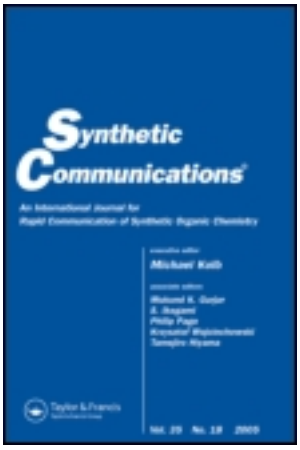

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Microwave-Assisted Synthesis of New Spiro[indoline-3,4′-quinoline] Derivatives via a One-Pot Multicomponent Reaction

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Published online: 19 Mar 2009.

To cite this article: Song-Lei Zhu , Kai Zhao , Xiao-Ming Su & Shun-Jun Ji (2009): Microwave-Assisted Synthesis of New Spiro[indoline-3,4′-quinoline] Derivatives via a One-Pot Multicomponent Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:8, 1355-1366

To link to this article: http://dx.doi.org/10.1080/00397910802527714

Synthetic Communications®, 39: 1355–1366, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802527714

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Microwave-Assisted Synthesis of New Spiro[indoline-3,4′-quinoline] Derivatives via a One-Pot Multicomponent Reaction

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Abstract: A simple and efficient synthesis of spiro[indoline-3,4′-quinoline] derivatives by a one-pot reaction of isatin, malononitrile, and enaminone under microwave irradiation was investigated. This protocol has the advantages of short reaction time, high yields of products, broad substrate scope, and easy workup procedure.

Keywords: Microwave irradiation, multicomponent reactions, spiro[indoline-3,4′-quinoline]

Multicomponent reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been used extensively in synthetic chemistry.[1] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding complicated purification operations and allowing savings of both solvents and reagents.[2] Organic reactions accelerated by microwave irradiation (MWI) have also attracted considerable attention over past years for the rapid and efficient synthesis of a variety of organic compounds.[3]

Received June 5, 2008.
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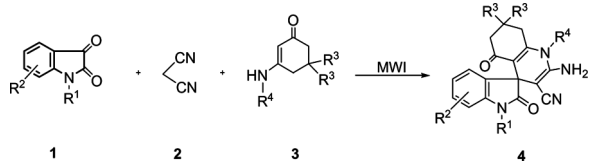
These technologies are particularly useful for the creation of diverse chemical libraries of druglike molecules for biological screening.[4]

Isatins (1*H*-indole-2,3-diones) are synthetically versatile substrates that are utilized for the synthesis of a large variety of heterocyclic compounds.[5] A number of spiro compounds derived from isatin are important pharmacophores and exhibit promising biological activities such as analgesic, fungicidal, antidepressant, antitumor, and antibiotic activities.[6,7] Likewise, polysubstituted quinoline, an important heterocyclic molecule, has also been reported for use in the pharmaceutical industry and possesses a broad spectrum of biological potency including antiasthmatic, anti-inflammatory, and antimalarial activities.[8] Therefore, the diverse biological activities reported for isatin and polysubstituted quinoline encouraged us to synthesize some new heterocyclic derivatives incorporating these moieties, which may lead to enhanced bioactivity.

Recently, Abdel-Rahman et al. have reported the synthesis and evaluation of some new spiro indoline-based heterocycles as potentially active antimicrobial agents by the reaction of isatin, malononitrile or ethyl cyanoacetate, and oxazolone derivatives.[7a] Dandia et al. have developed a microwave-assisted, one-pot, three-component, regioselective cyclocondensation of isatin, 3-amino-1,2,4-triazole or 2-aminobenzimidazole and thioacids to afford of a series of novel spiro[indole-thiazolidinones].[7b] In our previous work,[9] we synthesized a series of indole derivatives, which have shown some potential biological activities, under different conditions. In this article, we investigated a simple and facile protocol for the synthesis of a series of new spiro[indoline-3,4′-quinoline] derivatives.

The target compounds 2′-amino-1′-aryl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile **4** were synthesized by one-pot reactions of isatins **1**, malononitrile **2,** and enaminones **3** under MWI (Scheme 1).

Choosing an appropriate solvent is of crucial importance for a successful MW-assisted synthesis. In our initial study, various reaction conditions including solvent and temperature were tested in the one-pot, three-component synthesis of **4a** under MW irradiation. Among different polar solvents, such as ethanol, acetic acid, glycol,



Scheme 1. Synthesis of **4** by reaction of isatins, malonitrile, and enaminones.

