An Efficient One-pot Three-component Method for the Synthesis of 5-Amino-3-(2-oxo-2*H*-chromen-3-yl)-7-aryl-7*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitriles

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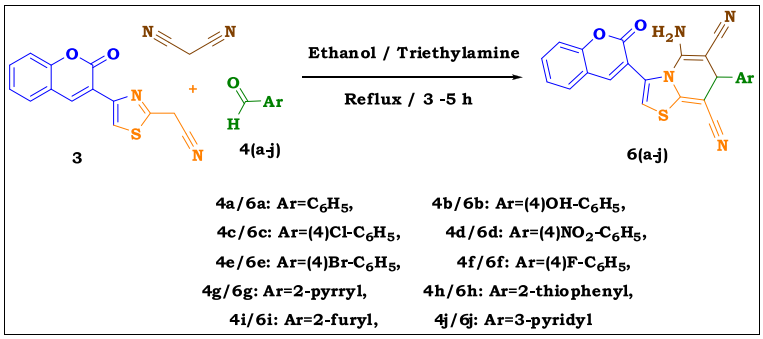


A facile, convenient, and adequate method has been developed for the synthesis of novel 5-amino-3-(2-oxo-2*H*-chromen-3-yl)-7-aryl-7*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitriles (**6**) by employing 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)acetonitrile (**3**) as an important precursor. Initially, we have synthesized the target compounds in a stepwise manner and then approached a tandem method to examine the feasibility of one-pot method. Subsequently, one-pot three-component protocol has been established for the synthesis of title compounds by the reaction of **3** with benzaldehyde and malononitrile in refluxing ethanol engender a new six-membered thiazolo[3,2-a] pyridine as a hybrid scaffold. Reaction conditions were optimized for this reaction and a broad substrate scope with various aryl and heteroaryl aldehydes make this protocol very practical, attractive, and worthy. Mechanistic aspects for the formation of these compounds were outlined comprehensively. Characterization of these newly synthesized compounds was achieved by means of IR, ^{1}H NMR, ^{13}C NMR, and HRMS.

INTRODUCTION

Heterocyclic compounds occupy central position in organic chemistry because they play vital role in the treatment of human ailments. Indeed, 80% of the drugs are constituted by heterocyclic ring systems. Among all, the fragrant compound coumarin and its derivatives are powerful scaffolds that exert remarkable applications in medicinal, materials chemistry, and agro-chemical fields, which have been recently reviewed by us [1]. They have been found to display various therapeutic activities that include anti-bacterial [2], anti-tumor [3], anti-inflammatory [4], anti-HIV [5], anticoagulant [6], anti-virus [7], anti-tubercular [8], anti-diabetic [9], anti-thrombotic [10], antioxidant [11], activity etc. Apart from these, coumarin and its related compounds have been found to exhibit various applications in materials chemistry, such as light emitting properties [12], fluorescent sensors [13], and as dyes [14].

On the other hand, 1,3-thiazoles are also prominent skeletal motif in number of drugs, few of them are ritonavir (anti-HIV), abafungin (antifungal), sulfathiazole (antimicrobial), riluzole (anticonvulsant), pramipexole (anti-Parkinson's), dasatinib (anti-cancer), melaxicam (anti-inflammatory), zopolrestat (anti-diabetic), febuxostat (anti-gout), nitazoxanide (antiparasitic), etc. Various researchers reported the diverse therapeutic applications of thiazoles as antihypertensive [15], anti-tubercular [16], anti-proliferative [17], antioxidant [18], and EP_1 receptor antagonist [19] agents. Literature review has disclosed that thiazoles in combination with coumarin ring in their core structure as a hybrid scaffold have unveiled significant pharmacological activities such as anticonvulsant [20], antimicrobial [21], anti-inflammatory [22], anti-tumor [23], antioxidant [24], etc. Also, thiazolo[3,2-a]pyridines with two or more fused heterocyclic rings in their structure have prominent diverse bioactivities such as CDK2-cyclin-A inhibitor [25], α-glucosidase inhibitor [26], uterus stimulant [27], and antimicrobial activities [28].

These aforementioned considerable biological activities have stimulated interest in the synthesis of a new class of coumarin derivatives with several new approaches for six-membered and five-membered rings, and their fused

hybrid scaffolds have been developed during our research that has base to frame this article. Although there are reports for the synthesis of thiazolo[3,2-a]pyridines, there is still no report for the preparation of coumarin-thiazolo[3,2-a]pyridines [29–31]. Thus, in continuation of our research on the synthesis of hybrid scaffolds of coumarins [32,33], herein, we wish to report efficient and environmentally benign methods for the synthesis of novel coumarin-thiazolo[3,2-a]pyridines *via* a one-pot three-component method.

