JOC The Journal of Organic Chemistry

Article

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Copper(II)-Catalyzed Carbon−Carbon Triple Bond Cleavage of Internal Alkynes for the Synthesis of Annulated Indolizines

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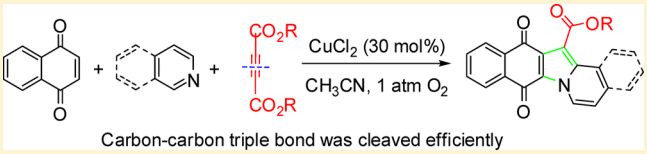
Supporting Information

ABSTRACT: Cleavage of C≡C bond in butynedioates via copper(II)-catalyzed reaction has been achieved, leading to the synthesis of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones in high yields by one-pot three-component reactions. In this unprecedented C≡C bond cleavage reaction of internal alkynes, both fragments from the alkyne are successively incorporated into the products.



INTRODUCTION

Carbon−carbon bond cleavage reactions have attracted considerable attention because of both fundamental scientific interest and potential utility in organic synthesis.[1] Over the past decades, various useful processes involving C−C single and double bonds cleavage have been developed.[2] In contrast, the cleavage of C−C triple bond is much less reported and remained one of the most challenging subjects in modern synthetic organic chemistry.[3] Most studies on alkyne cleavage have focused on stoichiometric organometallic reactions, such as alkyne ligand scission on metal complexes[4] and oxidative cleavage.[5] Except for metathesis of alkynes, examples for the metal-catalyzed C−C triple bond cleavage reactions are rare, and the limited reports usually used expensive and toxic transition metals such as rhodium, ruthenium, gold, or palladium.[6] Following our interest in copper(II)-catalyzed aerobic reactions,[7] we herein report the first example of copper(II)-catalyzed cleavage of C−C triple bond of internal alkyne under aerobic oxidation condition, which leads to an efficient access to benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones.

Indolizines have received much attention in recent years for their various pharmaceutical applications as antituberculosis agents,[8] PLA2 inhibitors,[9] histamine H3 receptor antagonists,[10] 5-HT3 receptor antagonists,[11] MPtpA/MPtpB phosphatases inhibitors,[12] TRPV1 antagonist,[13] and 15-lipoxygenase inhibitors.[14] As a class of benzo- annulated indolizines, benzo[*f*]-pyrido[1,2-*a*]indole-6,11-diones are important synthetic target molecules. Although a few synthetic routes for this class of compounds have been developed,[7c,15] there is still great demand to find new synthetic method using easily obtained substrates with high yields.

RESULTS AND DISCUSSION

Our investigation started with the reactions of 1,4-naphthoquinone **1** (1.0 mmol), pyridine **2a** (3.0 mmol), and dimethyl butynedioate **3a** (1.0 mmol) in acetonitrile in the presence of catalytic amount of hydrated copper(II) chloride (0.3 mmol) under an oxygen atmosphere of 1 atm. Interestingly, heating the reaction mixture at 80 °C for 16 h did not generate the [4 + 2] cycloaddition product via the nucleophilic addition of the zwitterion **I** to the naphthoquinone pyridinium salt **II**[7c] followed by *6-endo-trig* cyclization as shown in Scheme 1, but gave the benzo[*f*]pyrido[1,2-*a*]indole-6,11-dione product **4a** in 83% yield (Scheme 1). This indicates that carbon−carbon triple bond of butynedioate has been cleaved efficiently under this condition.

Encouraged by this promising result, we attempted to optimize the reaction conditions including solvent, the kind and amount of copper(II) salts, and reaction temperature. We first studied the influence of solvents and found DMF was a superior solvent (entries 1−7, Table 1). Regarding the copper(II) salts, hydrated copper(II) chloride proved to be the most promising (entry 7−11, Table 1). Decreasing the amount of copper chloride to 0.2 equiv led to a lower yield (entry 12, Table 1). Without copper(II) catalyst, no desired product was generated (entry 13, Table 1). When the reaction was carried out in the air instead of oxygen, 1.0 equiv of hydrated copper(II) chloride was needed to give the product in high yield (Table 1, entry 14). We finally optimized the reaction temperature with DMF as solvent and found the yield decreased with the lowering of the temperature (entry 15, Table 1). Therefore, the optimal reaction conditions should be heating the reactants in DMF at 80 °C under 1 atm O_2 in the presence of 30 mol % hydrated copper(II) chloride.

With the optimized conditions in hand, we then evaluated the scope of our procedure, applying various butynedioates **3** to react with naphthoquinone **1** and pyridines **2a**. Under the

Received: February 25, 2014
Published: April 8, 2014

   dx.doi.org/10.1021/jo500456d | *J. Org. Chem.* 2014, 79, 3992−3998

Scheme 1. Formation of Product 4a

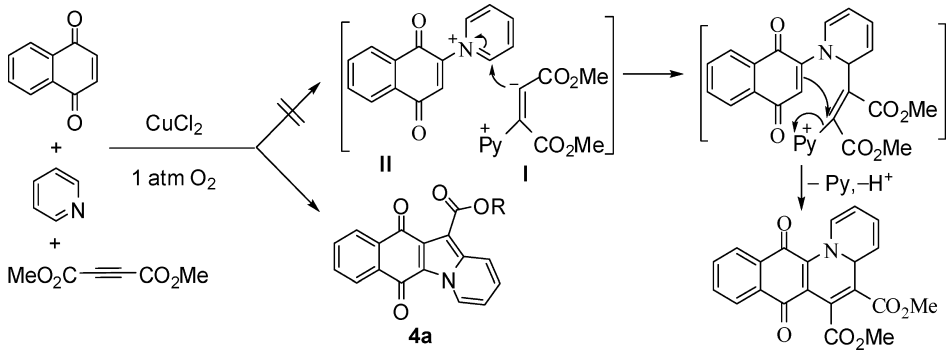
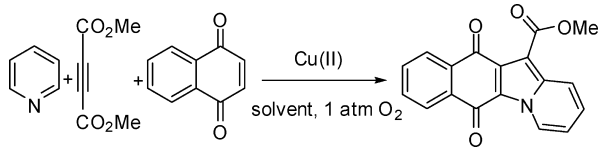


Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	copper (equiv)	temp (°C)	yield (%)[b]
1	CH_3CN	$CuCl_2$ (0.3)	reflux	83
2	C_6H_6	$CuCl_2$ (0.3)	reflux	32
3	toluene	$CuCl_2$ (0.3)	80	45
4	dioxane	$CuCl_2$ (0.3)	80	48
5	C_2H_5OH	$CuCl_2$ (0.3)	reflux	38
6	DMF	$CuCl_2$ (0.3)	100	88
7	**DMF**	**$CuCl_2$ (0.3)**	**80**	**93**
8	DMF	$CuBr_2$ (0.3)	80	85
9	DMF	$Cu(OTf)_2$ (0.3)	80	86
10	DMF	$Cu(OAc)_2$ (0.3)	80	83
11	DMF	$Cu(SO_4)_2$ (0.3)	80	75
12	DMF	$CuCl_2$ (0.2)	80	72
13	DMF	None	80	0
14	DMF	$CuCl_2$ (1.0)[c]	80	92
15	DMF	$CuCl_2$ (0.3)	60	65