Table 1. Optimization of reaction conditions of compound **4a**[a]

Entry	Solvent[b]	T (°C)	Time (min)	Yield[c] (%)
1	H_2O	80	15	Trace
2	EtOH	80	8	78
3	HOAc	80	10	50
4	DMF	80	10	42
5	Glycol	80	10	57
6	EtOH	60	10	65
7	EtOH	70	9	72
8	EtOH	90	8	76

[a]The reaction was carried out under MWI at the power of 150 W.
[b]The amount of solvent was 2 mL.
[c]Isolated yields.

dimethylformamide (DMF), and water, the best yield was found when ethanol was employed. The most suitable temperature should be 80 °C. The results are summarized in Table 1.

Moreover, when **4a** was synthesized under both MWI and classical heating at 80 °C, we found that MWI efficiently promoted the reaction and led to both a dramatic reduction of the reaction time, from 6 h to 8 min, and a remarkable increase in yield from 50% to 78%.

To expand the scope of the present method, different substituted isatins and enaminones containing either electron-withdrawing or electron-donating groups were applied in this reaction. From Table 2, it can be seen that the method works with a wide variety of substrates, and a series of spiro[indoline-3,4′-quinoline] derivatives **4** were obtained in good yields under the same reaction conditions.

The products were characterized by melting point, infrared (IR), ^{1}H NMR, and high-resolution mass spectrometry (HRMS) spectral data. Furthermore, the structure of **4 g** was further confirmed by x-ray diffraction (XRD) analysis (Fig. 1). Crystallographic data for the structure of **4 g** reported in this article have been deposited at the Cambridge Crystallographic Data Centre with No. CCDC-680112.

The proposed mechanism for the synthesis of spiro derivative **4** is described in Scheme 2. The process represents a typical cascade reaction in which the isatin **1** first condenses with malononitrile **2** to afford isatylidene malononitrile **5**. This step was regarded as a fast Knoevenagel condensation. Then, **5** is attacked via Michael addition with enaminone **3** to give the intermediate **6** and followed by the intramolecular cyclization to form the desired product **4**.

Evidence supporting this proposed mechanism was provided by the observation that when **5** and **3a** were subjected to the same conditions,

Table 2. Synthesis of compound **4** under MWI

Entry	R^1	R^2	R^3	R^4	Time (min)	Yield[a] (%)	M.p (°C)
4a	H	H	CH_3	C_6H_5	8	78	>300
4b	H	H	CH_3	4-ClC_6H_4	7	76	>300
4c	H	H	CH_3	4-$CH_3C_6H_4$	7	75	>300
4d	H	H	CH_3	4-$OCH_3C_6H_4$	8	77	>300
4e	H	H	CH_3	4-BrC_6H_4	7	85	>300
4f	H	H	CH_3	1-Naphthyl	10	66	>300
4g	$-CH_3$	H	CH_3	4-ClC_6H_4	9	81	>300
4h	$-CH_2Ph$	H	CH_3	4-ClC_6H_5	10	70	>300
4i	$-CH_2Ph$	H	CH_3	4-$CH_3C_6H_4$	9	72	>300
4j	H	4-Br	CH_3	4-$OCH_3C_6H_4$	10	67	>300
4k	H	6-Br	CH_3	4-ClC_6H_4	8	82	>300
4l	H	6-Br	CH_3	4-$CH_3C_6H_4$	8	75	>300
4m	H	H	H	4-ClC_6H_4	9	77	>300
4n	H	H	H	4-BrC_6H_4	9	80	>300
4o	H	H	H	4-$OCH_3C_6H_4$	9	75	>300

[a]Isolated yields.

the expected product **4a** was obtained in a yield similar to that obtained in the one-pot reaction (Scheme 3).

In conclusion, we have developed a facile, one-pot, three-component reaction involving isatins, malononitrile, and enaminones for the synthesis of a series of spirooxindoles derivatives under MWI. Particularly valuable features of this method include broad substrate scope, shorter reaction time, high yields of the products, and straightforward procedure, which make it a useful and attractive process for the synthesis of these important compounds.

