ONE-POT SYNTHESIS OF DENSELY FUNCTIONALIZED THIAZOLES
AND SYN-3-THIOACRYLATES

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Abstract – A sequential one-pot, two-step reaction has been established for efficient synthesis of densely functionalized thiazoles and syn-3-thioacrylates. Treatment of cyanoadetamide with isothiocyanates gave rise to 2-cyano-3-mercaptoacrylamides, trapped by but-2-yndioates through [3+2] cyclization to access functionalized thiazoles. Using propiolates to replace but-2-yndioates, the reaction resulted in highly substituted syn-3-thioacrylates. The present green synthesis shows several advantages including operational simplicity and fast reaction rates, which makes it a useful and attractive process of library generation for drug discovery.

INTRODUCTION

Thiazoles and their analogues, being as an important class of bioactive heterocycles, present in naturally occurring and non-naturally products, which show a wide spectrum of pharmacological properties4 such as antidiabetic, antibiotic, and antifungal activities.2,6 Particularly, thiazoles can serve as antidiabetic agents that increase the insulin sensitivity of target tissues, and they also acted as potent and selective activators of peroxisome proliferator-activated receptor γ (PPARγ).2 Owing to the biological significance of these molecules, the synthesis of thiazoles has attracted considerable attentions. For instance, Obydennov and co-workers reported the synthesis of 3-oxothien-2-ylidenes or 4-oxothiazol-2,5-ylidenes...
through a reaction of thioacetamides with dimethyl acetylenedicarboxylate but involved the narrow substrate scope. Basheer and co-workers employed cyanoacetamide to react with isothiocyanates, followed by treating cycloketones to generate several 1,3-thiazine derivatives, but demanded a two-step process. Although these limited syntheses, the explorations of a facile and practical protocol toward new thiazoles with diversity in their substituents is highly desirable. Recently, we developed a sequential one-pot, two-step reaction for efficient synthesis of spiro-substituted 1,3-thiazine library. In this report, 2-cyano-3-mercaptoacrylamides (Figure 1), derived from cyanoacetamide and isothiocyanatobenzene, were subjected with cyclic ketones through [5+1] cyclizations, affording spiro-substituted 1,3-thiazines. S1,N5-binucleophilic sites of 2-cyano-3-mercaptoacrylamides were involved in this transformation. Enlightened by cyclization reactions, we envisioned that [3+2] cyclization can be realized in a one-pot, two-step process using 1,2-bielectrophiles to react with S1,N3-binucleophilic sites of compounds A. As a continuation of our research devoted to domino reactions, in this paper, we would like to report a one-pot, two-step reaction for the domino synthesis of thiazole derivatives using cyanoacetamide 1, isothiocyanates 2 and but-2-yneioates 3a-b as starting materials. The syntheses were achieved by reacting cyanoacetamide with isothiocyanates to yield 2-cyano-3-mercaptoacrylamides A, which are trapped by but-2-yneioates through [3+2] cyclization, providing multi-functionalized thiazole derivatives 4. With exchanging but-2-yneioates 3a-b for propiolates 3c-d, the reaction gave an unexpected 3-thioacrylates 6 with syn-selectivity (only syn isomer) (Scheme 1).
RESULTS AND DISCUSSION

We firstly chose dimethyl but-2-ynedioate (DMAD) as 1,2-bielectrophiles to explore the feasibility of this reaction in one-pot two-step manner. Upon treatment with isothiocyanates and cyanoacetamide in the presence of sodium hydroxide in DMF at room temperature gave 2-cyano-3-mercaptoacrylamides in quantitative chemical yields. Without isolation, excess of HOAc (2.0 mL) was added into the above reaction system, followed by dimethyl but-2-ynedioate (DMAD) 3a, due to HOAc can promote the [3+2] cyclization. The new reaction system was heating at 60 °C under microwave irradiation (MWI) for 20 min. The pale yellow solid was obtained in 52% chemical yield (Table 1, entry 1). Its characterization by NMR and IR spectra indicated that the structure of resultant solid was thiazoles 4a. Next, we screened reaction temperatures and solvents for the reaction. The identical reaction was repeated many times at reaction temperatures ranging from 60 °C to 100 °C. The best result was obtained (4a, 78% yield, entry 2) when the reaction was conducted at 80 °C in HOAc. Increasing reaction temperature to 100 °C did not improve chemical yields (entry 3). Other solvents such as ethanol, formic acid (HCO2H), and propionic acid (EtCO2H) were inferior to HOAc in terms of reaction yields (entries 4-6).

Table 1. Optimization of reaction conditions under MWI

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>T/ °C</th>
<th>Yield a/%</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>HOAc</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>HOAc</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>HOAc</td>
<td>100</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>80</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>HCO2H</td>
<td>80</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>EtCO2H</td>
<td>80</td>
<td>68</td>
</tr>
</tbody>
</table>

a Isolated yield

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 isothiocyanates 2 were investigated and a series of new thiazole derivatives 4 were afforded in good yields through one-pot two-step strategy. As shown in Scheme 2, at the beginning, we made a search for the isothiocyanate substrate scope, cyanoacetamide 1 and DMAD 3a were used as model substrates, and the results indicated that arylated isothiocyanates bearing electron-withdrawing (fluoro, chloro) or electron-donating (methyl, methoxy) groups were found to be suitable for the synthesis of compound 4, giving good to excellent yields ranging from 73-81% (4b-4h). Notably, aliphatic counterparts such as benzyl group also exhibited a high reactivity, allowing [3+2] cyclization toward the formation of the corresponding densely functionalized thiazoles 4i in a 69%
yield. Alternatively, $N$-phenyl-cyanoacetamide $1b$ was successfully engaged in this transformation, affording highly substituted thiazoles $4j$ in a 67\% yield. Replacement of diethyl but-2-yne-dioate $3b$ with substrate $3a$ delivered a wide range of polysubstituted thiazoles $4k$-$4u$ in acceptable yields. The electronic property of arylated isothiocyanates shows no deducible impact on the reaction results. The structural elucidation and the attribution of stereoselectivity were unequivocally determined by NMR spectroscopic analysis and X-ray diffraction of single crystals that was obtained by slow evaporation of the solvent, as in the case of thiazole $4m$ (Figure 2).

