, 23.7; IR (KBr) v: 3332, 3137, 2937, 2853, 2179, 1633, 1610, 1531, 1508, 1465, 1453, 1417, 1386, 1301, 1284, 1247, 1175, 1103, 1058, 1032, 966, 835, 741 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{20}N_4OS$ $[M-H]^-$ 339.1274, found 339.1288.

(*E*)-3-Amino-3-(4-methylpiperidin-1-yl)-2-[4-(4-nitrophenyl)-thiazol-2-yl]-acrylonitrile (5k) Yellow solid, m.p. 292—293 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.29 (d, J=8.8 Hz, 2H, ArH), 8.12 (d, J=8.8 Hz, 2H, ArH), 7.96 (s, 1H, =CH), 3.90 (d, J=13.6 Hz, 2H, CH_2), 3.04 (t, J=12.0 Hz, 2H, CH_2), 1.71 (d, J=13.2 Hz, 2H, CH_2), 1.24—1.16 (m, 2H, CH_2), 0.94 (d, J=6.4 Hz, 3H, CH_3); IR (KBr) v: 3335, 3143, 2931, 2178, 1640, 1591, 1548, 1491, 1452, 1403, 1390, 1364, 1314, 1250, 1211, 1159, 1126, 1061, 968, 906, 773, 740, 705 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}N_5O_2S$ $[M-H]^-$ 368.1175, found 368.1156.

(*E*)-3-Amino-3-dimethylamino-2-[4-(4-nitrophenyl)-thiazol-2-yl]-acrylonitrile (5l) Yellow solid, m.p. 277—278 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.29 (d, J=8.8 Hz, 2H, ArH), 8.11 (d, J=8.8 Hz, 2H, ArH), 7.95 (s, 1H, =CH), 3.10 (s, 6H, CH_3); IR (KBr) v: 3343, 3164, 2173, 1645, 1598, 1565, 1539, 1515, 1463, 1441, 1409, 1373, 1339, 1270, 1197, 1115, 1065, 1028, 984, 619 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{13}N_5O_2S$ $[M-H]^-$ 314.0706, found 314.0706.

(*E*)-3-Amino-3-dimethylamino-2-[4-(3-nitrophenyl)-thiazol-2-yl]-acrylonitrile (5m) Yellow solid, m.p. 204—205 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.62 (s, 1H, ArH), 8.31 (d, J=8.0 Hz, 1H, ArH), 8.17 (dd, J=1.6, 8.0 Hz, 1H, ArH), 7.89 (s, 1H, =CH), 7.73 (t, J=8.0 Hz, 1H, ArH), 3.10 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.0, 162.3, 149.8, 148.3, 135.6, 131.9, 130.3, 122.3, 119.9, 114.9, 112.7, 109.0, 58.4; IR (KBr) v: 3334, 3105, 2170, 1647, 1553, 1513, 1497, 1462, 1421, 1344, 1321, 1253, 1196, 1104, 1060,

981, 897, 800, 733 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{13}N_5O_2S$ $[M-H]^-$ 314.0706, found 314.0723.

(*E*)-3-Amino-3-dimethylamino-2-(4-phenylthiazol-2-yl)-acrylonitrile (5n) Yellow solid, m.p. 181—182 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.84 (d, J=7.6 Hz, 2H, ArH), 7.57 (s, 1H, =CH), 7.43 (t, J=7.2 Hz, 2H, ArH), 7.33 (t, J=7.2 Hz, 1H, ArH), 3.09 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.4, 162.4, 152.1, 134.0, 128.7, 127.8, 125.7, 122.9, 112.7, 106.4, 58.4; IR (KBr) v: 3336, 3118, 2175, 1643, 1562, 1496, 1462, 1439, 1416, 1335, 1257, 1188, 1063, 1026, 972, 898, 846, 776, 709, 667 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{14}N_4S$ $[M-H]^-$ 269.0855, found 269.0854.

(*E*)-3-Amino-3-dimethylamino-2-[4-(4-methoxyphenyl)-thiazol-2-yl]-acrylonitrile (5o) Yellow solid, m.p. 240—241 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.77 (d, J=8.8 Hz, 2H, ArH), 7.40 (s, 1H, =CH), 6.99 (d, J=8.8 Hz, 2H, ArH), 3.79 (s, 3H, OCH_3), 3.08 (s, 6H, CH_3); IR (KBr) v: 3344, 3163, 2173, 1644, 1573, 1499, 1460, 1440, 1417, 1319, 1283, 1249, 1174, 1113, 981, 837, 741, 701, 618 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}N_4OS$ $[M-H]^-$299.0961, found 299.0945.