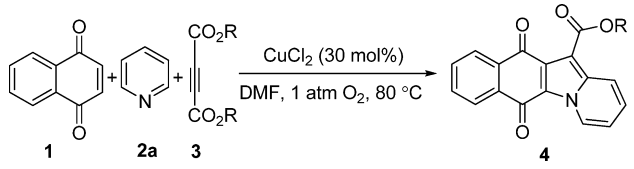
[a]Reagents and conditions: Under 1 atm of O_2, a mixture of naphthoquinone (1.0 mmol), pyridine (3.0 mmol), butynedioate (1.0 mmol), and hydrated copper(II) chloride was heated in solvent for 16 h. [b]Isolated yields. [c]Heated in the air.

optimized reaction conditions, reactions of different alkyl butynedioates **3a**–**3f** (1.0 mmol) with pyridine **2a** (1.0 mmol) and naphthoquinone **1** (1.0 mmol) are found to afford the corresponding products **4a**–**4f** in excellent yields (entry 1–7, Table 2). All products are fully characterized by analytical and spectral (NMR and HRMS) data. Moreover, the structure of **4e** was unambiguously established by X-ray crystallography (see Supporting Information).

Next, the scope of this reaction was extended to various substituted pyridines. 4-Substituted pyridines **2b**–**2f** also proved to be efficient substrates in this reaction. Pyridine with either EWG group (CO_2Et, CO_2Me, CN) or EDG group (OMe, *t*-Bu) reacted with butynedioate smoothly, yielding the desired products **5a**–**5s** in 73–96% yields (Table 3).

We also tried to use 3-bromopyridine **2g** to accomplish this reaction under the optimal conditions and found that two isomers **5t** and **5u** were formed simultaneously (Scheme 2). When 2-bromo pyridine was used as a substrate in this reaction, no desired product was formed, probably because of the steric effect.

Table 2. Reactions of Pyridine 2a and 1,4-Naphthoquinone 1 with Different Butynedioates 3[a]



1 2a 3 4

entry	3, R	product	yield (%)[b]
1	**3a**, R = CH_3	**4a**	93
2	**3b**, R = C_2H_5	**4b**	92
3	**3c**, R = $(CH_2)_2CH_3$	**4c**	85
4	**3d**, R = $CH(CH_3)_2$	**4d**	90
5	**3e**, R = $C(CH_3)_3$	**4e**	87
6	**3f**, R = $(CH_2)_3CH_3$	**4f**	85

[a]Reagents and conditions: Under 1 atm of O_2, a mixture of pyridine (3.0 mmol), butynedioate (1.0 mmol), naphthoquinone (1.0 mmol) and hydrated copper chloride (0.3 mmol) was heated in DMF at 80 °C for 16 h. [b]Isolated yields.

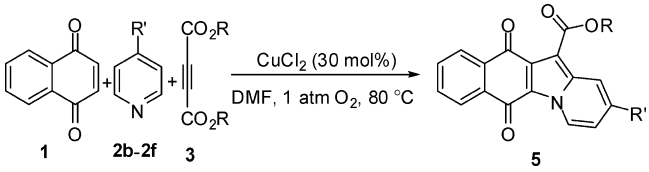
To further extend the utility of this reaction, we have investigated the reactions of isoquinoline **6** with butynedioates **3** and 1,4-naphthoquinone **1** for the synthesis of further annulated derivatives **7**. As expected, when naphthoquinone **1** (1.0 mmol) was heated with isoquinoline **6** (3.0 mmol), butynedioate **3** (3.0 mmol) and hydrated copper(II) chloride (0.3 mmol) under the optimized conditions, the corresponding products **7a**–**7e** were obtained in excellent yields (Table 4).

For a better understanding of the reaction mechanism, two control experiments were performed as shown in Scheme 3. First, when *N*-(2,7-dihydroxynaphthyl)-pyridinium chloride **8** (1.0 mmol)[16] was used as a substrate to react with pyridine **2a** (3.0 mmol) and butynedioate **3a** (1.0 mmol) by heating in DMF at 80 °C in O_2 atmosphere in the presence of 30 mol % copper(II) chloride, **4a** was generated in 90% yield (eq 1, Scheme 3). Meanwhile, this reaction cannot take place in the absence of $CuCl_2$ under otherwise the same conditions. Second, heating pyridinium salt **9** (1.0 mmol) with naphthoquinone **1** (1.0 mmol) and pyridine **2a** (3.0 mmol) in DMF at 80 °C in O_2 atmosphere in the presence of 30 mol % copper(II) chloride also led to the generation of **4a** in 92% yield (eq 1, Scheme 3). These results reveal that the pyridinium salt **II**[7c] generated in situ from naphthoquinone and pyridine under the action of $CuCl_2$ is a key intermediate in the reaction.

On the basis of the above experimental results, a possible mechanism for this reaction is suggested in Scheme 4. The reaction proceeded via two pathways. In the first, nucleophilic addition of pyridine to dimethyl butynedioate gave zwitterion

dx.doi.org/10.1021/jo500456d | J. Org. Chem. 2014, 79, 3992–3998

Table 3. Reaction of Pyridine 2b−2f, Terminal Alkynes 3, and 1,4-Naphthoquinone 1[a]



entry	2, R′	3, R	product	yield (%)[b]
1	**2b**, R′ = CO_2Me	**3a**, R = CH_3	**5a**	92
2	**2b**, R′ = CO_2Me	**3b**, R = C_2H_5	**5b**	91
3	**2b**, R′ = CO_2Me	**3c**, R = $(CH_2)_2CH_3$	**5c**	88
4	**2b**, R′ = CO_2Me	**3d**, R = $CH(CH_3)_2$	**5d**	89
5	**2c**, R′ = CO_2Et	**3a**, R = CH_3	**5e**	96
6	**2c**, R′ = CO_2Et	**3b**, R = C_2H_5	**5f**	95
7	**2c**, R′ = CO_2Et	**3d**, R = $CH(CH_3)_2$	**5g**	92
8	**2c**, R′ = CO_2Et	**3e**, R = $C(CH_3)_3$	**5h**	87
9	**2d**, R′ = CN	**3a**, R = CH_3	**5i**	81
10	**2d**, R′ = CN	**3b**, R = C_2H_5	**5j**	77
11	**2d**, R′ = CN	**3d**, R = $CH(CH_3)_2$	**5k**	73
12	**2e**, R′ = OMe	**3a**, R = CH_3	**5l**	95
13	**2e**, R′ = OMe	**3b**, R = C_2H_5	**5m**	89
14	**2e**, R′ = OMe	**3d**, R = $CH(CH_3)_2$	**5n**	87
15	**2e**, R′ = OMe	**3e**, R = $C(CH_3)_3$	**5o**	86
16	**2f**, R′ = $C(CH_3)_3$	**3a**, R = CH_3	**5p**	91
17	**2f**, R′ = $C(CH_3)_3$	**3b**, R = C_2H_5	**5q**	88
18	**2f**, R′ = $C(CH_3)_3$	**3c**, R = $(CH_2)_2CH_3$	**5r**	87
19	**2f**, R′ = $C(CH_3)_3$	**3d**, R = $CH(CH_3)_2$	**5s**	85