Scheme 2. Domino synthesis of products $4$. \textsuperscript{a}Second-step reaction times under MWI. \textsuperscript{b}Isolated yield.
In view of our success with one-pot/two-step protocol for the synthesis of functional thiazoles 4, we envisioned this reaction can proceed to yield 1,3-thiazin-4(3H)-ones 5 through [3+3] cyclization using propiolates 3c-d to replace substrates 3a-b. Unexpectedly, instead of 1,3-thiazin-4(3H)-ones 5, the reaction underwent another direction to form the syn-adducts 6 (Scheme 3). A range of isothiocyanates containing a variety of different functional groups, such as methyl, methoxy, chloride and bromide were tolerated leading to the corresponding syn-3-thioacrylates 6 with good yields (71%-82%). The results

Scheme 3. Synthesis of syn-3-thioacrylates 6. \(^{a}\)Second-step reaction times under MWI. \(^{b}\)Isolated yield
revealed that the electronic nature of the substituents on the benzene ring of isothiocyanates had no significant influence on the reactivity. In order to determine the stereochemistry of 3-thioacrylates 6, the single crystal of 6a was obtained by slow evaporation of the solvent. Its relative stereo-configuration was established by X-ray diffraction as shown in Figure 3.

Figure 3. X-Ray structure of compound 6a

In general, the present two new reactions showed the following attractive characteristics: (1) the reactions proceed efficiently with formation of alcohols as a major by-product under air conditions, which belongs to environmentally friendly chemistry; (2) the convenient workup is needed via simple filtration since the products directly precipitate out of solution after the reaction system is diluted with cold water, which belongs to GAP chemistry; (3) Excellent stereoselectivity of both reactions was achieved without using any metal catalysts.

Scheme 4. Proposed mechanism for products 4 and 6
On the basis of the above results, possible mechanisms have been proposed for the formation of products 4 and 6 as shown in Scheme 4. The formation of thiazoles 4 involved a successive S-addition / N-addition and elimination of alkoxy group sequence (Scheme 4(a)). Similar to the former reaction, the latter underwent tautomerization, S-addition and syn-tautomerization of enols to generate the final 3-thioacrylates 6 (Scheme 4(b)). The syn-selectivity may be attributed the intramolecular hydrogen bonds. In conclusion, we have developed one-pot two-step practical reactions for the efficient synthesis of densely functionalized thiazoles and syn-3-thioacrylates under microwave irradiation using commercially available starting materials. The reaction showed high stereoselectivity and broad scopes of substrates which can employ a wide range of common commercial starting materials. A new mechanism has been proposed to explain the reaction process and stereoselectivity. Both reactions feature mild conditions, simple operation, easy accessibility of reactants and workup procedure as well as metal-free catalysts. Further investigation on the biological evaluation of these resultant products is underway.

**EXPERIMENTAL**

Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage Company, 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. ¹H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d₆ with chemical shift (δ) given in ppm relative to TMS as internal standard. HRMS (ESI) was determined by using microTOF-Q II 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 4a**

Typically, in a 10 mL Initiator reaction vial, phenyl isothiocyanate (1.0 mmol) with cyanoacetamide (1.0 equiv) was performed in DMF catalyzed by sodium hydroxide (0.2 equiv) for 30 min at room temperature, and then HOAc (2.0 mL, excess) and dimethyl but-2-ynedioate (1.2 equiv) were added into the reaction system. Subsequently, the mixture was irradiated by microwave at 80 °C for 20 min. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and diluted with cold water, which then was filtered to give the crude products. The crude products were further purified by recrystallization from 95% EtOH as a pale yellow solid

**(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-3-phenylthiazolidin-5-ylidene)acetate (4a)**

A pale yellow solid; Mp >300 °C; IR (KBr, ν, cm⁻¹): 3469, 3355, 3319, 3248, 3168, 2110, 1731, 1699, 1667, 1591, 1536, 1493, 1446, 1373, 1326, 1245, 1202, 1014, 869; ¹H NMR (400 MHz, DMSO-d₆) (δ,
ppm): 7.77 (s, 1H, NH₂), 7.58-7.53 (m, 5H, Ar-H), 7.36 (s, 1H, NH₂), 6.80 (s, 1H, CH), 3.82 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 165.9, 164.7, 164.6, 161.6, 141.4, 134.5, 130.7, 129.4, 129.3, 116.9, 112.8, 81.4, 52.6. HRMS (ESI): m/z calcd for C₁₅H₁₁N₃NaO₄S, 352.0368 [M+Na]⁺; found: 352.0344.

(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-fluorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4b)
A pale yellow solid; Mp 288-289 °C; IR (KBr, v, cm⁻¹): 3509, 3430, 3404, 3337, 3293, 3242, 3196, 2202, 1737, 1715, 1666, 1602, 1536, 1508, 1437, 1373, 1229, 1262, 1053, 1026, 859, 706; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 7.78 (s, 1H, NH₂), 7.64-7.61 (m, 2H, Ar-H), 7.42 (s, 1H, NH₂), 3.79 (d, J = 8.4 Hz, 2H, Ar-H), 6.81 (s, 1H, CH), 3.35 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 165.8, 164.7, 164.5, 162.0, 141.4, 132.0, 131.9, 130.8, 117.0, 116.5, 116.2, 112.9, 81.3, 52.6. HRMS (ESI): m/z calcd for C₁₃H₁₀FN₃NaO₄S, 370.0274 [M+Na]⁺; found: 370.0270.

(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-chlorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4c)
A pale yellow solid; Mp 265-267 °C; IR (KBr, v, cm⁻¹): 3473, 3331, 3285, 3209, 3072, 2203, 1744, 1674, 1526, 1476, 1392, 1330, 1224, 1195, 1014, 875; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 7.78 (s, 1H, NH₂), 7.65-7.58 (m, 4H, Ar-H); 7.37 (s, 1H, NH₂), 6.81 (s, 1H, CH), 3.82 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 165.8, 164.6, 164.5, 161.7, 141.3, 135.5, 133.4, 131.4, 129.5, 117.0, 113.0, 81.2, 52.6. HRMS (ESI): m/z calcd for C₁₃H₁₀ClN₃NaO₄S, 385.9978 [M+Na]⁺; found: 385.9984.

