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Graphical Abstract

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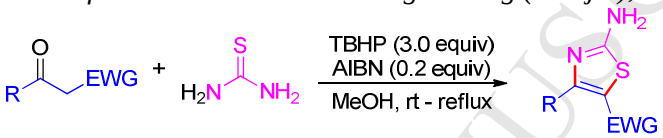

R = aryl, alkyl;
EWG = CO_2Me, CO_2Et, CN, COMe, COPh

18 examples
up to 95% yield

Tetrahedron
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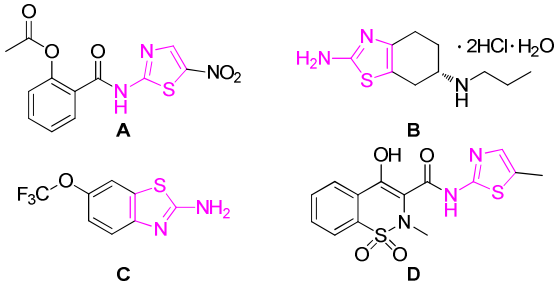
ABSTRACT

A new oxidative system of *tert*-butyl hydroperoxide (TBHP)/azodiisobutyronitrile (AIBN) has been used for the first time for a convenient, metal-free synthesis of substituted 2-aminothioazoles from active methylene ketone derivatives and thiourea. The reaction is postulated to proceed via an oxidative cyclization initiated by a radical process and followed by a condensation reaction.

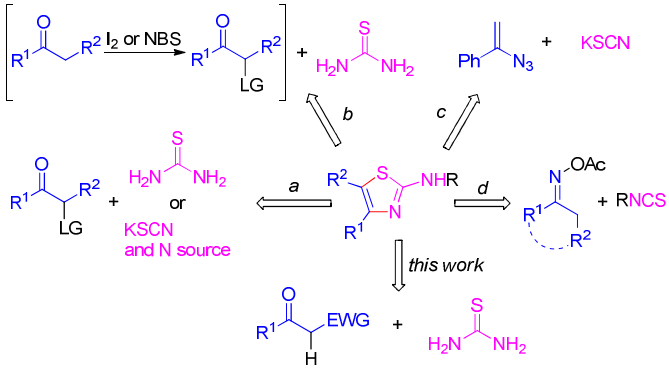
1. Introduction

2-Aminothioazole derivatives are known to have promising anti-HIV, antidiabetic, antibacterial, anti-oxidant, anti-inflammatory, antihypertensive, neuroprotective, anticancer, antifungal, and antitubercular activities.[1] Several popular drugs containing the 2-aminothioazole moiety in their chemical structure have proven to be effective for treating multiple diseases.[2-5] For examples, nitazoxanide (Scheme 1, **A**), known as a potent antiprotozoal agent, has entered clinical trials for the hepatitis B and C therapy.[2] Pramipexole dihydrochloride hydrate (Scheme 1, **B**) has been approved for treatment of Parkinsonism.[3] Among many other approved drugs, e.g., riluzole[4] (voltage-gated sodium channel blockers and glutamate release inhibitor, Scheme 1, **C**) and meloxicam[5] (antimalum, Scheme 1, **D**), all bear the 2-aminothioazole skeleton in their structures.

Scheme 1. Drug Molecules Containing the 2-Aminothioazole Moiety.



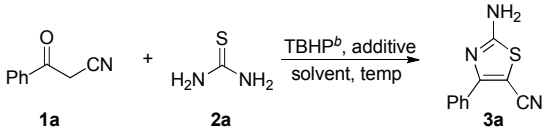
Scheme 2. The Synthetic Routes to Form 2-Aminothioazoles.



Owing to the fact that 2-aminothioazoles represent a privileged scaffold in medicinal chemistry, several strategies targeting the syntheses of such heterocycles have been developed.[6-9] A summary of the most commonly practiced synthetic strategies are listed in Scheme 2. Each approach has its own characteristic features in the preparation of the corresponding 2-aminothioazoles bearing the particular functional groups. The use of thiourea or potassium rhodanate as the sulfur source and a substrate containing a carbonyl group with a leaving group at the α-carbon is the most commonly applied strategy. The general reaction pathway is to allow a prefunctionalized ketone to undergo an intermolecular nucleophilic substitution with the sulfur nucleophile of thiourea or potassium rhodanate, followed

by a dehydration reaction at the formation of the C–S bond and a subsequent intramolecular condensation reaction (Scheme 2, **a**).[6,7] Furthermore, the prefunctionalization of ketone and intermolecular nucleophilic substitution with the sulfur nucleophile could occur in one-pot process by treatment with I_2 or NBS, etc.[6b-e] An alternative method is through the formation of the C–S and C–N bonds from vinyl azides and potassium thiocyanate, catalyzed and promoted by palladium(II) acetate and iron(III) bromide, respectively (Scheme 2, **c**).[8] The copper-catalyzed coupling of oxime acetates with isothiocyanates could also afford the 2-aminothioazole skeleton via N−O bond cleavage and C−S/C−N bond formation.[9] However, strategies targeting the synthesis of 2-aminothioazoles via direct C–H bond functionalization at the α-position of the carbonyl group have not yet been reported.

