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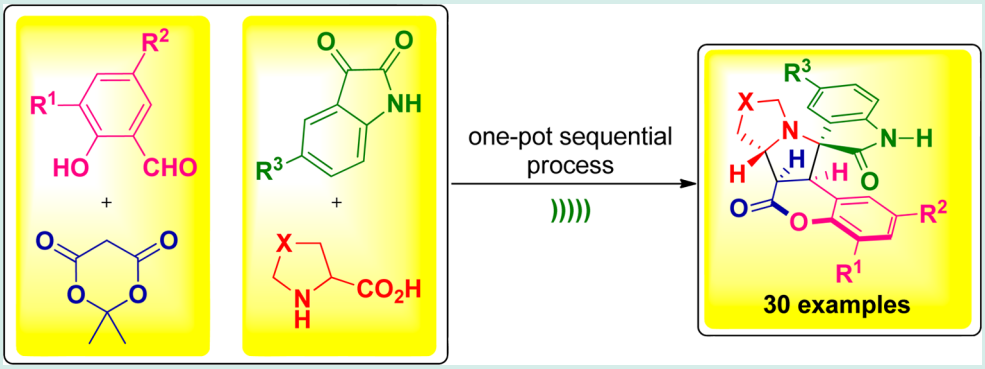
Ultrasound-Assisted Sequential Multicomponent Strategy for the Combinatorial Synthesis of Novel Coumarin Hybrids

Selvaraj Kanchithalaivan, Remani Vasudevan Sumesh, and Raju Ranjith Kumar*

Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, Tamil Nadu India

Supporting Information



ABSTRACT: The present investigation reports an easy access to a library of novel spiro-oxindole−pyrrolizine or pyrrolo[1,2-*c*]thiazole fused coumarin hybrid heterocycles through a one-pot sequential four-component reactions of 2,2-dimethyl-1,3-dioxane-4,6-dione, salicylaldehydes, isatins, and cyclic α-amino acids under ultrasound irradiation.

KEYWORDS: *sequential, spiro-oxindole, coumarin, pyrrolizine, pyrrolothiazole, 1,3-dipolar cycloaddition*

INTRODUCTION

The 1,3-dipolar cycloadditions (DPC) of azomethine ylides to activated olefins offer a facile entry toward five-membered nitrogen heterocycles.[1] In particular, investigations pertaining to the DPC of nonstabilized azomethine ylides generated in situ from the decarboxylative condensation of α-amino acids and nonenolizable ketones to dipolarophiles with exocyclic alkenes resulting in the formation of dispiro heterocycles have received significant attention.[2] However, reports on the DPC of these 1,3-dipoles with endocyclic alkenes to form monospiro fused heterocycles are scarce.[3] Consequently, the present work reports for the first time the synthesis of novel spiro-oxindole/acenaphthelene−pyrrolizine/pyrrolo[1,2-*c*]thiazole fused coumarin hybrid heterocycles through DPC of azomethine ylides under ultrasound-irradiation.

Recently, more focus is dedicated toward the DPC of azomethine ylides to olefins under ultrasound-irradiation, which offer a simple route for the construction of complex heterocycles.[4] Under these conditions, it has been observed that the cycloaddition proceeds through a diradical ylide rather than a concerted pathway. In general, organic reactions under ultrasound-irradiation are more advantageous when compared to conventional procedures in view of its milder reaction condition, improved selectivity, high yields in shorter reaction time, simple experimental procedure and workup and energy conservation.[5] Ultrasound-irradiation leads to cavitation, namely, formation, growth, and implosive collapse of bubbles in liquid. This induces intense local heating, which promotes organic reactions to occur.[4,5]

On the other hand, spiro-oxindoles are found in several bioactive natural products, such as spirotryprostatins A and B,[6] horsfiline,[7] rhynchophylline,[8] formosanine,[9] and elacomine.[10] The synthetic analogs of these heterocycles have also been shown to display significant biological activities.[11] In addition, coumarin containing natural products as well as its synthetic heterofused systems are endowed with wide array of biological properties which includes antidiabetic,[12] anticoagulant,[13] anticancer,[14] antitubercular,[15] anti-HIV[16] and AChE inhibition.[17] The present work also pertains to our continuous effort in the synthesis of novel heterocycles employing one-pot multicomponent reactions.[18]

