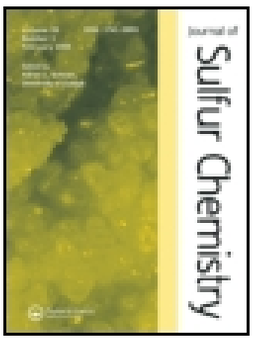

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An efficient one-pot four-component Gewald reaction: Synthesis of substituted 2-aminothiophenes with coumarin–thiazole scaffolds under environmentally benign conditions

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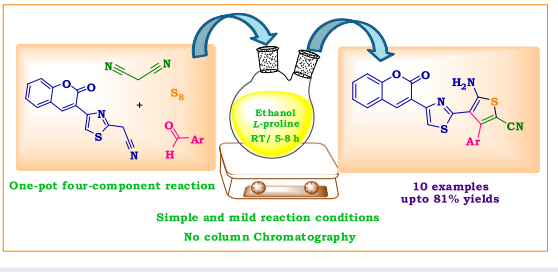
ABSTRACT

An elegant and efficient method has been outlined for the synthesis of novel 5-amino-4-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-3-arylthiophene-2-carbonitriles employing a one-pot four-component reaction of various aldehydes, 2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]acetonitrile, malononitrile and molecular sulfur independently in the presence of *L*-proline as a catalyst, under green reaction conditions. In an alternative approach, initially, the Knoevenagel condensation of these various aldehydes has been carried out with active methylene compounds malononitrile or 2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]acetonitrile to obtain the corresponding condensed compounds. These compounds then further subjected to a one-pot three-component Gewald reaction with molecular sulfur using sodium bicarbonate as a simple and inexpensive catalyst to obtain the target compounds. The effect of solvent and catalyst on these reactions has been screened to obtain the optimal conditions. The advantages of this protocol are the use of mild reaction conditions at ambient temperature, environmental friendliness, good yields in faster reaction times, convenient operation procedures, and broad substrate scope.



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2-aminothiophenes; one-pot four-component method; Knoevenagel condensation; Gewald reaction; environmentally benign conditions

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Introduction

Coumarin is a phytochemical that can be extracted from plants and microorganism natural sources. It was studied extensively due to its distinct applications in the field of synthetic organic chemistry, pharmacology, materials chemistry, and agrochemistry. Coumarin and its derivatives are the constituents of commercially available medicines namely fraxetin and esculetin which are known to exhibit anti-inflammatory and anti-oxidant activities, respectively [1]. They exhibit diverse pharmacological properties in particular anti-tumor [2], anti-diabetic [3], anti-microbial [4], and anti-thrombotic activities [5]. In addition to coumarins, thiazoles and its derivatives also have a significant role in the field of medicinal chemistry where they found to exhibit a wide variety of activities such as anti-tumor [6–8], anti-microbial [9], anti-convulsant [10], and anti-inflammatory activities [11].

Furthermore, sulfur is significant in the medicinal field as sulfa drugs, large number of sulfur-containing drugs and has various engineering applications. Sulfur is present in the human body in the form of amino acids specifically in methionine, cysteine, and substituted cysteines [12]. In addition, sulfur-containing heterocycles have paved a way for medicinal chemistry research [13]. On the other hand, thiophene derivatives in combination with other heterocyclic ring systems have wide variety of applications in pharmaceutical field such as antidepressants [14], analgesics [15], anti-inflammatory [16], and anti-microbial activities [17].

In particular, among the thiophene derivatives, 2-aminothiophenes are versatile materials and have wide scope to apply in every branch of the science. Aminothiophenes have significant roles in exhibiting potent biological activities such as allosteric enhancers of adenosine receptor [18] and glucagon receptor antagonist [19]. Moreover, they found applications in the field of materials science, such as dyes [20], conductivity-based sensors [21], and biodiagnostics [22,23]. Generally, these substituted 2-aminothiophenes are prepared by Gewald reaction by a base-promoted one-pot three-component reaction between active methylene compound, sulfur and an aldehyde or a ketone [24,25]. The core structure is formed in the multicomponent reaction between a ketone or an aldehyde, an activated nitrile and sulfur. Since 1961 when the Gewald reaction was first reported, it became a universal method for the synthesis of substituted 2-aminothiophenes. But still, the research and generation of new compounds with this method is rapidly expanding due to its easy adaptability in the field of pharmaceutical and material chemistry. Although this one-pot synthesis is well established, a step-wise procedure which involves the preparation of α, β-unsaturated nitrile by the condensation of ketone or aldehyde with an activated nitrile, followed by base-promoted reaction with sulfur will provide the better understanding in reaction mechanism.

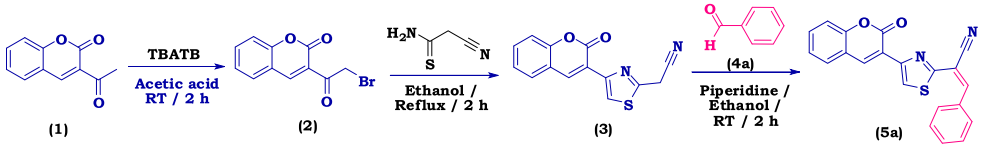
Nowadays, green and sustainable pathways are the ultimate goal, where reactions ideally include the advantages of fewer steps, faster reaction time, safer methods of synthesis, easy isolation procedures, viability in the laboratory, and high yield of the product. In continuation of our earlier work [26,27], the importance of this field of heterocyclic chemistry gave impetus to the present study. The data on synthesis, reactivity, mechanism for the formation of substituted 2-aminothiophenes containing coumarin and thiazole rings in a single framework as hybrid scaffolds and their structural characterization has been systematically studied and discussed in this article.