RESULTS AND DISCUSSION

Commercially available salicylaldehyde on reaction with ethyl acetoacetate in methanol containing a catalytic amount of piperidine afforded 3-acetyl-2*H*-chromen-2-one (**1**), which on bromination with tetrabutylammonium tribromide in acetic acid for 2 h resulted in the formation of 3-(2-bromoacetyl)-2*H*-chromen-2-one (**2**) [34]. 3-(2-Bromoacetyl)-2*H*-chromen-2-one (**2**) on reaction with 2-cyanothioacetamide in ethanol under reflux conditions for 2 h afforded the required synthon, 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)acetonitrile (**3**) (Scheme 1).

In our initial attempts, we have synthesized the title compounds in a stepwise method by the reaction of 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)acetonitrile (**3**) with aryl/heteroaryl aldehydes (**4**) using piperidine as a base in ethanol to obtain (*E*)-2-(4-(2-oxo-2*H*-chromen-3-yl) thiazol-2-yl)-3-arylacrylonitriles (**5**), followed by their reaction with malononitrile in refluxing ethanol using piperidine as a base. The structure of these compounds has been confirmed on the basis of their spectral data such as IR, ^{1}H NMR, ^{13}C NMR, and HRMS (please see Experimental section). In order to synthesize the target compounds in a one-pot method, we have bring about the aforementioned sequence of reactions in a tandem approach, where we have treated **3** with aryl/heteroaryl aldehyde (**4**), and after completion of reaction, (as indicated by the disappearance of starting materials on TLC) equimolar amount of malononitrile was added in the same reaction vessel. The mixture was further refluxed for 3–5 h to afford a product that is identical with compounds **6** that have been prepared earlier in the stepwise route (Scheme 2).

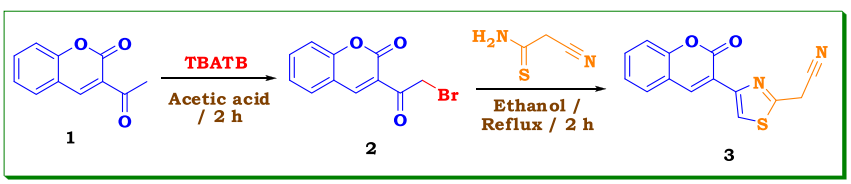
A plausible mechanism for the formation of products **6** by the aforementioned transformation *via* tandem method has been deliberated and given in Scheme 3. Initially, piperidine will facilitate the Knoevenagel condensation between active methylene center of **3** and aryl/heteroaryl aldehyde (**4**) to form α,β-unsaturated nitrile compound **5**. As well, piperidine available in the same reaction vessel will abstract the proton from the active methylene center of malononitrile and generates the carbanion that will undergo nucleophilic attack with **5** to give **A** that immediately starts the cyclization process to accord an intermediate **B**. The latter will abstract the proton from the protonated piperidine and undergoes tautomerism to get converted into a stabilized product **6**.

In another set of reactions, this stepwise and tandem method was performed by reacting aryl/heteroaryl aldehyde (**4**) and malononitrile initially to acquire an arylidene-malononitrile followed by their reaction with 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)acetonitrile (**3**). Thus, equimolar amounts of aryl/heteroaryl aldehyde (**4**) and malononitrile reacted together at RT for 2–3 h employing piperidine as a base to afford arylidene-malononitrile (**7**), which further on reaction with 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl) acetonitrile (**3**) under refluxing ethanol for 3–5 h resulted in the formation of required product **6**. In addition, in a tandem method, we have successfully synthesized the desired products **6**, where we have avoided the isolation of arylidene-malononitriles (**7**) (Scheme 4).

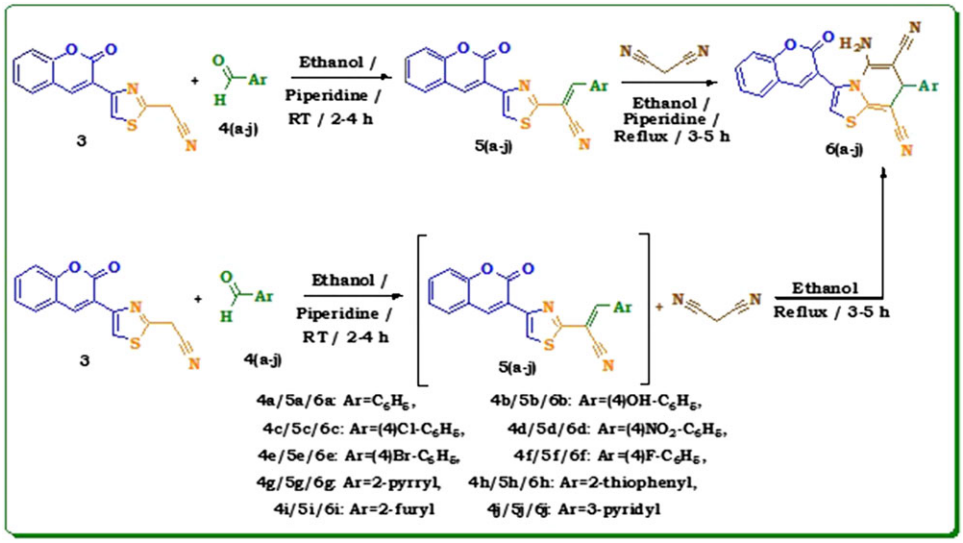
The mechanism for this approach has been proposed and depicted systematically in Scheme 5. Here, piperidine will first facilitate the Knoevenagel condensation reaction between aryl/heteroaryl aldehydes and malononitrile to give arylidene-malononitriles (**7**). As well, piperidine available in the vessel will abstract the proton from the active methylene center of **3** and generates carbanion; this will subsequently attack the arylidene-malononitriles by a nucleophilic approach to give an intermediate **A**. The latter undergoes cyclization process and generates intermediate **C**, which will further withdraw its proton from the protonated piperidine to obtain the product **6**.