RESULTS AND DISCUSSION

Initially, coumarin-3-carboxylic acid **2** was synthesized from the reaction of 2,2-dimethyl-1,3-dioxane-4,6-dione and salicylaldehyde **1**{*1*} following literature procedure.[19] In the next step, the 1,3-dipolar cycloaddition of **2** with azomethine ylide generated in situ from the reaction of isatin **3**{*1*} and proline **4**{*1*} was investigated under ultrasound irradiation (Scheme 1). The reaction occurred smoothly at 50 °C affording a colorless precipitate after 1 h of irradiation, which was filtered, washed

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Scheme 1. Synthesis of Spiro-oxindole−Pyrrolizine/pyrrolo[1,2-*c*]thiazole-Fused Coumarin Hybrids 5

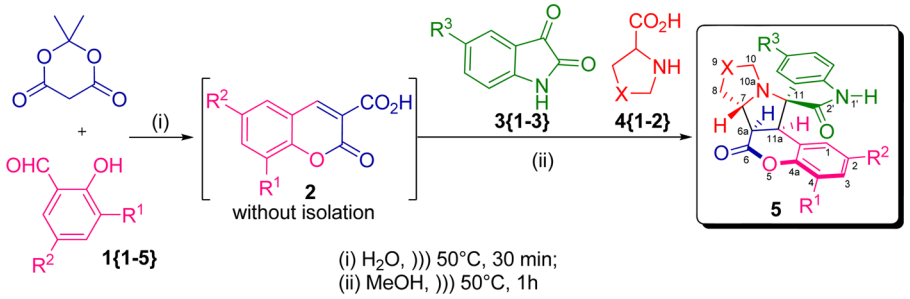

Table 1. Comparative Yield of 5 under Conventional and Ultrasound Conditions

entry	compd	R^1	R^2	R^3	X	yield (%)[a,b]	yield (%)[c]	mp (°C)
1	5{*1,1,1*}	H	H	H	CH_2	62	95	217−218
2	5{*1,2,1*}	H	H	Cl	CH_2	56	95	168−169
3	5{*1,3,1*}	H	H	CH_3	CH_2	60	94	166−167
4	5{*2,1,1*}	H	Br	H	CH_2	52	95	162−163
5	5{*2,2,1*}	H	Br	Cl	CH_2	60	94	217−218
6	5{*2,3,1*}	H	Br	CH_3	CH_2	55	96	241−242
7	5{*3,1,1*}	H	Cl	H	CH_2	58	95	210−211
8	5{*3,2,1*}	H	Cl	Cl	CH_2	59	95	217−218
9	5{*3,3,1*}	H	Cl	CH_3	CH_2	60	95	235−236
10	5{*4,1,1*}	H	NO_2	H	CH_2	64	94	172−173
11	5{*4,2,1*}	H	NO_2	Cl	CH_2	55	94	210−211
12	5{*4,3,1*}	H	NO_2	CH_3	CH_2	57	96	218−219
13	5{*5,1,1*}	Cl	Cl	H	CH_2	62	95	168−169
14	5{*5,2,1*}	Cl	Cl	Cl	CH_2	61	95	225−226
15	5{*5,3,1*}	Cl	Cl	CH_3	CH_2	59	96	168−169
16	5{*1,1,2*}	H	H	H	S	60	87	247−248
17	5{*1,2,2*}	H	H	Cl	S	55	82	156−157
18	5{*1,3,2*}	H	H	CH_3	S	58	89	257−258
19	5{*2,1,2*}	H	Br	H	S	54	81	217−218
20	5{*2,2,2*}	H	Br	Cl	S	56	86	193−194
21	5{*2,3,2*}	H	Br	CH_3	S	50	87	265−266
22	5{*3,1,2*}	H	Cl	H	S	60	80	257−258
23	5{*3,2,2*}	H	Cl	Cl	S	61	82	185−186
24	5{*3,3,2*}	H	Cl	CH_3	S	60	88	162−163
25	5{*4,1,2*}	H	NO_2	H	S	55	86	264−265
26	5{*4,2,2*}	H	NO_2	Cl	S	55	84	249−250
27	5{*4,3,2*}	H	NO_2	CH_3	S	58	91	263−264
28	5{*5,1,2*}	Cl	Cl	H	S	59	87	241−242
29	5{*5,2,2*}	Cl	Cl	Cl	S	56	90	233−234
30	5{*5,3,2*}	Cl	Cl	CH_3	S	55	92	239−240