EXPERIMENTAL

Melting points were recorded on an Electrothermal digital melting-point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FT-IR500 spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on a Varian Mercury 400-MHz spectrometer using dimethyl sulfoxide (DMSO)-d_6 as solvent and tetramethylsilane (TMS) as internal standard. HRMS were obtained using GCT-TOF instrument. X-ray diffraction data were made on a Rigaku Mercury CCD area detector with graphite monochromated Mo-Ka radiation. CHN analyses were recorded on a Carlo-Erba EA1110 CNNO-S analyzer.

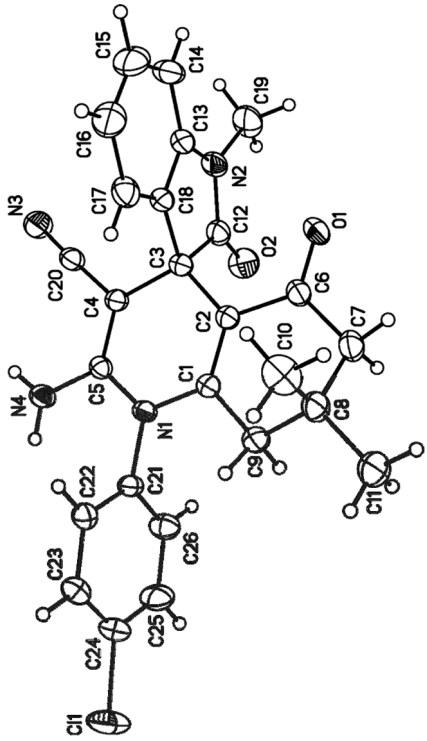
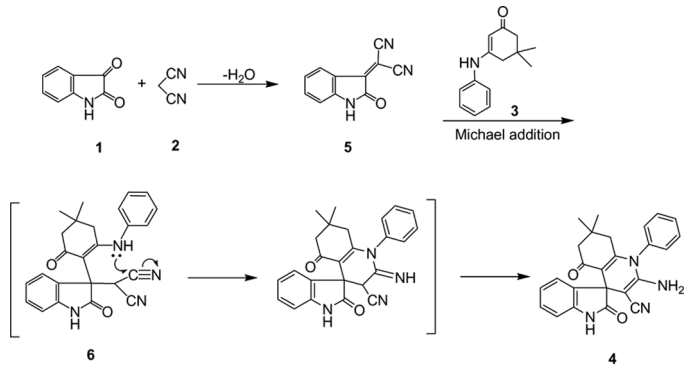
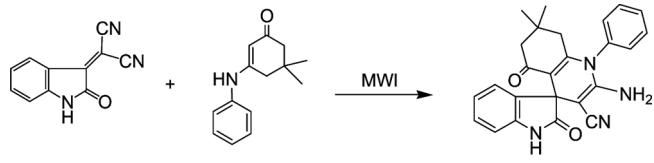


Figure 1. X-ray crystal structure of **4 g**.



Scheme 2. Plausible mechanism for the reaction of isatin and malononitrile with enaminones.



5 3a 4a

Scheme 3. Synthesis of **4a** by the reaction of isatylidene malononitrile with enaminone.

Typical Experimental Procedure: Preparation of Compounds 4

The reaction was performed in a monomodal Emrys Creator from Personal Chemistry, Uppsala, Sweden. In a 10-mL Emrys reaction vial, isatin **1** (1 mmol), malononitrile **2** (1 mmol), enaminone **3** (1 mmol), and ethanol (2 mL) were mixed and then capped. The mixture was irradiated at 80°C and the maximum power of 150 W for the given time. Upon completion, monitored by thin-layer chromatography (TLC), the reaction mixture was allowed to cool to room temperature and then poured into cold water (100 mL). The solid product was filtered and washed with EtOH (95%). The product was purified by recrystallization from EtOH–DMF (1:1) to afford **4a**–**4o**.

Data

2′-Amino-7′,7′-dimethyl-2,5′-dioxo-1′-phenyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4a**)

White solid; mp > 300°C; IR (KBr): ν 3442, 3334, 3218, 2184, 1715, 1643, 1551, 1366, 1258, 1049, 733 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.17 (br s, 1H, NH), 7.58–7.63 (m, 3H, Ar-H), 7.46–7.48 (m, 2H, Ar-H), 7.16 (d, $J = 7.2$ Hz, 1H, Ar-H), 7.12 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.91 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.76 (d, $J = 7.6$ Hz, 1H, Ar-H), 5.30 (s, 2H, NH_2), 2.07–2.14 (m, 2H, CH_2), 1.80–1.95 (m, 2H, CH_2), 0.88 (s, 3H, CH_3), 0.82 (s, 3H, CH_3). HRMS found: m/z 410.1738 (M^+); calcd. for $C_{25}H_{22}N_4O_2$: M, 410.1743. Anal. calcd. for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N, 13.65. Found: C, 73.27; H, 5.27; N, 13.72.