Table 1. Optimization of Reaction Conditions.[a]



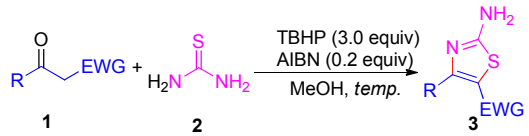
Entry	Additive	Solvent	Temp. (°C)	Yield (%)[c]
1	none	CH_3CN	reflux	45
2	TBAI	CH_3CN	reflux	55
3	BPO	CH_3CN	reflux	trace
4	$CoCl_2$	CH_3CN	reflux	66
5	AIBN	CH_3CN	reflux	70
6	AIBN	DCE	reflux	50
7	AIBN	DMF	100	72
8	AIBN	MeOH	reflux	83[d]
9	AIBN	MeOH	40	85
10	AIBN	MeOH	rt	87
11	TBAI	MeOH	rt	78
12	BPO	MeOH	rt	75
13	$CoCl_2$	MeOH	rt	85

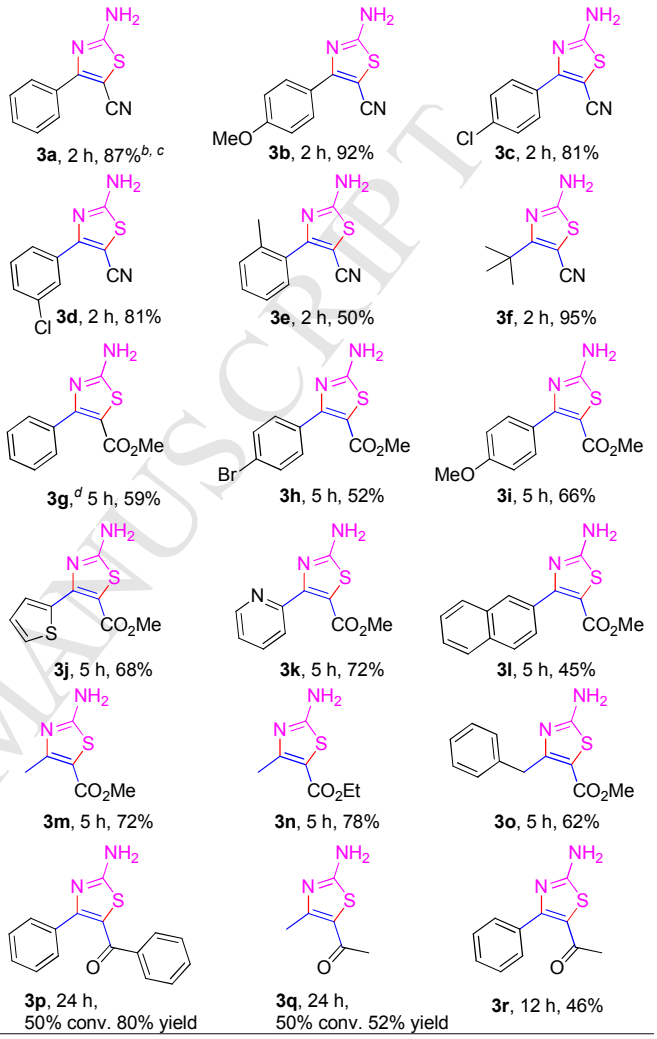
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), TBHP (3.0 mmol) and additive (0.2 mmol) in solvent (5 mL); stirred for 2 h unless otherwise stated. [b] TBHP (70% in water) was extracted with petroleum ether and was evaporated before use. [c] Isolated yield. [d] Attempts to isolate and characterize the byproducts from the model reaction at reflux temperature were unsuccessful.

As a powerful oxidant, *tert*-butyl hydroperoxide (TBHP) has found extensive applications in various oxidative reactions.[10-13] In combination with various catalysts such as iodine,[10] *N*-bromobutanimide (NBS),[11a] *N*-iodobutanimide (NIS),[11b,c] tetrabutylammonium iodide (TBAI),[12] and metal catalysts (Co,[13a] Cu,[13b-e] Fe,[13f,g] Ti,[13h] Ru,[13i] K[13j,k]), it has been applied to realize C–C, C–N, C–O, C–S, and N–N bond formations. However, to our best knowledge, TBHP has never been used in combination with AIBN as an oxidative system for the construction of 2-aminothioazoles.[14] Herein, we report for the first time an AIBN/TBHP-mediated synthesis of substituted 2-aminothioazoles from thiourea and ketone derivatives via C–S bond formation and dehydration processes (Scheme 2, "***this work***"), in which a leaving group at α-position of the carbonyl ketone is not needed at all.

2. Results and discussion

Table 2. Scope of the TBHP/AIBN-Mediated Reaction.[a,e]





[a] General conditions: substrate **1** (1.0 mmol), thiourea **2** (2.0 mmol), TBHP (3.0 mmol), and AIBN (0.2 mmol) in MeOH (5 mL) at rt. Substrate **1** was consumed completely unless otherwise stated. [b] Isolated yield. [c] The electron withdrawing group (EWG) in products **3** is the same as that in substrate **1**. [d] The reactions of **2g-r** were carried out at 65 °C in order for substrate **1** to be consumed completely. [e] The reaction of the *N*-substituted substrates including *N*-Boc thiourea and *N*-phenyl thiourea were also studied. However, no desired product was obtained in either case.