[a]Reagents and conditions: Under 1 atm of O_2, the mixture of substituted pyridine **2b−2f** (3.0 mmol), butynedioates **3** (1.0 mmol), naphthoquinone **1** (1.0 mmol) and hydrated copper chloride (0.3 mmol) was heated in DMF at 80 °C for 16 h. [b]Isolated yields.

I,[17] which reacted with intermediate **II** to yield **III**. Subsequent 5-*exo*-*trig* cyclization in **III** followed by proton transfer led to **IV**. Product **4a** was finally formed by *β*-elimination in **IV** with the loss of a pyridinium salt (path a, Scheme 4). The pyridinium salt was then deprotonated to give the pyridinium ylide **V**, which could also react with intermediate **II** to give **4a** as shown in path b, Scheme 4. The Cu^{2+} salt can be regenerated by oxygen oxidation.

In order to further clarify the mechanism, we used less than stoichiometric dimethyl butynedioate **3a** (0.6 mmol) to react with naphthoquinone **1** (1.0 mmol) and pyridine **2a** (3.0 mmol) by heating in DMF at 80 °C for 24 h in the presence of 30 mol % copper(II) chloride under the O_2 atmosphere. As expected, naphthoquinone could be consumed completely and the desired product **4a** was formed in 86% yield. Similarly, when less than stoichiometric diethyl butynedioate **3b** (0.6 mmol) was used to react with naphthoquinone **1** (1.0 mmol) and pyridine **2a** (3.0 mmol) under the same conditions, **4b** was obtained in 84% yield (Scheme 5). These results showed that both pieces of fragments from butynedioates participated in the reaction, further confirming our proposed mechanism.

CONCLUSION

In conclusion, we have reported a novel copper(II)-catalyzed reaction to cleave carbon−carbon triple bond of internal alkynes for the synthesis of benzo[*f*]pyrido[1,2-*a*]indole-6,11-diones. In this process, the two carbon atoms in the original C≡C bond, together with their substituents, are fully employed and incorporated into the products successively, leading to a perfect atomic economy of the entire synthesis. Further advantages of this synthesis include mild reaction condition, high product yields, and broad substrate scope. This protocol supplied an unprecedented avenue for the cleavage of carbon−carbon triple bond and may be further applied to synthesize other heterocyclic compounds. Studies toward elucidating the reaction mechanism and developing further applications of this type of C≡C triple bond cleavage reactions are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Methods. Melting points are uncorrected. ^1H NMR spectra were measured at 400 MHz with $CDCl_3$ as solvent. The chemical shifts (δ) are reported in parts per million relative to the residual deuterated solvent signal, and coupling constants (J) are given in Hertz. ^{13}C NMR spectra were measured at 100 MHz with $CDCl_3$ as solvent. HRMS (ESI) data were obtained in the electron impact (EI) (70 eV) mode.

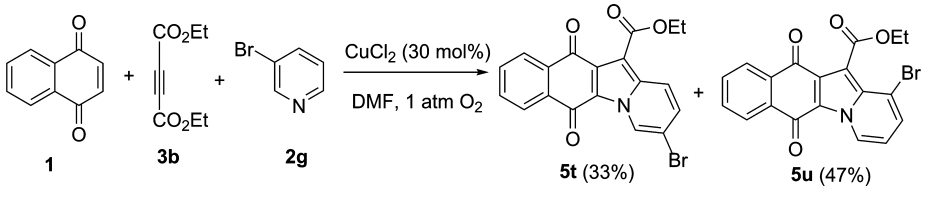
General Experimental Procedures of 4. Pyridine **2a** (3.0 mmol), 1,4-naphthaquionone **1** (1.0 mmol), butynedioates **3** (1.0 mmol), and hydrated copper(II) chloride (0.3 mmol) were mixed in 15 mL of DMF and heated at 80 °C for 16 h under 1 atm of O_2. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. Chromatographic separation (ethyl acetate/petroleum ether, 1:6) of the reaction mixture after removal of the solvent gave product **4**.

*Methyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**4a**).* Red solid: yield 283 mg (93%); mp 190−191 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.08 (t, J = 6.8 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 7.62−7.64 (m, 2H), 8.07−8.12 (m, 2H), 8.20 (d, J = 9.2 Hz, 1H), 9.69 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 174.7, 163.4, 139.3, 133.8, 133.3, 133.1, 132.9, 128.1, 127.9, 127.6, 126.9, 125.7, 122.1, 120.6, 117.1, 105.1, 51.7; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{11}NO_4Na$ 328.0586, found 328.0586.

*Ethyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**4b**).* Red solid: yield 292 mg (92%); mp 156−158 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (t, J = 7.2 Hz, 3H), 4.51 (q, J = 7.2 Hz, 2H), 7.17 (d, J = 7.2 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.69−7.72 (m, 2H), 8.20−8.23 (m, 2H), 8.30 (d, J = 9.2 Hz, 1H), 9.83 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 175.2, 163.3, 139.6, 134.2, 133.8, 133.7, 133.4, 133.2, 128.2, 127.8, 127.3, 126.0, 122.4, 120.9, 117.3, 106.1, 61.0, 14.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{19}H_{13}NO_4Na$ 342.0742, found 342.0740.

