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Efficient and Short Route for the Regioselective Synthesis of Highly Substituted, Angularly Fused Furano-, Pyrano-, and Pyrrolocoumarin/Quinolone Derivatives by Metal-Mediated Cyclization

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EFFICIENT AND SHORT ROUTE FOR THE REGIOSELECTIVE SYNTHESIS OF HIGHLY SUBSTITUTED, ANGULARLY FUSED FURANO-, PYRANO-, AND PYRROLOCOUMARIN/QUINOLONE DERIVATIVES BY METAL-MEDIATED CYCLIZATION

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A one-step efficacious method for the construction of a variety of substituted furano-, pyrano-, and pyrrolocoumarins and pyrroloquinolones in good to excellent yields has been developed.

Keywords: Claisen rearrangement; heterocycle; Lewis acid; palladium catalyst; regioselective cyclization

Many natural products contain coumarin moieties, and their analogs possess a wide range of valuable pharmacological or industrial relevance.[1,2] In particular, pyranoindole-bearing heterocycles[3] have been used extensively for their antibacterial, monoamine oxidase (MAO) inhibitory, and anthelmintic activities.[4] Both linearly and angularly fused furocoumarins are also important as photochemotherapeutic agents that are used to treat a variety of skin diseases, blocking cell growth and replication.[5,6] Moreover, many pyrano- and furocoumarins are isolated from natural sources and are reported to have a variety of biological activities.[1,7] Trioxsalen has photodynamic activity and is used in the treatment of leucoderma.[1] Furanocoumarins such as pimpinellin, isopimpinellin, bergaptene, and isobergaptene display high insect-antifeedant activity.[8]

A number of synthetic methodologies have been developed for the synthesis of benzofuran and benzopyran heterocycles.[9–13] Pd(II)-catalyzed reactions of 2-allylphenols are an important methodology.[14] The pioneering work of Hosokawa and Murahashi demonstrated the feasibility of this useful reaction including the influence of various factors such as additives and ligands on the Pd(II) salt on the regioselectivity.[15,16] Larock and coworkers reported that a catalytic amount of $Pd(dba)_2$ in the presence of oxygen and dimethylsulfoxide (DMSO) afforded benzopyrans as major products from *o*-allylic phenols.[17] Subsequently, Khan et al. reported the regioselective synthesis of tribromobenzofuran and pyran derivatives

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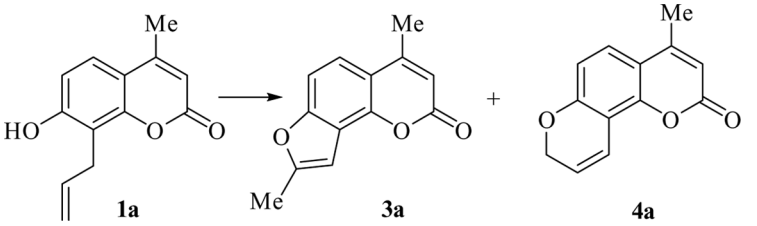
via Pd(II)-catalyzed oxidative cyclization.[18] In continuation of our effort to synthesize polycondensed coumarin derivatives,[19,20] we have very recently reported pyrrolocoumarin and quinolone derivatives from the acetylenic amines by Cu(I)-[21] and gold-catalyzed[22] cyclizations. In this communication, we report a short route for the regioselective synthesis of angularly fused furano-, pyrano-, and pyrrolocoumarin derivatives by Pd(II)- or Lewis acid–catalyzed cyclization strategy.