With the aforementioned enthusiastic and optimistic results, we intended to synthesize the title compounds in a one-pot method. Thus, in an initial model one-pot reaction, we have chosen equimolar amounts of 2-(4-(2-oxo-2*H*-

Scheme 1. Synthesis of 2-(4-(2-oxo-2*H*-chromen-3-yl)thiazol-2-yl)acetonitrile (**3**). [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 2. Stepwise and tandem syntheses of 5-amino-3-(2-oxo-2*H*-chromen-3-yl)-7-aryl-7*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitriles (**6**). [Color figure can be viewed at wileyonlinelibrary.com]



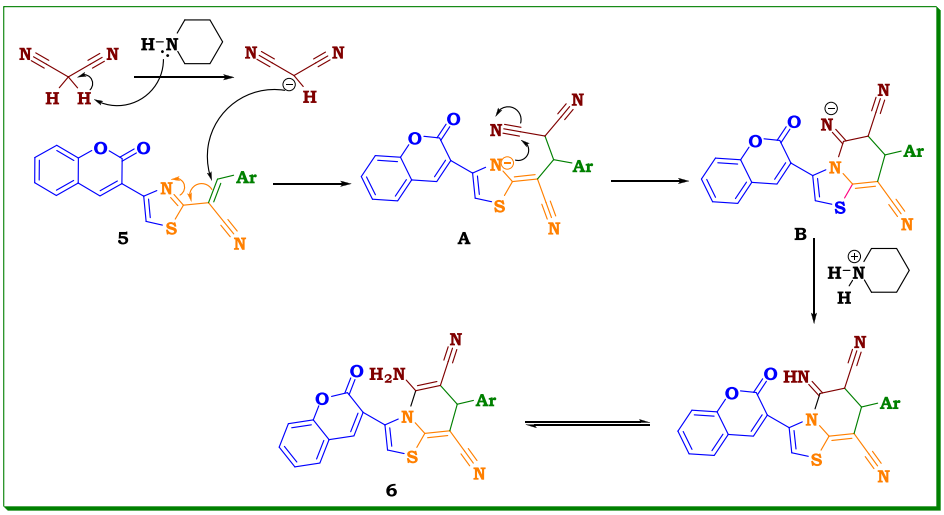
chromen-3-yl)thiazol-2-yl)acetonitrile (**3**), benzaldehyde (**4a**), and malononitrile as substrates and were reacted together in a single reaction vessel using piperidine as a catalyst and ethanol as a solvent under refluxing conditions. Fascinatingly, this reaction successfully completed to produce the desired product **6a** in a good yield, and it was found to be identical with the one that prepared earlier in the stepwise and tandem routes.

To find out the best reaction condition in terms of time and product yield, this one-pot three-component reaction has been screened for various catalysts in ethanol at reflux temperature by proceeding equimolar amounts of **3**, benzaldehyde (**4a**), and malononitrile. From this screening study, it is greatly notable that compared with other catalysts, triethylamine was found to impetus this one-pot three-component reaction with a high yield of product **6a** in a faster reaction time (Table 1).