(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(3-chlorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4d)
A pale yellow solid; Mp >300 °C; IR (KBr, v, cm⁻¹): 3473, 3339, 3285, 3208, 3173, 2204, 1744, 1695, 1677, 1524, 1438, 1330, 1219, 1054, 1014, 875; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 7.80 (s, 1H, NH₂), 7.76 (s, 1H, Ar-H), 7.69-7.66 (m, 1H, Ar-H), 7.60-7.55 (m, 2H, Ar-H), 7.43 (s, 1H, NH₂), 6.82 (s, 1H, CH), 3.82 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 165.8, 164.6, 164.4, 161.5, 141.2, 135.7, 133.4, 130.8(8), 130.8(6), 129.5, 128.5, 117.0, 113.0, 81.3, 52.6. HRMS (ESI): m/z calcd for C₁₃H₁₀ClN₃NaO₄S, 385.9978 [M+Na]⁺; found: 385.9965.

(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(3,4-dichlorophenyl)-4-oxothiazolidin-5-ylidene)acetate (4e)
A pale yellow solid; Mp >300 °C; IR (KBr, v, cm⁻¹): 3466, 3345, 3267, 3168, 3061, 2983, 2938, 2204, 1744, 1677, 1615, 1529, 1475, 1392, 1377, 1357, 1229, 1201, 1137, 919, 866; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 8.00 (d, J = 2.0 Hz, 1H, NH₂), 7.87 (d, J = 8.8 Hz, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.64-7.61 (m, 1H, Ar-H), 7.43 (s, 1H, NH₂), 6.83 (s, 1H, CH), 3.83 (s, 3H, OCH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 165.8, 164.5, 164.3, 161.5, 141.1, 134.2, 133.8, 131.6(9), 131.6(7), 131.3, 130.2,
117.2, 113.2, 81.2, 52.7. HRMS (ESI): m/z calcd for C_{15}H_{9}Cl_{2}N_{3}NaO_{4}S, 419.9589 [M+Na]^+; found: 419.9583.

(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-3-(p-tolyl)thiazolidin-5-ylidene)acetate
(4f)
A pale yellow solid; Mp 293-295 °C; IR (KBr, ν, cm^{-1}): 3486, 3352, 3324, 3260, 3179, 3079, 3039, 2204, 1741, 1683, 1599, 1532, 1448, 1371, 1326, 1238, 1205, 1009, 899, 858, 831; ^1H NMR (400 MHz, DMSO-d$_6$) (δ, ppm): 7.75 (s, 1H, NH$_2$), 7.38 (d, J = 8.4 Hz, 2H, Ar-H), 7.34-7.31 (m, 3H, NH$_2$ and Ar-H), 7.43 (s, 1H, NH$_2$), 6.79 (s, 1H, CH), 3.82 (s, 3H, OCH$_3$), 2.39 (s, 3H, CH$_3$); ^13C NMR (100 MHz, DMSO-d$_6$) (δ, ppm): 165.9, 164.7, 164.6, 161.8, 141.4, 140.4, 131.9, 129.8, 129.1, 116.9, 112.9, 81.3, 52.6, 21.0. HRMS (ESI): m/z calcd for C$_{16}$H$_{13}$N$_{3}$NaO$_{4}$S, 366.0524 [M+Na]^+; found: 366.0522.

(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-3-(m-tolyl)thiazolidin-5-ylidene)acetate
(4g)
A pale yellow solid; Mp 284-286 °C; IR (KBr, ν, cm^{-1}): 3472, 3314, 3165, 3064, 2949, 2202, 1744, 1698, 1602, 1539, 1439, 1332, 1245, 1058, 1017, 947, 915, 893, 857; ^1H NMR (400 MHz, DMSO-d$_6$) (δ, ppm): 7.75 (s, 1H, NH$_2$), 7.41 (d, 2H, J = 7.2 Hz, Ar-H), 7.33-7.30 (m, 3H, NH$_2$ and Ar-H), 6.79 (s, 1H, CH), 3.82 (s, 3H, OCH$_3$), 2.35 (s, 3H, CH$_3$); ^13C NMR (100 MHz, DMSO-d$_6$) (δ, ppm): 165.9, 164.7, 164.6, 161.6, 141.4, 138.9, 134.3, 131.4, 129.6, 129.1, 126.4, 116.9, 112.8, 81.4, 52.6, 20.8. HRMS (ESI): m/z calcd for C$_{16}$H$_{13}$N$_{3}$NaO$_{4}$S, 366.0524 [M+Na]^+; found: 366.0530.

(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-methoxyphenyl)-4-oxothiazolidin-5-ylidene)-acetate
(4h)
A pale yellow solid; Mp 265-266 °C; IR (KBr, ν, cm^{-1}): 3440, 3349, 3320, 3262, 3193, 2204, 1744, 1678, 1605, 1599, 1509, 1445, 1376, 1325, 1235, 1170, 1018, 943, 899; ^1H NMR (400 MHz, DMSO-d$_6$) (δ, ppm): 7.75 (s, 1H, NH$_2$), 7.43 (d, J = 9.2 Hz, 2H, Ar-H), 7.32 (s, 1H, NH$_2$), 7.06 (d, J = 8.8 Hz, 2H, Ar-H), 6.79 (s, 1H, CH), 3.82 (s, 6H, OCH$_3$); ^13C NMR (100 MHz, DMSO-d$_6$) (δ, ppm): 165.9, 164.7, 164.6, 162.3, 160.8, 141.5, 130.7, 126.9, 116.8, 114.5, 113.0, 81.3, 55.5, 52.6. HRMS (ESI): m/z calcd for C$_{16}$H$_{13}$N$_{3}$NaO$_{4}$S, 382.0474 [M+Na]^+; found: 382.0475.