Results and discussion

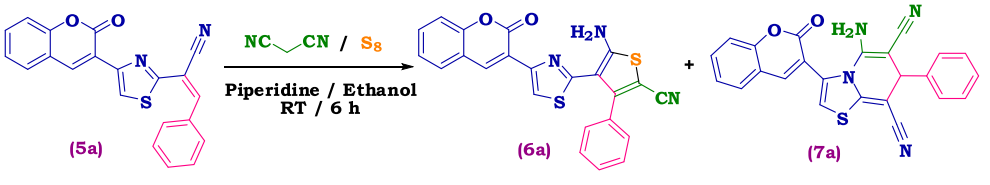
Commercially available salicylaldehyde upon reaction with ethyl acetoacetate in methanol containing a catalytic amount of piperidine at room temperature (RT) afforded 3-acetyl-2*H*-chromen-2-one (**1**), this on further bromination with tetrabutylammonium tribromide in acetic acid for 2 h at RT resulted in the formation of 3-(2-bromoacetyl)-2*H*-chromen-2-one (**2**) [28]. 3-(2-Bromoacetyl)-2*H*-chromen-2-one (**2**) on reaction with 2-cyanothioacetamide in ethanol under reflux for 2 h emerged in the origination of 2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]acetonitrile (**3**). Reaction of (**3**) with benzaldehyde (**4a**) at room temperature for 2 h in the presence of piperidine as catalyst afforded the corresponding condensed product, *i.e.* (*E*)-2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-3-phenylacrylonitrile (**5a**) (Scheme 1).

Further, a one-pot three-component reaction between **5a,** malononitrile and molecular sulfur in the presence of piperidine and ethanol at RT for 6 h afforded 5-amino-4-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-3-phenylthiophene-2-carbonitrile (**6a**) as the major product along with by-product 5-amino-3-(2-oxo-2*H*-chromen-3-yl)-7-phenyl-7*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (**7a**) (Scheme 2). Structure of these isolated compounds was confirmed based on their NMR, IR, and HRMS data. It has been observed from the literature that the formation of **7a** and its related compounds is generally possible under reflux conditions with the same starting materials without the use of elemental sulfur in the presence of a base catalyst [29,30].

With a view to obtain **6a** as a sole product in maximum yield, and to avoid the formation of unwanted side product **7a**, we have optimized this one-pot reaction conditions with various base catalysts in ethanol at RT. Catalysts such as morpholine, piperazine, and triethylamine being secondary and tertiary amines act as strong bases and exhibited the same results with the formation of side compound **7a** as an impurity. It was observed from the above catalyst screening that the use of mild organic bases instead of stronger bases will do the job for this reaction. *L*-Proline can act both as acid and base being amphoteric in nature, facilitates the chemical transformations in a concerted manner, indistinguishable with enzymatic catalysis. Indeed we have selected *L*-proline as a mild base catalyst and carried this experiment to achieve the desired product **6a** in good yield as a single compound.



Scheme 1. Synthesis of **5a** starting from 3-acetyl-2*H*-chromen-2-one.



Scheme 2. Synthesis of **6a** in a one-pot three-component method.

Furthermore, the literature survey reveals that the use of inorganic bases for the Gewald reaction instead of organic bases facilitates the formation of ylidene–sulfur intermediate and the corresponding ring closure reaction [31]. Hence we have screened several inorganic bases for this one-pot reaction and interestingly good-excellent results were obtained for the formation of desired product **6a** in significantly shorter reaction times. From this screening study, it is clearly observed that all the inorganic bases are selective and specific for the formation of the desired product **6a.** Among all the bases employed for this screening study, $NaHCO_3$ was found to be superior to other bases in terms of product yield and reaction times (Table 1).

After having the best optimal conditions in hand, we have generalized this method, *i.e.* the use of saturated sodium bicarbonate in ethanol has been extended to various other aryl and heteroaryl aldehydes. Achieved the synthesis of target compounds **6(a–j)** successfully with fair yields (Scheme 3).

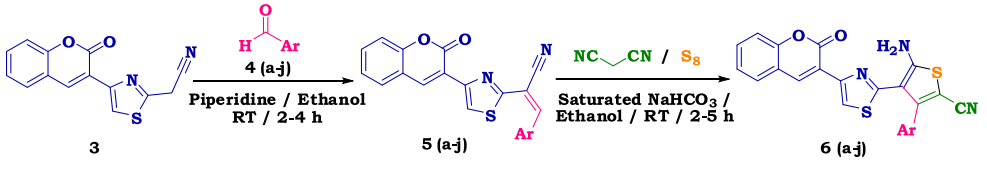
In another approach, we have synthesized the target compounds **6(a–j),** initially by the reaction of aryl/heteroaryl aldehydes **4(a–j)** with malononitrile to obtain arylidene-malononitriles **8(a–j)** followed by their reaction with 2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]acetonitrile (**3**) and molecular sulfur in ethanol using saturated sodium bicarbonate as a base catalyst (Scheme 4).

With the above encouraging results, we were curious to synthesize these compounds in a one-pot four-component reaction pathway. Thus, in an initial model one-pot

Table 1. Catalyst screening for the one-pot synthesis of **6a** at RT.