[a]Isolated yield after column chromatography. [b]Conventional heating. [c]Ultrasound irradiation.

with water and dried to obtain novel 6b,7,8,9-tetrahydro-6*H*-spiro[chromeno[3,4-*a*]pyrrolizine-11,3′-indoline]-2′,6-(6a*H*,11a*H*)-dione 5{*1,1,1*} in 97% yield.

In an attempt to synthesize 5{*1,1,1*} via a one-pot sequential procedure without isolating the intermediate **2**, the reactants 2,2-dimethyl-1,3-dioxane-4,6-dione and 1{*1*} in water was subjected to ultrasound irradiation at 50 °C. After 30−40 min a colorless precipitate was formed in the reaction mixture indicating the formation of **2**. To this, a mixture of isatin 3{*1*} and proline 4{*1*} dissolved in methanol was added and the ultrasound irradiation continued at 50 °C (Scheme 1). As the reaction progressed the mixture became homogeneous and after 45 min of irradiation, a colorless solid precipitated from the mixture, which was filtered and dried to obtain 5{*1,1, 1*} in 95% yield (Table 1).

It is significant to note that under ultrasound irradiation the stepwise, as well as the one-pot sequential, procedure afforded 5{*1,1,1*} in quantitative yields. As the product is precipitated in the reaction vessel, no column chromatographic purification is required thereby eliminating the use of large quantity of volatile solvents. Furthermore, under these conditions the necessity to monitor the reaction progress employing thin layer chromatography is not required as well.

Moreover, for comparison the above reaction was performed under conventional method, wherein the reactants **2**, isatin 3{*1*}, and proline 4{*1*} were refluxed in methanol. The reaction proceeds well with the formation of 5{*1,1,1*} but failed to attain completion even after 6 h of continuous reflux. At this stage the reaction mixture was cooled to room temperature and quenched with crushed ice. The precipitate after column

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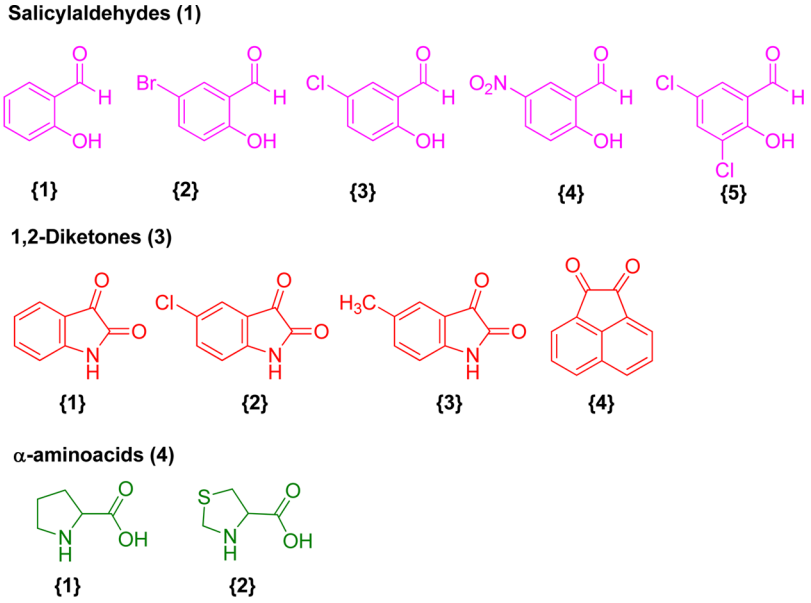

Figure 1. Diversity of reagents.

chromatographic purification afforded **5**{*1,1,1*} in 62% yield (Table 1). Apparently, the ultrasound irradiation method was found to be more advantageous over conventional heating for the synthesis of **5**{*1,1,1*}.

