Efficient One-Pot Synthesis of Novel Spirooxindole Derivatives via Three-Component Reaction in Aqueous Medium

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A novel and efficient one-pot synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*b*]quinoline]dione, spiro[furo-[3,4-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]dione, and spiro[indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]dione derivatives via three-component reaction of isatin, 5-amino-3-methylpyrazole, and 1,3-dicarbonyl compounds in aqueous medium is described. The advantages of this method include high efficiency, mild reaction conditions, convenient operation, and environmentally benign conditions.

Introduction

Multicomponent reactions (MCRs)[1] are special types of synthetically useful organic reactions in which three or more different starting materials react to give a final product in a one-pot procedure. Such reactions are one of the best tools in modern organic synthesis to generate compound libraries for screening purposes because of their productivity, simple procedures, convergence, and facile execution.[2] This methodology allows molecular complexity and diversity to be created by the facile formation of several new covalent bonds in a one-pot transformation quite closely approaching the concept of an ideal synthesis, and it is particularly well adapted for combinatorial synthesis.[3]

The indole nucleus is probably the most well-known heterocycle, a common and important feature of a variety of natural products and medicinal agents.[4] Compounds carrying the indole moiety exhibit antibacterial and antifungal activities.[5] Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity.[6−8] The spirocyclic oxindole core is featured in a number of natural alkaloids as well as medicinally relevant compounds.[9−14] For example, spirotryprostatin B, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly,[10] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors (Figure 1).[12] Therefore, a number of methods have been reported for the preparation of spirooxindole derivatives.[15−17]

Heterocycles containing the pyrazole ring are important targets in synthetic and medicinal chemistry because this fragment is a key moiety in numerous biologically active compounds,[18] among them such prominent drug molecules as Viagra, Celebrex, Analginum, and many others. On the other hand, pyrazolopyridines have received more and more attention in the recent years. Pharmaceutical researches of this kind of compounds have been reported, such as a potent cyclin dependent kinase 1 (CDK1) inhibitor,[19] human immunodeficiency virus (HIV) reverse transcriptase inhibitors,[20] CCR1 antagonists,[21] protein kinase inhibitors,[22] and inhibitors of cGMP degradation, together with studies of several herbicidal and fungicidal activities.[23] Numerous methods for the synthesis of pyrazolopyridines in the past 20 years have been reported with respect to their different structures.[24]

The development of organic reactions in water has become highly desirable in recent years to meet environmental considerations.[25,26] The unique properties of water in aqueous medium like high dielectric constant and cohesive energy density showed an extraordinary effect on reaction rates. Moreover, its cost-effectiveness, high abundance, noninflammability and non-toxic nature increased its applicability.[27]

However, to the best of our knowledge, there have been few reports about the synthesis of spirooxindole derivatives in aqueous medium lately.[28−31] As a part of our research program, which aims to develop new selective and environmentally friendly methodologies for the preparation of

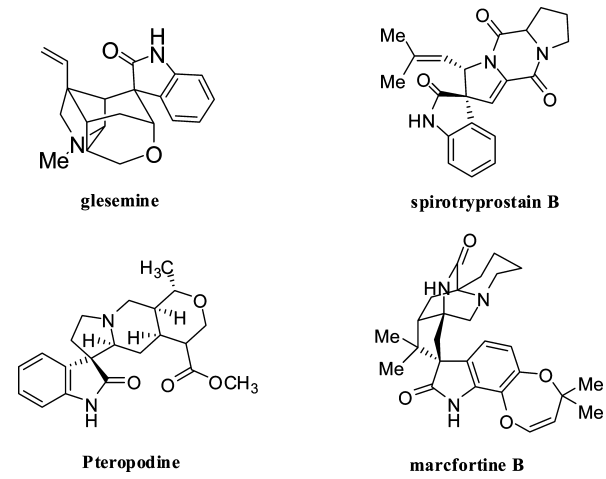

Figure 1. Naturally occurring and biologically active spirocyclic oxindoles.