(Z)-Methyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-benzyl-4-oxothiazolidin-5-ylidene)acetate
(4i)
A pale yellow solid; Mp 268-269 °C; IR (KBr, ν, cm^{-1}): 3451, 3338, 3282, 3204, 3171, 3059, 2199, 1738, 1688, 1674, 1603, 1520, 1433, 1347, 1321, 1218, 1077; ^1H NMR (400 MHz, DMSO-d$_6$) (δ, ppm): 7.86 (s, 1H, NH$_2$), 7.58 (s, 1H, NH$_2$), 7.37 (t, J = 7.2 Hz, 2H, Ar-H), 7.29 (t, J = 7.2 Hz, 1H, Ar-H), 7.18 (d, J = 7.6 Hz, 2H, Ar-H), 6.86 (s, 1H, CH), 5.48 (s, 2H, CH$_2$), 3.81 (s, 3H, OCH$_3$); ^13C NMR (100 MHz, DMSO-d$_6$) (δ, ppm): 165.8, 165.4, 164.3, 161.4, 140.1, 134.9, 128.7, 127.4, 125.8, 117.8, 115.3, 80.6, 52.6, 47.5. HRMS (ESI): m/z calcd for C$_{16}$H$_{13}$N$_{3}$NaO$_{4}$S, 366.0524 [M+Na]^+; found: 366.0502.

(Z)-methyl 2-(2-(1-cyano-2-oxo-2-(phenylamino)ethylidene)-4-oxo-3-phenylthiazolidin-5-ylidene)-
acetate (4j)
A pale yellow solid; Mp 271-273 °C; IR (KBr, ν, cm\(^{-1}\)): 3468, 3435, 3285, 3200, 3063, 2203, 1731, 1693, 1654, 1600, 1531, 1442, 1364, 1321, 1219, 912, 869; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) (δ, ppm): 9.81 (s, 1H, NH\(_2\)), 7.58 (s, 7H, Ar-H), 7.34 (s, 2H, Ar-H), 7.14 (s, 1H, Ar-H), 6.85 (s, 1H, CH), 6.85 (s, 1H, CH), 3.83 (s, 3H, OCH\(_3\)); \(^1^3\)C NMR (100 MHz, DMSO-\(d_6\)) (δ, ppm): 165.8, 164.7, 162.4, 161.9, 140.7, 137.7, 134.4, 130.8, 129.4(2), 129.3(7), 128.5, 124.5, 121.3, 117.4, 112.5, 82.0, 52.7. HRMS (ESI): \(m/z\) calcd for C\(_{21}\)H\(_{15}\)N\(_3\)NaO\(_8\), 428.0681 [M+Na]\(^+\); found: 428.0681.

(Z)-Ethyl 2-(2-(amino-1-cyano-2-oxoethylidene)-4-oxo-3-phenylthiazolidin-5-ylidene)acetate (4k)
A pale yellow solid; Mp: 248-249 °C; IR (KBr, ν, cm\(^{-1}\)): 3460, 3358, 3322, 3240, 3172, 2204, 1720, 1699, 1660, 1598, 1539, 1493, 1444, 1379, 1326, 1245, 1200, 1011, 868; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) (δ, ppm): 7.70 (s, 1H, NH\(_2\)), 7.60-7.53 (m, 3H, Ar-H), 7.49-7.46 (m, 2H, NH\(_2\) and Ar-H), 6.78 (s, 1H, CH), 4.28 (m, 2H, CH\(_2\)), 1.31 (t, \(J = 7.2\) Hz, 3H, CH\(_3\)); \(^1^3\)C NMR (100 MHz, DMSO-\(d_6\)) (δ, ppm): 165.3, 164.6, 164.5, 161.7, 140.8, 134.2, 130.8, 129.3, 129.2, 117.6, 112.8, 81.4, 61.5, 13.9. HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{13}\)N\(_3\)NaO\(_4\), 366.0524 [M+Na]\(^+\); found: 366.0520.

(Z)-Ethyl 2-(2-(amino-1-cyano-2-oxoethylidene)-3-(4-fluorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4l)
A pale yellow solid; Mp 262-263 °C; IR (KBr, ν, cm\(^{-1}\)): 3477, 3341, 3285, 3200, 3167, 2203, 1742, 1675, 1525, 1371, 1325, 1227, 1195, 1027, 883; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) (δ, ppm): 7.78 (s, 1H, NH\(_2\)), 7.64-7.60 (m, 2H, Ar-H), 7.40 (t, \(J = 8.8\) Hz, 3H, NH\(_2\) and Ar-H), 6.78 (s, 1H, CH), 4.31-4.26 (m, 2H, CH\(_2\)), 1.28 (t, \(J = 7.2\) Hz, 3H, CH\(_3\)); \(^1^3\)C NMR (100 MHz, DMSO-\(d_6\)) (δ, ppm): 165.4, 164.7, 164.5, 162.0, 141.2, 132.0, 131.9, 130.8, 117.3, 116.5, 116.2, 113.0, 81.2, 61.5, 14.0. HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{12}\)FN\(_3\)NaO\(_8\), 384.0430 [M+Na]\(^+\); found: 384.0418.

(Z)-Ethyl 2-(2-(amino-1-cyano-2-oxoethylidene)-3-(4-chlorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4m)
A pale yellow solid; Mp 251-252 °C; IR (KBr, ν, cm\(^{-1}\)): 3448, 3289, 3207, 3056, 2205, 1735, 1692, 1653, 1609, 1530, 1493, 1393, 1361, 1320, 1229, 1195, 1090, 1019, 850; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) (δ, ppm): 7.78 (s, 1H, NH\(_2\)), 7.63 (d, \(J = 8.8\) Hz, 2H, Ar-H), 7.59 (d, \(J = 8.8\) Hz, 2H, Ar-H), 7.39 (s, 1H, NH\(_2\)), 6.77 (s, 1H, CH), 4.31-4.26 (m, 2H, CH\(_2\)), 1.28 (t, \(J = 7.2\) Hz, 3H, CH\(_3\)); \(^1^3\)C NMR (100 MHz, DMSO-\(d_6\)) (δ, ppm): 165.3, 164.6, 164.5, 161.7, 141.2, 135.5, 133.4, 131.4, 129.4, 117.3, 113.0, 81.2, 61.5, 14.0. HRMS (ESI): \(m/z\) calcd for C\(_{16}\)H\(_{12}\)ClN\(_3\)NaO\(_8\), 400.0135 [M+Na]\(^+\); found: 400.0122.