The above ultrasound-assisted one-pot sequential procedure was then employed for the synthesis of a library of novel spiro-oxindolo-pyrrolizine/pyrrolo[1,2-*c*]thiazole fused coumarin hybrid heterocycles **5** by varying the salicylaldehyde **1**, isatin **3** and cyclic *α*-amino acid **4** (Figure 1). The data in Table 1 disclose that this protocol works well with all the substrates affording excellent yields of the products when compared to the conventional heating, wherein the yields were less than 62%.

The structure of all the coumarin hybrid heterocycles **5** is in complete agreement with the elemental analysis, ESI mass, IR, and NMR spectroscopic data. As a representative example, the mass spectrum of **5**{*1,1,1*} has a characteristic molecular ion peak at 347.25 (M^+). The IR spectrum of **5**{*1,1,1*} shows strong absorptions at 1758 and 1729 cm^{-1} due to the two carbonyl groups. In the proton NMR spectrum of **5**{*1,1,1*}, a doublet at 3.93 ppm (J = 11.1 Hz) can be readily assigned to 11a-CH on the basis of its multiplicity. From the H,H-COSY of 11a-CH, the doublets of doublets at 3.11 ppm (J = 11.1, 3.3 Hz) is due to 6a-CH. The coupling constant value of 11.1 Hz discloses that 11a-H and 6a-H are cis. Further, it is evident from the H,H-COSY of 6a-CH that the triplets of doublets at 4.73 ppm (J = 7.1, 3.3 Hz) accounting for one proton is due to 7-CH. The C,H-COSY correlations assigns the carbon signals at 44.0, 47.9, and 67.8 ppm to C-11a, 6a, and 7 respectively. The 8-, 9-, and 10-CH_2 protons appear as multiplets in the range 1.71−3.14 ppm and the NH of the oxindole ring gives a broad singlet at 8.16 ppm. The carbon signals at 76.9, 167.6, and 177.8 ppm are due to spiro carbon C-11 and the carbonyl carbons at C-6 and C-2′ respectively (Figure 2).

The structure of **5** elucidated from the NMR spectroscopic studies was further confirmed from single crystal X-ray data. The ORTEP diagram of **5**{*5,3,1*} shown in Figure 3 discloses that H-11a and H-6a are cis, whereas H-6a and H-7 are trans.[20]

A plausible mechanism for the formation of spiro-coumarin hybrid heterocycles **5** via ultrasound irradiation, as well as conventional heating is depicted in Scheme 2. Initially, the aldol

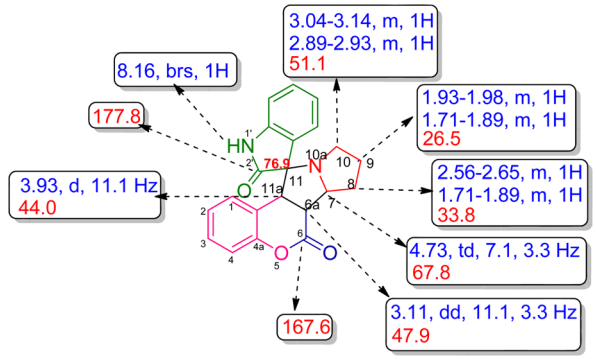

Figure 2. ^1H and ^{13}C chemical shifts of **5**{*1,1,1*}.

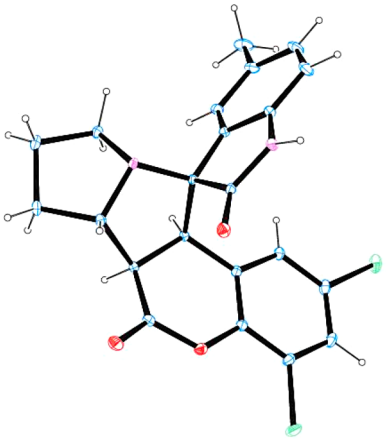

Figure 3. ORTEP diagram of **5**{*5,3,1*}.

reaction of 2,2-dimethyl-1,3-dioxane-4,6-dione and salicylaldehydes **1** affords the intermediate arylidene **6**, which undergoes an intramolecular cyclization via nucleophilic attack of OH on the carbonyl carbon followed by elimination of acetone to yield the coumarin-3-carboxylic acid **2**. Simultaneously, the condensation of isatins and proline or 1,3-thiazolone-4-carboxylic acid affords the spiro intermediate **7**.[21] The decarboxylation of