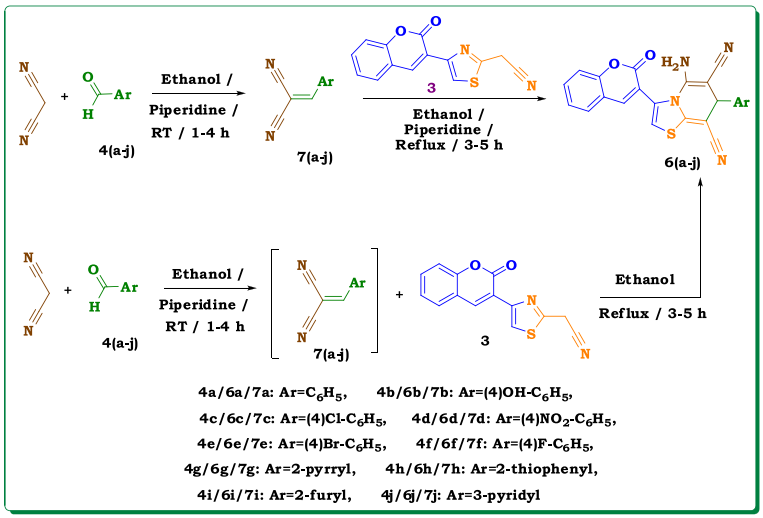
After having the best reaction condition in hand, that is, the use of triethylamine in ethanol, we have extended this method to various other aldehyde derivatives (**4**) and generalized the method to achieve the title compounds (**6**) in good to excellent yields (Scheme 6).

Experimental. Melting points are uncorrected and were determined in open capillary tubes using hot sulfuric acid bath. TLC analyses were carried out on silica gel-G coated sheets supplied by Merck Company, and visualization was performed using UV lamp and iodine staining. IR spectra were recorded using Perkin

Scheme 3. Plausible mechanism for the formation of **6** by a stepwise method. [Color figure can be viewed at wileyonlinelibrary.com]



Scheme 4. Stepwise and tandem syntheses of 5-amino-3-(2-oxo-2*H*-chromen-3-yl)-7-aryl-7*H*-thiazolo[3,2-a]pyridine-6,8-dicarbonitriles (**6**). [Color figure can be viewed at wileyonlinelibrary.com]



Elmer model-446 FTIR in KBr. NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard using Varian 400-MHz spectrometer instrument. Mass spectra were recorded on Agilent instrument using ESI method. Chemicals like salicylaldehydes, malononitrile, and solvents were purchased from commercial suppliers and were used as such.

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 the completion of 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, and air-dried at RT. The product was recrystallized from methanol to obtain a pure white colored compound **3**.

White solid; yield: 2.35 g (88%); mp 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 (complex, m, 4H, Ar—**H**), 8.43 (s, 1H, Ar—**H**), 8.78 (s, 1H, Ar—**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 21.5, 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), and a catalytic amount of piperidine and ethanol (30 mL) was stirred at RT for a period of 2–4 h. Completion of the reaction was monitored by TLC analysis. After completion of reaction, the mixture was poured into ice-cold water (100 mL), and the separated solid was filtered and washed with water (2 × 50 mL). These crude compounds were recrystallized from a suitable solvent to give pure **5**.

Scheme 5. Plausible mechanism for the formation of **6** by a stepwise method. [Color figure can be viewed at wileyonlinelibrary.com]

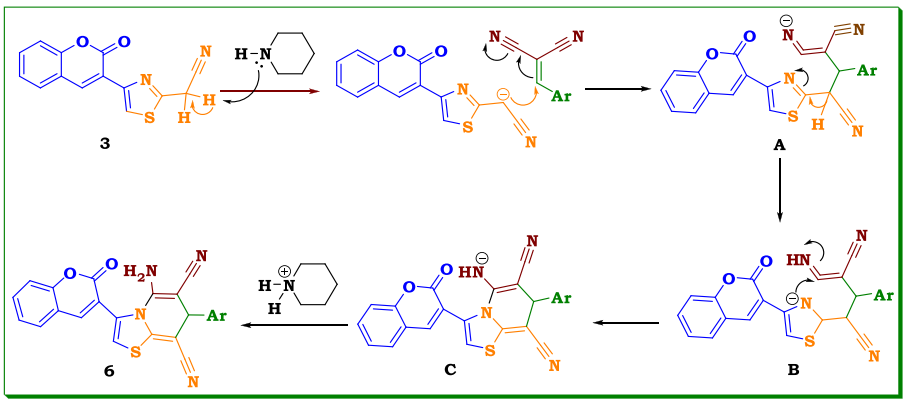


Table 1

Optimization for the suitable catalyst in one-pot method to obtain **6a**.

S. No.	Catalyst	Solvent	Reaction condition	Reaction time	Yield[a] (%)
1	Piperidine	Ethanol	Reflux	5 h	75
2	Morpholine	Ethanol	Reflux	7 h	69
3	Piperazine	Ethanol	Reflux	6 ½ h	65
4	*N*-methylpiperazine	Ethanol	Reflux	7 ½ h	61
5	*N*-ethylpiperazine	Ethanol	Reflux	6 h	60
6	DABCO	Ethanol	Reflux	8 h	55
7	DBU	Ethanol	Reflux	8 ½ h	47
8	Diethylamine	Ethanol	Reflux	7 ½ h	68
9	**Triethylamine**	**Ethanol**	**Reflux**	**3 ½ h**	**82**
10	Imidazole	Ethanol	Reflux	12 h	44

[a]Yield refer to crude product.
Bold text signifies best optimized condition for the reaction to get the product in high yield.