The requisite precursors **1a** and **b** were prepared according to standard published procedure.[23] When 8-allyl-7-hydroxy coumarin derivative **1a** was subjected to palladium(II)-catalyzed oxidative cyclization in the presence of $PdCl_2$ (4 mol%), $Cu(acac)_2 \cdot H_2O$ (3 equiv) and LiCl (3 equiv) in DMF–water (9:1) at 25 °C for 3 h[18] furnished a 70% overall yield of furanocoumarin **3a** and pyranocoumarin derivative **4a** in a 35:65 ratio. The formation of the furanocoumarin and pyranocoumarin may proceed through a 5-exo-trig and a 6-endo-trig modes of cyclization respectively. The two modes of cyclization compete, and the endo-selectivity predominates over the exo-selectivity as expected. Pleasingly, when the same reaction is performed under the same reaction conditions but with changing the temperature from 25 °C to 80 °C, the overall yield reaches to 80%, along with a dramatic change in the exo- vs. endo-selectivity. The ratio becomes 20:80 (i.e., the yield of the pyranocoumarin increases from 65% to 80% and thereby lowers the yield of the furanocoumarin from 35 to 20%). The outcome of this reaction and the mechanistic rationalization is quite interesting. When the reaction was conducted in the presence of $PdCl_2$ (4 mol%), $CuCl_2$ (0.5 equiv), and O_2 (bubbling) in methanol–water (9:1) at room temperature, 63% overall yield of **3a** and **4a** with reversed regioselectivity

Table 1. Palladiuim(II)-catalyzed oxidative cyclization of 8-allyl-7-hydroxy-4-methyl-2*H*-chromen-2-one (**1a**)



1a **3a** **4a**

Entry	Reaction conditions	Time (h)	Yield[a] (%) **3a** + **4a**	Ratio **3a**:**4a**
1	$PdCl_2$ (4 mol%), $Cu(acac)_2 \cdot H_2O$ (3 eq), LiCl (3 eq), DMF–water (9:1), 25 °C	3	70	35:65
2	$PdCl_2$ (4 mol%), $Cu(acac)_2 \cdot H_2O$ (3 eq), LiCl (3 eq), DMF–water (9:1), 80 °C	1	80	20:80
3	$PdCl_2$ (4 mol%), $CuCl_2$ (0.5 eq), O_2 (bubbling), MeOH-water (9:1), 25 °C	3.5	63	60:40
4	$Pd(acac)_2$ (5 mol%), $KHCO_3$ (0.5 eq), air, DMF–water (9:1), 80 °C	12	65	19:81
5	$Pd(acac)_2$ (2 mol%), $Cu(acac)_2 \cdot H_2O$ (0.5 eq), O_2 (bubbling), MeOH-water (9:1), 60 °C	2.5	67	70:30

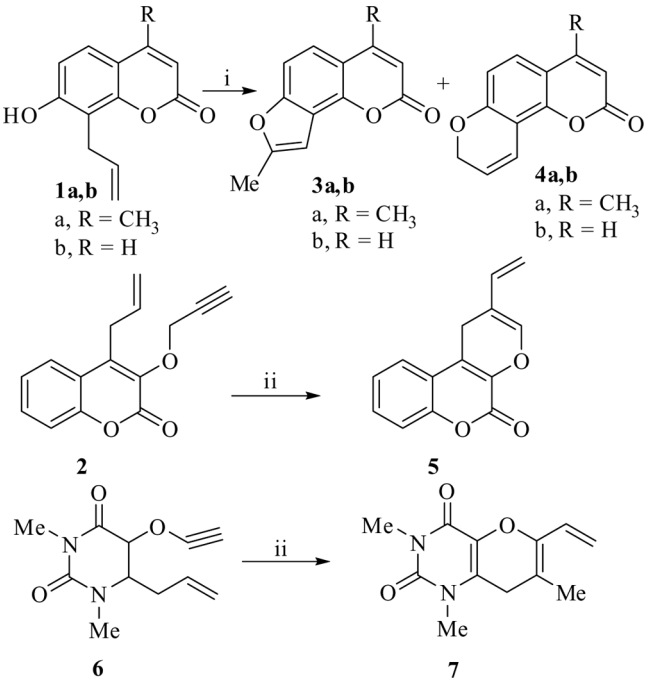
[a]Overall yield.

(60:40) was obtained. The same observation was also made when **1b** was subjected to the same aforesaid reaction conditions. The results are summarized in Table 1.

The aforesaid result for the construction of furano- and pyranocoumarin derivatives by the implementation of Pd-mediated intramolecular cyclization turned our attention toward the synthesis of potentially bioactive fused pyranocoumarins. For this purpose, the required starting material **2** was prepared according to a previously published procedure.[24] Substrate **2** bearing allyl and alkynyl moieties is an excellent precursor for the ring closing metathesis (RCM) reaction where seven-membered ring heterocycles are expected to be formed. Pd-mediated cyclization of this type of precursor also gives a similar type of the seven-membered heterocyclic ring, as expected from the RCM reaction.[25] Here we opted for a methodology of Pd-mediated cyclization where a six-membered heterocyclic skeleton is formed.