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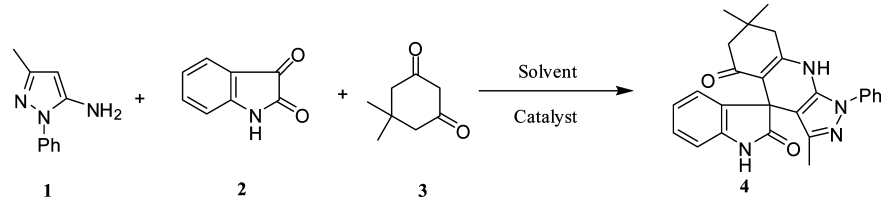
Scheme 1. Model Reaction



1 2 3 4

Table 1. Optimization of Reaction Conditions

entry	solvent	temperature (°C)	catalyst	time (h)	yield (%)
1	water	80		24	<20
2	water	80	HCl (10%)	8	69
3	water	80	*p*-TSA (10%)	8	73
4	water	80	CAN (10%)	8	87
5	water	80	$FeCl_3$ (10%)	8	54
6	water	80	$CoCl_2$ (10%)	8	31
7	water	80	$Cu(OAc)_2$ (10%)	8	29
8	water	r.t.	CAN (10%)	24	23
9	AcOH	95	CAN (10%)	8	82
10	CH_3CN	80	CAN (10%)	8	79
11	THF	65	CAN (10%)	8	75
12	DMF	90	CAN (10%)	8	77
13	EtOH	80	CAN (10%)	8	80
14	water	80	CAN (5%)	8	72
15	water	80	CAN (15%)	8	86
16	water	80	CAN (20%)	8	88

heterocyclic compounds,[32] herein, we investigated a three-component reaction of isatin, 5-amino-3-methylpyrazole, and 1,3-dicarbonyl compounds to afford a series of spiro[indoline-3,4′-pyrazolo[3,4-*b*]quinoline]dione, spiro[furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]dione, and spiro[indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]dione derivatives in water catalyzed by CAN (Ceric Ammonium Nitrate).

Results and Discussion

Initially, to get spiro[indoline-3,4′-pyrazolo[3,4-*b*]quinoline]dione derivatives **4a**, we tested the reaction of 5-amino-1-phenyl-3-methylpyrazole **1a**, isatin **2a**, dimedone **3** as a simple model substrate in various reaction conditions (Scheme 1). The results are shown in Table 1.

It was found that when the reaction was carried out without any catalysts the yield of product was very low (Table 1, <20%, entry 1) even after 24 h. To improve the yields, we examined this reaction using different Brønsted and Lewis acids (Table 1, entries 2−7). Some Brønsted acids such as HCl and *p*-TSA (*p*-toluenesulfonic acid) can catalyze this reaction with moderate yields (Table 1, entries 2−3). However, the use of some Lewis acids, for example, $FeCl_3$, $CoCl_2$, $Cu(OAc)_2$ led to low product formation (Table 1, entries 5−7). Finally, CAN was identified as the optimal catalyst, with **4a** being isolated in 87% yield (Table 1, entry 4). Performing the reaction in the presence of CAN at room temperature led to low conversion of **4a** in 23% yield even with prolonged time (Table 1, entry 8). Subsequently, we further turned to testing the effect of solvents. AcOH, CH_3CN, tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), or EtOH showed no superiority to water (Table 1, entry 9−13) as solvents.

Table 2. Synthesis of Compound **4** in Aqueous Medium

entry	R^1	X	R^2	R^3	products	time (h)	yield (%)
1	C_6H_5	H	H	CH_3	**4a**	8	87
2	C_6H_5	5-CH_3	H	CH_3	**4b**	10	87
3	C_6H_5	5-Br	H	CH_3	**4c**	12	88
4	C_6H_5	5-F	H	CH_3	**4d**	6	85
5	C_6H_5	H	CH_3	CH_3	**4e**	8	86
6	C_6H_5	H	H	H	**4f**	9	82
7	CH_3	H	CH_3	CH_3	**4g**	10	85

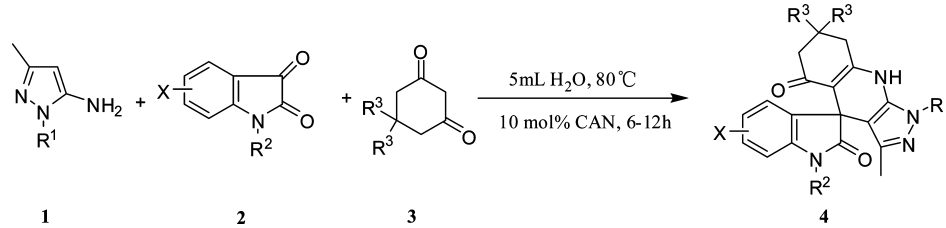
We also evaluated the amount of CAN required for this reaction. It was found that when increasing the amount of CAN from 5 mol % to 10, 15, and 20 mol %, the yields increased from 72% to 87, 86, and 88%, respectively (Table 1, entries 14−16). Using 10 mol % CAN in water is sufficient to push this reaction forward. More amounts of the catalyst did not improve the yields.