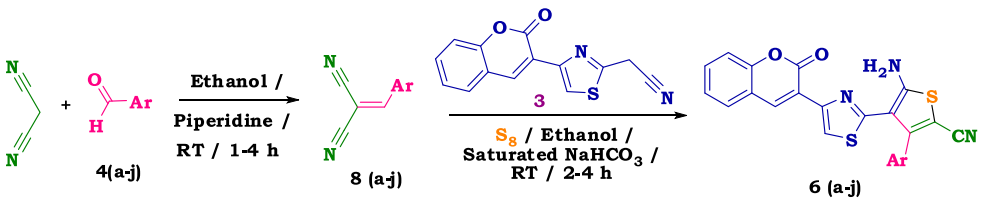
S. no.	Catalyst	Solvent	Reaction time	Yield[a] (%)	
				6a	**7a**
1	Piperidine	Ethanol	6 h	61	8
2	Morpholine	Ethanol	5½ h	64	5
3	Piperazine	Ethanol	7½ h	67	9
4	Triethylamine	Ethanol	5½ h	56	12
5	*L*-proline	Ethanol	6 h	75	0
6	Sodium bicarbonate[b]	Ethanol	2 h	90	0
7	Sodium carbonate[b]	Ethanol	3½ h	86	0
8	Potassium carbonate[b]	Ethanol	2½ h	84	0

[a]Yield refers to the pure product.
[b]Saturated aqueous solution.



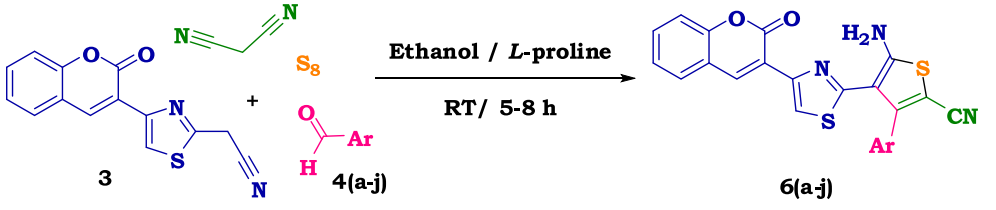
4a/5a/6a: Ar=C_6H_5, **4b/5b/6b: Ar=(4)OH-C_6H_5,**
4c/5c/6c: Ar=(4)Cl-C_6H_5, **4d/5d/6d: Ar=(4)NO_2-C_6H_5,**
4e/5e/6e: Ar=(4)Br-C_6H_5, **4f/5f/6f: Ar=(4)F-C_6H_5,**
4g/5g/6g: Ar=2-pyrryl, **4h/5h/6h: Ar=2-thiophenyl,**
4i/5i/6i: Ar=2-furyl **4j/5j/6j: Ar=3-pyridyl**

Scheme 3. Synthesis of **6(a–j)** in one-pot three-component method starting from **3**.



4a/6a/8a: Ar=C_6H_5, 4b/6b/8b: Ar=(4)OH-C_6H_5,
4c/6c/8c: Ar=(4)Cl-C_6H_5, 4d/6d/8d: Ar=(4)NO_2-C_6H_5,
4e/6e/8e: Ar=(4)Br-C_6H_5, 4f/6f/8f: Ar=(4)F-C_6H_5,
4g/6g/8g: Ar=2-pyrryl, 4h/6h/8h: Ar=2-thiophenyl,
4i/6i/8i: Ar=2-furyl 4j/6j/8j: Ar=3-pyridyl

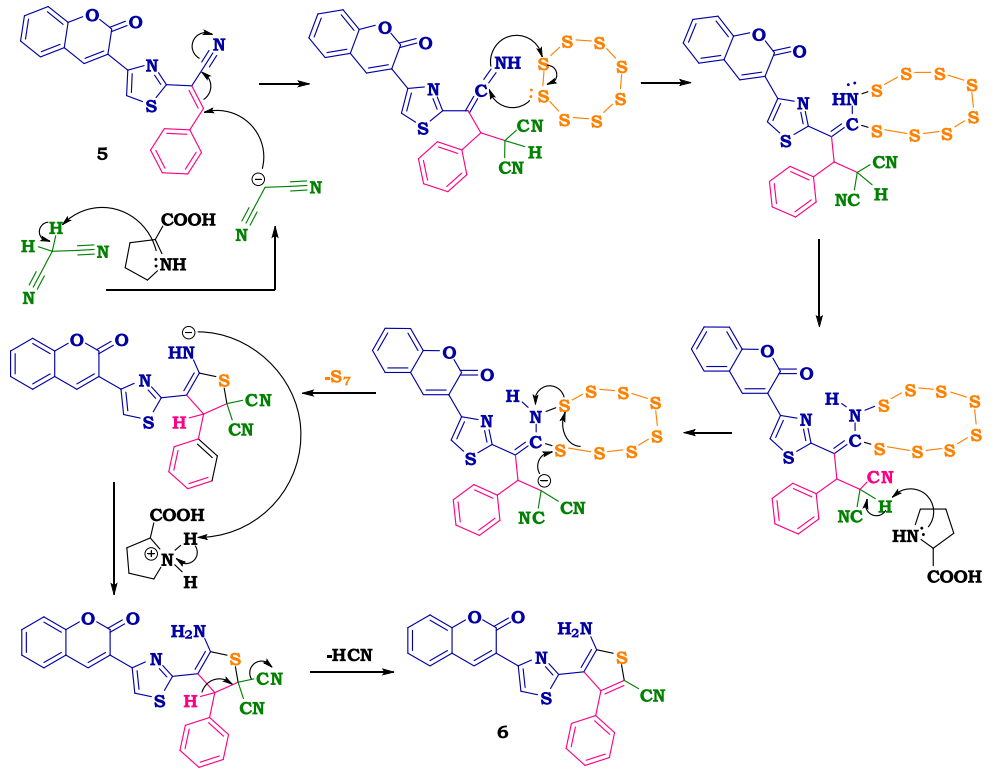
Scheme 4. Alternative approach for the synthesis of **6(a–j)**.