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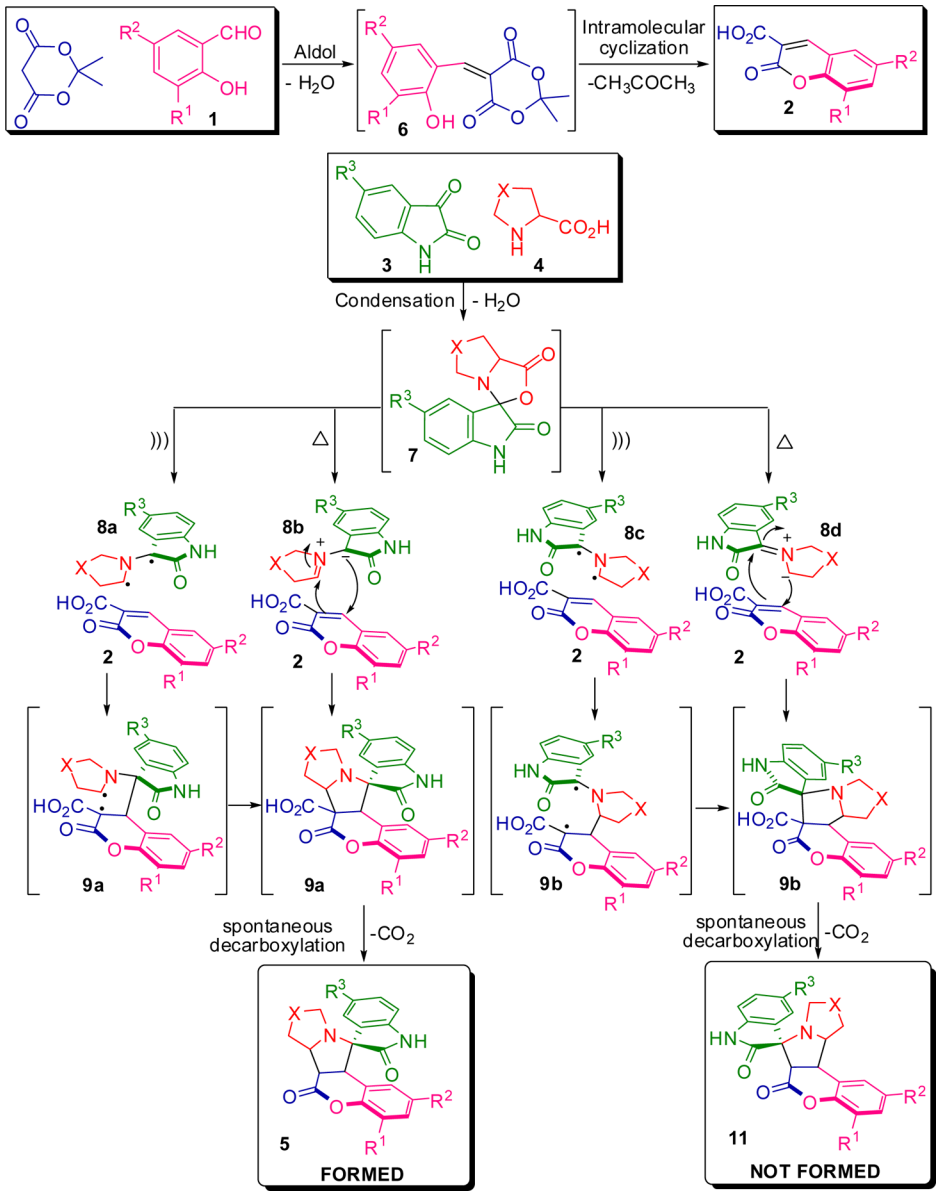
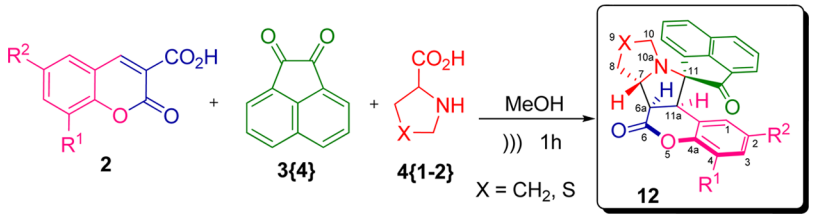
Scheme 2. Plausible mechanism for the formation of 5



