ACS Combinatorial Science

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Efficient Synthesis of Functionalized Benzo[*b*][1,8]naphthyridine Derivatives via Three-Component Reaction Catalyzed by L-Proline

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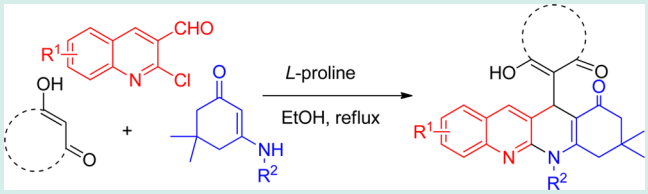
Supporting Information

ABSTRACT: A facile and efficient one-pot procedure for the preparation of functionalized benzo[*b*][1,8]naphthyridine derivatives by three-component reaction of 2-chloroquinoline-3-carbaldehyde, 1,3-dicarbonyl compounds, and enaminones catalyzed by L-proline is described. This new protocol has the advantages of environmental friendliness, good yields, and convenient operation.



KEYWORDS: *benzo[b][1,8]naphthyridine, three-component reaction, L-proline*

INTRODUCTION

1,8-Naphthyridine, tetrahydro-1,8-naphthyridine, and its annelated derivatives are present in many natural and synthetic compounds. 1,8-Naphthyridine derivatives show a broad range of interesting physiological activities, such as anti-inflammatory,[1] analgesic,[2] antiaggressive,[3] anticancer,[4] antibacterial,[5] antitumor,[6] antihypertensive,[7] and antiallergitic.[8] Although many synthetic methods for the preparation of 1,8-naphthyridines have been reported, examination of literature reveals considerable scope for refinement of the existing procedures.[9] Thus, because of their great biological importance and employment of these compounds as starting material for the synthesis of various linearly tri- and tetracyclic heterocycles of biological interest, the development of effective ways to synthesize these compounds utilizing inexpensive reagents continues to be an active area of research for synthetic organic chemists.[10]

Multicomponent reactions (MCRs) are chemical transformations in which three or more different starting materials combine together via a one-pot procedure to give a final complex product. Obviation of the need for isolation and purification of the intermediates results in maximization of yields and reduction of waste, and thus renders the protocols ecofriendly.[11] These features make multicomponent reactions well suited for the construction of complex molecules from readily available starting materials.[12]

Small organic molecules like L-proline, and their derivatives are readily available commercial catalysts and have been used in various transformations with excellent yields.[13] L-Proline has been found to be very effective in enamine-based direct catalytic asymmetric Aldol,[14] Mannich,[15] Michael,[16] Diels–Alder,[17] α-amination reaction,[18] Knoevenagel-type reactions,[19] unsymmetric Biginelli reaction,[20] and some domino reactions.[21] Recently, we have reported the synthesis of a series of heterocycles using MCRs or domino reactions catalyzed by L-proline.[22] In the current paper, we report a novel three-component domino reaction for the synthesis of functionalized benzo[*b*][1,8]-naphthyridine derivatives using L-proline as the catalyst.

RESULTS AND DISCUSSION

We initially evaluated the three-component reaction of the 2-chloroquinoline-3-carbaldehyde **1**{*1*}, 4-hydroxycoumarin **2**{*1*}, and enamine **3**{*1*}(Scheme 1). The reaction mixture, which was composed of a 1:1:1 mixture of **1**{*1*}, **2**{*1*}, and **3**{*3*}, was tested under a variety of different conditions. The effects of solvents and catalysts were evaluated for this reaction, and the results are summarized in Table 1. It was found that when the reaction was carried out in water without any catalyst the yield of product was low (Table 1, entry 1). Ethanol as solvent provided higher yields than those using other organic solvents (CH_3CN, THF, DMF, $CHCl_3$, and toluene) (Table 1, entry 7 vs entries 2–6). To improve the yields, we examined this reaction using different catalysts. Acid (*p*-toluenesulfonic acid, *p*-TSA) and some bases (Cs_2CO_3, NaOH, and piperidine) can not catalyze this reaction (Table 1, entries 8–11). However, L-proline was identified as the optimal catalyst with **4**{*1,1,1*} in 80% yield (Table 1, entry 12). So L-proline was chosen as the catalyst for this reaction. We also evaluated the amount of L-proline required for this reaction. The results from Table 1 (entries 12–14) show that 10 mol % L-proline at reflux in ethanol is optimal for the reaction.