(Z)-Ethyl 2-(2-(amino-1-cyano-2-oxoethylidene)-3-(3-chlorophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4n)
A pale yellow solid; Mp >300 °C; IR (KBr, ν, cm\(^{-1}\)): 3494, 3418, 3289, 3208, 2205, 1708, 1601, 1508, 1453, 1371, 1294, 1226, 1135, 1053, 860; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) (δ, ppm): 7.78 (s, 1H, NH\(_2\)),
7.76 (d, \( J = 1.6 \) Hz, 1H, Ar-H), 7.69-7.66 (m, 1H, Ar-H), 7.60-7.54 (m, 2H, Ar-H), 7.42 (s, 1H, NH₂), 6.78 (s, 1H, CH), 4.31-4.26 (m, 2H, CH₂), 1.28 (t, \( J = 7.2 \) Hz, 3H, CH₃); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) (δ, ppm): 165.3, 164.6, 164.4, 161.5, 141.1, 135.7, 133.4, 130.9, 129.5, 128.5, 117.4, 113.0, 81.3, 61.6, 14.0. HRMS (ESI): \( m/z \) calcld for C\(_{16}\)H\(_{12}\)Cl\(_3\)N\(_2\)NaO\(_4\)S, 400.0135 [M+Na]; found: 400.0135.

(Z)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(3,4-dichlorophenyl)-4-oxothiazolidin-5-ylidene) acetate (4o)

A pale yellow solid; Mp >300 °C; IR (KBr, ν, cm\(^{-1}\)): 3476, 3344, 3286, 3166, 3061, 2992, 2938, 2205, 1744, 1677, 1605, 1529, 1473, 1392, 1371, 1327, 1229, 1201, 1127, 1137, 919, 864; \(^{1}\)H NMR (400 MHz, DMSO-\(d_6\)) (δ, ppm): 7.99 (d, \( J = 0.8 \) Hz, 1H, NH₂), 7.87 (d, \( J = 8.8 \) Hz, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.64-7.61 (m, 1H, Ar-H), 7.43 (s, 1H, NH₂), 6.80 (s, 1H, CH), 4.32-4.26 (m, 2H, CH₂), 1.28 (t, \( J = 7.2 \) Hz, 3H, CH₃); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) (δ, ppm): 165.3, 164.5, 164.3, 161.6, 141.0, 134.3, 133.8, 131.7, 131.3, 130.2, 117.5, 113.2, 81.2, 61.6, 14.0. HRMS (ESI): \( m/z \) calcld for C\(_{16}\)H\(_{11}\)Cl\(_2\)N\(_3\)NaO\(_4\)S, 433.9745 [M+Na]+; found: 433.9738.

(Z)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-bromophenyl)-4-oxothiazolidin-5-ylidene)-acetate (4p)

A pale yellow solid; Mp 258-259 °C; IR (KBr, ν, cm\(^{-1}\)): 3448, 3341, 3287, 3208, 3178, 2203, 1733, 1692, 1607, 1582, 1529, 1490, 1371, 1319, 1229, 1195, 1112, 1015, 847; \(^{1}\)H NMR (400 MHz, DMSO-\(d_6\)) (δ, ppm): 7.78 (s, 2H, Ar-H), 7.76 (s, 1H, NH₂), 7.52 (d, \( J = 8.8 \) Hz, 2H, Ar-H), 7.39 (s,1H, NH₂), 6.77 (s, 1H, CH), 4.31-4.26 (m, 2H, CH₂), 1.28 (t, \( J = 14.4 \) Hz, 3H, CH₃); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) (δ, ppm): 165.3, 164.6, 164.4, 161.7, 141.2, 133.8, 132.4, 131.7, 124.1, 117.3, 113.0, 81.2, 61.6, 14.0. HRMS (ESI): \( m/z \) calcld for C\(_{16}\)H\(_{12}\)Br\(_2\)N\(_2\)NaO\(_4\)S, 443.9630 [M+Na]+; found: 443.9643.

(Z)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-(p-tolyl)thiazolidin-5-ylidene)acetate (4q)

A pale yellow solid; Mp 259-261 °C; IR (KBr, ν, cm\(^{-1}\)): 3476, 3337, 3266, 2200, 1750, 1688, 1590, 1536, 1444, 1369, 1321, 1234, 1003, 899, 858, 829, 761; \(^{1}\)H NMR (400 MHz, DMSO-\(d_6\)) (δ, ppm): 7.76 (s, 1H, NH₂), 7.38 (d, \( J = 7.6 \) Hz, 2H, Ar-H), 7.34-7.19 (m, 3H, NH₂ and Ar-H), 6.76 (s, 1H, CH), 4.30-4.26 (m, 2H, CH₂), 2.39 (s, 3H, CH₃) , 1.28 (t, \( J = 6.8 \) Hz, 3H, CH₃); \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) (δ, ppm): 165.4, 164.7, 164.6, 161.9, 141.4, 140.4, 131.9, 129.8, 129.1, 117.1, 112.9, 81.3, 61.5, 20.9, 14.0. HRMS (ESI): \( m/z \) calcld for C\(_{17}\)H\(_{15}\)N\(_2\)NaO\(_4\)S, 380.0681 [M+Na]+; found: 380.0668.