Scheme 3. Synthesis of Spiro-acenaphthenequinone−Pyrrolizine/Pyrrolo[1,2-*c*]thiazole-Fused Coumarin Hybrids 12



7 under ultrasound irradiation forms the diradical ylide **8a**, whereas under conventional heating forms the ylide **8b**. The 1,3-dipolar cycloaddition of **8a** and **8b** with **2** proceeds through a diradical mechanism (via **9a**) and a concerted pathway, respectively, to afford the adduct **10a** followed by the spontaneous decarboxylation of **10a** to afford **5**.

The above sequential reaction proceeds regioselectively affording a single isomer of the product **5** under both ultrasound irradiation as well as conventional heating. The other regioisomer **11** is not formed during the course of the reaction. However, formation of **11** can be visualized from the cycloaddition of either **8c** or **8d** with **2** via **10b**, which presumably is less favored due to the electrostatic repulsion between the carbonyl of coumarin ring and that of the approaching azomethine ylide dipole (Scheme 2). This regiochemistry is also evident from the single crystal X-ray studies (Figure 3).

Further, with a view to extend the scope of the above one-pot four-component sequential protocol, isatins were replaced with acenaphthenequinone **3{4}** (Scheme 3). Because of the

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solubility issue of acenaphthenequinone in aqueous conditions, the reaction failed to occur. However, the three-component reaction of **2**, **3**{*4*} and **4**{*1*−*2*} under ultrasound irradiation afforded novel spiro-acenaphthenequinone−pyrrolizine/pyrrolo[1,2-*c*]thiazole fused coumarin hybrids **12** in good yields in 45−60 min (Table 2). The structure of these heterocycles **12** was elucidated with the help of NMR spectroscopy.

Table 2. Yield and Melting Point of 12

entry	compd	R^1	R^2	X	yield (%)	mp (°C)
31	**12**{*1,4,1*}	H	H	CH_2	90	197−198
32	**12**{*2,4,1*}	H	Br	CH_2	89	234−235
33	**12**{*3,4,1*}	H	Cl	CH_2	84	228−229
34	**12**{*4,4,1*}	H	NO_2	CH_2	82	217−218
35	**12**{*5,4,1*}	Cl	Cl	CH_2	88	211−212
36	**12**{*1,4,2*}	H	H	S	92	226−227
37	**12**{*2,4,2*}	H	Br	S	86	238−239
38	**12**{*3,4,2*}	H	Cl	S	80	240−241
39	**12**{*4,4,2*}	H	NO_2	S	89	230−231
40	**12**{*5,4,2*}	Cl	Cl	S	92	247−248

CONCLUSIONS

In conclusion, we have developed a facile one-pot four-component sequential protocol for the regioselective synthesis of hitherto unreported spiro-oxindole−pyrrolizine or pyrrolothiazole fused coumarin hybrid heterocycles under ultrasound-irradiation. The reaction afforded excellent yields of the products in significantly lesser time in contrast to the conventional heating wherein yields were less than 62%. The reaction proceeds through a sequential aldol condensation−intramolecular cyclization−1,3-dipolar cycloaddition−decarboxylation in one-pot without the isolation and/or purification of intermediates. Furthermore, spiro-acenaphthenequinone−pyrrolizine or pyrrolothiazole fused coumarins were also obtained following a three-component protocol under ultrasound-irradiation.