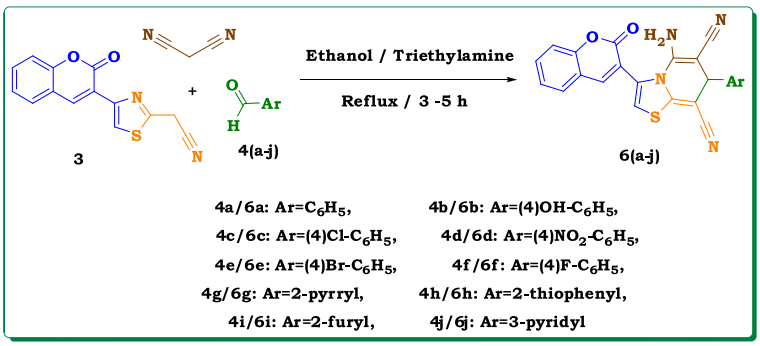
2-(4-(2-Oxo-2H-chromen-3-yl)thiazol-2-yl)-3-phenylacrylonitrile (5a). Yellow color solid; yield: 2.52 g (71%); mp 222–224°C (methanol); IR (KBr): 1718 cm^{-1} (strong, sharp, —CO of coumarin ring), 2156 cm^{-1} (strong, sharp, —CN group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.38–8.07 (complex, m, 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, 116.5, 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.

3-(4-Hydroxyphenyl)-2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)acrylonitrile (5b). Yellow color solid; yield: 2.52 g (68%); mp 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 (complex, m, 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, 115.781, 115.8, 116.3, 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, 153.1, 157.0, 158.5, 158.0; HRMS calculated for $C_{21}H_{13}N_2O_3S$ $[M + H]^+$: 373.0646, found: 373.0662.

3-(4-Chlorophenyl)-2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)acrylonitrile (5c). Yellow color solid; yield: 2.84 g (73%); mp 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 (complex, m, 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, 116.1, 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.

3-(4-Nitrophenyl)-2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl) acrylonitrile (5d). Yellow color solid; yield: 3.12 g (78%); mp 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 (complex, m, 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, 116.1, 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.

Scheme 6. One-pot three-component synthesis of title compounds using triethylamine. [Color figure can be viewed at wileyonlinelibrary.com]



3-(4-Bromophenyl)-2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)acrylonitrile (5e). Yellow color solid; yield: 3.20 g (74%); mp 211–213°C (ethyl acetate); IR (KBr): 1731 cm^{-1} (strong, sharp, —CO of coumarin ring), 2205 cm^{-1} (strong, sharp, —CN group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.44–8.04 (complex, m, 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, 111.5, 111.7, 116.7, 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; HRMS calculated for $C_{21}H_{12}BrN_2O_2S$ $[M + H]^+$: 434.9802, found: 434.9854.

3-(4-Fluorophenyl)-2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)acrylonitrile (5f). Yellow color solid; yield: 2.61 g (70%); mp 188–190°C (methanol); IR (KBr): 1714 cm^{-1} (strong, sharp, —CO of coumarin ring), 2190 cm^{-1} (strong, sharp, —CN group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.42–8.05 (complex, m, 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.

2-(4-(2-Oxo-2H-chromen-3-yl)thiazol-2yl)-3-(1H-pyrrol-2-yl) acrylonitrile (5g). Yellow color solid; yield: 2.48 g (72%); mp 198–200°C (methanol); IR (KBr): 1718 cm^{-1} (strong, sharp, —CO of coumarin ring), 2336 cm^{-1} (strong, sharp, —CN group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.33–7.91 (complex, m, 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.

2-(4-(2-Oxo-2H-chromen-3-yl)thiazol-2yl)-3-(thiophen-2-yl) acrylonitrile (5h). Yellow color solid; yield: 2.49 g (69%); mp 187–189°C (methanol); IR (KBr): 1718 cm^{-1} (strong, sharp, —CO of coumarin ring), 2185 cm^{-1} (strong, sharp, —CN group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.30–7.92 (complex, m, 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.

3-(Furan-2-yl)-2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl) acrylonitrile (5i). Yellow color solid; yield: 2.50 g (67%); mp 192–194°C (methanol); IR (KBr): 1734 cm^{-1} (strong, sharp, —CO of coumarin ring), 2210 cm^{-1} (strong, sharp, —CN group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.32–7.93 (complex, m, 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: 347.0487.