The optimized reaction conditions were then tested for library construction with seven 2-chloroquinoline-3-carbaldehydes **1**{*1*–*7*}, four 1,3-dicarbonyl compounds **2**{*1*–*4*}, and 11 enamines **3**{1-11} (Figure 1). The corresponding functionalized benzo[*b*]-[1,8]naphthyridine derivatives **4** were obtained in good yields at refluxing temperature in ethanol catalyzed by L-proline. The results are summarized in Table 2. This protocol was efficient with 1,3-dicarbonyl compounds with either 1,3-diketones or β-ketoesters (such as 4-hydroxycoumarin, 4-hydroxy-6-methyl-2*H*-pyran-2-one, 4-hydroxyquinolin-2(1*H*)-one). However, when other 1,3-diketones such as 2-hydroxynaphthalene-1,4-dione,

Received: December 2, 2013
Revised: March 19, 2014
Published: March 26, 2014

Scheme 1. Model Reaction

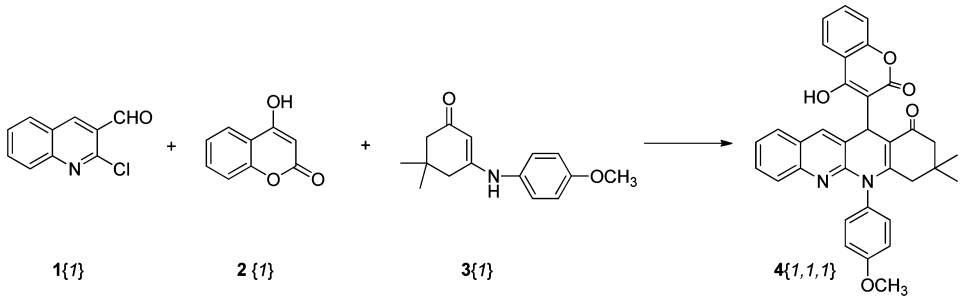


Table 1. Optimizing the Reaction Conditions for the Synthesis of 4{1,1,1}

entry	solvent	catalyst (mol %)	temperature (°C)	time (h)	yield[a] (%)
1	H_2O	no	reflux	8	30
2	CH_3CN	no	reflux	8	52
3	THF	no	reflux	8	53
4	DMF	no	120	8	22
5	$CHCl_3$	no	reflux	8	26
6	Toluene	no	115	8	46
7	EtOH	no	reflux	8	58
8	EOH	*p*-TSA (10%)	reflux	8	52
9	EtOH	Cs_2CO_3 (10%)	reflux	8	27
10	EtOH	NaOH (10%)	reflux	8	28
11	EtOH	piperidine (10%)	reflux	8	28
12	EtOH	L-proline (10%)	reflux	8	80
13	EtOH	L-proline (5%)	reflux	8	73
14	EtOH	L-proline (15%)	reflux	8	79

[a]Yield was determined by HPLC-MS.

5,5-dimethylcyclohexane-1,3-dione, cyclohexane-1,3-dione, furan-2,4(3*H*,5*H*)-dione, cyclopentane-1,3-dione and 1*H*-indene-1,3(2*H*)-dione were used the products were obtained in low yields (**4**{*2,4,7*} and **4**{*5,4,5*}) or complex mixture were obtained. It was also found that phenyl groups bearing either electron-withdrawing or electron-donating groups on the enaminone ring, were tolerated under the reaction conditions, leading to the final products in satisfactory yields (up to 87%). Because the enaminones were prepared previously from the reaction of dimedone with arylamine, we thought enaminones might no need prior preparation, but could be formed in the reaction system. So the four-component reaction of 6-*tert*-butyl-2-chloroquinoline-3-carbaldehyde **1**{*7*}, 4-hydroxycoumarin **2**{*1*}, dimedone, and aniline was carried out under the optimal conditions. However, the product **4**{*7,1,5*} was obtained only in low yield (42% isolated yield) (Scheme 2).