2′-Amino-1′-(4-chlorophenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4b**)

Yellow solid; mp > 300°C; IR (KBr): ν 3457, 3334, 3218, 2191, 1721, 1644, 1566, 1489, 1366, 1188, 1049, 756 cm^{-1}; ^1H NMR (400 MHz,

DMSO-d_6): δ 10.21 (br s, 1H, NH), 7.56 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.45–7.53 (m, 2H, Ar-H), 7.17 (d, $J = 7.2$ Hz, 1H, Ar-H), 7.11 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.89 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.75 (d, $J = 7.6$ Hz, 1H, Ar-H), 5.55 (s, 2H, NH_2), 2.07–2.16 (m, 2H, CH_2), 1.79–1.93 (m, 2H, CH_2), 0.89 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). HRMS found: m/z 444.1342 (M^+); calcd. for $C_{25}H_{21}ClN_4O_2$: M, 444.1353. Anal. calcd. for $C_{25}H_{21}ClN_4O_2$: C, 67.49; H, 4.76; N, 12.59. Found: C, 67.38; H, 4.67; N, 12.65.

2′-Amino-7′,7′-dimethyl-2,5′-dioxo-1′-p-tolyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4c**)

White solid; mp > 300°C; ν 3434, 3318, 3218, 2191, 1721, 1643, 1559, 1366, 1258, 1196, 1048, 748 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.16 (br s, ^{1}H, NH), 7.41 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.30–7.41 (m, 2H, Ar-H), 7.09–7.15 (m, 2H, Ar-H), 6.90 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.75 (d, $J = 7.6$ Hz, 1H, Ar-H), 5.27 (s, 2H, NH_2), 2.41 (s, 3H, CH_3), 2.06–2.14 (m, 2H, CH_2), 1.82–1.94 (m, 2H, CH_2), 0.88 (s, 3H, CH_3), 0.82 (s, 3H, CH_3). HRMS found: m/z 424.1892 (M^+); calcd. for $C_{26}H_{24}N_4O_2$: M, 424.1899. Anal. calcd. for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20. Found C, 73.62; H, 5.77; N, 13.12.

2′-Amino-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4d**)

White solid; mp > 300°C; IR (KBr): ν 3435, 3337, 3218, 2184, 1716, 1643, 1592, 1470, 1361, 1195, 1051, 725 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.20 (br s, 1H, NH), 7.32–7.41 (m, 2H, Ar-H), 7.09–7.16 (m, 4H, Ar-H), 6.89 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.75 (d, $J = 7.2$ Hz, 1H, Ar-H), 5.37 (s, 2H, NH_2), 3.84 (s, 3H, OCH_3), 2.06–2.15 (m, 2H, CH_2), 1.82–1.93 (m, 2H, CH_2), 0.88 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). HRMS found: m/z 440.1860 (M^+); calcd. for $C_{26}H_{24}N_4O_3$: M, 440.1848. Anal. calcd. for $C_{26}H_{24}N_4O_3$: C, 70.89; H, 5.49; N, 12.72. Found: C, 70.80; H, 5.56; N, 12.78.

2′-Amino-1′-(4-bromophenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4e**)

Yellow solid; mp > 300°C; IR (KBr): ν 3417, 3340, 3291, 2190, 1745, 1657, 1485, 1364, 1261, 1193, 1012, 751 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (br s, 1H, NH), 7.78 (d, $J = 8.8$ Hz, 2H, Ar-H),

7.40–7.48 (m, 2H, Ar-H), 7.17 (d, $J = 7.6$ Hz, 1H, Ar-H), 7.11 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.89 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.75 (d, $J = 7.6$ Hz, 1H, Ar-H), 5.56 (s, 2H, NH_2), 2.07–2.15 (m, 2H, CH_2), 1.79-1.93 (m, 2H, CH_2), 0.88 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). HRMS found: m/z 488.0843 (M^+); calcd. for $C_{25}H_{21}BrN_4O_2$: M, 488.0848. Anal. calcd. for $C_{25}H_{21}BrN_4O_2$: C, 61.36; H, 4.33; N, 11.45. Found: C, 61.43; H, 4.40; N, 11.52.