The reaction of substrate **2** is carried out in the presence of $Pd(acac)_2$, a catalytic amount of AcOH, and $(o\text{-tolyl})_3P$ as cocatalyst in boiling CH_3CN for 1 h to afford the six-membered heterocycle **5** in 82% yield. Addition of excess AcOH gave the deprogylated product. Excess cocatalyst gave a complicated reaction mixture. After having achieved satisfactory result on the coumarin system, we explored this methodology on pyrimidine system **6**, which also afforded pyranopyrimidine **7** in 80% yield (Scheme 1).

It is well known that generally nitrogenated polycyclic compounds possess greater capacity to bind with DNA and replication-related enzymes,[26] and this

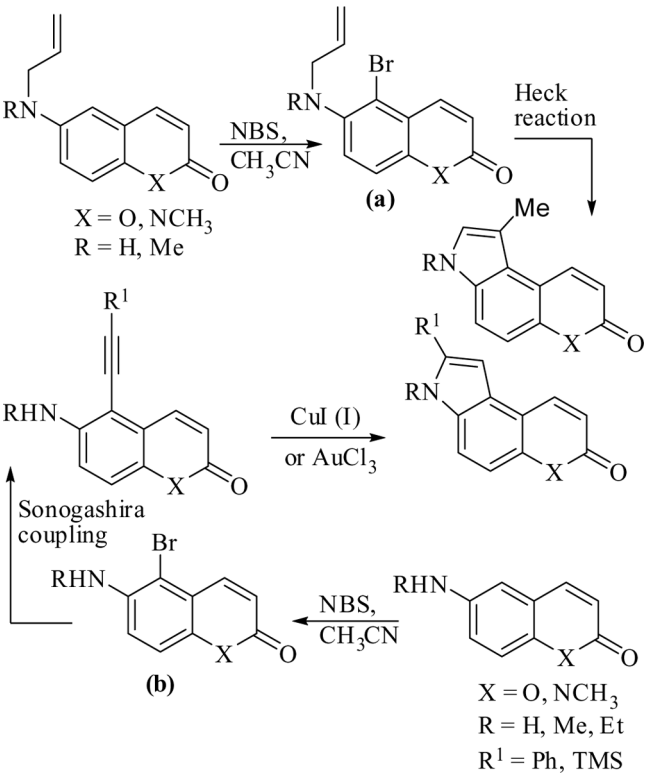


Scheme 1. Synthesis of furano- and pyranocoumarin derivatives. Reagent and conditions: (i) $PdCl_2$ (4 mol%), $Cu(acac)_2 \cdot H_2O$ (3 eq), LiCl (3 equiv), DMF-water (9:1), rt, 3 h (ii) $Pd(acac)_2$ (20 mol%), $(o\text{-tolyl})_3P$, acetic acid, acetonitrile, reflux, 1 h.

prompted us to undertake the synthesis of pyrrolocoumarin and quinolone derivatives from N-allyl coumarin and quinolone derivatives in one step. Recently, we reported pyrrolo coumarin and quinolone derivatives by the Heck coupling reaction[27] and also by CuI(I)-[21] or gold-catalyzed[22] cycloisomerization (Scheme 2).

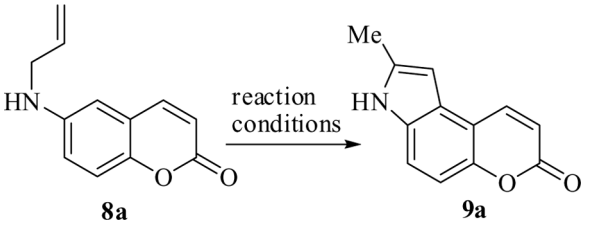
From Scheme 2, it is clear that the synthetic routes of variedly substituted pyrrolocoumarin derivatives are quite long and the required starting materials and reagents are expensive. Therefore, this led us to explore a shorter as well as a cheaper route. For this purpose, the starting materials **8a**–**c** were prepared by the conventional allylation reaction. Initial attempts at cyclization under thermal conditions were of no avail. Starting materials remained unchanged. We then carried out the cyclization reaction mediated by Pd with the three effective conditions described in Table 2.