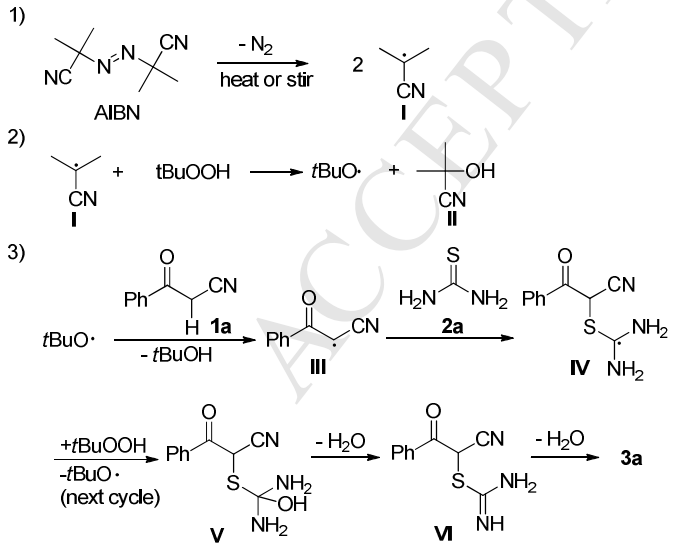
For the investigation of the reaction, 3-oxo-3-phenylpropanenitrile (**1a**) and thiourea (**2a**) were selected as model substrates. Optimization of the reaction conditions were carried out under various additive, solvents, and reaction temperatures. Additive-screening studies showed that the reaction did not need an additive if the oxidant TBHP was present (Table 1, entry 1); however, the yield, in general, improved in the presence of an initiator. Among the four additives of common choices - TBAI (*tetra-n*-butylammonium iodide),[12] $CoCl_2$,[13a] AIBN (2,2'-azo *bis*isobutyronitride)[14] and BPO (benzoyl peroxide)[15] - tested, we found that AIBN was the most effective one for the reaction (Table 1, entries 2-5). Under the newly defined oxidant-initiator system consisting of TBHP and 20 mol% of AIBN, reactions were carried out in three different solvents (Table 1, entries 6-8). Relative to CH_3CN, DCE and

DMF, reaction in MeOH gave the highest, satisfactory yield of 83% (Table 1, entry 8). Further studies on the temperature effect indicated that lower temperature slightly favored the reaction through hampering the formation of side products (Table 1, entries 8-10). However, when the temperature was reduced to below room temperature, it took longer time for the substrate to be consumed completely. Furthermore, additive-screening studies at room temperature in MeOH also indicated AIBN was the most appropriate initiator for this transformation (Table 1, entries 11-13). In summary, the optimal reaction conditions were identified as 20 mol% of AIBN (initiator) and 3.0 equiv. of TBHP (oxidant) in 5.0 mL of MeOH (solvent) at room temperature for 2 h.

Under the optimized reaction conditions, the scope of the reaction was studied using a series of ketones (Table 2). Results show that the reaction could tolerate a range of electron-withdrawing groups at the α-position, including CN, CO_2Me, CO_2Et, COMe, and COPh, with the desired 2-aminothioazoles all obtained in satisfactory to high yields. The electronic effect of the substituent on the phenyl ring in the R group in ketone was shown to be small as the yield values were all rather close among **3a-e** as well as **3g-i** (Table 2). Within the small variances in the yield values, electron-donating groups seemed to favorably affect the reaction while electron-withdrawing groups, negatively. On the other hand, steric effect was evident, as the yield of **3e** was significantly lower than the counterparts of **3a-d**. In addition, other aromatic motifs such as 2-thienyl, 2-pyridyl and 2-naphthyl (Table 2, **3j-l**) adjacent to the carbonyl group, were also successfully tolerated in this process. Notably, for the substrates bearing alkyl groups, the corresponding products were obtained in better yields than those bearing aromatic substituents (Table 2, **3f** compared to **3a-e** and **3m-o** compared to **3g-l**).

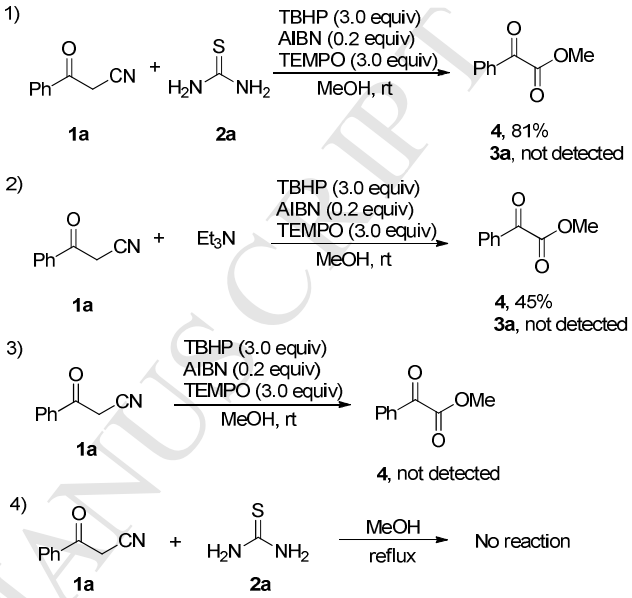
Regarding the electron-withdrawing group (EWG) at the α-carbon, the nitrile group gave better yields than all the rest bearing a carbonyl group (**3a-f** compared to **3g-r**). Finally, the method could be applied to 1,3-dione compounds, although the overall yields were, in general, relatively low (Table 2, **3p-r**).