EXPERIMENTAL PROCEDURE

General. Melting points were measured in open capillary tubes and are uncorrected. Electrospray ionization mass spectrometry (ESI-MS) analyses were recorded in LCQ Fleet, Thermo Fisher Instrument in negative ion mode. The collision voltage and ionization voltage were −70 V and −4.5 kV, respectively, using nitrogen as atomization and desolvation gas. The desolvation temperature was set at 300 °C. The scan range of mass spectrum was 300−2000 *m*/*z*. The relative amount of each component was determined from the LC−MS chromatogram, using the area normalization method. Infrared spectra were recorded on a JASCO FT-IR instrument using KBr pellets. The ^{1}H ^{13}C and 2D NMR spectra were recorded on Bruker Avance 300 MHz spectrometer with TMS as the internal standard and $CDCl_3$ or DMSO-d_6 was used as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Elemental analyses were performed on PerkinElmer 2400 Series II CHNS analyzer. The single crystal X-ray data set for compound **5**{*5,3,1*} was collected on Bruker Kappa APPEXII diffractometer with Mo Kα (λ = 0.71073 Å) radiation. SHELXTL software was used for structure solution and refinement. Ultrasonication was performed in a Bandelin-Sonorex Ultrasonic Bath (Super RK) with a frequency of 35 kHz and a power of 230 W. The internal dimensions of the ultrasonic cleaner tank were 240 × 140 × 100 mm with liquid holding capacity of 3L. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60−80 °C) and ethyl acetate as eluent. The solvents and all reagents used in this study were purchased from commercial suppliers.

General Procedure for the Synthesis of 5. *Ultrasound Irradiation.* A reaction flask with the appropriate salicylaldehyde (**1**{*1*−*5*}, 1 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (1 mmol) in water (7 mL) was located at the maximum energy area in the ultrasonic bath and the surface of the reactants was placed slightly lower than the level of the water. The mixture was subjected to ultrasonic irradiation of low power at 50 °C for about 30 min. To this, a mixture of appropriate isatin (**3**{*1*−*3*}, 1 mmol) and proline or 4-thiazolidinecarboxylic acid (**4**, 1 mmol) dissolved in methanol (7 mL) was added. The irradiation was continued until the completion of the reaction (∼45−60 min), during which the product precipitated from the reaction mixture, which was filtered and dried to obtain pure **5**.

Conventional Method. A reaction flask with appropriate salicylaldehyde (**1**{*1*−*5*}, 1 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (1 mmol) in water (7 mL) was refluxed for 30 min. To this a mixture of appropriate isatin (**3**{*1*−*3*}, 1 mmol) and proline or 4-thiazolidinecarboxylic acid (**4**, 1 mmol) dissolved in methanol (7 mL) was added. The heating was continued for 5−6 h with regular TLC analysis. Then the reaction mixture was poured into ice cold water and the precipitate was filtered and subjected to column chromatographic purification (80:20 v/v petroleum ether:ethyl acetate mixture) to afford pure **5**.

Compound ***5****{1,1,1}:* Obtained as colorless solid; yield 95%; mp 217−218 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71−1.89 (m, 2H), 1.93−1.98 (m, 1H), 2.56−2.65 (m, 1H), 2.89−2.93 (m, 1H), 3.11 (dd, *J* = 11.3, 3.2 Hz, 1H), 3.04−3.14 (m, 1H), 3.93 (d, *J* = 11.1 Hz, 1H), 4.73 (td, *J* = 7.1, 3.1 Hz, 1H), 6.34 (d, *J* = 7.8 Hz, 1H), 6.70−6.76 (m, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 7.01−7.18 (m, 2H), 7.31−7.36 (m, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 8.16 (brs, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5, 33.7, 44.0, 47.9, 51.1, 67.9, 76.9, 110.7, 116.8, 117.3, 122.3, 123.7, 125.9, 127.4, 129.0, 130.2, 142.6, 151.2, 167.6, 177.8 ppm; Anal. Calcd for $C_{21}H_{18}N_2O_3$ C, 72.82; H, 5.24; N, 8.09; Found C, 72.98; H, 5.14; N, 8.11; ESI-MS *m*/*z* calcd $[M + H]^+$ 347.13, found 347.25; FT IR (cm^{-1}) 3434, 3058, 1758, 1729, 1619, 1471, 1168, 773.