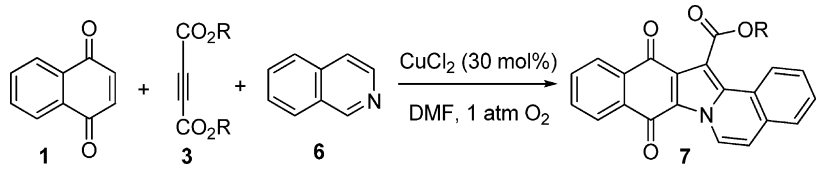
*Propyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**4c**).* Red solid: yield 284 mg (85%); mp 133−135 °C;

Scheme 2. Formation of Two Isomers



dx.doi.org/10.1021/jo500456d | J. Org. Chem. 2014, 79, 3992−3998

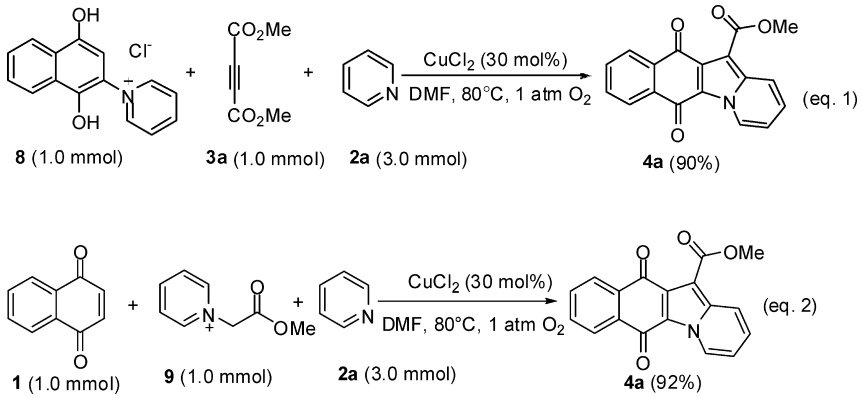
Table 4. Reaction of Isoquinoline 6, Butynedioate 3, and 1,4-Naphthoquinone 1[a]



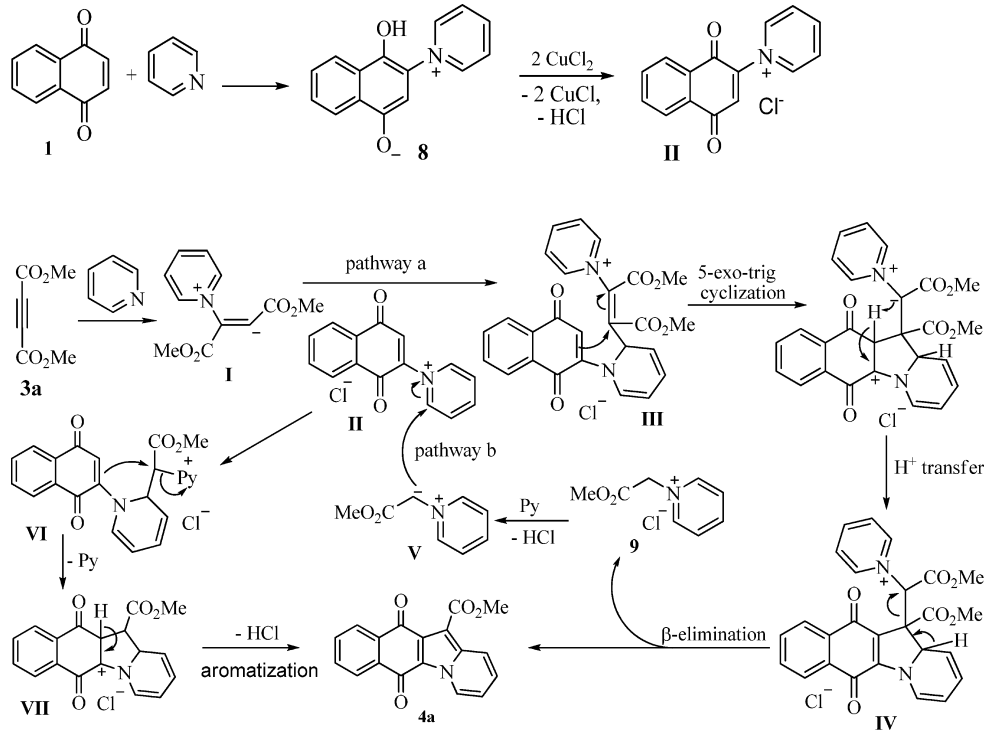
entry	3, R	product	yield (%)[b]
1	**3a**, R = CH_3	**7a**	93
2	**3b**, R = CH_2CH_3	**7b**	91
3	**3c**, R = $(CH_2)_2CH_3$	**7c**	89
4	**3d**, R = $CH(CH_3)_2$	**7d**	88
5	**3e**, R = $C(CH_3)_3$	**7e**	85

[a]Reagents and conditions: Under 1 atm of O_2, the mixture of isoquinoline **6** (3.0 mmol), butynedioate **3** (1.0 mmol), naphthoquinone **1** (1.0 mmol), and hydrated copper chloride (0.3 mmol) was heated in DMF at 80 °C for 16 h. [b]Isolated yields.

Scheme 3. Control Experiment



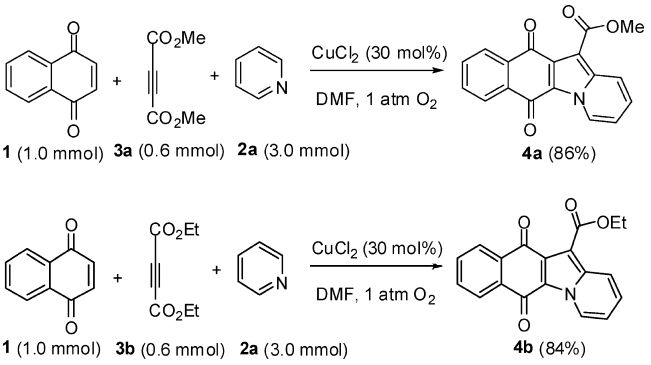
Scheme 4. Proposed Mechanism



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, J = 7.2 Hz, 3H), 1.88−1.93 (m, 2H), 4.41 (t, J = 6.8 Hz, 2H), 7.14 (td, J = 6.8, 1.2 Hz, 1H), 7.39−7.43 (m, 1H), 7.68−7.71 (m, 2H), 8.18−8.22 (m, 2H), 8.29 (d, J = 8.8 Hz, 1H), 9.81 (dt, J = 6.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)

dx.doi.org/10.1021/jo500456d | J. Org. Chem. 2014, 79, 3992−3998

Scheme 5. Mechanism Confirmation



δ 180.2, 175.1, 163.4, 139.6, 134.2, 133.7, 133.4, 133.1, 128.7, 128.2, 127.8, 127.3, 126.0, 122.4, 120.9, 117.3, 106.0, 66.7, 21.2, 10.7; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{15}NO_4Na$ 356.0899, found 356.0897.

*Isopropyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**4d**).* Red solid: yield 299 mg (90%); mp 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, *J* = 6.0 Hz, 6H), 5.39−5.42 (m, 1H), 7.16 (td, *J* = 7.2, 1.6 Hz, 1H), 7.40−7.44 (m, 1H), 7.69−7.73 (m, 2H), 8.21−8.24 (m, 2H), 8.28 (d, *J* = 9.2 Hz, 1H), 9.84 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 174.8, 162.4, 139.0, 133.9, 133.4, 133.0, 132.7, 128.3, 127.9, 127.3, 126.9, 125.6, 122.0, 120.5, 116.9, 106.3, 68.3, 21.7; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{15}NO_4Na$ 356.0899, found 356.0899.