(Z)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-4-oxo-(m-tolyl)thiazolidin-5-ylidene)acetate (4r)

A pale yellow solid; Mp 277-279 °C; IR (KBr, ν, cm\(^{-1}\)): 3480, 3342, 3266, 3164, 3060, 2991, 2199, 1742, 1675, 1613, 1524, 1491, 1453, 1371, 1324, 1223, 1032, 914, 888; \(^{1}\)H NMR (400 MHz, DMSO-\(d_6\)) (δ, ppm): 7.74 (s, 1H, NH₂), 7.43-7.38 (m, 2H, Ar-H), 7.33-7.30 (m, 3H, NH₂ and Ar-H), 6.75 (s, 1H, CH), 4.31-4.25 (m, 2H, CH₂), 2.36 (s, 3H, CH₃) , 1.28 (t, \( J = 7.2 \) Hz, 3H, CH₃); \(^{13}\)C NMR (100 MHz,
Subsequently, the mixture was irradiated by microwave at 100 °C and then HOAc (2.0 mL, excess) and methyl propiolate (1.5 equiv) were added into the reaction system. The auto-oxidation was catalyzed by sodium hydroxide (0.2 equiv) for 30 min at room temperature, then dissolved in DMSO-d₆. The reaction mixture was analyzed by NMR, IR, and HRMS to obtain the following data:

### (Z)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-(4-methoxyphenyl)-4-oxothiazolidin-5-ylidene)acetate (4s)

A pale yellow solid; Mp 257-259 °C; IR (KBr, ν, cm⁻¹): 3480, 3431, 3390, 3254, 3176, 2205, 1731, 1694, 1530, 1368, 1320, 1228, 1193, 1022, 885; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 7.76 (s, 1H, NH₂), 7.42 (d, J = 8.8 Hz, 2H, Ar-H), 7.32 (s, 1H, NH₂), 7.06 (d, J = 8.4 Hz, 2H, Ar-H), 6.75 (s, 1H, CH), 4.31-4.26 (m, 2H, CH₂), 3.82 (s, 3H, OCH₃) (4t)

### (Z)-Ethyl 2-(2-(2-amino-1-cyano-2-oxoethylidene)-3-benzyl-4-oxothiazolidin-5-ylidene)acetate (4t)

A pale yellow solid; Mp 232-233 °C; IR (KBr, ν, cm⁻¹): 3471, 3342, 3287, 3169, 3062, 2201, 1735, 1676, 1607, 1528, 1372, 1352, 1219, 1184, 1029, 964; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 7.85 (s, 1H, NH₂), 7.57 (s, 1H, NH₂), 7.37 (t, J = 7.2 Hz, 2H, Ar-H), 7.29 (t, J = 7.2 Hz, 1H, Ar-H), 7.18 (d, J = 7.6 Hz, 2H, Ar-H), 6.83 (s, 1H, CH), 5.48 (s, 2H, CH₂), 4.30-4.25 (m, 2H, CH₂), 1.28 (t, J = 6.8 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 165.4, 165.3, 164.3, 161.4, 140.0, 134.9, 128.7, 127.4, 125.8, 118.1, 115.4, 80.6, 61.6, 47.5, 14.0. HRMS (ESI): m/z calcd for C₁₇H₁₅N₅NaO₅S, 396.0630 [M+Na⁺]; found: 396.0630.

### (Z)-Ethyl 2-(2-(1-cyano-2-oxo-2-(phenylamino)ethylidene)-4-oxo-3-phenylthiazolidin-5-ylidene)acetate (4u)

A pale yellow solid; Mp 221-222 °C; IR (KBr, ν, cm⁻¹): 3544, 3479, 3468, 3391, 3050, 2196, 1726, 1687, 1661, 1521, 1441, 1367, 1319, 1221, 1018, 931, 886; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 9.81 (s, 1H, NH₂), 7.57-7.55 (m, 7H, Ar-H), 7.33 (t, J = 7.6 Hz, 2H, Ar-H), 7.12 (t, J = 7.2 Hz, 1H, Ar-H), 6.81 (s, 1H, CH), 4.31-4.26 (m, 2H, CH₂), 1.28 (t, J = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 165.3, 164.7, 162.4, 161.9, 140.6, 137.7, 134.4, 130.8, 129.4(3), 129.3(5), 128.5, 124.5, 121.3, 117.6, 112.5, 81.9, 61.6, 14.0. HRMS (ESI): m/z calcd for C₂₂H₁₇N₅NaO₅S, 442.0837 [M+Na⁺]; found: 442.0838.

### General Procedure for the Synthesis of Compounds 6a

Typically, in a 10 mL Initiator reaction vial, phenyl isothiocyanate (1.0 mmol) with cyanoacetaldehyde (1.0 equiv) was performed in DMF catalyzed by sodium hydroxide (0.2 equiv) for 30 min at room temperature, and then HOAc (2.0 mL, excess) and methyl propiolate (1.5 equiv) were added into the reaction system. Subsequently, the mixture was irradiated by microwave at 100 °C for 28 min. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the
reaction mixture was cooled to room temperature and filtered to give the crude products, which were further purified by recrystallization from 95% EtOH as a pale yellow solid.

(Z)-Methyl 3-((3-amino-2-cyano-3-oxo-1-(phenylamino)prop-1-en-1-yl)thio)acrylate (6a)

A pale yellow solid; Mp 156-157 °C; IR (KBr, v, cm⁻¹): 3524, 3501, 3479, 3468, 3430, 2198, 1707, 1675, 1559, 1411, 1325, 1232, 1166, 1034, 883; ¹H NMR (400 MHz, CDCl₃) (δ, ppm): 12.54 (s, 1H, NH), 7.39-7.35 (m, 2H, Ar-H), 7.28-7.26 (m, 2H, Ar-H), 7.22 (d, J = 7.6 Hz, 2H, NH), 6.94 (d, J = 9.6 Hz, 1H, CH=), 3.73 (s, 3H, CH₃), 1.60 (s, 1H, CH=); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm): 168.0, 166.0, 163.4, 143.2, 137.6, 129.1, 126.5, 125.4, 118.1, 114.9, 80.6, 51.6. HRMS (ESI): m/z calcd for C₁₄H₁₃N₃NaO₃S, 326.0575 [M+Na]+; found: 326.0578.