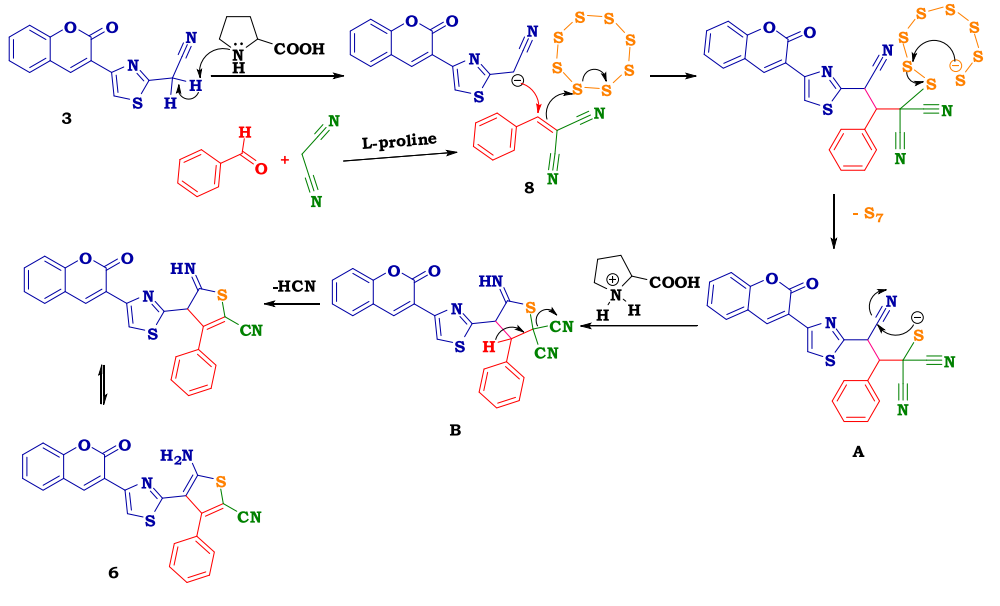
4a/6a: Ar=C_6H_5, 4b/6b: Ar=(4)OH-C_6H_5,
4c/6c: Ar=(4)Cl-C_6H_5, 4d/6d: Ar=(4)NO_2-C_6H_5,
4e/6e: Ar=(4)Br-C_6H_5, 4f/6f: Ar=(4)F-C_6H_5,
4g/6g: Ar=2-pyrryl, 4h/6h: Ar=2-thiophenyl,
4i/6i: Ar=2-furyl, 4j/6j: Ar=3-pyridyl

Scheme 5. One-pot four-component synthesis of **6(a–j)**.

four-component reaction, we have reacted 2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]acetonitrile (**3**), benzaldehyde (**4a**), molecular sulfur, and malononitrile using saturated sodium bicarbonate as a base and ethanol as a solvent media. But the reaction did not proceed even after stirring for 20 h at RT and also at reflux temperature. This reaction has also carried out by replacing $NaHCO_3$ base with other inorganic bases such as Na_2CO_3 and K_2CO_3. But product formation was not observed. It has been noted that these inorganic bases were not able to catalyze the Knoevenagel condensation between either **3** and **4a** to give **5a** or **4a** and malononitrile to give **8a**, as described in our earlier communication [32]. Hence to overcome this problem and to synthesize the target compounds in a one-pot four-component method, we have adopted *L*-proline, as an efficient catalyst (without the side product formation) from the screening study (Table 1) and carried out the same experiment. Thus equimolar amounts of **3**, **4a**, malononitrile, and molecular sulfur were reacted together in a single reaction vessel using *L*-proline as the catalyst. This reaction successfully completed to accord corresponding product **6a** in 73% yield. Further, we have extended this method to various other aryl/heteroaryl aldehyde derivatives **4(b–j)** and generalized the method to produce the target compounds **6(b–j)** in high yield (Scheme 5).



Scheme 6. Plausible rationale for the formation of '**6'** from **5**.



Scheme 7. Plausible rationale for the formation of '**6**' from **8**.

The formation of the products **6 (a–j)** is assumed to proceed by two parallel mechanisms. The first mechanism involves the initial condensation of aryl/heteroaryl aldehydes with 2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]acetonitrile (**3**) to afford the corresponding 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)-3-arylacrylonitriles (**5**). Michael addition of malononitrile with **5** followed by its reaction with molecular sulfur and subsequent cyclization gives the desired product **6**(**a–j)** (Scheme 6).

The second mechanism involves initial condensation of aldehyde with malononitrile to form arylidene-malononitriles (**8)** followed by their reaction with **3** and molecular sulfur. *L*-Proline will abstract the proton form the active methylene center of 2-[4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]acetonitrile (**3**) to generate the carbanion that undergoes Michael addition with the ylidenic bond of **8**, followed by its subsequent reaction with elemental sulfur to form an intermediate **A**, this further cyclized by nucleophilic attack of the sulfur atom with nitrile group to generate the intermediate **B**. The latter loses a molecule of HCN followed by tautomerization to give the final product **6** (Scheme 7).

Conclusion

In summary, we have reported a mild and efficient protocol for the preparation of various 2-aminothiophenes containing coumarin–thiazole hybrid scaffolds via a four-component Gewald reaction. Thus we have successfully demonstrated the one-pot reaction of various aldehydes with 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)acetonitrile (**3**), malononitrile, and sulfur at room temperature using *L*-proline as an efficient green catalyst. The use of readily available starting materials, inexpensive and nontoxic catalysts like *L*-proline and sodium bicarbonate for this Gewald reaction in environmentally friendly reaction media are supremacy of this method. Furthermore, operational simplicity, good to excellent product yields, and easy work-up procedures are prominent advantages of this method. Given the large number of commercially available building blocks, this present method is applicable for the synthesis of libraries with high diversity.

Experimental section

Melting points are uncorrected and were determined in open capillary tubes using hot sulfuric acid bath. TLC analysis was performed using silica gel-G coated sheets supplied by Merck Company with visualization using a UV lamp and iodine staining. IR spectra were recorded using a Perkin Elmer model-446 FTIR in KBr. ^{1}H NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard using a Varian 400-MHz spectrometer instrument. Mass spectra were recorded on an Agilent instrument using the ESI method. Chemicals such as salicylaldehydes, malononitrile, and solvents were purchased from commercial suppliers and were used directly without purification.