*tert-Butyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**4e**).* Red solid: yield 301 mg (87%); mp 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (s, 9H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.68−7.73 (m, 2H), 8.20 (dd, *J* = 6.0, 2.0 Hz, 2H), 8.25 (d, *J* = 8.8 Hz, 1H), 9.81 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 175.1, 162.6, 139.3, 134.3, 133.9, 133.3, 133.1, 128.6, 128.2, 127.5, 127.2, 126.0, 122.1, 120.8, 117.2, 108.1, 81.8, 28.4; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{17}NO_4Na$ 370.1055, found 370.1055.

*Butyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**4f**).* Red solid: yield 294 mg (85%); mp 89−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, *J* = 7.6 Hz, 3H), 1.52−1.58 (m, 2H), 1.84−1.88 (m, 2H), 4.46 (t, *J* = 6.8 Hz, 2H), 7.16 (t, *J* = 6.8 Hz, 1H), 7.40−7.44 (m, 1H), 7.70−7.73 (m, 2H), 8.18−8.23 (m, 2H), 8.29 (d, *J* = 8.8 Hz, 1H), 9.82 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 175.5, 163.7, 139.8, 134.5, 134.0, 133.7, 133.4, 129.0, 128.5, 128.1, 127.6, 126.3, 122.7, 121.2, 117.6, 106.3, 65.3, 31.1, 19.6, 14.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{17}NO_4Na$ 370.1055, found 370.1053.

General Procedure for the Preparation of 5. Substituted pyridine **2b**−**2g** (3.0 mmol), 1,4-naphthaquionone **1** (1.0 mmol), butynedioates **3** (1.0 mmol), and hydrated copper(II) chloride (0.3 mmol) were mixed in 15 mL of DMF and heated at 80 °C for 16 h under 1 atm of O_2. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. Chromatographic separation (ethyl acetate/petroleum ether, 1:6) of the reaction mixture after removal of the solvent gave product **5**.

*Dimethyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-2,12-dicarboxylate (**5a**).* Yellow solid: yield 333 mg (92%); mp 224−225 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 4.08 (s, 3H), 7.70 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.74−7.77 (m, 2H), 8.24−8.26 (m, 2H), 8.97 (s, 1H), 9.85 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 175.6, 164.7, 163.4, 138.1, 134.1, 133.7, 133.6, 128.9, 128.6, 127.7, 127.5, 126.3, 123.3, 116.2, 108.5, 52.9, 52.4; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{13}NO_6Na$ 386.0641, found 386.0632.

*12-Ethyl 2-methyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-2,12-dicarboxylate (**5b**).* Yellow solid: yield 342 mg (91%); mp 214−215 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (t, *J* = 7.2 Hz, 3H), 4.00 (s, 3H), 4.55 (q, *J* = 7.2 Hz, 2H), 7.68 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.74−7.76 (m, 2H), 8.24−8.26 (m, 2H), 8.97 (s, 1H), 9.83 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 175.7, 164.7, 162.9, 138.0, 134.2, 133.7, 133.6, 133.5, 129.0, 128.4, 127.7, 127.5, 126.3, 123.4, 116.2, 109.1, 61.5, 52.9, 14.3; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{15}NO_6Na$ 400.0797, found 400.0789.

*12-Propyl 2-methyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-2,12-dicarboxylate (**5c**).* Red solid: yield 345 mg (88%); mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (t, *J* = 7.2 Hz, 3H), 1.90−1.95 (m, 2H), 4.00 (s, 3H), 4.46 (t, *J* = 6.8 Hz, 2H), 7.69 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.74−7.76 (m, 2H), 8.24−8.27 (m, 2H), 8.99 (s, 1H), 9.85 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 175.7, 164.7, 162.9, 138.1, 134.2, 133.7, 133.6, 129.1, 128.4, 127.7, 127.5, 126.3, 123.4, 116.1, 109.1, 67.1, 52.9, 22.1, 10.7; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{17}NO_6Na$ 414.0954, found 414.0947.

*12-Isopropyl 2-methyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido-[1,2-a]indole-2,12-dicarboxylate (**5d**).* Red solid: yield 348 mg (89%); mp 209−211 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, *J* = 6.8 Hz, 6H), 4.02 (s, 3H), 5.41−5.48 (m, 1H), 7.69 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.74−7.77 (m, 2H), 8.25−8.28 (m, 2H), 8.98 (s, 1H), 9.84 (dd, *J* = 7.6, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):δ 179.8, 175.6, 164.7, 162.4, 137.9, 134.2, 133.7, 133.6, 133.5, 129.0, 128.3, 127.7, 127.6, 127.5, 126.3, 123.4, 116.0, 109.7, 69.2, 52.9, 21.9; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{17}NO_6Na$ 414.0954, found 414.0954.

*12-Methyl 2-ethyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]-indole-2,12-dicarboxylate (**5e**).* Yellow solid: yield 363 mg (96%); mp 212−214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, *J* = 7.2 Hz, 3H), 4.08 (s, 3H), 4.46 (q, *J* = 7.2 Hz, 2H), 7.68−7.75 (m, 3H), 8.22−8.24 (m, 2H), 8.94 (s, 1H), 9.82 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 175.8, 164.4, 163.6, 138.3, 134.3, 133.9, 133.8, 133.7, 129.1, 129.0, 127.8, 127.6, 126.4, 123.5, 123.3, 116.4, 108.6, 62.3, 52.5, 14.4; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{15}NO_6Na$ 400.0797, found 400.0791.

*Diethyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-2,12-dicarboxylate (**5f**).* Yellow solid: yield 371 mg (95%); mp 176−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, *J* = 7.2 Hz, 3H), 1.52 (t, *J* = 7.2 Hz, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 4.54 (q, *J* = 7.2 Hz, 2H), 7.67 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.71−7.74 (m, 2H), 8.21−8.24 (m, 2H), 8.94 (s, 1H), 9.80 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 174.9, 163.7, 162.2, 137.5, 133.6, 133.2, 133.1, 133.0, 128.4, 128.3, 127.2, 127.0, 125.7, 122.8, 122.7, 115.7, 108.4, 61.6, 60.9, 13.9; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{17}NO_6Na$ 414.0954, found 414.0959.

*12-Isopropyl 2-ethyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-2,12-dicarboxylate (**5g**).* Yellow solid: yield 374 mg (92%); mp 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, *J* = 7.2 Hz, 3H), 1.51 (d, *J* = 6.4 Hz, 6H), 4.45 (q, *J* = 7.2 Hz, 2H), 5.42−5.46 (m, 1H), 7.68 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.72−7.76 (m, 2H), 8.22−8.26 (m, 2H), 8.95 (s, 1H), 9.82 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 175.3, 163.9, 161.9, 137.6, 133.9, 133.3, 133.2, 128.7, 128.3, 127.3, 127.1, 125.9, 122.9, 115.8, 109.3, 68.8, 61.7, 21.6, 13.9; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{19}NO_6Na$ 428.1110, found 428.1101.