(*E*)-3-Amino-3-diethylamino-2-[4-(4-nitrophenyl)-thiazol-2-yl]-acrylonitrile (5p) Yellow solid, m.p. 251—252 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.29 (d, J=8.8 Hz, 2H, ArH), 8.10 (d, J=9.2 Hz, 2H, ArH), 7.96 (s, 1H, =CH), 3.52 (dd, J=6.8, 13.6 Hz, 4H, CH_2), 1.20 (t, J=7.2 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 170.5, 163.4, 160.4, 146.4, 139.9, 126.5, 124.1, 111.2, 61.7, 58.3, 43.9, 13.1; IR (KBr) v: 3370, 3112, 2165, 1646, 1598, 1547, 1510, 1456, 1385, 1340, 1244, 1114, 983, 854, 838, 714, 618 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}N_5O_2S$ $[M-H]^-$ 342.1019, found 342.1004.

(*E*)-3-Amino-3-diethylamino-2-[4-(4-methoxyphenyl)-thiazol-2-yl]-acrylonitrile (5q) Yellow solid, m.p. 172—173 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.77 (d, J=8.0 Hz, 2H, ArH), 7.40 (s, 1H, =CH), 6.99 (d, J=8.0 Hz, 2H, ArH), 3.79 (s, 3H, OCH_3), 3.50 (d, J=6.4 Hz, 4H, CH_2), 1.20 (t, J=5.6 Hz, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 169.7, 160.5, 159.0, 151.9, 127.0, 126.9, 123.1, 114.1, 104.4, 58.3, 55.2, 43.8, 13.2; IR (KBr) v: 3353, 3117, 2170, 1643, 1608, 1558, 1532, 1493, 1461, 1434, 1415, 1360, 1318, 1281, 1249, 1176, 1112, 1086, 1028, 895, 837, 810, 744, 709 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}N_4OS$ $[M-H]^-$ 327.1274, found 327.1291.

(*E*)-3-Amino-3-(4-{(*E*)-1-amino-2-cyano-2-[4-(3-nitrophenyl)-thiazol-2-yl]-vinyl}-piperazin-1-yl)-2-[4-(3-nitro-phenyl)-thiazol-2-yl]-acrylonitrile (5r) Yellow solid, m.p. >300 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.66 (s, 2H, ArH), 8.34 (d, J=7.6 Hz, 2H, ArH), 8.19 (d, J=8.0 Hz, 2H, ArH), 7.97 (s, 2H, =CH), 7.74 (t, J=8.0 Hz, 2H, ArH), 3.68 (s, 8H, CH_2), 3.51 (s, 2H, NH_2), 2.89 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 158.7, 154.6, 151.6, 148.7, 147.9, 141.5, 131.4, 130.7, 128.6, 127.8, 126.4, 122.1, 121.7, 113.9, 111.0, 101.2, 55.5, 33.9, 25.0, 25.0; IR (KBr) v: 3333, 3115, 2176, 1659, 1633, 1536, 1513, 1496, 1452, 1377, 1344, 1261, 1199, 1116, 983, 730, 617 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{22}N_{10}O_4S_2$ $[M-H]^-$ 625.1183, found 625.1196.

(*E*)-3-Amino-3-(4-{(*E*)-1-amino-2-[4-(3-chlorophenyl)-thiazol-2-yl]-2-cyano-vinyl}-piperazin-1-yl)-2-[4-(3-chloro-phenyl)-thiazol-2-yl]-acrylonitrile (5s) Yellow solid, m.p. >300 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.93 (s, 2H, ArH), 7.85 (d, J=7.6 Hz, 2H, ArH), 7.81 (s, 2H, =CH), 7.47 (t, J=8.0 Hz, 2H, ArH), 7.40 (d, J=7.6 Hz, 2H, ArH), 3.66 (s, 8H, CH_2), 3.30 (s, 4H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 188.0, 164.5, 131.7, 131.5, 131.3, 130.2, 128.2, 122.6, 114.4, 112.8, 112.7, 55.8, 37.5, 34.4, 15.0; IR (KBr) v: 3328, 3118, 2175, 1631, 1595, 1523, 1501, 1446, 1380, 1295, 1143, 983, 802, 750, 731, 600 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{22}Cl_2N_8S_2$ $[M-H]^-$ 603.0702, found 603.0724.