Under the optimized reaction conditions, a series of spiro[indoline-3,4′-pyrazolo[3,4-*b*]quinoline]dione derivatives **4** were synthesized (Scheme 2). The results are summarized in Table 2.

To further expand the scope of the present method, we investigated one-pot reactions involving tetronic acid **5** and 1,3-indanedione **7**. To our delight, under the above optimized conditions, the reactions proceeded smoothly, and a variety of the desired spirooxindoles products **6** and **8** were obtained in good yields (Scheme 3 and Table 3).

As shown in Tables 2 and 3, it was found that this method works with a wide variety of substrates. A series of different position substituted isatins including either electron-withdrawing or electron-donating groups and different 1,3-dicarbonyl compounds were used in this reaction. However, the yield of 5-amino-1,3-dimethylpyrazole with 4-chloroisatin and tetronic acid (Table 3, Entry 10) was relatively low, which is probably due to the low reactivity of the carbonyl in 4-chloroisatin.

Scheme 2. Synthesis of Spiro[indoline-3,4′-pyrazolo[3,4-*b*]quinoline]dione Derivatives **4**



1 2 3 4

Scheme 3. Synthesis of Spirooxindole Derivatives **6** and **8**

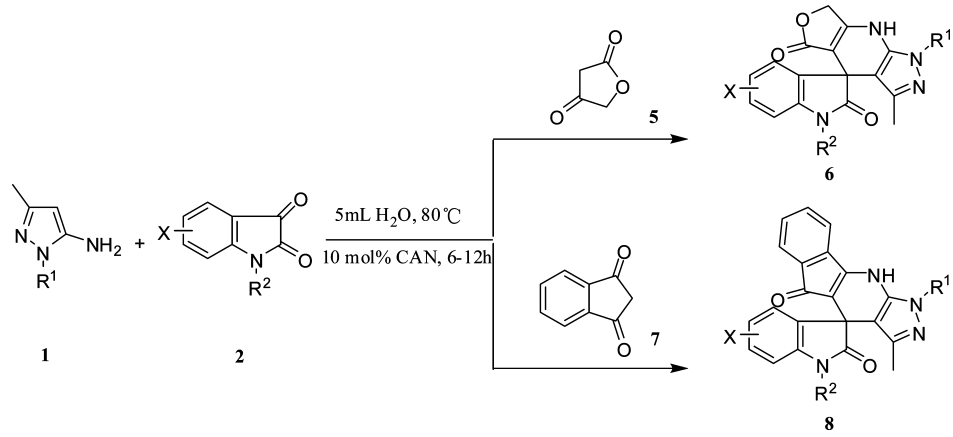


Table 3. Synthesis of Compound **6** and **8** in Aqueous Medium

entry	R^1	X	R^2	products	time (h)	yield (%)
1	C_6H_5	H	H	**6a**	6	86
2	C_6H_5	5-F	H	**6b**	8	87
3	C_6H_5	5-CH_3	H	**6c**	6	88
4	C_6H_5	H	CH_3	**6d**	10	85
5	CH_3	H	H	**6e**	8	86
6	CH_3	5-Br	H	**6f**	12	89
7	CH_3	5-Cl	H	**6g**	12	85
8	CH_3	5-F	H	**6h**	8	86
9	CH_3	5-CH_3	H	**6i**	10	81
10	CH_3	4-Cl	H	**6j**	12	57
11	CH_3	H	CH_3	**6k**	6	88
12	C_6H_5	H	H	**8a**	6	91
13	C_6H_5	5-F	H	**8b**	8	90
14	CH_3	H	H	**8c**	6	88

According to the literature,[33] we proposed the plausible mechanism for the formation of spirooxindole derivatives **4**. The first step involves the formation of 3-(5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-hydroxyindolin-2-one **9** by the nucleophilic addition of 1-phenyl-3-methyl-5-pyrazolone **1** to isatin **2** as a key intermediate, which lost a water to afford **10**. Then, **10** is attacked via Michael addition of dimedone **3** to give the intermediate **11** followed by cycloaddition and dehydration to form the desired product **4** (Scheme 4).