Scheme 3. Proposed Mechanism.



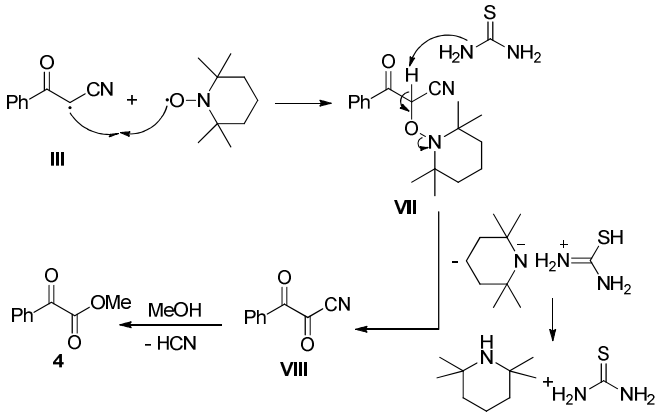
Although the results of the above experimental results are not enough for a convincing mechanism, we postulated a plausible radical mechanistic pathway for this process. As illustrated in Scheme 3, Initially, AIBN, a radical initiator, was converted to radical **I** under heat or stir accompanied by the release of a molecule of N_2.[16] Then the reaction of radical **I** and *tert*-butyl hydroperoxide gave the *tert*-butoxyl radical and a molecule of 2-hydroxy-2-methylpropanenitrile.[17] Hydrogen abstraction of the α-hydrogen of the ketone by the *tert*-butoxyl radical produced the carbon radical **III**. Addition reaction across the double bond of C=S in thiourea **2a** by **III** formed radical intermediate **IV**. Then **IV** further reacted with *tert*-butyl hydroperoxide to afford intermediate **V** along with the formation of another *tert*-butoxyl radical, which could be used in the next cycle. At the end of the radical process, two dehydration reactions and an isomerization process followed, leading to the title product, 2-aminothioazole.

Scheme 4. Control Studies.



Control experiments were carried out to verify the proposed mechanism (Scheme 4). When 3.0 equiv of TEMPO, an efficient radical scavenger, was added to the reaction mixture under standard conditions, no desired product **3a** was detected (Scheme 4, eq 1). However, methyl 2-oxo-2-phenylacetate **4** was isolated in 81% yield. The result supported a radical process in the reaction sequence. However, no compound **4** was formed when the reaction was run in the absence of thiourea **2a** (Scheme 4, eq 3). When thiourea **2a** was replaced with 1.5 equiv of Et_3N (Scheme 4, eq 2), compound **4** could be obtained in 45% yield. This result indicated that the formation of compound **4** required the involvement of a base, which, we propose here the role of thiourea **2a** in the formation of **4** as described in Scheme 4, eq 1. Furthermore, no condensation reaction occurred when **1a** reacted with **2a** in the absence of TBHP and AIBN. This result implied that the radical reaction occurred prior to the dehydration condensation reaction.

Scheme 5. A Probable Process for the Generation of **4**.



Scheme 5 describes the proposed pathway for the formation of **4**. The reaction sequence starts from the cross-coupling of the radical intermediate **III** and TEMPO leading to the formation of intermediate **VII**.[18] With a β-hydrogen elimination under basic conditions, **VII** was converted to 2-oxo-2-phenylacetyl cyanide **VIII** after the release of 2,2,6,6-tetramethylpiperidine as a byproduct.[19] In the presence of MeOH, 2-oxo-2-phenylacetyl cyanide **VIII** was finally converted to compound **4** via a known process.[20]

Conclusion

In conclusion, we have disclosed for the first time a new, effective oxidative system consisting of TBHP and AIBN, which allowed successful synthesis of substituted 2-aminothioazoles from ketone derivatives and thiourea via a novel, metal-free protocol. The mechanism of the reaction involves the oxidative C–S bond formation via a radical process, subsequently the C-N bond formation via an intramolecular condensation reaction. Further investigation on reaction mechanism is in progression in our group.

3. Experimental Section

3.1. General Information

All reactions were carried out at room temperature under air unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on 600 MHz or 400 MHz spectrometer at 25 ^{o}C. Chemical shifts values are given in ppm and referred as the internal standard to TMS: 0.00 ppm. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; m, multiplet and dd, doublet of doublets, brs, broad singlet. The coupling constants J, are reported in Hertz (Hz). High resolution mass spectrometry (HRMS) was obtained on a Q-TOF micro spectrometer. Melting points were determined with a Micromelting Point Apparatus without corrections. Organic solutions were concentrated by rotary evaporation below 40 °C in vacuum. TLC plates were visualized by exposure to ultraviolet light.