However, only deallylated product was obtained in each case. Subsequently, we turned our attention to the cyclization in the presence of Lewis acid catalysts. Initially, we conducted the reaction by using $BF_3 \cdot Et_2O$ as the catalyst (which is mostly used in this type of aromatic aza-Claisen rearrangement). Unfortunately, this protocol also failed to give an appreciable amount of the desired product (only <5% of the cyclized product was obtained). However, when the reaction was performed in



Scheme 2. Synthesis of pyrrolo coumarin and quinolone derivatives by (a) Heck reaction and (b) Cu(I)- or $AuCl_3$-catalyzed cyclization.

Table 2. Optimization of cyclization reaction of **8a** to **9a**



8a **9a**

Entry	Reaction conditions	Yield (%)
1	$PdCl_2$ (4 mol%), Cu $(acac)_2 \cdot H_2O$ (3 equiv), LiCl (3 equiv), DMF–water, rt, 1 h	dp
2	Pd $(acac)_2$ (2 mol%), Cu $(acac)_2 \cdot H_2O$ (1 equiv), acetic acid, reflux, 1 h	dp
3	Pd $(acac)_2$ (2 mol%), $(o\text{-tolyl})_3P$ (4 mol%), acetic acid (1 equiv), acetonitrile, 60 °C, 2.5 h	dp
4	$BF_3 \cdot Et_2O$ (1.5 equiv), xylene, reflux, 5–6 h	<5
5	$AlCl_3$ (1.5 equiv), dichlorobenzene, reflux, 1 h	85
6	$SnCl_4$ (2 equiv), toluene, reflux, 3.5 h	nr

dp – deallylated product.
nr – no reaction.

$AlCl_3$ in *o*-dichlorobenzene (DCB) at refluxing conditions for 1 h, the pyrrolo coumarin derivative **9a** was obtained in 85% yield. We attempted this reaction using another Lewis acid, $SnCl_4$, but in this case the reaction did not proceed at all. Therefore, $AlCl_3$-catalyzed reaction in *o*-DCB was employed as the optimized condition. Other substrates, **8b** and **8c**, were subjected to this optimized condition to give the corresponding cyclized products in excellent yields. The results are presented in Table 3.

The mechanistic rationale of the reaction attracts attention because two consecutive reactions occur, leading to the ultimate synthesis of the potentially bioactive pyrrolocoumarin and pyrroloquinolone derivatives **7a**–**c** in excellent yields. Usually, aromatic aza-Claisen rearrangement affords the corresponding C-allyl products in case of the N-alkyl protected-N-allyl derivatives, but, in our case, the aza-Claisen rearrangement and subsequent cyclization occur simultaneously.

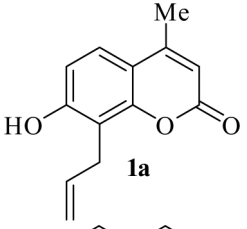
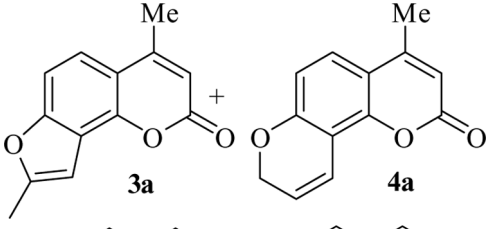
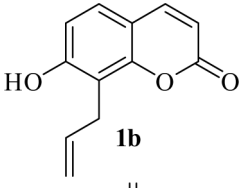
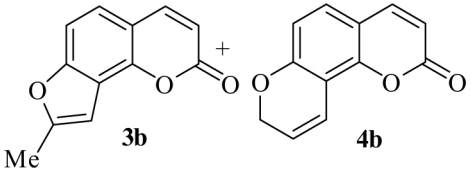
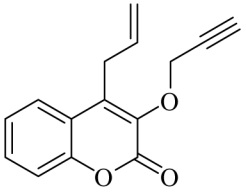
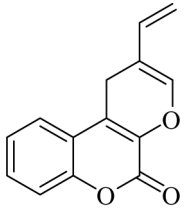
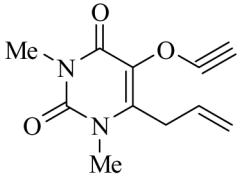
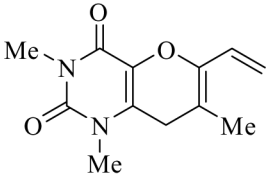
In summary, we have developed an efficient regioselective protocol to synthesize a series of angularly fused furano-, pyrano-, and pyrrolocoumarin derivatives by Pd(II)-catalyzed oxidative cyclization or by Lewis acid–mediated cyclization in one step. For the oxidative cyclization, air is the sole reoxidant for palladium. The method is simple, straightforward, and high yielding.