To prove the mechanism, when the reaction of 5-amino-1-phenyl-3-methylpyrazole **1**, isatin **2a**, dimedone **3** was carried out for 1 h, the intermediate 3-(5-amino-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-3-hydroxyindolin-2-one **9** was isolated and characterized by spectroscopic methods. We were pleased to find that the reaction of intermediate **9** with dimedone **3** in the presence of CAN under the same reaction conditions proceeded smoothly giving the 3′,7′,7′-trimethyl-1′-phenyl-6′,7′,8′,9′-tetrahydrospiro[indoline-3,4′-pyrazolo-[3,4-*b*]quinoline]-2,5′(1′*H*)-dione **4a** in 84% yield. (Scheme 5).

Finally, to further explore the potential of this protocol for synthesis of spiro-heterocyclic compounds, we investigated the reaction involving acenaphthylene-1,2-dione **12** and obtained 1′,3′,7′,7′-tetramethyl-6′,7′,8′,9′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-pyrazolo[3,4-*b*]quinoline]-2,5′(1′*H*)-dione **13** and spiro[acenaphthylene-1,4′-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine]dione derivatives **14** in good yields (Scheme 6).

The structures of the products **4a**−**g**, **6a**−**k**, **8a**−**c**, **13**, and **14a**,**b** were characterized by IR, ^{1}H NMR, ^{13}C NMR spectra as well as high resolution mass spectrometry (HRMS). The structure of **14a** was further confirmed by X-ray diffraction analysis. The molecular structure **14a** is shown in Figure 2.

In summary, we have described a simple one-pot three component reaction involving isatin, 5-amino-3-methylpyrazole, and 1,3-dicarbonyl compounds for the synthesis of spiro[indoline-3,4′-pyrazolo[3,4-*b*]quinoline]dione, spiro-[furo[3,4-*e*]pyrazolo[3,4-*b*] pyridine-4,3′-indoline]dione, and spiro[indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-4,3′- indoline]dione derivatives in water. Particularly, valuable features of this method include the good yields of the products, broader substrate scope, mild reaction conditions, reduced environmental impact, and the straightforwardness of the procedure, which make it a useful and attractive process for the synthesis of these important compounds.