2′-Amino-7′,7′-dimethyl-1′-(naphthalen-1-yl)-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4f**)

White solid; mp > 300°C; IR (KBr): ν 3446, 3334, 3221, 2182, 1728, 1661, 1557, 1418, 1242, 1192, 1054, 920, 805, 726 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.28 (br s, 1H, NH), 8.11–8.18 (m, 2H, Ar-H), 7.89–7.94 (m, 2H, Ar-H), 7.67–7.75 (m, 3H, Ar-H), 7.20 (d, $J = 9.6$ Hz, 1H, Ar-H), 7.14 (t, $J = 8.8$ Hz, 1H, Ar-H), 6.93 (t, $J = 10.0$ Hz, 1H, Ar-H), 6.79 (d, $J = 9.6$ Hz, 1H, Ar-H), 5.47 (s, 2H, NH_2), 2.12 (d, $J = 23.2$ Hz, 1H, CH_2), 1.99 (s, 2H, CH_2), 1.55 (d, $J = 22.8$ Hz, 1H, CH_2), 0.79 (s, 3H, CH_3), 0.69 (s, 3H, CH_3). HRMS found: m/z 460.1882 (M^+); calcd. for $C_{29}H_{24}N_4O_2$: M, 460.1899. Anal. calcd. for $C_{29}H_{24}N_4O_2$: C, 75.63; H, 5.25; N, 12.17. Found: C, 75.53; H, 5.30; N, 12.25.

2′-Amino-1′-(4-chlorophenyl)-1,7′,7′-trimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4g**)

White solid; mp > 300°C; IR (KBr): ν 3463, 3312, 2190, 1716, 1650, 1568, 1491, 1364, 1090, 1018, 915, 753 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.65 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.51–7.54 (m, 2H, Ar-H), 7.23 (t, $J = 8.0$ Hz, 2H, Ar-H), 6.93–6.70 (m, 2H, Ar-H), 5.55 (s, 2H, NH_2), 3.13 (s, 3H, $-NCH_3$), 2.05–2.17 (m, 2H, CH_2), 1.81–1.93 (m, 2H, CH_2), 0.89 (s, 3H, CH_3), 0.81 (s, 3H, CH_3). HRMS found: m/z 458.1501 (M^+); calcd. for $C_{25}H_{23}ClN_4O_2$: M, 458.1510. Anal. calcd. for $C_{25}H_{23}ClN_4O_2$: C, 68.04; H, 5.05; N, 12.21. Found: C, 68.13; H, 5.12; N, 12.30.

2′-Amino-1-benzyl-1′-(4-chlorophenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4h**)

White solid; mp > 300°C; IR (KBr): ν 3454, 3365, 2182, 1703, 1644, 1556, 1487, 1362, 1259, 1094, 917, 850, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.67 (d, $J = 11.6$ Hz, 2H, Ar-H), 7.55 (d, $J = 9.2$ Hz, 4H, Ar-H),

7.25–7.33 (m, 4H, Ar-H), 7.10 (t, $J = 10.4$ Hz, 1H, Ar-H), 6.97 (t, $J = 9.6$ Hz, 1H, Ar-H), 6.61 (d, $J = 10.4$ Hz, 1H, Ar-H), 5.67 (s, 2H, NH_2), 4.83–4.96 (m, 2H, CH_2), 2.11–2.22 (m, 2H, CH_2), 1.81–1.98 (m, 2H, CH_2), 0.90 (s, 3H, CH_3), 0.82 (s, 3H, CH_3). HRMS found: m/z 534.1831 (M^+); calcd. for $C_{32}H_{27}ClN_4O_2$: M, 534.1823. Anal. calcd. for $C_{32}H_{27}ClN_4O_2$: C, 71.83; H, 5.09; N, 10.47. Found: C, 71.76; H, 5.17; N, 10.35.