Reagents were purchased as reagent grade and were used without further purification except for TBHP (70% in water, extracted with petroleum ether and was evaporated for use). Solvents were dried by CaH_2 before use. All reactions were performed in standard glassware, heated at 70 ^{o}C for 3 h before use. Flash column chromatography was performed over silica gel 200-300 mesh and the eluent was a mixture of ethyl acetate (EA) and petroleum ether (PE).

4.2. General Procedure for Preparation of Substrate 1.

Substrates **1m**, **1n** and **1p-r** were purchased as reagent grade and were used without further purification.

Procedure A[21, 22d-e]: Substrates **1a-f** were prepared adapted from a previously reported procedure. To a suspension of acetonitrile (20 mmol) in THF (80 mL) was added NaH (40 mmol, 60%). After the reaction mixture was stirred at 0 ^{o}C for about 1 h, the ester was added dropwise at the same temperature. The mixture was then refluxed until TLC indicated the complete consumption of the ester. The reaction mixture was poured into ice-water (100 mL), acidified with aqueous HCl (3 M) to pH 2~3 and extracted with EA (100 mL × 3). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The desired pure product was obtained by silica gel chromatography using a mixture of EA/PE (v/v = 2/8) as eluent.

Procedure B[22]: Substrates **1g-j** and **1l** were prepared adapted from a previously reported procedure with some modifications: to a solution of ketone (20 mmol) in THF (80 mL) was added methyl dicarbonate (60 mmol) and NaH (40 mmol, 60%). The reaction mixture was refluxed until TLC indicated complete consumption of the ketone. After cooling, the reaction mixture was poured into ice-water (100 mL), acidified with aqueous HCl (3 M) to pH 2~3 and extracted with EA (100 mL × 3). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The desired pure product was obtained by silica gel chromatography using a mixture of EA/PE (v/v = 1/9) as eluent.

Substrate **1k** was prepared adapted from a previously reported procedure.[22f]

Procedure C[23]: Substrate **1o** was prepared adapted from a previously reported procedure: to an ice-cooled solution of Meldrum's acid (10 mmol) and pyridine (2 mL, 25 mmol) in CH_2Cl_2 (20 mL) was added phenylacetyl chloride (10 mmol) dropwise over a span of 0.5 h. After being stirred at 0 °C for 4 h and at room temperature for 1 h, the mixture was diluted with EtOAc, washed with 1 M HCl and then brine, dried and concentrated. The residue was dissolved in MeOH (30 mL) and heated at 90 °C for 2 h. The desired pure product was obtained by silica gel chromatography using a mixture of EA/PE (v/v = 1/19) as eluent.

4.2.1. 3-Oxo-3-phenylpropanenitrile ***(1a)***. Following the general procedure A, **1a** was purified by silica gel chromatography (20% EA/PE). Yield: 92%, yellow solid, mp. 79-80 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.2 Hz, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.8 Hz, 2H), 4.12 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 187.3, 134.8, 134.2, 129.2, 128.5, 114.0, 29.5.

4.2.2. 3-(4-Methoxyphenyl)-3-oxopropanenitrile ***(1b)***. Following the general procedure A, **1b** was purified by silica gel chromatography (20% EA/PE). Yield: 72%, yellow solid, mp. 119-120 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 4.04 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.5, 164.8, 131.0, 127.2, 114.4, 114.2, 55.7, 29.1.

4.2.3. 3-(4-Chlorophenyl)-3-oxopropanenitrile ***(1c)***. Following the general procedure A, **1c** was purified by silica gel chromatography (20% EA/PE). Yield: 84%, yellow solid, mp. 124-126 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 4.08 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.1, 141.5, 132.6, 129.9, 129.6, 113.6, 29.5.

4.2.4. 3-(3-Chlorophenyl)-3-oxopropanenitrile ***(1d).*** Following the general procedure A, **1d** was purified by silica gel chromatography (20% EA/PE). Yield: 80%, yellow solid, mp. 73-74 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 4.15 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 186.1, 135.6 (d, *J* = 4.8Hz), 134.7, 130.6, 128.5, 126.6, 113.4, 29.6.

4.2.5. 3-Oxo-3-(o-tolyl)propanenitrile ***(1e)***. Following the general procedure A, **1e** was purified by silica gel chromatography (20% EA/PE). Yield: 73%, yellow solid, mp. 83-84 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 2H), 4.07 (s, 2H), 2.58 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 189.3, 140.6, 133.8, 133.4, 132.9, 129.3, 126.2, 114.1, 31.5, 21.9.

4.2.6. 4,4-Dimethyl-3-oxopentanenitrile ***(1f).*** Following the general procedure A, **1f** was purified by silica gel chromatography (20% EA/PE). Yield: 55%, coloerless solid, mp. 67-68 ^{o}C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.64 (s, 2H), 1.21 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.0, 114.3, 44.6, 27.6, 26.1.

4.2.7. Methyl 3-oxo-3-phenylpropanoate ***(1g).*** Following the general procedure B, **1g** was purified by silica gel chromatography (10% EA/PE). Yield: 95%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.51 (s, 0.19H), 7.95 (d, *J* = 7.3 Hz, 2H),

7.78 (d, *J* = 8.4 Hz, 0.41H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.45(m, 2.25H), 7.42 (t, *J* = 7.4 Hz, 0.42H), 5.68 (s, 0.2H), 4.02 (s, 2H), 3.80 (s, 0.61H), 3.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.4, 173.6, 171.5, 168.0, 135.9, 133.9, 133.3, 131.3, 128.9, 128.6, 128.6, 126.1, 87.1, 52.6, 51.5, 45.7.