The structures of all products **4** were characterized using IR, ^{1}H NMR and ^{13}C NMR spectroscopies, and HRMS analysis. Compound **4**{*1,1,1*} exhibited characteristic IR stretching frequencies in the 3461, 1749, 1719, and 1644 cm^{-1} regions for OH, C═O(ester), C═O(ketone), and C═C, respectively. In the ^{1}H NMR spectrum of compound **4**{*1,1,1*} the hydroxy group proton show a singlet at δ 12.25 ppm. The methyl group protons show two singlets at δ 0.87 and 0.76 ppm because of the two methyl groups. A singlet appearing at δ 5.77 ppm was assigned to the C-12 proton of the pyridine ring. In addition, HRMS analyses were consistent with the structures. The structure of compound **4**{*1,1,1*} was further confirmed by X-ray diffraction analysis[23] (Figure 2).

Although the detailed mechanism of this reaction remains to be fully clarified, the formation of compound **4** could be explained by the reaction sequence in Scheme 3. We suggest that L-proline catalyze the formation of iminum **5** in a reversible reaction with the 2-chloroquinoline-3-carbaldehyde **1**. The higher reactivity of the iminum ion compared with the carbonyl species could faciliate Knoevenagel condensation with 4-hydroxycoumarin **2**, via intermediate **6**, and after the elimination of L-proline, **7** might be produced as an intermediate. The addition of **7** to enaminones **3** then could funish the intermediate product **8**, which upon intermolecular cyclization would give rise to products **4**.

CONCLUSION

In conclusion, we have developed a simple and efficient method for the preparation of functionalized benzo[*b*][1,8]naphthyridine derivatives by three-component reaction of 2-chloroquinoline-3-carbaldehyde, 1,3-dicarbonyl compounds and enaminones catalyzed by L-proline. This method has the advantages of good yields and convenient procedure.

EXPERIMENTAL PROCEDURES

Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H NMR and ^{13}C NMR were determined on Varian Invoa-400 MHz or Invoa-300 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS analyses were carried out using Bruker micrOTOF-Q or Accurate-Mass TOF LC/MS instrument.

General Procedure for the Synthesis of 4. A dry 50 mL flask was charged with 2-chloroquinoline-3-carbaldehyde **1** (1 nmol), 1,3-dicarbonyl compounds **2** (1 mmol), enaminones **3** (1 mmol), L-proline (0.1 mmol, 10 mol %), and ethanol (5 mL). The mixture was stirred at refluxing temperature for 8 h. After completion of the reaction (confirmed by TLC), the reaction mixture was cooled to room temperature. The crystalline solids were collected and purified by recrystallization from DMF and water to give the pure products **4**.

2-(4-Hydroxy-2-oxo-2H-chromen-3-yl)-5-(4-methoxyphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2H)-one 4{1,1,1}: Red solid; m.p. 228−230 °C; IR (KBr, ν, cm^{-1}) 3461, 2935, 1749, 1719, 1644, 1552, 1379, 1335, 1263, 1164, 1039, 808, 787, 744; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 12.25 (s, 1H, OH), 7.97 (d, *J* = 8.0 Hz, 1H, ArH), 7.94 (s, 1H, ArH), 7.68 (d, *J* = 8.0 Hz, 1H, ArH), 7.53 (t, *J* = 8.0 Hz, 1H, ArH), 7.42 (t, *J* = 7.6 Hz, 1H, ArH), 7.34−7.29 (m, 4H, ArH), 7.26 (d, *J* = 8.0 Hz, 1H, ArH), 7.22 (d, *J* = 8.8 Hz, 1H, ArH), 7.11−7.07 (m, 2H, ArH), 5.77 (s, 1H, CH), 3.82 (s, 3H, OCH_3), 2.24 (d, *J* = 17.2 Hz, 2H, CH_2), 2.05 (d, *J* = 16.4 Hz, 1H, CH), 1.94 (d, *J* = 16.8 Hz, 1H, CH), 0.87 (s, 3H, CH_3), 0.76 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 159.7, 159.3, 152.8, 151.8, 144.2, 134.5, 133.0, 132.6, 132.0, 127.8, 126.6, 124.7, 117.2, 116.7, 107.0 114.95, 107.00, 56.0,