2′-Amino-1-benzyl-7′,7′-dimethyl-2,5′-dioxo-1′-p-tolyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4i**)

White solid; mp > 300°C; IR (KBr): ν 3441, 3330, 2183, 1716, 1644, 1559, 1486, 1362, 1259, 1185, 1052, 917, 751 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 7.55 (d, $J = 7.6$ Hz, 2H, Ar-H), 7.35–7.43 (m, 4H, Ar-H), 7.31 (t, $J = 7.2$ Hz, 2H, Ar-H), 7.25 (d, $J = 7.6$ Hz, 2H, Ar-H), 7.09 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.97 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.61 (d, $J = 8.0$ Hz, 1H, Ar-H), 5.37 (s, 2H, NH_2), 4.85–4.95 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.11–2.19 (m, 2H, CH_2), 1.86–1.98 (m, 2H, CH_2), 0.90 (s, 3H, CH_3), 0.83 (s, 3H, CH_3). HRMS found: m/z 514.2391 (M^+); calcd. for $C_{33}H_{30}N_4O_2$: M, 514.2369. Anal. calcd. for $C_{33}H_{30}N_4O_2$: C, 77.02; H, 5.88; N, 10.89. Found: C, 77.12; H, 5.79; N, 10.95.

2′-Amino-4-bromo-1′-(4-methoxyphenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4j**)

Yellow solid; mp > 300°C; IR (KBr): ν 3457, 3334, 3218, 2184, 1721, 1643, 1512, 1443, 1366, 1250, 1180, 1049, 910, 764 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.47 (br s, 1H, NH), 7.34–7.36 (m, 1H, Ar-H), 7.26–7.29 (m, 1H, Ar-H), 7.06–7.13 (m, 4H, Ar-H), 6.78–6.80 (m, 1H, Ar-H), 5.48 (s, 2H, NH_2), 3.83 (s, 3H, OCH_3), 2.07–2.17 (m, 2H, CH_2), 1.77–1.95 (m, 2H, CH_2), 0.89 (s, 3H, CH_3), 0.86 (s, 3H, CH_3). HRMS found: m/z 518.0954 (M^+); calcd. for $C_{26}H_{23}BrN_4O_3$: M, 518.0930. Anal. calcd. for $C_{26}H_{23}BrN_4O_3$: C, 60.12; H, 4.46; N, 10.79. Found: C, 60.18; H, 4.51; N, 10.85.

2′-Amino-6-bromo-1′-(4-chlorophenyl)-7′,7′-dimethyl-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4k**)

Yellow solid; mp > 300°C; IR (KBr): ν 3462, 3328, 3210, 2186, 1721, 1644, 1560, 1470, 1362, 1261, 1049, 782 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.40 (br s, 1H, NH), 7.59–7.61 (m, 3H, Ar-H), 7.42–7.54

(m, 2H, Ar-H), 7.08–7.17 (m, 2H, Ar-H), 6.90 (s, 1H, Ar-H), 5.47 (s, 2H, NH_2), 2.07–2.12 (m, 2H, CH_2), 1.78–1.96 (m, 2H, CH_2), 0.86 (s, 3H, CH_3), 0.80 (s, 3H, CH_3). HRMS found: m/z 522.0448 (M^+); calcd. for $C_{25}H_{20}BrClN_4O_2$: M, 522.0458. Anal. calcd. for $C_{25}H_{20}BrClN_4O_2$: C, 57.32; H, 3.85; N, 10.70. Found: C, 57.28; H, 3.91; N, 10.78.

2′-Amino-6-bromo-7′,7′-dimethyl-2,5′-dioxo-1′-p-tolyl-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4l**)

Yellow solid; mp > 300°C; IR (KBr): ν 3442, 3323, 3217, 2183, 1729, 1645, 1555, 1477, 1362, 1317, 1258, 1052, 919, 747 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.33 (br s, 1H, NH), 7.40–7.42 (m, 3H, Ar-H), 7.27–7.34 (m, 2H, Ar-H), 7.07–7.14 (m, 2H, Ar-H), 6.90 (s, 1H, Ar-H), 5.36 (s, 2H, NH_2), 2.41 (s, 3H, CH_3), 2.06–2.12 (m, 2H, CH_2), 1.83–1.95 (m, 2H, CH_2), 0.88 (s, 3H, CH_3), 0.82 (s, 3H, CH_3). HRMS found: m/z 502.1022 (M^+); calcd. for $C_{26}H_{23}BrN_4O_2$: M, 502.1004. Anal. calcd. for $C_{26}H_{23}BrN_4O_2$: C, 62.03; H, 4.61; N, 11.13. Found: C, 62.13; H, 4.52; N, 11.21.