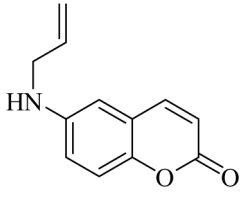
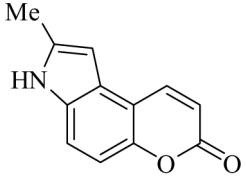
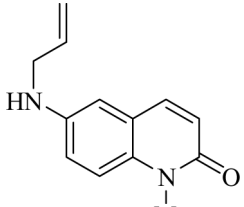
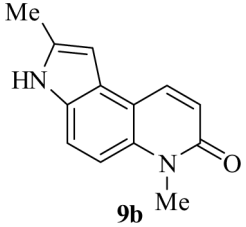
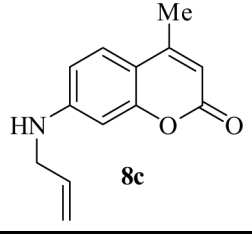
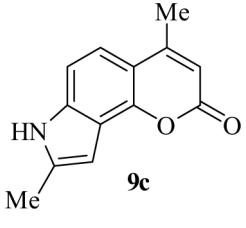
EXPERIMENTAL

General

Melting points were determined in open capillaries and are uncorrected. Infrared (IR) spectra were run for KBr discs on a Perkin-Elmer 120–000A apparatus

Table 3. Synthesis of furano-, pyrano- and pyrrolocoumarin and quinolone derivatives

Entry	Starting material	Product	Reaction condition	Yield (%)
1	 **1a**	 **3a** **4a**	A	70 (**3a:4a** 35:65)
2	 **1b**	 **3b** **4b**	A	75 (**3b**:**4b** 36:64)
3	 **2**	 **5**	B	82
4	 **6**	 **7**	B	80

5	 **8a**	 **9a**	C	85
6	 **8b**	 **9b**	C	76
7	 **8c**	 **9c**	C	83

A = $PdCl_2$ (4 mol %), $Cu(acac)_2 \cdot H_2O$ (3 equiv), LiCl (3 equiv), DMF-water (9:1), rt, 3 h.
B = $Pd(acac)_2$ (20 mol%), (*0*-tolyl)$_3$P (40 mol %), acetic acid (10 equiv), CH_3CN, 110 °C, 1 h.
C = $AlCl_3$ (1.5 equiv), dichlorobenzene, reflux, 1 h.

(ν_{max} in cm^{-1}), and ^1H NMR spectra were determined for solutions in $CDCl_3$ with tetramethylsilane (TMS) as internal standard on a Bruker DPX-400. ^{13}C NMR spectra were determined for solutions in $CDCl_3$ on a Bruker DPX-400. High-resolution mass spectra (HRMS) were recorded on a Qtof Micro YA263 instrument. Silica gel (60–120 mesh) was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for thin-layer chromatography (TLC). Petroleum ether refers to the fraction between 60 and 80 °C.

Typical Procedure for the Oxidative Cyclization of Compound 1a

LiCl (58.81 mg, 1.39 mmol), $Cu(acac)_2 \cdot H_2O$ (277 mg, 1.39 mmol), and $PdCl_2$ (3.28 mg, 4 mol%) were added to a solution of compound **1a** (100 mg, 0.46 mmol) in DMF–H_2O (9 mL : 1 mL). The suspension was stirred for 3 h at rt. The reaction mixture was poured into water (30 mL) and extracted with $CHCl_3$ (20 mL). The organic layer was washed with water (15 ml) and brine (15 ml) and then dried (Na_2SO_4), and the solvent was removed. The residue was purified by column chromatography over silica gel to afford **3a** (24.3 mg, 24.5%) and **4a** (45 mg, 45.5%). Overall yield: 70% (ratio **3a**:**4a** = 35:65). Compound **1b** was subjected to the same reaction condition to afford products **3b** and **4b**.