4.2.8. Methyl 3-(4-bromophenyl)-3-oxopropanoate ***(1h).*** Following the general procedure B, **1h** was purified by silica gel chromatography (10% EA/PE). Yield: 86%, yellow solid, mp. 45-46 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.49 (s, 0.3H), 7.81 (d, *J* = 7.1 Hz, 2H), 7.63 (d, *J* = 6.3 Hz, 2.6H), 7.55 (d, *J* = 7.9 Hz, 0.63H), 5.66 (s, 0.3H), 3.98 (s, 2H), 3.81 (s, 1H), 3.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 191.4, 173.4, 170.2, 167.7, 134.6, 132.2, 131.8, 130.0, 129.2, 127.6, 125.8, 87.4, 52.7, 51.6, 45.6.

4.2.9. Methyl 3-(4-methoxyphenyl)-3-oxopropanoate ***(1i).*** Following the general procedure B, **1i** was purified by silica gel chromatography (10% EA/PE). Yield: 77%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 7.6 Hz, 2H), 3.97 (s, 2H), 3.87 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 190.9, 168.2, 164.1, 130.9, 129.0, 127.8, 114.0, 113.9, 85.6, 55.6, 52.5, 51.5, 45.6.

4.2.10. Methyl 3-oxo-3-(thiophen-2-yl)propanoate ***(1j).*** Following the general procedure B, **1j** was purified by silica gel chromatography (10% EA/PE). Yield: 60%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 3.6 Hz, 1H), 7.72 (d, *J* = 4.8 Hz, 1H), 7.16 (t, *J* = 4.2 Hz , 1H), 3.95 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 184.9, 167.5, 143.2, 135.2, 133.4, 128.4, 52.6, 46.2.

4.2.11. Methyl 3-(naphthalen-2-yl)-3-oxopropanoate ***(1l).*** Following the general procedure B, **1l** was purified by silica gel chromatography (10% EA/PE). Yield: 76%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.61 (s, 0.2H), 8.44 (s, 1H), 8.35 (s, 0.2H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.88 – 7.85 (m, 2.6H), 7.64 – 7.54 (m, 2.6H), 5.82 (s, 0.2H), 4.14 (s, 2H), 3.82 (s, 0.6H), 3.77 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.4, 173.6, 171.3, 168.1, 135.9, 134.7, 132.8, 132.4, 130.7, 130.5, 129.7, 129.0, 128.8, 128.3, 127.9, 127.7, 127.6, 127.0, 126.8, 126.7, 126.5, 123.8, 122.6, 87.8, 52.6, 51.6, 45.8.

4.2.12. Methyl 3-oxo-4-phenylbutanoate ***(1o).*** Following the general procedure C, **1o** was purified by silica gel chromatography (10% EA/PE). Yield: 60%, yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 3.83 (s, 2H), 3.71 (s, 3H), 3.47 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.5, 167.6, 133.2, 129.6, 128.9, 127.4, 52.4, 50.1, 48.0.

4.3. General Procedure for Preparation of 2-amino-thiozoles 3.

General procedure: The substrate **1** (1.0 mmol) and thiourea **2** (2.0 mmol) were added to solvent (5 mL methanol) at room temperature. To the reaction mixture, TBHP (3.0 mmol) and AIBN (0.2 mmol) were added respectively. The reaction mixture was stirred at room temperature (for substrates **1a-f**) or reflux temperature (for substrates **1g-r**) until TLC indicated the total consumption of **1** (for substrates **1p-q**, the reaction time is 24 h). The residue was treated with saturated aqueous $NaHCO_3$ (50 mL) and then extracted with EA (30 mL × 3). The organic phase was washed with brine (50 mL × 1), dried over anhydrous Na_2SO_4. The solvent was removed and the residue was purified by flash column chromatography on silica gel (EA/PE) to afford the desired compound **3**.

4.3.1 2-Amino-4-phenylthiazole-5-carbonitrile ***(3a).*** Following the general procedure, **3a** was purified by silica gel chromatography (30% EA/PE). Yield: 87%, white solid, mp. >200 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.25 (s, 2H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.56 – 7.39 (m, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.6, 161.0, 132.5, 130.0, 128.8, 127.4, 115.3, 83.6. HRMS (ESI) calcd for $C_{10}H_8N_3S^+$ [M + H^+] 202.0433, found 202.0428.

4.3.2 2-Amino-4-(4-methoxyphenyl)thiazole-5-carbonitrile ***(3b).*** Following the general procedure, **3b** was purified by silica gel chromatography (30% EA/PE). Yield: 92%, white solid, mp. 193 – 194 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.19 (s, 2H), 7.90 (d, *J* = 9.0 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.3, 160.8, 160.5, 129.0, 125.1, 115.7, 114.2, 81.8, 55.3. HRMS (ESI) calcd for $C_{11}H_{10}N_3OS^+$ [M + H^+] 232.0539, found 232.0533.