2-(4-(2-Oxo-2H-chromen-3-yl)thiazol-2-yl)-3-(pyridin-3-yl) acrylonitrile (5j). Yellow color solid; yield: 2.59 g (73%); mp 196–198°C (methanol); IR (KBr): 1718 cm^{-1} (strong, sharp, —CO of coumarin ring), 2179 cm^{-1} (strong, sharp, —CN group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ = 7.34–7.96 (complex, m, 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: 358.0662.

General procedure for the synthesis of 6 from 5. A mixture of **5** (10 mmol), malononitrile (10 mmol), and a catalytic amount of piperidine and ethanol (30 mL) was refluxed on a water bath for a period of 3–5 h. Completion of the reaction was monitored by TLC analysis. After completion of reaction, the mixture was poured into ice-cold water (100 mL), and the separated solid was filtered and washed with water (2 × 50 mL). These crude compounds were recrystallized from suitable solvent to give the pure **6**.

5-Amino-3-(2-oxo-2H-chromen-3-yl)-7-phenyl-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6a). Yellow color solid; yield: 3.08 g (73%); mp >250°C (ethanol); IR (KBr): 1718 cm^{-1} (strong, sharp, —CO of coumarin ring), 2205 cm^{-1} (strong, sharp, —CN group), 3400–3440 (broad medium, —NH_2 group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.68 (s, 1H, —C**H**—), 7.41–8.89 (complex, m, 13H, Ar—**H** & N$\mathbf{H}_2$); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 37.7, 104.5, 115.9, 116.3, 118.9, 119.7, 121.5, 124.8, 129.1, 129.2, 129.8, 132.0, 132.2, 132.4, 140.1, 146.0, 148.3, 152.6, 158.7, 162.0; HRMS calculated for $C_{24}H_{15}N_4O_2S$ $[M + H]^+$: 423.0914, found: 423.0918.

5-Amino-7-(4-hydroxyphenyl)-3-(2-oxo-2H-chromen-3-yl)-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6b). Yellow color solid; yield: 3.06 g (70%); mp 235–237°C (methanol); IR (KBr): 1720 cm^{-1} (strong, sharp, —CO of coumarin ring), 2209 cm^{-1} (strong, sharp, —CN group), 3300–3340 (broad medium, —NH_2 group), 3520–3570 (broad medium, —OH group); ^1H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.65 (s, 1H, —C**H**—), 7.40–8.89 (complex, m, 12H, Ar—**H** & N$\mathbf{H}_2$), 10.15 (s, 1H, O**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 36.9, 104.8, 116.5, 117.9, 118.9, 119.4, 119.8, 121.2, 121.8, 122.1, 125.2, 127.2, 129.3, 129.5, 130.1, 132.7, 137.0, 139.5, 143.0, 146.7, 151.2, 153.8, 159.8, 162.1; HRMS calculated for $C_{24}H_{15}N_4O_3S$ $[M + H]^+$: 439.0864, found: 439.0859.

5-Amino-7-(4-chlorophenyl)-3-(2-oxo-2H-chromen-3-yl)-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6c). Yellow color solid; yield: 3.05 g (67%); mp 196–198°C (acetonitrile); IR (KBr): 1715 cm^{-1} (strong, sharp, —CO of coumarin ring), 2224 cm^{-1} (strong, sharp, —CN group), 3350–3400 (broad medium, —NH_2 group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.64 (s, 1H, —C**H**—), 7.42–8.90 (complex, m, 12H, Ar—**H** & N**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 37.8, 59.3, 72.3, 105.0, 115.9, 116.6, 117.1, 118.5, 118.8, 125.0, 125.7, 127.5, 128.0, 129.2, 130.5, 131.0, 135.5, 138.9, 152.6, 153.7, 158.7, 163.1; HRMS calculated for $C_{24}H_{14}ClN_4O_2S$ $[M + H]^+$: 457.0526, found: 457.0545.

5-Amino-7-(4-nitrophenyl)-3-(2-oxo-2H-chromen-3-yl)-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6d). Yellow color solid; yield: 3.31 g (71%); mp >250°C (chloroform); IR (KBr): 1717 cm^{-1} (strong, sharp, —CO of coumarin ring), 2205 cm^{-1} (strong, sharp, —CN group), 3320–3410 (broad medium, —NH_2 group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.65 (s, 1H, —C**H**—), 7.42–8.88 (complex, m, 12H, Ar—**H** & N**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 37.4, 59.4, 72.7, 105.1, 116.2, 117.6, 118.1, 118.5, 123.4, 125.1, 125.6, 127.3, 128.0, 129.4, 130.4, 139.5, 145.6, 149.3, 152.9, 153.5, 158.8, 162.8; HRMS calculated for $C_{24}H_{14}N_5O_4S$ $[M + H]^+$: 468.0766, found: 468.0755.