*12-tert-Butyl 2-ethyl 6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-2,12-dicarboxylate (**5h**).* Yellow solid: yield 366 mg (87%); mp 198−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (t, *J* = 7.2 Hz, 3H), 1.74 (s, 9H), 4.47 (q, *J* = 7.2 Hz, 2H), 7.81−7.83 (m, 3H), 8.02−8.22 (m, 2H), 8.97 (s, 1H), 9.83 (dd, *J* = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 175.5, 164.3, 161.7, 143.5, 137.8, 133.5, 133.4, 130.9, 129.1, 128.5, 127.6, 127.4, 126.2, 123.3, 116.0, 111.0, 82.4, 62.0, 28.3, 14.3; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{21}NO_6Na$ 442.1267, found 442.1268.

*Methyl 2-cyano-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]-indole-12-carboxylate (**5i**).* Yellow solid: yield 267 mg (81%); mp 287−289 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (s, 3H), 7.19 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.77−7.79 (m, 2H), 8.25−8.28 (m, 2H), 9.03 (s, 1H), 9.38 (dd, *J* = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5, 175.9, 162.9, 136.9, 134.1, 134.0, 133.2, 129.1, 128.6, 127.7, 127.3, 126.4, 116.7, 110.5, 108.5, 52.6; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{10}N_2O_4Na$ 353.0538, found 353.0539.

*Ethyl 2-cyano-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]-indole-12-carboxylate (**5j**).* Yellow solid: yield 265 mg (77%); mp

dx.doi.org/10.1021/jo500456d | J. Org. Chem. 2014, 79, 3992−3998

225−226 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (t, J = 7.2 Hz, 3H), 4.55 (q, J = 7.2 Hz, 2H), 7.22 (dd, J = 7.2, 1.6 Hz, 1H), 7.76−7.78 (m, 2H), 8.23−8.27 (m, 2H), 8.70 (s, 1H), 9.88 (dd, J = 7.2, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3, 175.9, 162.4, 136.8, 134.1, 134.0, 133.9, 133.2, 129.1, 128.5, 127.7, 127.3, 126.4, 123.8, 116.7, 116.6, 110.3, 109.1, 61.7, 14.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{20}H_{12}N_2O_4Na$ 367.0695, found 367.0694.

*Isopropyl 2-cyano-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**5k**).* Yellow solid: yield 261 mg (73%); mp 183−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (d, J = 6.4 Hz, 6H), 5.40−5.45 (m, 1H), 7.21 (dd, J = 7.2, 1.6 Hz, 1H), 7.75−7.79 (m, 2H), 8.23−8.27 (m, 2H), 8.67 (s, 1H), 9.87 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 175.6, 161.6, 136.3, 133.8, 133.6, 133.5, 133.0, 128.8, 128.2, 127.3, 127.0, 126.9, 126.1, 116.5, 116.2, 109.9, 109.4, 69.3, 21.6; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{14}N_2O_4Na$ 381.0851, found 381.0839.

*Methyl 2-methoxy-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**5l**).* Red solid: yield 319 mg (95%); mp 242−243 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 4.03 (s, 3H), 6.84 (dd, J = 7.6, 2.4 Hz, 1H), 7.67−7.71 (m, 3H), 8.17−8.20 (m, 2H), 9.68 (d. J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 174.6, 164.4, 159.7, 142.7, 134.0, 133.5, 133.3, 132.9, 129.4, 129.2, 127.1, 125.7, 122.0, 111.9, 102.9, 98.1, 55.8, 51.7; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{19}H_{13}NO_5Na$ 358.0691, found 358.0683.

*Ethyl 2-methoxy-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]-indole-12-carboxylate (**5m**).* Red solid: yield 312 mg (89%); mp 183−185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (t, J = 7.2 Hz, 3H), 3.96 (s, 3H), 4.50 (q, J = 7.2 Hz, 2H), 6.84 (dd, J = 7.6, 2.8 Hz, 1H), 7.67−7.72 (m, 3H), 8.17−8.21 (m, 2H), 9.68 (d, J = 7..6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 174.7, 164.0, 159.7, 142.7, 134.2, 133.7, 133.4, 133.0, 129.5, 127.3, 125.8, 122.1, 112.0, 103.7, 98.2, 60.8, 55.9, 14.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{20}H_{15}NO_5Na$ 372.0848, found 372.0844.

*Isopropyl 2-methoxy-6,11-dioxo-6,11-dihydrobenzo[f]pyrido-[1,2-a]indole-12-carboxylate (**5n**).* Red solid: yield 316 mg (87%); mp 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (d, J = 6.0 Hz, 6H), 3.95 (s, 3H), 5.34−5.40 (m, 1H), 6.83 (dd, J = 7.6, 2.8 Hz, 1H), 7.64−7.71 (m, 3H), 8.17−8.21 (m, 2H), 9.67 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 174.3, 163.0, 159.2, 142.1, 133.9, 133.3, 132.9, 132.6, 129.1, 126.9, 125.4, 121.7, 111.5, 103.9, 97.8, 68.0, 55.4, 21.7; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{17}NO_5Na$ 386.1004, found 386.1003.

*t-Butyl 2-methoxy-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**5o**).* Red solid: yield 325 mg (86%); mp 215−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (s, 9H), 3.92 (s, 3H), 6.76 (dd, J = 7.6, 1.8 Hz, 1H), 7.56 (d, J = 2.8 Hz, 1H), 7.62−7.69 (m, 2H), 8.12−8.16 (m, 2H), 9.60 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 174.4, 162.9, 159.4, 142.2, 134.3, 133.7, 133.1, 132.8, 129.5, 129.4, 127.1, 125.7, 121.8, 111.7, 105.6, 98.1, 81.3, 55.8, 28.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{22}H_{19}NO_5Na$ 400.1161, found 400.1161.

*Methyl 2-tert-butyl-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**5p**).* Red solid: yield 328 mg (91%); mp 212−214 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 4.05 (s, 3H), 7.24 (dd, J = 7.6, 2.0 Hz, 1H), 7.68−7.72 (m, 2H), 8.19−8.22 (m, 2H), 8.27 (s, 1H), 9.73 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 174.6, 163.9, 152.2, 140.0, 133.9, 133.4, 133.1, 132.7, 128.5, 127.3, 126.9, 125.6, 121.7, 116.5, 115.1, 104.4, 51.6, 35.0, 29.9; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{22}H_{19}NO_4Na$ 384.1212, found 384.1216.

*Ethyl 2-tert-butyl-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]-indole-12-carboxylate (**5q**).* Red solid: yield 330 mg (88%); mp 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.51 (t, J = 7.2 Hz, 3H), 4.52 (q, J = 7.2 Hz, 2H), 7.23 (d, J = 7.2 Hz, 1H), 7.70−7.72 (m, 2H), 8.21−8.26 (m, 3H), 9.74 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 174.9, 163.5, 152.3, 140.1, 134.3, 133.8, 133.3, 133.0, 129.0, 127.7, 127.3, 125.9, 122.1, 116.8, 115.5, 105.3, 60.9, 35.4, 30.2, 14.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{23}H_{21}NO_4Na$ 398.1368, found 398.1372.