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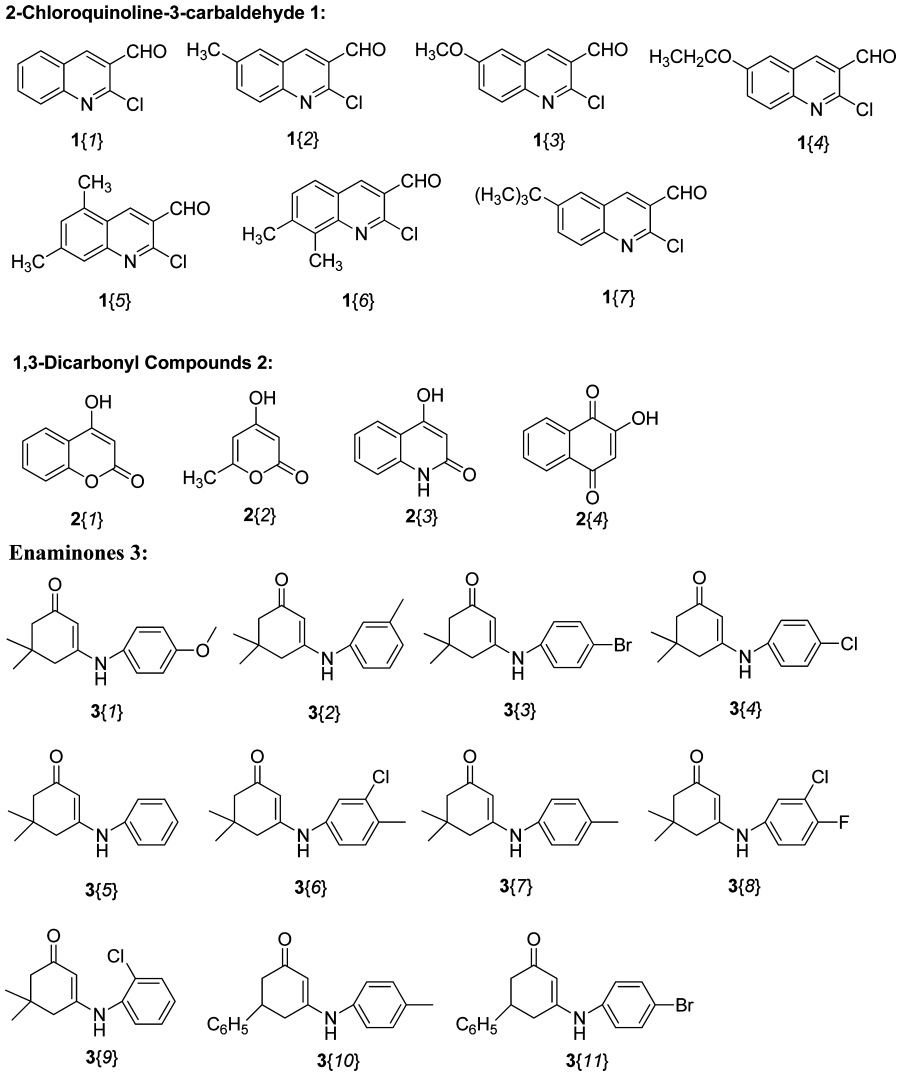
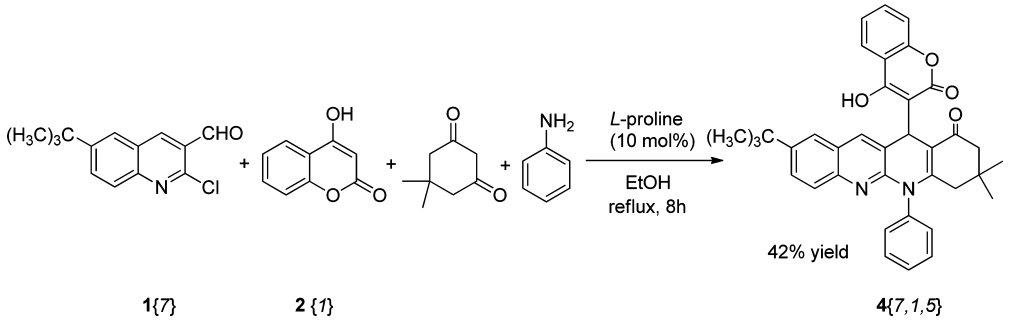