(*E*)-3-Amino-3-(4-{(*E*)-1-amino-2-cyano-2-[4-(4-methoxyphenyl)-thiazol-2-yl]-vinyl}-piperazin-1-yl)-2-[4-(4-methoxy-phenyl)-thiazol-2-yl]-acrylonitrile (5t) Yellow solid, m.p. >300 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.80 (d, J=8.8 Hz, 4H, ArH), 7.48 (s, 2H, =CH), 7.00 (d, J=8.4 Hz, 4H, ArH), 3.80 (s, 6H, OCH_3), 3.65 (s, 8H, CH_2); IR (KBr) v: 3332, 3121, 2904, 2175, 1631, 1529, 1501, 1447, 1381, 1287, 1249, 1173, 1142, 1059, 1031, 980, 837, 740, 703, 583 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{28}N_8O_2S_2$ $[M-H]^-$ 595.1698, found 595.1663.

(*E*)-3-Amino-3-(4-chloro-phenylamino)-2-[4-(3-nitrophenyl)-thiazol-2-yl]-acrylonitrile (5u) Yellow solid, m.p. 228—230 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H, NH), 8.61 (s, 1H, ArH), 8.32 (d, J=7.2 Hz, 1H, ArH), 8.18 (d, J=7.2 Hz, 1H, ArH), 7.99 (s, 1H, =CH), 7.73 (t, J=8.0 Hz, 1H, ArH), 7.47 (d, J=7.6 Hz, 2H, ArH), 7.34 (s, 2H, ArH); IR (KBr) v: 3476, 3344, 3230, 3115, 2183, 1663, 1619, 1574, 1541, 1517, 1493, 1422, 1395, 1348, 1276, 1162, 1116, 996, 828, 729, 620 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{12}ClN_5O_2S$ $[M-H]^-$ 396.0317, found 396.0333.

(*E*)-3-Amino-3-(4-bromo-phenylamino)-2-[4-(3-nitrophenyl)-thiazol-2-yl]-acrylonitrile (5v) Yellow solid, m.p. 236—237 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 9.26 (s, 1H, NH), 8.61 (s, 1H, ArH), 8.31 (d, J=7.6 Hz, 1H, ArH), 8.18 (d, J=8.4 Hz, 1H, ArH), 7.99 (s, 1H, =CH), 7.73 (t, J=8.0 Hz, 1H, ArH), 7.59 (d, J=6.4 Hz, 2H, ArH), 7.29—7.27 (m, 2H, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 183.0, 168.3, 148.3, 143.1, 136.6, 132.2, 132.1, 131.9, 130.4, 125.5, 122.4, 120.6, 120.0, 112.7, 56.0, 18.5; IR (KBr) v: 3467, 3352, 3228, 2181, 1663, 1619, 1572, 1540, 1515, 1489, 1420, 1390, 1346, 1274, 1173, 1116, 1064, 1009, 974, 828, 728 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{12}BrN_5O_2S$ $[M-H]^-$ 439.9811, found 439.9811.

(*E*)-3-Amino-3-(4-methylphenylamino)-2-(4-phenylthiazol-2-yl)-acrylonitrile (5w) Yellow solid, m.p. 209—211 ℃; ^1H NMR (400 MHz, DMSO-d_6) δ: 9.03 (s, 1H, NH), 7.84 (d, J=6.4 Hz, 2H, ArH), 7.63 (s,

1H, =CH), 7.42 (t, J=7.2 Hz, 2H, ArH), 7.34—7.22 (m, 5H, ArH), 2.33 (s, 3H, OCH_3); IR (KBr) ν: 3437, 3306, 3206, 2191, 1645, 1603, 1573, 1514, 1480, 1442, 1419, 1396, 1289, 1265, 1253, 1176, 1060, 1027, 965, 894, 819, 776, 723, 706 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}N_4S$ $[M-H]^-$ 332.1090, found 332.1017.

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[14] The single-crystal growth was carried out in DMF at room temperature. Crystal data for **5a**: Empirical formula $C_{16}H_{15}N_5O_3S$, Formula weight 357.39, crystal dimension 0.17 mm×0.08 mm×0.06 mm, Monoclinic, space group $P2(1)/c$, a=7.2560(8) Å, b=14.7641(15) Å, c=16.1849(16) Å, α=90°, β=97.9370(10)°, γ=90°, μ=0.214 mm^{-1}, V=1717.3(3) $Å^3$, Z=4, D_c=1.382 Mg/m^3, $F(000)$=744, S=0.924, R_1=0.0712, wR_2=0.0740.

(Cheng, F.)