*Propyl 2-tert-butyl-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]indole-12-carboxylate (**5r**).* Red solid: yield 338 mg (87%); mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (t, J = 7.2 Hz, 3H), 1.38 (s, 9H), 1.68−1.92 (m, 2H), 4.39 (t, J = 6.8 Hz, 2H), 7.19 (dd, J = 7.6, 2.0 Hz, 1H), 7.63−7.66 (m, 2H), 8.11−8.17 (m, 2H), 8.22 (d, J = 1.2 Hz, 1H), 9.67 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 174.8, 163.6, 152.3, 140.1, 134.3, 133.7, 133.3, 132.9, 129.0, 127.7, 127.2, 125.8, 122.1, 116.7, 115.5, 105.4, 66.6, 35.4, 30.3, 22.2, 10.7; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{24}H_{23}NO_4Na$ 412.1525, found 412.1527.

*Isopropyl 2-tert-butyl-6,11-dioxo-6,11-dihydrobenzo[f]pyrido-[1,2-a]indole-12-carboxylate (**5s**).* Red solid: yield 332 mg (85%); mp 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.49 (d, J = 6.4 Hz, 6H), 5.37−5.43 (m, 1H), 7.21 (dd, J = 7.2, 2.0 Hz, 1H), 7.67−7.71 (m, 2H), 8.18−8.23 (m, 3H), 9.72 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 175.1, 163.1, 152.4, 140.1, 134.5, 134.0, 133.5, 133.2, 129.3, 127.9, 127.5, 126.1, 122.3, 116.9, 115.7, 106.2, 68.7, 35.6, 30.5, 22.4; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{24}H_{23}NO_4Na$ 412.1525, found 412.1525.

*Ethyl 3-bromo-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]-indole-12-carboxylate (**5t**).* Yellow solid: yield 131 mg (33%); mp 186−188 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50 (t, J = 7.2 Hz, 3H), 4.51 (q, J = 7.2 Hz, 2H), 7.48 (dd, J = 9.6, 1.6 Hz, 1H), 7.72−7.75 (m, 2H), 8.20−8.24 (m, 3H), 10.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 175.4, 163.0, 137.7, 134.2, 133.6, 133.5, 133.4, 131.1, 128.4, 128.1, 127.5, 126.1, 122.3, 121.4, 112.8, 106.8, 61.2, 14.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{19}H_{12}BrNO_4Na$ 419.9847, found 419.9841.

*Ethyl 1-bromo-6,11-dioxo-6,11-dihydrobenzo[f]pyrido[1,2-a]-indole-12-carboxylate (**5u**).* Red solid: yield 188 mg (47%); mp 260−262 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (t, J = 7.2 Hz, 3H), 4.56 (q, J = 7.2 Hz, 2H), 6.94 (t, J = 7.2 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.68−7.76 (m, 2H), 8.18 (d, J = 7.2 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 9.68 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 174.8, 165.1, 134.7, 134.3, 133.6, 133.5, 129.8, 127.3, 127.2, 126.9, 121.2, 116.9, 114.0, 110.8, 62.7, 14.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{19}H_{12}BrNO_4Na$ 419.9847, found 419.9845.

General Procedure for the Preparation of 7. Isoquinoline **6** (3.0 mmol), 1,4-naphthaquionone **1** (1.0 mmol), butynedioates **3** (1.0 mmol), and hydrated copper(II) chloride (0.3 mmol) were mixed in 15 mL of DMF and heated at 80 °C for 16 h under 1 atm of O_2. After completion of the reaction, the reaction mixture was allowed to cool to room temperature. Chromatographic separation (ethyl acetate/petroleum ether, 1:6) of the reaction mixture after removal of the solvent gave product **7**.

*14-Methoxycarbonylbenz[5,6]indolo[2,1-a]isoquinoline-8,13-dione (**7a**).* Yellow solid: yield 329 mg (93%); mp 245−247 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (s, 3H), 7.26−7.28 (m, 1H), 7.59−7.62 (m, 2H), 7.69−7.74 (m, 3H), 8.17−8.24 (m, 3H), 9.41−9.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 174.9, 166.9, 134.2, 133.6, 133.3, 133.1, 132.5, 129.3, 129.2, 128.8, 127.5, 126.7, 126.4, 124.2, 124.1, 124.0, 122.3, 117.3, 109.4, 53.2; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{22}H_{13}NO_4Na$ 378.0742, found 378.0734.

*14-Ethoxycarbonylbenz[5,6]indolo[2,1-a]isoquinoline-8,13-dione (**7b**).* Yellow solid: yield 337 mg (91%); mp 238−240 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (t, J = 7.2 Hz, 3H), 4.67 (q, J = 7.2 Hz, 2H), 7.25 (d, J = 7.2 Hz, 1H), 7.57−7.59 (m, 2H), 7.68−7.71 (m, 3H), 8.16−8.25 (m, 3H), 9.39 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.8, 175.4, 166.8, 134.6, 133.9, 133.7, 133.4, 132.9, 129.7, 129.6, 129.2, 127.9, 127.1, 127.0, 126.8, 124.7, 124.6, 122.7, 117.6, 110.4, 62.7, 14.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{23}H_{15}NO_4Na$ 392.0899, found 392.0889.

*14-Propoxycarbonylbenz[5,6]indolo[2,1-a]isoquinoline-8,13-dione (**7c**).* Yellow solid: yield 340 mg (89%); mp 228−229 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, J = 7.2 Hz, 3H), 1.89−1.95 (m, 2H), 4.57 (t, J = 6.8 Hz, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.62−7.64 (m, 2H), 7.71−7.78 (m, 3H), 8.19−8.27 (m, 3H), 9.46 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 175.2, 166.7, 134.4, 133.7, 133.5, 133.2, 132.6, 129.5, 129.4, 129.0, 127.7, 126.8, 126.6,

dx.doi.org/10.1021/jo500456d | J. Org. Chem. 2014, 79, 3992−3998

124.4, 124.3, 122.4, 117.4, 110.2, 68.1, 21.9, 10.5; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{17}NO_4Na$ 406.1055, found 406.1053.

*14-Isopropoxycarbonylbenz[5,6]indolo[2,1-a]isoquinoline-8,13-dione (**7d**).* Yellow solid: yield 336 mg (88%); mp 261−263 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (d, J = 6.4 Hz, 6H), 5.58−5.61 (m, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.59−7.62 (m, 2H), 7.69−7.75 (m, 3H), 8.19−8.29 (m, 3H), 9.42 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 174.9, 165.8, 134.2, 133.4, 133.3, 132.9, 132.2, 129.2, 129.0, 128.6, 127.4, 126.6, 126.4, 126.3, 124.1, 122.1, 117.1, 110.5, 69.9, 21.5; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{17}NO_4Na$ 406.1055, found 406.1054.