Procedure for the preparation of 3 from 2

A mixture of **2** (10 mmol) and 2-cyanothioacetamide (10 mmol) was refluxed in ethanol (30 mL) for a period of 2 h. After completion of the reaction as indicated by TLC, the reaction mixture was poured into ice-cold water (100 mL). The separated solid was filtered,

washed with water (2×50 mL) thoroughly, air dried at RT. The product was recrystallized from methanol to obtain a pure colorless compound **3**.

White solid. Yield: 2.35 g (88%); M.p. 177–179°C; IR (KBr): 1730 cm^{-1} (strong, sharp, –CO of coumarin ring), 2206 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.66 (s, 2H, –C**H**$_2$) 7.38–7.98 (multiplet, 4H, Ar-**H**), 8.43 (s, 1H, Ar-**H**), 8.78 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 21.50, 115.8, 116.9, 118.9, 119.8, 121.1, 124.7, 129.1, 132.1, 139.5, 147.3, 152.5, 158.6, 158.9; HRMS calculated for $C_{14}H_9N_2O_2S$ $[M+H]^+$: 269.0384, Found: 269.0321.

General procedure for the synthesis of 5 from 3 and 4

A mixture of **3** (10 mmol), various aldehydes (10 mmol), catalytic amount of piperidine and ethanol (30 mL) was stirred at RT for a period of 2–4 h. The completion of the reaction was monitored by TLC analysis. After completion of the reaction, the mixture was poured into ice cold water (100 mL) and the separated solid was filtered, washed with water (2×50 mL). These crude compounds were recrystallized from suitable solvent to give the pure **5**.

(E)-2-[4-(2-Oxo-2H-chromen-3-yl)thiazol-2-yl]-3-phenylacrylonitrile (5a)

Yellow solid. Yield: 2.52 g (71%); M.p. 222–224°C (methanol); IR (KBr): 1718 cm^{-1} (strong, sharp, –CO of coumarin ring), 2156 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.38–8.07 (multiplet, 9H, Ar-**H**), 8.41 (s, 1H, vinylic-**H**), 8.54 (s, 1H, Ar-**H**), 8.85 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 109.8, 117.9, 118.9, 119.4, 119.8, 121.2, 121.8, 122.1, 125.2, 127.2, 129.3, 129.5, 132.7, 137.0, 143.0, 146.7, 151.2, 153.8, 163.0; HRMS calculated for $C_{21}H_{13}N_2O_2S$ $[M+H]^+$: 357.0697, Found: 357.0621.

(E)-3-(4-Hydroxyphenyl)-2-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl]acrylonitrile (5b)

Yellow solid. Yield: 2.52 g (68%); M.p. 179–181°C (acetonitrile); IR (KBr): 1712 cm^{-1} (strong, sharp, –CO of coumarin ring), 2208 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.42–8.04 (multiplet, 8H, Ar-**H**), 8.43 (s, 1H, vinylic-**H**), 8.55 (s, 1H, Ar-**H**), 8.89 (s, 1H, Ar-**H**), 9.45 (s, 1H, -O**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 108.7, 115.7, 115.8, 118.9, 120.6, 120.9, 121.1, 124.3, 125.7, 127.7, 128.0, 129.4, 130.3, 143.4, 146.4, 153.1, 153.5, 157.0, 163.4; HRMS calculated for $C_{21}H_{13}N_2O_3S$ $[M+H]^+$: 373.0646, Found: 373.0662.

(E)-3-(4-Chlorophenyl)-2-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl]acrylonitrile (5c)

Yellow solid. Yield: 2.84 g (73%); M.p. 202–204°C (methanol); IR (KBr): 1720 cm^{-1} (strong, sharp, –CO of coumarin ring), 2205 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.42–8.04 (multiplet, 8H, Ar-**H**), 8.43 (s, 1H, vinylic-**H**), 8.57 (s, 1H, Ar-**H**), 8.83 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 109.1, 118.5, 120.7, 125.1, 125.4, 128.0, 128.4, 128.7, 128.9, 129.1, 129.6, 133.0, 133.4, 134.5, 143.6, 146.3, 153.2, 153.4, 163.1; HRMS calculated for $C_{21}H_{12}ClN_2O_2S$ $[M+H]^+$: 391.0308, Found: 391.0323.

(E)-3-(4-Nitrophenyl)-2-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl]acrylonitrile (5d)

Yellow solid. Yield: 3.12 g (78%); M.p. 196–198°C (acetone); IR (KBr): 1723 cm^{-1} (strong, sharp, –CO of coumarin ring), 2198 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz,

DMSO-d_6/TMS): δ = 7.42–8.08 (multiplet, 8H, Ar-**H**), 8.42 (s, 1H, vinylic-**H**), 8.55 (s, 1H, Ar-**H**), 8.88 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 108.7, 118.3, 120.9, 124.9, 125.4, 127.9, 128.3, 128.7, 128.7, 129.0, 129.4, 133.3, 133.4, 134.4, 143.7, 146. 1, 153.0, 153.5, 162.9; HRMS calculated for $C_{21}H_{12}N_3O_4S$ $[M+H]^+$: 402.0548, Found: 402.0565.

(E)-3-(4-Bromophenyl)-2-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl]acrylonitrile (5e)

Yellow solid. Yield: 3.20 g (74%); M.p. 211–213°C (ethyl acetate); IR (KBr): 1731 cm^{-1} (strong, sharp, –CO of coumarin ring), 2205 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.44–8.04 (multiplet, 8H, Ar-**H**), 8.44 (s, 1H, vinylic-**H**), 8.55 (s, 1H, Ar-**H**), 8.83 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 109.1, 111.7, 116.8, 118.3, 120.9, 122.6, 124.9, 125.9, 127.3, 128.7, 128.7, 129.0, 143.4, 146.3, 149.6, 149.9, 153.1, 153.8, 162.2; HRMS calculated for $C_{21}H_{12}BrN_2O_2S$ $[M+H]^+$: 434.9802, Found: 434.9854.