5-Amino-7-(4-bromophenyl)-3-(2-oxo-2H-chromen-3-yl)-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6e). Yellow color solid; yield: 3.55 g (71%); mp >250°C (ethanol); IR (KBr): 1722 cm^{-1} (strong, sharp, —CO of coumarin ring), 2214 cm^{-1} (strong, sharp, —CN group), 3380–3430 (broad medium, —NH_2 group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): 4.66 (s, 1H, —C**H**—), 7.41–8.89 (complex, m, 12H, Ar—**H** & N**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 37.6, 58.9, 71.8, 105.0, 115.5, 116.7, 118.0, 119.4, 121.1, 125.3, 125.8, 127.6, 129.4, 130.6, 131.8, 132.1, 139.6, 142.4, 152.4, 153.8, 159.6, 162.1; HRMS calculated for $C_{24}H_{14}BrN_4O_2S$ $[M + H]^+$: 501.0020, found: 501.0034.

5-Amino-7-(4-fluorophenyl)-3-(2-oxo-2H-chromen-3-yl)-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6f). Yellow color solid; yield: 2.75 g (63%); mp >250°C (methanol); IR (KBr): 1719 cm^{-1} (strong, sharp, —CO of coumarin ring), 2210 cm^{-1} (strong, sharp, —CN group), 3410–3460 (broad medium, —NH_2 group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.65 (s, 1H, —C**H**—), 7.38–8.87 (complex, m, 12H, Ar—**H** & N**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 37.7, 59.4, 72.3, 105.2, 115.6, 116.6, 118.2, 119.6, 120.2, 125.5, 125.9, 127.7, 128.6, 130.7, 131.1, 138.2, 138.9, 152.3, 153.9, 158.9, 159.5, 162.3; HRMS calculated for $C_{24}H_{13}FN_4O_2S$ $[M + H]^+$: 440.0743, found: 440.0768.

5-Amino-3-(2-oxo-2H-chromen-3-yl)-7-(1H-pyrrol-2-yl)-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6g). Yellow color solid; yield: 2.58 g (63%); mp 205–207°C (methanol); IR (KBr): 1730 cm^{-1} (strong, sharp, —CO of coumarin ring), 2206 cm^{-1} (strong, sharp, —CN group), 3400–3440 (broad medium, —NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.65 (s, 1H, —C**H**—), 7.40–7.89 (complex, m, 11H, Ar—**H** & N**H**$_2$), 11.62 (s, 1H, N**H**); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 37.6, 105.3, 116.3, 117.5, 119.7, 120.7, 121.9, 125.1, 129.4, 129.6, 132.1, 139.0, 141.4, 144.0, 152.7, 159.2, 162.9; HRMS calculated for $C_{22}H_{14}N_5O_2S$ $[M + H]^+$: 412.0868, found: 412.0863.

5-Amino-3-(2-oxo-2H-chromen-3-yl)-7-(thiophen-2-yl)-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6h). Yellow color solid; yield: 2.99 g (70%); mp 223–225°C (acetonitrile); IR (KBr): 1726 cm^{-1} (strong, sharp, —CO of coumarin ring), 2190 cm^{-1} (strong, sharp, —CN group), 3390–3430 (broad medium, —NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.66 (s, 1H, —C**H**—), 7.38–7.85 (complex, m, 11H, Ar—**H** & N**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 37.2, 58.4, 71.0, 105.4, 116.5, 117.2, 118.2, 118.7, 123.5, 125.3, 125.6, 125.9, 127.1, 128.2, 128.6, 130.6, 138.7, 139.9, 152.4, 153.2, 159.6, 162.4; HRMS calculated for $C_{22}H_{13}N_4O_2S_2$ $[M + H]^+$: 429.0479, found: 429.0460.

5-Amino-7-(furan-2-yl)-3-(2-oxo-2H-chromen-3-yl)-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6i). Yellow color solid; yield: 2.76 g (67%); mp >250°C (ethanol); IR (KBr): 1720 cm^{-1} (strong, sharp, —CO of coumarin ring), 2234 cm^{-1} (strong, sharp, —CN group), 3390–3430 (broad medium, —NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.65 (s, 1H, —C**H**—), 7.40–7.90 (complex, m, 11H, Ar—**H** & N**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 37.3, 58.6, 70.8, 105.6, 116.8, 117.4, 118.0, 118.6, 123.0, 125.5, 126.0, 126.3, 127.6, 128.4, 128.8, 130.0, 138.1, 139.6, 152.3, 153.1, 158.9, 162.1; HRMS calculated for $C_{22}H_{13}N_4O_3S$ $[M + H]^+$: 413.0708, found: 413.0715.