4.3.3 2-Amino-4-(4-chlorophenyl)thiazole-5-carbonitrile ***(3c)***. Following the general procedure, **3c** was purified by silica gel chromatography (30% EA/PE). Yield: 81%, white solid, mp. >200 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.27 (s, 2H), 7.93 (d, *J* = 9.0 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.7, 159.5, 134.6, 131.3, 129.1, 128.9, 115.1, 84.1. HRMS (ESI) calcd for $C_{10}H_7ClN_3S^+$ [M + H^+] 236.0044, found 236.0045.

4.3.4. 2-Amino-4-(3-chlorophenyl)thiazole-5-carbonitrile ***(3d)***. Following the general procedure, **3d** was purified by silica gel chromatography (30% EA/PE). Yield: 81%, white solid, mp. >200 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (s, 2H), 7.93 (s, 1H), 7.92 – 7.85 (m, 1H), 7.56 (d, *J* = 4.8 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.7, 158.9, 134.3, 133.5, 130.8, 129.7, 127.1, 125.8, 114.9, 84.7. HRMS (ESI) calcd for $C_{10}H_7ClN_3S^+$ [M + H^+] 236.0044, found 236.0049.

4.3.5. 2-Amino-4-(o-tolyl)thiazole-5-carbonitrile ***(3e)***. Following the general procedure, **3e** was purified by silica gel chromatography (30% EA/PE). Yield: 50%, white solid, mp. >200 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.21 (s, 2H), 7.38 (dd, *J* = 15.0, 7.8 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 170.8, 163.7, 136.3, 132.6, 130.6, 129.4, 129.3, 125.7, 114.6, 86.5, 19.6. HRMS (ESI) calcd for $C_{11}H_{10}N_3S^+$ [M + H^+] 216.0590, found 216.0580.

4.3.6 2-Amino-4-(tert-butyl)thiazole-5-carbonitrile ***(3f)***. Following the general procedure, **3f** was purified by silica gel chromatography (30% EA/PE). Yield: 95%, white solid, mp. 188 – 189 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.99 (s, 2H), 1.32 (s, 9H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 173.1, 169.8, 115.1, 82.2, 36.4, 29.6. HRMS (ESI) calcd for $C_8H_{12}N_3S^+$ [M + H^+] 182.0746, found 182.0737.

4.3.7 Methyl 2-amino-4-phenylthiazole-5-carboxylate ***(3g)***. Following the general procedure, **3g** was purified by silica gel chromatography (30% EA/PE). Yield: 59%, white solid, mp. 176 – 177 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.87 (s, 2H), 7.63 – 7.64 (m, 2H), 7.37 – 7.38 (m, 3H), 3.62 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 169.9, 161.5, 159.0, 134.5, 129.6, 128.7, 127.3, 107.6, 51.3. HRMS (ESI) calcd for $C_{11}H_{11}N_2O_2S^+$ [M + H^+] 235.0536, found 235.0529.

4.3.8 Methyl 2-amino-4-(4-bromophenyl)thiazole-5-carboxylate ***(3h)***. Following the general procedure, **3h** was purified by silica gel chromatography (30% EA/PE). Yield: 52%, white solid, mp. >200 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.92 (s, 2H), 7.65 – 7.53 (m, 4H), 3.63 (s, 3H). ^{13}C NMR (1510 MHz, DMSO-d_6) δ 167.0, 161.4, 157.6, 133.6, 131.7, 130.4, 122.1, 108.0, 51.5. HRMS (ESI) calcd for $C_{11}H_{10}Br^{79}N_2O_2S^+$ [M + H^+] 312.9641, found 312.9645.

4.3.9 Methyl 2-amino-4-(4-methoxyphenyl)thiazole-5-carboxylate ***(3i)***. Following the general procedure, **3i** was purified by silica gel chromatography (30% EA/PE). Yield: 66%, white solid, mp. 160 – 161 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 9.0 Hz, 2H), 6.93 (d, J = 9.0 Hz, 2H), 5.91 (s, 2H), 3.84 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.0, 162.2, 160.4, 158.8,

131.2, 126.3, 113.1, 109.9, 55.3, 51.8. HRMS (ESI) calcd for $C_{12}H_{13}N_2O_3S^+$ [M + H$^+$] 265.0641, found 265.0648.

4.3.10. Methyl 2-amino-4-(thiophen-2-yl)thiazole-5-carboxylate ***(3j)***. Following the general procedure, **3j** was purified by silica gel chromatography (30% EA/PE). Yield: 68%, white solid, mp. 172 – 173 °C. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.43 – 8.35 (m, 1H), 7.94 (s, 2H), 7.65 (d, J = 4.8 Hz, 1H), 7.14 (dd, J = 4.8, 3.6 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 169.1, 161.6, 151.0, 137.5, 130.1, 129.1, 127.7, 105.4, 51.7. HRMS (ESI) calcd for $C_9H_9N_2O_2S_2^+$ [M + H$^+$] 241.0100, found 241.0007.