Compound 3a. White solid, mp 182–184 °C; IR (KBr, cm^{-1}) ν_{max}: 1730, 1601; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.48 (s, 3H), 2.50 (s, 3H), 6.24 (s, 1H), 6.72 (s, 1H), 7.33 (d, 1H, $J = 8.7$ Hz), 7.42 (d, 1H, $J = 8.7$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 14.5, 19.8, 100.6, 108.2, 113, 114.6, 119.6, 120.3, 147.6, 152.8, 156.7, 157.2, 160.8. MS (m/z): 214 [M^+]. Anal. calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71%. Found: C, 72.98; H, 4.57%. Solvent of recrystallization: EtOAc/hexane (8:2), 2 mL/100 mg.

Compound 4a. White solid, mp 157–159 °C; IR (KBr, cm^{-1}) ν_{max}: 1726, 1601; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.36 (s, 3H), 4.92 (d, 2H, $J = 2.0$ Hz), 5.83–5.87 (m, 1H), 6.12 (s, 1H), 6.72 (d, 1H, $J = 8.7$ Hz), 6.97 (d, 1H, $J = 9.9$ Hz), 7.32 (d, 1H, $J = 8.7$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 19.1, 66.4, 111.7, 112.3, 112.9, 114.2, 118.1, 122.2, 124.9, 146.4, 152.6, 157.3, 160.8; MS (m/z): 214 [M^+]. Anal. calcd. for $C_{13}H_{10}O_3$: C, 72.89; H, 4.71%. Found: C, 72.78; H, 4.77%. Solvent of recrystallization: EtOAc/hexane (8:2), 2 mL/100 mg.

Compound 3b. White solid, mp 148–150 °C; IR (KBr, cm^{-1}) ν_{max}: 1728, 1601; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.49 (s, 3H), 6.35 (d, 1H, $J = 9.4$ Hz), 6.72 (s, 1H), 7.32 (d, 2H, $J = 8.5$ Hz), 7.77 (d, 1H, $J = 9.4$ Hz); MS (m/z): 200 [M^+]. Anal. calcd. for $C_{12}H_8O_3$: C, 72.00; H, 4.03%. Found: C, 71.89; H, 4.15%. Solvent of recrystallization: EtOAc/hexane (8:2), 2 mL/100 mg.

Compound 4b. White solid, mp 151–153 °C; IR (KBr, cm^{-1}) ν_{max}: 1730, 1603; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.75 (s, 2H), 5.83–5.87 (m, 1H), 6.22 (d, 1H, $J = 9.2$ Hz), 6.69 (d, 1H, $J = 8.5$ Hz), 6.95 (d, 1H, $J = 10.2$ Hz), 7.19 (d, 1H, $J = 8.6$ Hz), 7.58 (d, 1H, $J = 9.2$ Hz); MS (m/z): 200 [M^+]. Anal. calcd. for $C_{12}H_8O_3$: C, 72.00; H, 4.03%. Found: C, 72.28; H, 3.92%. Solvent of recrystallization: EtOAc/hexane (8:2), 2 mL/100 mg.

Typical Procedure for the Pd-Catalyzed Cyclization of 2 and 6

A solution of (*0*-tolyl)$_3$P (51.53 mg, 0.166 mmol) and Pd(acac)$_2$ (18.59 mg, 0.083 mmol) in acetonitrile (8 mL) was refluxed for 20 min. Then acetic acid (0.25 mL) was added to it and refluxed for another 5 min. A solution of compound **2** (100 mg, 0.416 mmol) in acetonitrile (5 mL) was added to the reaction mixture and refluxed for an additional 1 h. After cooling the reaction mixture, solvent was evaporated, the mixture was neutralized with $NaHCO_3$ solution, and the product was extracted with $CHCl_3$ (15 mL). The organic extract was washed with water (10 ml) and brine (10 ml), dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography over silica gel to afford the cyclized product **5** in 82% yield. Compound **6** was subjected to the same reaction condition to afford product **7**.