(Z)-Methyl 3-((1-(4-chlorophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6b)

A pale yellow solid; Mp 173-175 °C; IR (KBr, v, cm⁻¹): 3189, 2201, 1720, 1552, 1217, 1179, 828; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 12.48 (s, 1H, NH), 7.45-7.43 (m, 2H, Ar-H), 7.35 (m, 2H, Ar-H), 7.33 (d, J = 4.4 Hz, 1H, CH=), 6.04 (d, J = 9.8 Hz, 1H, CH=), 3.65 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 168.1, 166.5, 163.6, 143.6, 137.3, 131.1, 129.5, 127.6, 118.4, 115.6, 81.9, 52.1. HRMS (ESI): m/z calcd for C₁₄H₁₂ClN₃NaO₃S, 360.0186 [M+Na]+; found: 326.0578.

(Z)-Methyl 3-((3,4-dichlorophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6c)

A dark yellow solid; Mp 173-175 °C; IR (KBr, v, cm⁻¹): 3192, 2198, 1694, 1525, 1215, 1167, 823; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 12.34 (s, 1H, NH), 7.66-7.62 (m, 2H, Ar-H), 7.36 (d, J = 9.8 Hz, 1H, CH=), 7.32 (d, J = 11.2 Hz, 1H, Ar-H), 6.08 (d, J = 9.8 Hz, 1H, CH=), 3.66 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 168.1, 166.1, 163.7, 143.4, 137.3, 131.1, 129.5, 127.5, 118.4, 115.9, 81.8, 60.9, 14.5. HRMS (ESI): m/z calcd for C₁₄H₁₂Cl₂N₃NaO₃S, 393.9796 [M+Na]+; found: 326.0578.

(Z)-Methyl 3-((1-(4-bromophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6d)

A white solid; Mp 159-161 °C; IR (KBr, v, cm⁻¹): 3186, 2201, 1719, 1557, 1217, 1175, 811; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 12.46 (s, 1H, NH), 7.58-7.56 (m, 2H, Ar-H), 7.35 (d, J = 9.8 Hz, 1H, CH=), 7.28-7.26 (m, 2H, Ar-H), 6.04 (d, J = 9.8 Hz, 1H, CH=), 3.65 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 168.1, 166.5, 163.4, 143.6, 137.7, 132.4, 127.8, 119.4, 118.4, 115.6, 82.0, 52.1. HRMS (ESI): m/z calcd for C₁₄H₁₂BrN₃NaO₃S, 403.968 [M+Na]+; found: 326.0578.

(Z)-Methyl 3-((1-(p-tolylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6e)

A pale yellow solid; Mp 135-137 °C; IR (KBr, v, cm⁻¹): 3191, 2218, 1711, 1544, 1242, 1169, 818; ¹H NMR (400 MHz, DMSO-d₆) (δ, ppm): 12.55 (s, 1H, NH), 7.35 (d, J = 9.8 Hz, 1H, CH=), 7.18 (s, 4H, Ar-H), 6.01 (d, J = 9.8 Hz, 1H, CH=), 3.64 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-d₆) (δ, ppm): 168.6, 166.5, 164.1, 144.0, 136.5, 135.6, 130.1, 125.8, 115.3, 80.5, 52.1, 31.2, 21.5, 21.0. HRMS (ESI): m/z calcd for C₁₅H₁₅N₃NaO₃S, 340.0732 [M+Na]+; found: 326.0578.

(Z)-Methyl 3-((1-(4-methoxyphenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6f)
A gray solid; Mp: 139-141 °C; IR (KBr, v, cm⁻¹): 3109, 2193, 1702, 1559, 1224, 1162, 804; ¹H NMR (400 MHz, DMSO-­d₆) (δ, ppm): 12.49 (s, 1H, NH), 7.36 (d, J = 9.8 Hz, 1H, CH=), 7.23-7.21 (m, 2H, Ar-H), 6.95-6.93 (m, 2H, Ar-H), 6.01 (d, J = 9.8 Hz, 1H, CH=), 3.75 (s, 3H, CH₃), 3.64 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-­d₆) (δ, ppm): 168.7, 166.5, 164.6, 158.2, 144.1, 130.9, 127.7, 115.2, 114.8, 79.9, 55.8, 52.1. HRMS (ESI): m/z calcld for C₁₅H₁₂N₂NaO₆S, 356.0681 [M+Na]⁺; found: 326.0578.

(Z)-Methyl 3-(1-(3,4-dimethoxyphenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6g)
A yellow solid; Mp 215-217 °C; IR (KBr, v, cm⁻¹): 3183, 2193, 1701, 1574, 1224, 1169, 812; ¹H NMR (400 MHz, DMSO-­d₆) (δ, ppm): 12.50 (s, 1H, NH), 7.38 (d, J = 9.8 Hz, 1H, CH=), 6.95 (m, 2H, Ar-H), 6.83-6.80 (m, 1H, Ar-H), 6.02 (d, J = 9.8 Hz, 1H, CH=), 3.74 (s, 3H, CH₃), 3.71 (s, 3H, CH₃), 3.64 (s, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-­d₆) (δ, ppm): 168.7, 166.5, 164.4, 149.2, 147.9, 144.1, 131.0, 118.8, 118.4, 115.1, 112.0, 110.6, 80.0, 56.1, 56.0, 52.1. HRMS (ESI): m/z calcld for C₁₆H₁₇N₃NaO₆S, 386.0787 [M+Na]⁺; found: 326.0578.

(Z)-Ethyl 3-((3-amino-2-cyano-3-oxo-1-(phenylamino)prop-1-en-1-yl)thio)acrylate (6h)
A pale yellow solid; Mp 146-147 °C; IR (KBr, v, cm⁻¹): 3528, 3511, 3474, 3469, 3422, 2203, 1706, 1675, 1559, 1424, 1343, 1229, 1159, 1036, 888; ¹H NMR (400 MHz, CDCl₃) (δ, ppm): 12.54 (s, 1H, NH), 7.39-7.37 (m, 2H, Ar-H), 7.27 (s, 3H, Ar-H), 7.22 (d, J = 7.6 Hz, 2H, NH), 6.93 (d, J = 10.0 Hz, 1H, CH=), 5.92 (d, J = 8.0 Hz, 1H, CH=) 4.21-4.15 (m, 2H, CH₂), 1.27 (t, J = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃) (δ, ppm): 168.0, 165.5, 163.5, 142.9, 137.6, 129.1, 126.4, 125.3, 118.0, 115.2, 80.5, 60.3, 14.0. HRMS (ESI): m/z calcld for C₁₆H₁₇N₃NaO₆S, 340.0732 [M+Na]⁺; found: 340.0726.