(E)-3-(4-Fluorophenyl)-2-[4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl]acrylonitrile (5f)

Yellow solid. Yield: 2.61 g (70%); M.p. 188–190°C (methanol); IR (KBr): 1714 cm^{-1} (strong, sharp, –CO of coumarin ring), 2190 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.42–8.05 (multiplet, 8H, Ar-**H**), 8.43 (s, 1H, vinylic-**H**), 8.56 (s, 1H, Ar-**H**), 8.85 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 108.4, 115.5, 115.7, 117.4, 118.6, 120.6, 124.7, 125.7, 127.2, 128.8, 129.6, 130.9, 143.9, 146.2, 150.7, 153.6, 153.9, 154.4, 163.3; HRMS calculated for $C_{21}H_{12}FN_2O_2S$ $[M+H]^+$: 375.0603, Found: 375.0610.

(E)-2-[4-(2-Oxo-2H-chromen-3-yl)thiazol-2yl]-3-(1H-pyrrol-2-yl)acrylonitrile (5g)

Yellow solid. Yield: 2.48 g (72%); M.p. 198–200°C (Methanol); IR (KBr): 1718 cm^{-1} (strong, sharp, –CO of coumarin ring), 2336 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.33–7.91 (multiplet, 7H, Ar-**H**), 8.17 (s, 1H, vinylic-**H**), 8.40 (s, 1H, Ar-**H**), 8.76 (s, 1H, Ar-**H**), 11.93 (s, 1H, N**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 109.8, 116.5, 117.9, 118.9, 119.4, 119.8, 121.2, 121.8, 122.1, 125.2, 127.2, 129.3, 129.5, 139.5, 143.0, 146.7, 151.2, 153.8, 161.8; HRMS calculated for $C_{19}H_{12}N_3O_2S$ $[M+H]^+$: 346.0650, Found: 346.0661.

(E)-2-[4-(2-Oxo-2H-chromen-3-yl)thiazol-2yl]-3-(thiophen-2-yl)acrylonitrile (5h)

Yellow solid. Yield: 2.49 g (69%); M.P. 187–189°C (Methanol); IR (KBr): 1718 cm^{-1} (strong, sharp, –CO of coumarin ring), 2185 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.30–7.92 (multiplet, 7H, Ar-**H**), 8.21 (s, 1H, vinylic-**H**), 8.43 (s, 1H, Ar-**H**), 8.78 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 109.5, 113.4, 116.5, 118.7, 119.4, 120.6, 124.6, 125.7, 127.7, 128.2, 128.8, 129.6, 130.9, 141.9, 143.2, 146.9, 151.7, 154.1, 162.0; HRMS calculated for $C_{19}H_{11}N_2O_2S2$ $[M+H]^+$: 363.0261, Found: 363.0258.

(E)-3-(Furan-2-yl)-2-[4-(2-oxo-2H-chromen-3-yl)thiazol-2yl]acrylonitrile (5i)

Yellow solid. Yield: 2.50 g (67%); M.P. 192–194°C (Methanol); IR (KBr): 1734 cm^{-1} (strong, sharp, –CO of coumarin ring), 2210 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.32–7.93 (multiplet, 7H, Ar-**H**), 8.18 (s, 1H, vinylic-**H**), 8.42 (s, 1H, Ar-**H**), 8.76 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 109.4, 112.5, 113.7, 116.4, 118.6, 119.5, 120.7, 124.7, 125.7, 127.2, 128.7, 129.8, 131.0, 142.0, 143.3, 146.7, 151.8, 154.3, 162.2; HRMS calculated for $C_{19}H_{11}N_2O_3S$ $[M+H]^+$: 347.0490, Found: 375.0487.

(E)-2-[4-(2-Oxo-2H-chromen-3-yl)thiazol-2yl]-3-(pyridin-3-yl)acrylonitrile (5j)

Yellow solid. Yield: 2.59 g (73%); M.p. 196–198°C (Methanol); IR (KBr): 1718 cm^{-1} (strong, sharp, –CO of coumarin ring), 2179 cm^{-1} (strong, sharp, –CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.34–7.96 (multiplet, 8H, Ar-**H**), 8.22 (s, 1H, vinylic-**H**), 8.46 (s, 1H, Ar-**H**), 8.76 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 109.3, 112.6, 113.7, 116.7, 118.5, 119.7, 120.3, 122.5, 124.6, 125.1, 125.8, 127.2, 128.6, 128.9, 136.0, 143.2, 146.6, 152.7, 154.8, 162.0; HRMS calculated for $C_{20}H_{12}N_3O_2S$ $[M+H]^+$: 358.0650, Found: 357.0662.

General procedure for the synthesis of 6 from 5

A mixture of **5** (10 mmol), malononitrile (10 mmol), elemental sulfur (10 mmol), saturated sodium bicarbonate solution in water (10 mL), and ethanol (50 mL) was stirred at RT for a period of 2–5 h. Progress of the reaction was monitored by TLC analysis. After completion of the reaction, the mixture was poured into ice cold water (150 mL) and the separated solid was filtered, washed with water (2×50 mL). These crude products were recrystallized from a suitable solvent to give the pure **6.**

5-Amino-4- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] -3-phenylthiophene-2-carbonitrile (6a)

Yellow solid. Yield: 3.62 g (85%); M.p. 236–238°C (benzene); IR (KBr): 1723 cm^{-1} (strong, sharp, –CO of coumarin ring), 2227 cm^{-1} (strong, sharp, –CN group), 3380–3440 (broad medium, –NH_2 group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.40–8.45 (multiplet, 11H, Ar-**H**, N**H**$_2$), 8.57 (s, 1H, Ar-**H**), 8.89 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 111.9, 117.9, 118.9, 119.4, 119.8, 121.2, 121.8, 122.1, 125.2, 127.2, 129.3, 129.5, 130.1, 132.7, 137.0, 139.5, 143.0, 151.2, 153.8, 154.7, 162.1; HRMS calculated for $C_{23}H_{14}N_3O_2S_2$ $[M+H]^+$: 428.0527, Found: 428.0541.