4.3.11. Methyl 2-amino-4-(pyridin-2-yl)thiazole-5-carboxylate ***(3k)***. Following the general procedure, **3k** was purified by silica gel chromatography (30% EA/PE). Yield: 72%, white solid, mp. 180 – 181 °C. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.58 (d, J = 4.8 Hz, 1H), 7.88 (s, 2H), 7.83 (td, J = 7.8, 1.5 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.39 (dd, J = 7.2, 5.4 Hz, 1H), 3.59 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 170.0, 161.4, 157.6, 153.2, 148.6, 135.9, 124.2, 123.3, 110.0, 51.4. HRMS (ESI) calcd for $C_{10}H_9N_3NaO_2S^+$ [M + Na$^+$] 258.0308, found 258.0307.

4.3.12. Methyl 2-amino-4-(naphthalen-2-yl)thiazole-5-carboxylate ***(3l)***. Following the general procedure, **3l** was purified by silica gel chromatography (30% EA/PE). Yield: 45%, white solid, mp. 74 – 75 °C. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.23 (s, 1H), 7.93 – 7.96 (m, 4H), 7.89 (d, J = 8.4 Hz, 1H), 7.76 (dd, J = 8.4, 1.5 Hz, 1H), 7.53 – 7.56 (m, 2H), 3.64 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 169.9, 161.6, 158.9, 132.9, 132.2, 132.0, 129.0, 128.4, 127.4, 126.7, 126.5, 126.2, 107.9 51.5. Two carbon peaks overlapped. HRMS (ESI) calcd for $C_{15}H_{13}N_2O_2S^+$ [M + H$^+$] 285.0692, found 285.0690.

4.3.13. Methyl 2-amino-4-methylthiazole-5-carboxylate ***(3m)***. Following the general procedure, **3m** was purified by silica gel chromatography (30% EA/PE). Yield: 72%, white solid, mp. 160 – 161 °C. 1H NMR (600 MHz, DMSO-d$_6$) δ 7.74 (s, 2H), 3.67 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 170.3, 162.3, 159.6, 106.8, 51.2, 17.1. HRMS (ESI) calcd for $C_6H_9N_2O_2S^+$ [M + H$^+$] 173.0379, found 173.0384.

4.3.14. Ethyl 2-amino-4-methylthiazole-5-carboxylate ***(3n)***. Following the general procedure, **3n** was purified by silica gel chromatography (30% EA/PE). Yield: 78%, white solid, mp. 170 – 171 °C. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.70 (s, 2H), 4.15 (q, J = 7.2 Hz, 2H), 2.38 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 170.2, 161.9, 159.3, 107.3, 59.7, 17.1, 14.3. HRMS (ESI) calcd for $C_7H_{11}N_2O_2S^+$ [M + H$^+$] 187.0536, found 187.0525.

4.3.15. Methyl 2-amino-4-benzylthiazole-5-carboxylate ***(3o)***. Following the general procedure, **3o** was purified by silica gel chromatography (30% EA/PE). Yield: 62%, white solid, mp. 199 – 200 °C. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.81 (s, 2H), 7.29 – 7.22 (m, 4H), 7.19 – 7.14 (m, 1H), 4.19 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 170.6, 162.3, 161.7, 139.1, 128.7, 128.2, 126.0, 107.3, 51.4, 35.6. HRMS (ESI) calcd for $C_{12}H_{13}N_2O_2S^+$ [M + H$^+$] 249.0692, found 249.0697.

4.3.16. (2-Amino-4-phenylthiazol-5-yl)(phenyl)methanone ***(3p)***. Following the general procedure, **3p** was purified by silica gel chromatography (30% EA/PE). Yield: 80% (50% conv.), white solid, mp. 183 – 184 °C. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 8.06 (s, 2H), 7.40 – 7.33 (m, 2H), 7.32 – 7.26 (m, 1H), 7.23 (d, J = 7.2 Hz, 2H), 7.13 (dd, J = 14.4, 7.2 Hz, 3H), 7.07 (t, J = 7.5 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 187.5, 170.9, 158.9, 138.5, 134.8, 131.1, 129.6, 128.5, 128.3, 127.6, 127.3, 120.5. HRMS (ESI) calcd for $C_{16}H_{13}N_2OS^+$ [M + H$^+$] 281.0743, found 281.0741.

4.3.17. 1-(2-Amino-4-methylthiazol-5-yl)ethanone ***(3q)***. Following the general procedure, **3q** was purified by silica gel chromatography (30% EA/PE). Yield: 52% (50% conv.), white solid, mp. >200 °C. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 12.02 (s, 1H), 6.72 (s, 1H), 2.25 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 168.1, 157.3, 146.5, 107.4, 22.5, 16.9. HRMS (ESI) calcd for $C_6H_9N_2OS^+$ [M + H$^+$] 157.0430, found 157.0423.

4.3.18. 1-(2-Amino-4-phenylthiazol-5-yl)ethanone ***(3r)***. Following the general procedure, **3r** was purified by silica gel chromatography (30% EA/PE). Yield: 46%, white solid, mp. 138 – 139 °C. ^{1}H NMR (600 MHz, DMSO-d$_6$) δ 7.96 (s, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 2.18 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d$_6$) δ 186.6, 171.6, 160.0, 140.9, 131.1, 128.3, 127.5, 118.7, 18.6. HRMS (ESI) calcd for $C_{11}H_{11}N_2OS^+$ [M + H$^+$] 219.0587, found 219.0587.

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Supplementary Material

Supplementary related to this article can be found at…

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