(Z)-Ethyl 3-((1-(4-chlorophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6i)
A white solid; Mp 164-167 °C; IR (KBr, v, cm⁻¹): 3178, 2201, 1713, 1558, 1215, 1174, 832; ¹H NMR (400 MHz, DMSO-­d₆) (δ, ppm): 12.47 (s, 1H, NH), 7.45-7.43 (m, 2H, Ar-H), 7.34-7.33 (m, 2H, Ar-H), 7.32 (d, J = 4.8 Hz, 1H, CH=), 6.02 (d, J = 9.8 Hz, 1H, CH=), 4.11 (q, J = 7.2 Hz, 2H, CH₂), 1.19 (t, J = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-­d₆) (δ, ppm): 168.1, 166.1, 163.7, 143.4, 143.4, 137.3, 133.8, 131.1, 130.5, 129.5, 127.9, 127.5, 127.4, 118.4, 118.2, 115.9, 81.8, 60.9, 14.5. HRMS (ESI): m/z calcld for C₁₅H₁₄ClN₂NaO₆S, 374.0342 [M+Na]⁺; found: 326.0578.

(Z)-Ethyl 3-(1-(3,4-dichlorophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6j)
A pale yellow solid; Mp 170-172 °C; IR (KBr, v, cm⁻¹): 3197, 2199, 1697, 1549, 1223, 1172, 815; ¹H NMR (400 MHz, DMSO-­d₆) (δ, ppm): 12.34 (s, 1H, NH), 7.66-7.62 (m, 2H, Ar-H), 7.35-7.32 (m, 1H, Ar-H), 7.31 (d, J = 2.6 Hz, 1H, CH=), 6.05 (d, J = 9.8 Hz, 1H, CH=), 4.12 (q, J = 7.2 Hz, 2H, CH₂), 1.20 (t, J = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-­d₆) (δ, ppm): 167.6, 166.1, 163.1, 143.2, 138.6, 131.6, 131.2, 128.8, 127.4, 125.9, 118.3, 116.2, 83.1, 60.9, 14.5. HRMS (ESI): m/z calcld for C₁₅H₁₃Cl₂N₂NaO₆S, 407.9952 [M+Na]⁺; found: 326.0578.

(Z)-Ethyl 3-(1-(4-bromophenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6k)
A white solid; Mp 166-168 °C; IR (KBr, v, cm⁻¹): 3177, 2203, 1712, 1552, 1212, 1179, 817; ¹H NMR (400 MHz, DMSO-δ6) (δ, ppm): 12.45 (s, 1H, NH), 7.58-7.56 (m, 2H, Ar-H), 7.34-7.31 (m, 2H, Ar-H), 7.27 (d, J = 8.8 Hz, 1H, CH=), 6.02 (d, J = 9.8 Hz, 1H, CH=); ¹³C NMR (100 MHz, DMSO-δ6) (δ, ppm): 168.1, 166.1, 163.6, 143.4, 137.7, 132.4, 127.8, 119.4, 118.4, 116.0, 81.9, 60.9, 14.5. HRMS (ESI): m/z calcd for C₁₅H₁₄BrN₃NaO₃S, 417.9837 [M+Na]⁺; found: 326.0578.

(Z)-Ethyl 3-(1-(4-methoxyphenylamino)-2-carbamoyl-2-cyanovinylthio)acrylate (6l)

A gray solid; Mp 134-136 °C; IR (KBr, v, cm⁻¹): 3142, 2196, 1693, 1530, 1214, 1186, 810; ¹H NMR (400 MHz, DMSO-δ6) (δ, ppm): 12.49 (s, 1H, NH), 7.34-7.21 (m, 4H, Ar-H), 6.94 (d, J = 9.0 Hz, 1H, CH=), 5.98 (d, J = 9.8 Hz, 1H, CH=), 4.09 (q, J = 7.2 Hz, 2H, CH₂), 3.75 (s,3H, CH₃), 1.18 (t, J = 7.2 Hz, 3H, CH₃); ¹³C NMR (100 MHz, DMSO-δ6) (δ, ppm): 168.7, 166.1, 164.7, 158.2, 143.9, 130.9, 127.7, 118.8, 115.5, 114.8, 79.9, 60.8, 55.8, 14.5. HRMS (ESI): m/z calcd for C₁₆H₁₇N₃NaO₄S, 370.0837 [M+Na]⁺; found: 326.0578.

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REFERENCES AND NOTES


12. Crystal data for **4m**: C₁₆H₁₂ClN₃O₄S, pale yellow, block, Triclinic, space group P-1, a = 5.1991(9) Å, b = 10.9259(13) Å, c = 14.8466(16) Å, α = 86.570(2)°, β = 81.3180(10)°, γ = 84.3840(10)°, V = 828.8(2) Å³, Mr = 377.80, Z = 2, Dc = 1.514 Mg/m³, λ = 0.71073 Å, μ(Mo Kα) = 0.384 mm⁻¹, F(000) = 388, R = 0.0547, wR² = 0.0963, largest diff. Peak and hole: 0.315 and -0.353 e/Å³.

13. Crystal data for **6a**: C₁₄H₁₃N₃O₃S, pale yellow, block, Monoclinic, space group c2/c, a = 30.309(3) Å, b = 9.2416(8) Å, c = 10.0704(9) Å, α = γ = 90°, β = 96.2810(10)°, V = 2803.8(4) Å³, Mr = 303.33, Z = 8, Dc = 1.437 Mg/m³, λ = 0.71073 Å, μ(Mo Kα) = 0.245 mm⁻¹, F(000) = 1264, R = 0.0470, wR² = 0.1029, largest diff. Peak and hole: 0.283 and -0.246 e/Å³.