Figure 1. Diversity of reagents.

Scheme 2. Synthesis of Compound 4{*7,1,5*} via Four-Component Reaction



49.7, 42.7, 32.7, 31.4, 29.7, 27.0, 21.6; HRMS calcd for $C_{34}H_{28}N_2O_5$ $[M]^+$ 544.1998, found 544.2012.

12-(4-Hydroxy-5-methyl-2-oxo-2H-pyran-3-yl)-5-(4-methoxyphenyl)-3,3,9-trimethyl-3,4,5,12-tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2H)-one ***4****{2,2,1}:* Red solid; m.p. 238−240 °C; IR (KBr, ν, cm^{-1}) 3462, 2972, 1738, 1720, 1644, 1639, 1562, 1369, 1345, 1226, 1165, 962, 936, 765; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 11.45 (s, 1H, OH), 7.77 (s, 1H, ArH), 7.47 (s, 1H, ArH), 7.27−7.20 (m, 4H, ArH), 7.06 (d, J = 8.0 Hz, 2H, ArH), 5.94 (s, 1H, ArH), 5.59 (s, 1H, CH), 3.82 (s, 3H, CH_3O), 2.31 (s, 3H, CH_3), 2.18−2.11 (m, 2H, CH_2), 2.04 (s, 3H, CH_3), 1.96 (d, J = 16.0 Hz, 1H, CH), 1.88 (d, J = 17.6 Hz, 1H, CH), 0.86 (s, 3H, CH_3), 0.80 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 194.6, 164.4, 160.8, 158.9, 155.4, 151.3, 143.9, 135.2, 133.9, 132.9, 132.4, 131.5, 130.7, 127.4, 126.3, 123.5, 115.0, 114.6, 107.2, 100.6, 55.7, 50.0, 42.2, 32.3, 29.8, 21.3, 19.6; HRMS calcd for $C_{32}H_{30}N_2O_5$ $[M]^+$ 522.2155, found 522.2170.

12-(4-Hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3,3-dimethyl-5-(4-methylphenyl)-3,4,5,12-tetrahydrodibenzo[b,g][1,8]naphthyridin-1(2H)-one ***4****{1,3,7}:* Red solid; m.p. 254−256 °C;

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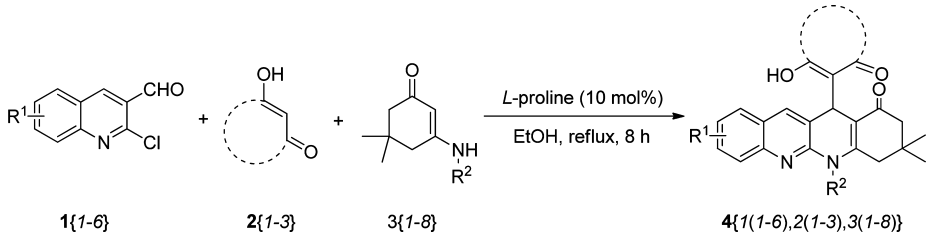
Table 2. Synthesis of Functionalized Indole Derivatives 4