5-Amino-3-(4-hydroxyphenyl)-4- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] thiophene-2-carbonitrile (6b)

Yellow solid. Yield: 3.49 g (79%); M.p. > 250°C (benzene); IR (KBr): 1715 cm^{-1} (strong, sharp, –CO of coumarin ring), 2210 cm^{-1} (strong, sharp, –CN group), 3400–3440 (broad medium, –NH_2 group), 3530–3580 (broad medium, –OH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.38-8.42 (multiplet, 10H, Ar-**H** & N**H**$_2$), 8.54 (s, 1H, Ar-**H**), 8.82 (s, 1H, Ar-**H**), 10.21 (s, 1H, O**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 112.2, 117.4, 119.1, 119.7, 120.1, 121.4, 121.9, 122.7, 124.9, 127.5, 129.6, 129.9, 131.0, 132.5, 137.3, 139.9, 143.5, 151.3, 154.5, 154.9, 162.0; HRMS calculated for $C_{23}H_{14}N_3O_3S_2$ $[M+H]^+$: 444.0476, Found: 444.0459.

5-Amino-3-(4-chlorophenyl)-4- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] thiophene-2-carbonitrile (6c)

Yellow solid. Yield: 3.87 g (84%); M.p. > 250°C (ethanol); IR (KBr): 1719 cm^{-1} (strong, sharp, –CO of coumarin ring), 2210 cm^{-1} (strong, sharp, –CN group), 3380–3420 (broad medium, –NH_2 group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.41–8.47 (multiplet, 10H, Ar-**H** & N**H**$_2$), 8.58 (s, 1H, Ar-**H**), 8.87 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz,

DMSO-d_6/TMS): 111.7, 117.0, 118.6, 119.3, 119.7, 121.4, 121.9, 122.4, 125.7, 127.7, 129.8, 130.2, 130.8, 132.6, 137.4, 139.7, 143.2, 151.3, 153.9, 154.8, 162.3; HRMS calculated for $C_{23}H_{13}ClN_3O_2S_2$ $[M+H]^+$: 462.0137, Found: 462.0116.

5-Amino-3-(4-nitrophenyl)-4- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] thiophene-2-carbonitrile (6d)

Yellow solid. Yield: 4.10 g (87%); M.p. 245-247°C (benzene); IR (KBr): 1721 cm^{-1} (strong, sharp, –CO of coumarin ring), 2214 cm^{-1} (strong, sharp, –CN group), 3400–3450 (broad medium, $–NH_2$ group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): $\delta = 7.42$-8.48 (multiplet, m, 10H, Ar-**H** & N**H**$_2$), 8.59 (s, 1H, Ar-**H**), 8.90 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 112.2, 116.8, 118.8, 120.2, 120.8, 121.4, 121.9, 122.5, 125.5, 127.8, 130.6, 130.8, 131.4, 132.8, 137.2, 139.7, 142.9, 151.4, 153.9, 154.8, 162.4; HRMS calculated for $C_{23}H_{13}N_4O_4S_2$ $[M+H]^+$: 473.0378, Found: 473.0358.

5-Amino-3-(4-bromophenyl)-4- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] thiophene-2-carbonitrile (6e)

Yellow solid. Yield: 4.03 g (80%); M.p. >250°C (ethanol); IR (KBr): 1724 cm^{-1} (strong, sharp, –CO of coumarin ring), 2226 cm^{-1} (strong, sharp, –CN group), 3420–3480 (broad medium, $–NH_2$ group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): $\delta = 7.40$-8.46 (multiplet, 10H, Ar-**H** & N**H**$_2$), 8.55(s, 1H, Ar-**H**), 8.88 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 112.7, 118.2, 118.8, 119.6, 120.2, 121.5, 121.9, 122.5, 125.5, 127.0, 129.0, 129.7, 130.5, 132.8, 137.3, 140.2, 143.2, 151.3, 153.9, 154.8, 161.8; HRMS calculated for $C_{23}H_{13}BrN_3O_2S_2$ $[M+H]^+$: 505.9632, Found: 505.9612.

5-Amino-3-(4-fluorophenyl)-4- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] thiophene-2-carbonitrile (6f)

Yellow solid. Yield: 3.47 g (78%); M.p. >250°C (benzene); IR (KBr): 1718 cm^{-1} (strong, sharp, –CO of coumarin ring), 2198 cm^{-1} (strong, sharp, –CN group), 3400–3450 (broad medium, $–NH_2$ group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): $\delta = 7.43$–8.49 (multiplet, 10H, Ar-**H** & N**H**$_2$), 8.56 (s, 1H, Ar-**H**), 8.90 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 111.8, 118.4, 119.4, 119.9, 120.4, 121.4, 122.2, 122.8, 125.6, 127.2, 129.5, 129.9, 130.6, 132.9, 137.1, 140.4, 143.5, 151.5, 154.2, 155.7, 162.2; HRMS calculated for $C_{23}H_{13}FN_3O_2S_2$ $[M+H]^+$: 446.0433, Found: 446.0415.