Compound 5. White solid, mp 189–191 °C; IR (KBr, cm^{-1}) ν_{max}: 2922, 1692, 1223; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.59–3.61 (m, 2H), 5.11–5.17 (m, 2H), 5.89–5.98 (m, 1H), 6.27 (s, 1H), 7.28–7.35 (m, 2H), 7.38–7.42 (m, 1H), 7.56 (dd, 1H, $J = 7.9$, 1.4 Hz); MS (m/z): 226 [M$^+$]. Anal. calcd. for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46%. Found: C, 74.65; H, 4.21%. Solvent of recrystallization: $CHCl_3$/hexane (8:2), 2 mL/100 mg.

Compound 7. White solid, mp 166–168 °C; IR (KBr, cm^{-1}) ν_{max}: 2922, 1694, 1637; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.59 (t, 3H, $J = 1.8$ Hz), 3.38 (s, 3H), 3.39 (s, 3H), 3.46–3.48 (q, 2H, $J = 1.8$ Hz), 5.11–5.21 (m, 2H), 5.83–5.90 (m, 1H); MS (m/z): 234 [M$^+$]. Anal. calcd. for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02%; N, 11.96%. Found: C, 61.82; H, 5.93%; N, 12.03%. Solvent of recrystallization: $CHCl_3$/hexane (8:2), 2 mL/100 mg.

Typical Procedure for the Lewis Acid–Catalyzed Cyclization of 8a

$AlCl_3$ (148.5 mg, 0.745 mmol) was added to a solution of compound **8a** (100 mg, 0.496 mmol) in DCB (5 mL) and refluxed for 1 h. The reaction mixture was cooled and diluted with slow addition of water (30 mL) and extracted with $CHCl_3$ (20 mL). The organic layer was washed with water (15 ml) and brine (15 ml) and then dried (Na_2SO_4), and the solvent was removed. The residue was purified by column chromatography over silica gel to afford **9a** (84.2 mg, 85%). Compounds **8b** and **8c** were subjected to the same reaction condition to afford products **9b** and **9c**.

Compound 9a. White solid, mp 272–274 °C; IR (KBr, cm^{-1}) ν_{max}: 3233, 1679, 1599; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.44 (s, 3H), 6.41 (d, 1H, $J = 9.3$ Hz), 6.61 (s, 1H), 7.01 (d, 1H, $J = 8.4$ Hz), 7.51 (d, 1H, $J = 8.4$ Hz), 8.38 (d, 1H, $J = 9.3$ Hz), 11.40 (s, 1H); MS (m/z): 199 [M$^+$]. Anal. calcd. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03%. Found: C, 72.09; H, 4.33; N, 7.13%. Solvent of recrystallization: EtOH, 2 mL/100 mg.

Compound 9b. Yellow solid, mp 242–244 °C; IR (KBr, cm^{-1}) ν_{max}: 3243, 1642, 1585; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.44 (s, 3H), 3.66 (s, 3H), 5.56 (s, 1H), 6.57 (d, 1H, $J = 9.4$ Hz), 7.18 (d, 1H, $J = 8.8$ Hz), 7.55 (d, 1H, $J = 8.8$ Hz), 8.21 (d, 1H, $J = 9.4$ Hz), 11.40 (s, 1H); MS (m/z): 212 [M$^+$]. Anal. calcd. for

$C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20%. Found: C, 73.26; H, 5.77; N, 13.28%. Solvent of recrystallization: EtOH, 2 mL/100 mg.

Compound 9c. Yellow solid, mp 304–306 °C; IR (KBr, cm^{-1}) ν_{max}: 3267, 1691, 1598; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.43 (s, 3H), 2.46 (s, 3H), 6.18 (s, 1H), 6.43 (s, 1H), 7.27 (d, 1H, $J = 8.6$ Hz), 7.35 (d, 1H, $J = 8.6$ Hz), 11.52 (s, 1H); MS (m/z): 213 [M^+]. Anal. calcd. for $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57%. Found: C, 73.51; H, 5.13; N, 6.77%. Solvent of recrystallization: EtOH, 2 mL/100 mg.

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