1{*1-6*} **2**{*1-3*} 3{*1-8*} **4**{*1*(*1-6*),*2*(*1-3*),*3*(*1-8*)}

entry	products	isolated yield (%)	mp (°C)
1	4{*1,1,1*}	80	228−230
2	4{*1,1,2*}	79	233−234
3	4{*2,1,1*}	83	234−236
4	4{*2,1,3*}	84	246−248
5	4{*3,1,3*}	85	256−258
6	4{*4,1,4*}	83	260−262
7	4{*5,1,5*}	86	256−257
8	4{*6,1,1*}	87	244−246
9	4{*6,1,4*}	82	246−248
10	4{*6,1,5*}	85	256−258
11	4{*6,1,6*}	84	244−246
12	4{*6,1,9*}	76	236−237
13	4{*7,1,5*}	84	252−254
14	4{*2,2,1*}	82	238−240
15	4{*2,2,3*}	76	258−259
16	4{*2,2,4*}	83	256−257
17	4{*2,2,7*}	84	232−234
18	4{*3,2,3*}	84	256−257
19	4{*3,2,6*}	82	258−260
20	4{*4,2,5*}	87	254−256
21	4{*6,2,5*}	85	246−248
22	4{*7,2,7*}	86	246−248
23	4{*7,2,10*}	78	256−258
24	4{*7,2,11*}	75	260−262
25	4{*1,3,7*}	82	254−256
26	4{*2,3,1*}	85	238−240
27	4{*3,3,7*}	84	234−236
28	4{*5,3,5*}	83	254−256
29	4{*5,3,7*}	82	254−256
30	4{*5,3,8*}	76	279−280
31	4{*6,3,1*}	82	243−245
32	4{*2,4,7*}	36	258−259
33	4{*5,4,5*}	35	263−265

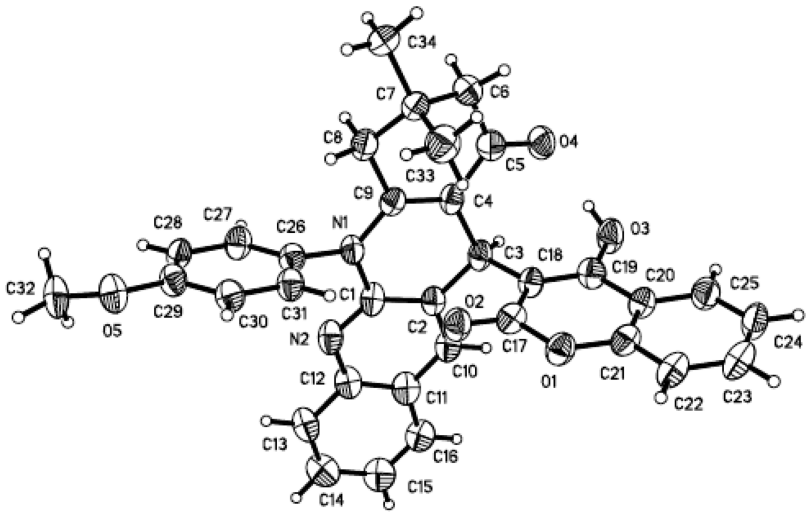


Figure 2. X-ray structure of compound 4{*1,1,1*}.

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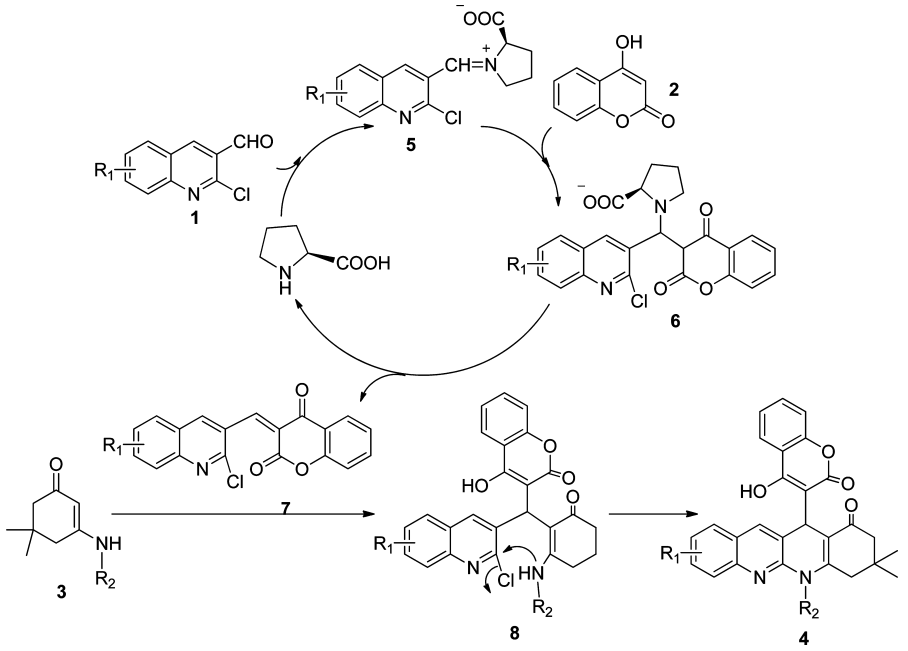
Scheme 3. Proposed Mechanism for the Synthesis of 4