5-Amino-4- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] -3-(1H-pyrrol-2-yl)thiophene-2-carbonitrile (6g)

Yellow solid. Yield: 3.03 g (73%); M.p. >250°C (benzene); IR (KBr): 1728 cm^{-1} (strong, sharp, –CO of coumarin ring), 2225 cm^{-1} (strong, sharp, –CN group), 3410–3460 (broad medium, –NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): $\delta = 7.41$-8.42 (multiplet, 9H, Ar-**H** & N**H**$_2$), 8.55 (s, 1H, Ar-**H**), 8.87 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 107.9, 117.7, 118.5, 119.6, 119.6, 119.8, 120.6, 125.2, 129.2, 132.1, 138.6, 138.6, 139.0, 143.9, 145.2, 145.6, 146.3, 151.2, 152.7, 153.6, 162.5; HRMS calculated for $C_{21}H_{13}N_4O_2S_2$ $[M+H]^+$: 417.0479, Found: 417.0455.

5′-Amino-4′- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] -2,3′-bithiophene-2′-carbonitrile (6h)

Yellow solid. Yield: 3.07 g (71%); M.P. >250°C (benzene); IR (KBr): 1724 cm^{-1} (strong, sharp, –CO of coumarin ring), 2204 cm^{-1} (strong, sharp, –CN group), 3390–3450 (broad medium, –NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): $\delta = 7.40$–8.40 (multiplet, 9H, Ar-**H** & N**H**$_2$), 8.56 (s, 1H, Ar-**H**), 8.89 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 108.2, 117.8, 118.4, 119.7, 119.7, 119.9, 120.9, 125.5, 129.7, 132.3, 138.7, 138.7, 139.2, 144.3, 145.1, 145.4, 146.2, 151.5, 152.9, 154.1, 161.8; HRMS calculated for $C_{21}H_{12}N_3O_2S_3$ $[M+H]^+$: 434.0091, Found: 434.0105.

5-Amino-3-(furan-2-yl)-4- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] thiophene-2-carbonitrile (6i)

Yellow solid. Yield: 3.09 g (75%); M.P. >250°C (methanol); IR (KBr): 1724 cm^{-1} (strong, sharp, –CO of coumarin ring), 2242 cm^{-1} (strong, sharp, –CN group), 3410–3460 (broad medium, –NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): $\delta = 7.39$–8.42 (multiplet, 9H, Ar-**H** & N**H**$_2$), 8.57 (s, 1H, Ar-**H**), 8.91 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 107.7, 117.5, 118.6, 119.6, 119.6, 119.8, 120.5, 121.3, 125.7, 129.9, 132.4, 138.8, 139.5, 144.4, 145.3, 145.6, 146.5, 151.6, 153.2, 154.4, 161.7; HRMS calculated for $C_{21}H_{12}N_3O_3S_2$ $[M+H]^+$: 418.0320, Found: 418.0308.

5-Amino-4- [4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl] -3-(pyridin-3-yl)thiophene-2-carbonitrile (6j)

Yellow solid. Yield: 2.99 g (70%); M.p. 228–230°C (ethanol); IR (KBr): 1718 cm^{-1} (strong, sharp, –CO of coumarin ring), 2223 cm^{-1} (strong, sharp, –CN group), 3410–3470 (broad medium, –NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): $\delta = 7.38$–8.40 (multiplet, 10H, Ar-**H** & N**H**$_2$), 8.55 (s, 1H, Ar-**H**), 8.90 (s, 1H, Ar-**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 107.9, 118.3, 118.8, 119.2, 119.3, 119.7, 120.6, 120.8, 121.7, 126.2, 130.2, 132.6, 139.2, 139.9, 141.7, 145.7, 148.5, 149.6, 151.8, 153.5, 155.5, 161.9; HRMS calculated for $C_{22}H_{13}N_4O_2S_2$ $[M+H]^+$: 429.0479, Found: 429.0468.

General procedure the synthesis of 6 from 8 and 3

A mixture of **8** (10 mmol), **3** (10 mmol), elemental sulfur (10 mmol), saturated sodium bicarbonate solution in water (10 mL), and ethanol (50 mL) was stirred at RT for a period of 2–4 h. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, the mixture was poured into ice cold water (150 mL) and the separated solid was filtered and washed with water (2×50 mL). These crude products were recrystallized from a suitable solvent to give the pure **6.**

6a: Yield: 3.50 g (82%); **6b**: Yield: 3.01 g (68%); **6c**: Yield: 3.82 g (83%); **6d**: Yield: 4.01 g (85%); **6e**: Yield: 3.88 g (77%); **6f**: Yield: 3.29 g (74%); **6g**: Yield: 2.91 g (70%); **6h**: Yield: 3.16 g (73%); **6i:** Yield: 3.12 g (75%); **6j**: Yield: 2.99 g (70%).

General procedure for the one-pot four-component synthesis of 6

A mixture of **3** (10 mmol), **4** (10 mmol), malononitrile (10 mmol), elemental sulfur (10 mmol), *L*-proline (10 mol%), and ethanol (50 mL) was stirred at RT for a period of

5–8 h. The completion of the reaction was monitored by TLC analysis. After completion of the reaction, the mixture was poured into ice-cold water (150 mL) and the separated solid was filtered and washed with water (2×50 mL). These crude products were recrystallized from a suitable solvent to give the pure **6.**

6a: Yield: 3.28 g (77%); **6b**: Yield: 3.10 g (70%); **6c**: Yield: 3.47 g (75%); **6d**: Yield: 3.82 g (81%); **6e**: Yield: 3.98 g (79%); **6f**: Yield: 3.20 g (72%); **6g**: Yield: 2.82 g (68%); **6h**: Yield: 3.03 g (70%); **6i:** Yield: 2.75 g (66%); **6j**: Yield: 2.95 g (69%).

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No potential conflict of interest was reported by the authors.

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