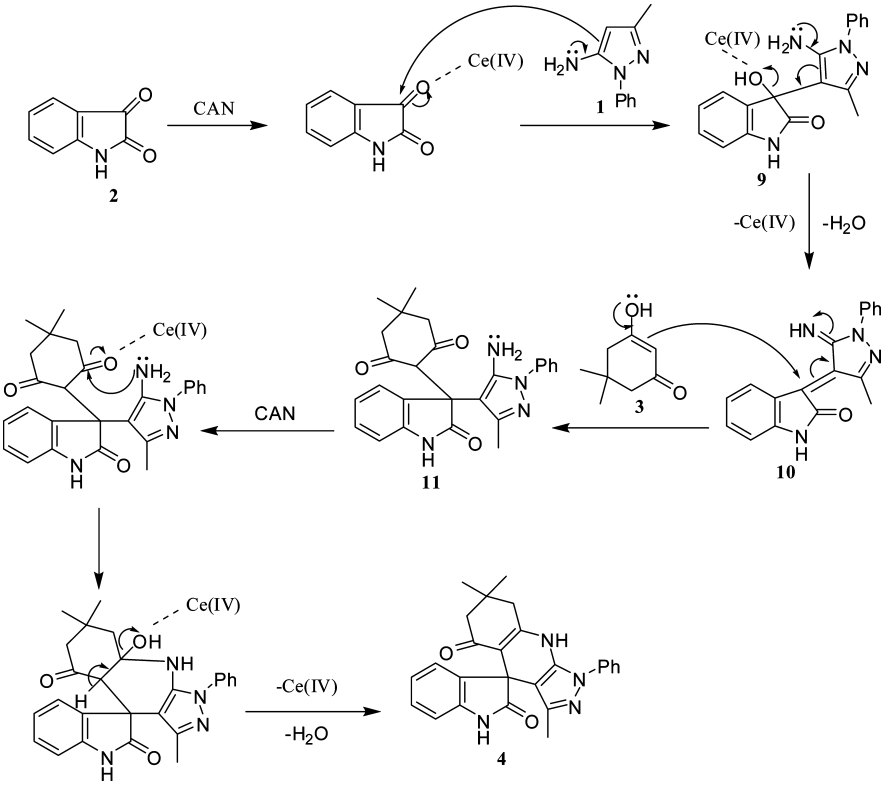
Experimental Section

Melting points were determined in open capillaries and uncorrected. IR spectra were recorded on a Varian F-1000 spectrometer in KBr pellet. ^{1}H NMR and ^{13}C NMR spectra were obtained from a solution in DMSO-d_6 with Me_4Si as internal standard using Varian Inova-400 MHz or Inova-300 MHz spectrometer. HRMS analyses were carried out using time-of-flight mass spectrometry (TOF-MS) or GCT-TOF instrument.

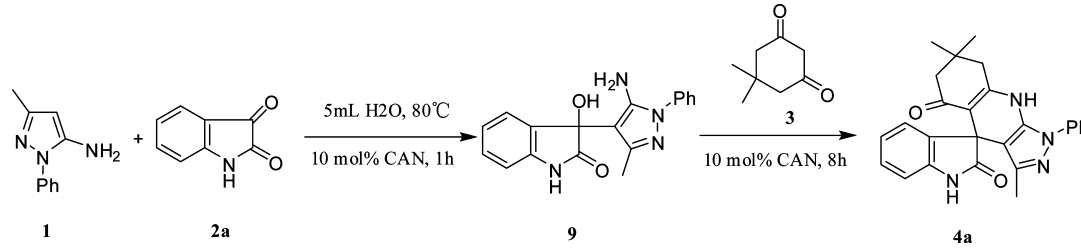
General Procedure for the Synthesis of 4, 6, and 8. A mixture of 5-amino-3-methylpyrazole (1 mmol), isatin (1 mmol), 1,3-dicarbonyl compounds (1 mmol), and CAN (10 mol %) in H_2O (5 mL) was stirred at 80 °C for 6−12 h. After completion of the reaction confirmed by thin-layer chromatography (TLC; eluent acetone/petroleum ether, 1:2), the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered, dried, and recrystallized from DMF and ethanol to afford the pure **4**, **6**, or **8** as a white powder.

3′,7′,7′-Trimethyl-1′-phenyl-6′,7′,8′,9′-tetrahydrospiro[indoline-3,4′-pyrazolo[3,4-*b*]quinoline]-2,5′(1′*H*)-dione (4a). M.p.: >300 °C. IR (KBr) ν: 3284, 3157, 2955, 1710, 1618, 1532, 1467, 1366, 1123, 751, 684 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.97 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.55

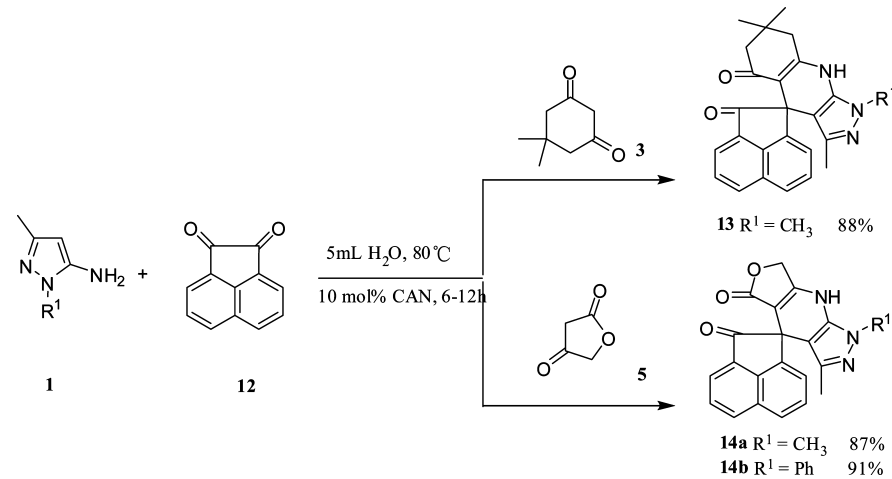
Scheme 4. Proposed Mechanism for the Synthesis of Spirooxindole Derivatives **4**