IR (KBr, ν, cm^{-1}) 3463, 2812, 1680, 1506, 1458, 1380, 1329, 1255, 1160, 1102, 1034, 904, 859, 753, 671; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 11.12 (s, 1H, OH), 7.97 (s, 1H, ArH), 7.88 (s, 1H, ArH), 7.69 (d, J = 8.0 Hz, 1H, ArH), 7.48 (s, 1H, ArH), 7.44 (s, 1H, ArH), 7.40 (d, J = 7.6 Hz, 3H, ArH), 7.36 (s, 1H, ArH), 7.28 (s, 1H, ArH), 7.16 (s, 3H, ArH), 5.65 (s, 1H, CH), 2.45 (s, 3H, CH_3), 2.42 (s, 1H, CH), 2.29 (d, J = 16.0 Hz, 2H, 2 × CH), 2.11 (d, J = 16.0 Hz, 1H, CH), 1.95 (d, J = 17.2 Hz, 1H, CH), 0.91 (s, 3H, CH_3), 0.78 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm) 197.0, 162.5, 152.4, 145.2, 138.2, 137.8, 135.3, 131.4, 131.3, 131.1, 130.6, 129.8, 129.4, 127.6, 127.4, 126.5, 124.8, 123.9, 121.6, 116.1, 115.1, 42.4, 36.3, 32.4, 30.3, 29.5, 26.5, 21.3; HRMS calcd for $C_{34}H_{28}N_3O_3$ $[M - H]^+$ 526.2131, found 526.2135.

■ ASSOCIATED CONTENT

Supporting Information

The spectroscopic characterization for compounds **4** and crystallographic information file for compound **4**{*1,1,1*}. This material is available free of charge via the Internet at http://pubs.acs.org/.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by the Major Basic Research Project of the Natural Science Foundation of the Jiangsu Higher Education Institutions (No. 10KJA150049), A Project of the Natural Science Foundation of Jiangsu Province (No. BK20131160), A Project Funded by the Priority Academic Project Development of Jiangsu Higher Education Institutions and the Foundation of Key Laboratory of Organic Synthesis of Jiangsu Province (No. JSK1210).

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(23) Crystallographic data for the structure of compounds **4**{*1,1,1*} have been deposited at the Cambridge Crystallographic Data Center, and the deposit number is CCDC-990533. Copy of available meterial can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax +44 1223 336 033; e-mail deposit@ccdc.cam.ac.uk). Crystal data of **4**{*1,1,1*}: molecular formula = $C_{34}H_{28}N_2O_5$, formula weight = 544.58, (crystal system) monoclinic, (space group) $P2_1/c$, a = 8.3089(11) Å, b = 16.1429(15) Å, c = 20.651(2) Å, β = 100.411(2)°, V = 2724.3(5) Å^3, T = 293(2) K, Z = 4, D_c = 1.328 Mg m^{-3}, μ(Mo Kα) = 0.725 mm^{-1}, 9166 reflection measured, 4722 independent reflections, R_1 = 0.0691, R_2 = 0.0782.