5-Amino-3-(2-oxo-2H-chromen-3-yl)-7-(pyridin-3-yl)-7H-thiazolo[3,2-a]pyridine-6,8-dicarbonitrile (6j). Yellow color solid; yield: 2.70 g (64%); mp >250°C (methanol); IR (KBr): 1725 cm^{-1} (strong, sharp, —CO of coumarin ring), 2210 cm^{-1} (strong, sharp, —CN group), 3420–3480 (broad medium, —NH group); ^{1}H NMR (400 MHz, DMSO-d_6/TMS): δ = 4.66 (s, 1H, —C**H**—), 7.39–7.88 (complex, m, 12H, Ar—**H** & N**H**$_2$); ^{13}C NMR (100 MHz, DMSO-d_6/TMS): 37.5, 58.4, 70.6, 105.2, 116.7, 116.9, 117.5, 119.9, 121.5, 121.7, 125.5, 129.7, 130.3, 132.6, 140.1, 141.9, 142.4, 144.4, 148.0, 150.1, 152.2, 158.5, 162.0; HRMS calculated for $C_{23}H_{14}N_5O_2S$ $[M + H]^+$: 424.0868, found: 424.0855.

General procedure for the tandem synthesis of 6 from 3 and 4. A mixture of **3** (10 mmol), various aldehydes (10 mmol), and a catalytic amount of piperidine and ethanol (30 mL) was stirred at RT for a period of 2–4 h. Completion of the reaction was monitored by TLC analysis. After completion of reaction, malononitrile

(10 mmol) was added into the same reaction vessel and refluxed on a water bath for a period of 3–5 h. Completion of the reaction was monitored by TLC analysis. After completion of reaction, the mixture was poured into ice-cold water (100 mL), and the separated solid was filtered and washed with water (2 × 50 mL). These crude compounds were recrystallized from suitable solvent to give the pure **6**.

6a: Yield: 3.08 g (73%);
6b: Yield: 3.06 g (70%);
6c: Yield: 3.37 g (74%);
6d: Yield: 3.59 g (77%);
6e: Yield: 3.55 g (71%);
6f: Yield: 3.38 g (77%);
6g: Yield: 3.20 g (78%);
6h: Yield: 3.12 g (73%);
6i: Yield: 2.84 g (69%);
6j: Yield: 2.87 g (68%).

General procedure for the tandem synthesis of 6 from 4 and malononitrile. A mixture of **4** (10 mmol), malononitrile (10 mmol), and a catalytic amount of piperidine and ethanol (30 mL) was stirred at RT for a period of 1–4 h. Completion of the reaction was monitored by TLC analysis. After completion of reaction, **3** (10 mmol) was added into the same reaction vessel and refluxed on a water bath for a period of 3–5 h. Completion of the reaction was monitored by TLC analysis. After completion of reaction, the mixture was poured into ice-cold water (100 mL), and the separated solid was filtered and washed with water (2 × 50 mL). These crude compounds were recrystallized from suitable solvent to give the pure **6**.

6a: Yield: 3.12 g (74%);
6b: Yield: 3.10 g (71%);
6c: Yield: 3.42 g (75%);
6d: Yield: 3.45 g (74%);
6e: Yield: 3.80 g (76%);
6f: Yield: 3.02 g (69%);
6g: Yield: 3.08 g (75%);
6h: Yield: 3.03 g (71%);
6i: Yield: 2.88 g (70%);
6j: Yield: 2.83 g (67%).

General procedure for the one-pot three-component synthesis of 6. A mixture of **3** (10 mmol), **4** (10 mmol), malononitrile (10 mmol), and a catalytic amount of triethylamine and ethanol (30 mL) was refluxed on a water bath for a period of 3–5 h. Completion of the reaction was monitored by TLC analysis. After completion of reaction, the mixture was poured into ice-cold water (100 mL), and the separated solid was filtered and washed with water (2 × 50 mL). These crude compounds were recrystallized from suitable solvent to give the pure **6**.

6a: Yield: 3.58 g (85%);
6b: Yield: 3.50 g (80%);
6c: Yield: 4.01 g (88%);
6d: Yield: 3.64 g (78%);
6e: Yield: 4.15 g (83%);
6f: Yield: 3.38 g (77%);
6g: Yield: 3.24 g (79%);
6h: Yield: 3.59 g (84%);
6i: Yield: 3.05 g (74%);
6j: Yield: 3.34 g (79%).

CONCLUSIONS

In summary, we have demonstrated efficient stepwise, tandem, and one-pot three-component approach for the synthesis of title compounds. Further, we have optimized the reaction conditions by screening various catalysts to obtain optimal conditions. Among all the methods approached for the synthesis, one-pot three-component method has been regarded as satisfactory and eminent approach. The methods applied are operationally simple, environmentally viable, atom economy, easy accessibility of reactants, simple workup procedures, use of ethanol as green solvent, and high yielding. The capacity of various aldehydes including some heteroaryl aldehyde partners makes this approach very attractive for the construction of high-value and biologically significant heterocycles.

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