Compound ***5****{1,1,2}:* Obtained as colorless solid; yield 87%; mp 247−248 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.89 (dd, *J* = 10.8, 6.9 Hz, 1H), 3.31 (d, *J* = 9.3 Hz, 1H), 3.49 (dd, *J* = 10.8, 6.9 Hz, 1H), 3.88 (d, *J* = 9.3 Hz, 1H), 4.01 (d, *J* = 10.5 Hz, 1H), 4.13 (d, *J* = 10.5 Hz, 1H), 4.85 (t, *J* = 6.9 Hz, 1H), 6.29 (d, *J* = 7.5 Hz, 1H), 6.77−6.85 (m, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 7.14−7.23 (m, 2H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 6.9 Hz, 1H), 7.68 (brs, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 39.1, 45.9, 48.2, 55.7, 70.4, 76.6, 77.2, 110.8, 116.9, 117.2, 123.1, 124.0, 125.5, 126.1, 127.5, 129.6, 130.7, 142.1, 151.4, 165.9, 178.1 ppm; Anal. Calcd for $C_{20}H_{16}N_2O_3S$ C, 65.92; H, 4.43; N, 7.69; Found C, 65.94; H, 4.40; N, 7.64.

General Procedure for the Synthesis of 12. A reaction flask with appropriate coumarin-3-carboxylic acid (**2**, 1 mmol), acenaphthenequinone (**3**{*4*}, 1 mmol) and proline or 4-

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thiazolidinecarboxylic acid (**4**, 1 mmol) in methanol (10 mL) was located at the maximum energy area in the ultrasonic bath and the surface of the reactants was placed slightly lower than the level of the water. The mixture was subjected to ultrasonic irradiation of low power at 50 °C for about 45−60 min until the completion of the reaction during which the product precipitated from the reaction mixture, which was filtered and dried to obtain pure **12**.

Compound ***12****{1,4,1}*. Obtained as colorless solid; yield 90%; mp 197−198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81−2.00 (m, 3H), 2.68−2.80 (m, 2H), 3.13−3.18 (m, 2H), 3.24 (dd, J = 11.4, 3.0 Hz, 1H), 4.23 (d, J = 11.4 Hz, 1H), 4.72−4.76 (m, 1H), 6.33 (d, J = 7.5 Hz, 1H), 6.94−7.02 (m, 2H), 7.58−7.63 (m, 1H), 7.70−7.80 (m, 2H), 7.87 (d, J = 6.9 Hz, 1H), 7.97 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 26.4, 33.9, 42.8, 48.6, 51.6, 68.1, 80.2, 117.1, 117.3, 122.3, 122.4, 123.4, 126.0, 127.3,128.0, 128.3, 128.5, 130.7, 131.3, 131.4, 136.0, 143.0, 151.0, 167.8, 201.7 ppm; Anal. Calcd for $C_{25}H_{19}NO_3$ C, 78.72; H, 5.02; N, 3.67; Found C, 78.79; H, 4.93; N, 3.63.

Compound ***12****{1,4,2}:* Obtained as colorless solid; yield 92%; mp 226−227 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98 (dd, J = 10.5, 7.2 Hz, 1H), 3.41 (d, J = 9.9 Hz, 1H), 3.55 (dd, J = 10.8, 7.2 Hz, 1H), 3.86 (d, J = 9.9 Hz, 1H), 4.08−4.16 (m, 2H), 4.91 (t, J = 6.9 Hz, 1H), 6.00 (d, J = 7.5 Hz, 1H), 6.46−6.51 (m, 1H), 6.99−7.09 (m, 2H), 7.60−7.66 (m, 2H), 7.81−7.86 (m, 1H), 8.01 (d, J = 7.5 Hz, 2H), 8.09−8.11 (m, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) δ 39.3, 46.2, 47.6, 56.0, 70.8, 80.0, 117.1, 117.4, 122.3, 122.4, 123.7, 126.3, 127.3, 128.6, 128.7, 129.4, 130.6, 130.8, 131.5, 135.3, 143.0, 151.3, 166.0, 203.0 ppm; Anal. Calcd for $C_{24}H_{17}NO_3S$ C, 72.16; H, 4.29; N, 3.51; Found C, 72.19; H, 4.33; N, 3.49.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic characterization of **5** and **12** and ^{1}H and ^{13}C spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: raju.ranjithkumar@gmail.com. Phone: +919655591445.

Notes

The authors declare no competing financial interest.

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