Scheme 5. Two-Step Synthesis of Spirooxindole **4a**



Scheme 6. Synthesis of Spirocyclic Acenaphthyleneones **13** and **14**



(s, 3H, CH_3), 1.97 (d, J = 15.9 Hz, 1H, CH_2), 2.08 (d, J = 15.9 Hz, 1H, CH_2), 2.56 (s, 2H, CH_2), 6.79 (d, J = 7.5 Hz, 1H, ArH), 6.84 (d, J = 3.6 Hz, 2H, ArH), 7.06−7.12 (m, 1H, ArH), 7.40−7.43 (m, 1H, ArH), 7.48−7.56 (m, 4H, ArH), 9.68 (s, 1H, NH), 10.32 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.0, 27.6, 28.9, 32.8, 41.6, 49.4, 51.0, 102.3, 108.6, 109.2, 122.1, 123.8, 124.1, 127.9, 127.9, 130.1, 137.3, 137.7, 138.5, 142.4, 145.7, 153.7, 180.3, 194.0. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{24}N_4O_2$: 425.1972 $[M+H]^+$, found: 425.1972.

1′,3-Dimethyl-1-phenyl-7,8-dihydrospiro[furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]-2′,5(1*H*)-dione (6d). M.p.: >300 °C. IR (KBr) ν: 3189, 3052, 2940, 1704, 1651, 1549, 1475, 1363, 1118, 1019, 753, 689 cm^{-1}. ^{1}H NMR (300

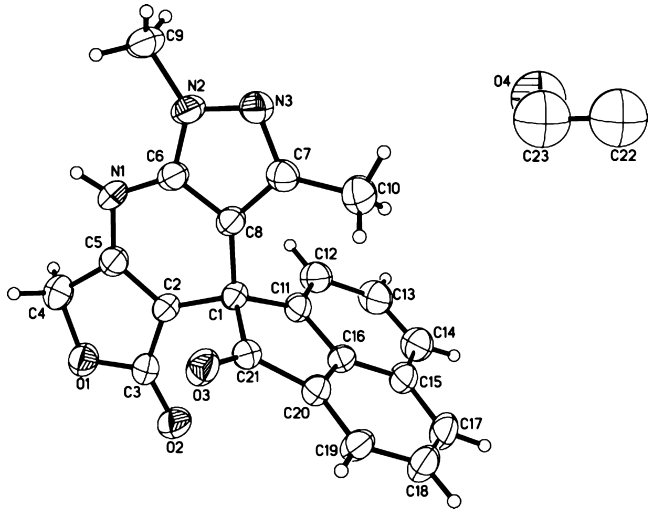


Figure 2. Crystal structure of **14a**.

MHz, DMSO-d_6): δ_H 1.42 (s, 3H, CH_3), 3.22 (s, 3H, CH_3), 4.94 (s, 2H, CH_2), 7.02 (t, $J = 7.5$ Hz, 1H, ArH), 7.08 (d, $J = 8.1$ Hz, 2H, ArH), 7.31 (t, $J = 7.5$ Hz, 1H, ArH), 7.41−7.46 (m, 1H, ArH), 7.51−7.59 (m, 4H, ArH), 10.67 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 10.7, 25.8, 45.8, 65.2, 96.7, 100.5, 107.7, 122.3, 122.7, 123.8, 127.0, 128.1, 129.1, 132.8, 136.9, 137.8, 142.3, 144.7, 159.3, 169.4, 175.5. HRMS [Found: *m*/*z* 398.1379 (M^+), calcd for $C_{23}H_{18}N_4O_3$: M, 398.1379].