2′-Amino-1′-(4-chlorophenyl)-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4m**)

Light yellow solid; mp > 300°C; IR (KBr): ν 3442, 3334, 2190, 1719, 1655, 1561, 1491, 1357, 1200, 1087, 1008, 743 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.21 (br s, 1H, NH), 7.64 (d, $J = 8.8$ Hz, 2H, Ar-H), 7.50–7.54 (m, 2H, Ar-H), 7.18 (d, $J = 7.2$ Hz, 1H, Ar-H), 7.11 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.89 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.74 (d, $J = 7.6$ Hz, 1H, Ar-H), 5.57 (s, 2H, NH_2), 2.11–2.17 (m, 2H, CH_2), 1.95–2.07 (m, 2H, CH_2), 1.68–1.77 (m, 2H, CH_2). HRMS found: m/z 416.1024 (M^+); calcd. for $C_{23}H_{17}ClN_4O_2$: M, 416.1040. Anal. calcd. for $C_{23}H_{17}ClN_4O_2$: C, 66.27; H, 4.11; N, 13.44. Found: C, 66.38; H, 4.20; N, 13.27.

2′-Amino-1′-(4-bromophenyl)-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4n**)

Yellow solid; mp > 300°C; IR (KBr): ν 3446, 3337, 3288, 2190, 1718, 1653, 1560, 1488, 1357, 1302, 1200, 1013, 743 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.16 (br s, 1H, NH), 7.77 (d, $J = 8.4$ Hz, 2H, Ar-H), 7.45 (d, $J = 8.0$ Hz, 2H, Ar-H), 7.17 (d, $J = 7.2$ Hz, 1H, Ar-H), 7.11 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.89 (t, $J = 7.2$ Hz, 1H, Ar-H), 6.74

(d, $J = 7.6$ Hz, 1H, Ar-H), 5.48 (s, 2H, NH_2), 1.96–2.18 (m, 4H, CH_2), 1.62–1.80 (m, 2H, CH_2). HRMS found: m/z 460.0523 (M^+); calcd. for $C_{23}H_{17}BrN_4O_2$: M, 460.0535. Anal. calcd. for $C_{23}H_{17}BrN_4O_2$: C, 59.88; H, 3.71; N, 12.15. Found: C, 59.98; H, 3.79; N, 12.23.

2′-Amino-1′-(4-methoxyphenyl)-2,5′-dioxo-5′,6′,7′,8′-tetrahydro-1′*H*-spiro[indoline-3,4′-quinoline]-3′-carbonitrile (**4o**)

White solid; mp > 300°C; IR (KBr): ν 3469, 3327, 3206, 2179, 1637, 1510, 1421, 1359, 1252, 1195, 1009, 952, 755 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 10.15 (br s, 1H, NH), 7.36–7.41 (m, 2H, Ar-H), 7.09–7.17 (m, 4H, Ar-H), 6.89 (t, $J = 7.6$ Hz, 1H, Ar-H), 6.74 (d, $J = 7.6$ Hz, 1H, Ar-H), 5.31 (s, 2H, NH_2), 3.84 (s, 3H, OCH_3), 1.99–2.19 (m, 4H, CH_2), 1.69–1.79 (m, 2H, CH_2). HRMS found: m/z 412.1536 (M^+); calcd. for $C_{24}H_{20}N_4O_3$: M, 412.1535. Anal. calcd. for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.75; H, 4.79; N, 13.65.

Preparation of Compound 5

A mixture of isatin **1** (2 mmol) and malononitrile **2** (2 mmol) in absolute ethanol (5 mL) was irritated for 2 min at a maximum power of 100 W and 80 °C. Upon completion, monitored by TLC, the reaction mixture was allowed to cool to room temperature and washed with EtOH (95%) to give pure deep red product **5**.

2-Oxo-(3*H*)-indol-3-ylidene Malononitrile (**5**)

Mp 239–240 °C (lit.[6c] 239 °C).

ACKNOWLEDGMENTS

This work was partially supported by the Key Laboratory of Organic Synthesis of Jiangsu Province at Suzhou University (No. S8109108), the Natural Science Foundation of Jiangsu Province (No. BK2006048), and the National Science Foundation of China (Nos. 20472062 and 20672079), Nature Science Key Basic Research of Jiangsu Province for Higher Education (Nos. 06KJA15007 and 05KJB150116), Jiangsu Provincial Key Laboratory of Fine Petrochemical Technology (No. KF0402), and a research grant from the Innovation Project for Graduate Students of Jiangsu Province.

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