*14-tert-Butoxycarbonylbenz[5,6]indolo[2,1-a]isoquinoline-8,13-dione (**7e**).* Yellow solid: yield 339 mg (85%); mp 240−241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 9H), 7.28 (d, J = 7.6 Hz, 1H), 7.61−7.65 (m, 2H), 7.70−7.77 (m, 3H), 8.21−8.26 (m, 2H), 8.35−8.37 (m, 1H), 9.44 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 175.2, 165.6, 134.5, 133.6, 133.5, 133.1, 132.2, 129.4, 129.2, 128.8, 127.6, 126.8, 126.5, 126.4, 124.5, 124.4, 122.1, 117.3, 112.1, 83.3, 28.0; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{19}NO_4Na$ 420.1212, found 420.1205.

■ ASSOCIATED CONTENT

Supporting Information

X-ray crystallographic structures and crystal data (CIF) on compound **4e**. ^{1}H NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge National Natural Science Foundation of China (NSFC 21172188, 21202058), and Open Project Program of Jiangsu Province Key Laboratory of Green Synthetic for Functional Materials (K201308) for financial support of this work.

■ REFERENCES

(1) For selected reviews, see: (a) Jun, C. H. *Chem. Soc. Rev.* **2004**, *33*, 610. (b) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222. (c) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100.

(2) See for examples: (a) Miyamoto, K.; Tada, N.; Ochiai, M. *J. Am. Chem. Soc.* **2007**, *129*, 2772. (b) Seiser, T.; Roth, O. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6320. (c) Najera, C.; Sansano, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2452. (d) Seiser, T.; Cramer, N. *J. Am. Chem. Soc.* **2010**, *132*, 5340. (e) Li, H.; Li, Y.; Zhang, X. S.; Chen, K.; Wang, X.; Shi, Z. J. *J. Am. Chem. Soc.* **2011**, *133*, 15244.

(3) (a) For reviews, see: (a) Jennings, P. W.; Johnson, L. L. *Chem. Rev.* **1994**, *94*, 2241. (b) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (c) Murakami, M.; Ito,Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, 1999; p 97.

(4) (a) Cairns, G. A.; Carr, N.; Green, M.; Mahon, M. F. *Chem. Commun.* **1996**, 2431. (b) Chamberlin, R. L. M.; Rosenfeld, D. C.; Wolczanski, P. T.; Lobkovsky, E. B. *Organometallics* **2002**, *21*, 2724. (c) Adams, H.; Guio, L. V. Y.; Morris, M. J.; Spey, S. E. *J. Chem. Soc., Dalton Trans.* **2002**, 2907.

(5) (a) Moriarty, R. M.; Penmasta, R.; Awasthi, A. K.; Prakash, I. *J. Org. Chem.* **1988**, *53*, 6124. (b) Sawaki, Y.; Inoue, H.; Ogata, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1133.

(6) (a) Jun, C.-H.; Lee, H.; Moon, C.-W.; Hong, H.-S. *J. Am. Chem. Soc.* **2001**, *123*, 8600. (b) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 6646. (c) Datta, S.; Chang, C.-L.; Yeh, K.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 9294. (d) Liu, Y.-H.; Song, F.-J.; Guo, S.-H. *J. Am. Chem. Soc.* **2006**, *128*, 11332. (e) Wang, A.-Z.; Jiang, H.-F. *J. Am. Chem. Soc.* **2008**, *130*, 5030. (f) Liu, Q.-L.; Chen, P.-H.; Liu, G.-S. *ACS Catal.* **2013**, *3*, 178.

(7) (a) Sun, J.-W.; Wang, X.-S.; Liu, Y. *J. Org. Chem.* **2013**, *78*, 10560. (b) Liu, Y.; Hu, H.-Y.; Su, X.-B.; Sun, J.-W.; Cao, C.-S.; Shi, Y.-H. *Eur. J. Org. Chem.* **2013**, 2020. (c) Liu, Y.; Sun, J.-W. *J. Org. Chem.* **2012**, *77*, 1191.

(8) Gundersen, L.-L.; Charnock, C.; Negussie, A. H.; Rise, F.; Teklu, S. *Eur. J. Pharm. Sci.* **2007**, *30*, 26.

(9) Hagishita, S.; Yamada, M.; Shirahase, K.; Okada, T.; Murakami, Y.; Ito, Y.; Matsuura, T.; Wada, M.; Kato, T.; Ueno, M.; Chikazawa, Y.; Yamada, K.; Ono, T.; Teshirogi, I.; Ohtani, M. *J. Med. Chem.* **1996**, *39*, 3636.

(10) Chai, W.; Breitenbucher, J. G.; Kwok, A.; Li, X.; Wong, V.; Carruthers, N. I.; Lovenberg, T. W.; Mazur, C.; Wilson, S. J.; Axe, F. U.; Jones, T. K. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1767.

(11) Bermudez, J.; Fake, C. S.; Joiner, G. F.; Joiner, K. A.; Kim, F. D.; Miner, W. D.; Sanger, G. J. *J. Med. Chem.* **1990**, *33*, 1924.

(12) Weide, T.; Arve, L.; Prinz, H.; Waldmann, H.; Kessler, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 59.

(13) Dorange, I.; Forsblom, R.; Macsari, I.; Svensson, M.; Bylund, J.; Besidski, Y.; Blid, J.; Sohn, D.; Gravenfors, Y. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6888.

(14) Teklu, S.; Gundersen, L.-L.; Larsen, T.; Malterud, K. E.; Rise, F. *Bioorg. Med. Chem.* **2005**, *13*, 3127.

(15) (a) Pratt, E. F.; Rice, R. G.; Luckenbaugh, R. W. *J. Am. Chem. Soc.* **1957**, *79*, 1212. (b) Citterio, A.; Fochi, M.; Marion, A.; Mele, A.; Sebastiano, R.; Delcanale, M. *Heterocycles* **1998**, *48*, 1993. (c) Liu, Y.; Hu, H.-Y.; Liu, Q.-J.; Hu, H.-W.; Xu, J.-H. *Tetrahedron* **2007**, *63*, 2024.

(16) For the generation of **8**, see: Schmidt, A.; Topp, M.; Mordhorst, T.; Schneider, O. *Tetrahedron* **2007**, *63*, 1842.

(17) For the generation of intermediate **I**, see for examples: (a) Nair, V.; Pillai, A. N.; Menon, R. S.; Suresh, E. *Org. Lett.* **2005**, *7*, 1189. (b) Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2001**, *3*, 3495. (c) Asghari, S.; Habibi, A. K. *Tetrahedron* **2012**, *68*, 8890.