1,3-Dimethyl-1*H*-spiro[indeno[2,1-*e*]pyrazolo[3,4-*b*]pyridine-4,3′-indoline]-2′,5(10*H*)-dione (8c). M.p.: >300 °C. IR (KBr) ν: 3361, 3196, 3125, 3059, 2932, 1693, 1602, 1540, 1505, 1340, 1229, 1189, 863, 757, 720, 632 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 1.44 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 6.85−6.88 (m, 2H, ArH), 6.92 (d, $J = 6.8$ Hz, 1H, ArH), 7.15−7.21 (m, 2H, ArH), 7.36 (t, $J = 7.2$ Hz, 1H, ArH), 7.50 (t, $J = 7.6$ Hz, 1H, ArH), 7.73 (d, $J = 7.2$ Hz, 1H, ArH), 10.54 (s, 1H, NH), 11.05 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ_C 16.8, 41.0, 52.6, 107.2, 111.1, 114.7, 125.3, 125.9, 127.5, 129.9, 133.7, 136.1, 137.3, 139.6, 140.8, 141.9, 144.2, 147.2, 148.7, 162.0, 184.2, 194.7. HRMS [Found: *m*/*z* 368.1273 (M^+), calcd for $C_{22}H_{16}N_4O_2$: M, 368.1273].

General Procedure for the Synthesis of 13 and 14. A mixture of 5-amino-3-methylpyrazole (1 mmol), acenaphthylene-1,2-dione (1 mmol), dimedone or tetronic acid (1 mmol), and CAN (10 mol %) in H_2O (5 mL) was stirred at 80 °C for 6−12 h. After completion of the reaction confirmed by TLC (eluent acetone/petroleum ether, 1:2), the reaction mixture was cooled to room temperature. Then, the precipitated product was filtered, dried and recrystallizated from DMF and ethanol to afford the pure **13** or **14** as a yellow powder.

1′,3′,7′,7′-Tetramethyl-6′,7′,8′,9′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-pyrazolo[3,4-*b*]quinoline]-2,5′(1′*H*)-dione (13). M.p.: >300 °C. IR (KBr) ν: 3280, 3183, 3047, 2949, 1720, 1603, 1544, 1465, 1366, 1251, 1149, 1042, 989, 781 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 0.78 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.90 (d, $J = 16.4$ Hz, 1H, CH_2), 2.00 (d, $J = 16.0$ Hz, 1H, CH_2), 2.54 (d, $J = 17.2$ Hz, 1H, CH_2), 2.61 (d, $J = 16.8$ Hz, 1H, CH_2), 3.64 (s, 3H, CH_3), 7.10 (d, $J = 6.0$ Hz, 1H, ArH), 7.54 (t, $J = 6.8$ Hz, 1H, ArH), 7.76−7.82 (m, 2H, ArH), 7.87 (d, $J = 6.8$ Hz, 1H, ArH), 8.18 (d, $J = 7.6$ Hz, 1H, ArH), 9.99 (s, 1H, NH). HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}N_3O_2$: 398.1863 $[M+H]^+$, found: 398.1863.

3′-Methyl-1′-phenyl-7′,8′-dihydro-2*H*-spiro[acenaphthylene-1,4′-furo[3,4-*e*]pyrazolo[3,4-*b*]pyridine]-2,5′(1′*H*)-dione (14b). M.p.: >300 °C. IR (KBr) ν: 3190, 3053, 2948, 1750, 1699, 1651, 1541, 1472, 1332, 1120, 1027, 786, 658 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 0.99 (s, 3H, CH_3), 4.99 (s, 2H, CH_2), 7.40−7.47 (m, 2H, ArH), 7.53−7.60 (m, 4H, ArH), 7.71 (t, $J = 7.8$ Hz, 1H, ArH), 7.89 (t, $J = 7.8$ Hz, 1H, ArH), 8.00 (d, $J = 8.4$ Hz, 1H, ArH), 8.06 (d, $J = 6.9$ Hz, 1H, ArH), 8.35 (d, $J = 8.1$ Hz, 1H, ArH), 10.71 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.5, 52.3, 66.6, 99.2, 102.9, 122.2, 123.0, 124.0, 125.4, 128.3, 129.5, 130.0, 130.3, 132.5, 132.8, 138.2, 139.1, 141.6, 143.0, 145.9, 160.6, 171.1, 204.4. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{17}N_3O_3$: 420.1343 $[M+H]^+$, found: 420.1329.

Acknowledgment. We are grateful to the foundation of Key Laboratory of Organic Synthesis of Jiangsu Province for financial support.

Supporting Information Available. Representative experimental procedures, spectral data of compounds **4a**−**g**, **6a**−**k**, **8a**−**c**, **9**, **13**, and **14a**,**b**, and crystal data for **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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