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Sequential Photo-oxidative [3 + 2] Cycloaddition/Oxidative Aromatization Reactions for the Synthesis of Pyrrolo[2,1-*a*]isoquinolines Using Molecular Oxygen as the Terminal Oxidant

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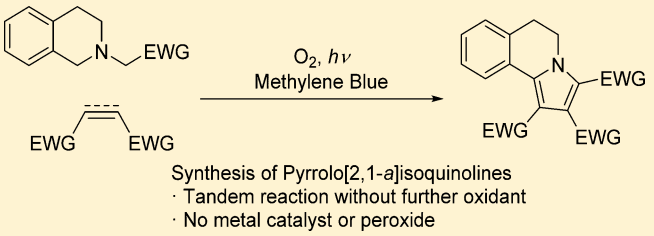
Supporting Information

ABSTRACT: We report an efficient method for the synthesis of pyrrolo[2,1-*a*]isoquinoline derivatives using sequential [3 + 2] cycloaddition/oxidative aromatization reactions catalyzed by methylene blue with fluorescent light irradiation under an oxygen atmosphere. The products were obtained in moderate to good yields.



Pyrrolo[2,1-*a*]isoquinoline, often found in the core of marine polycyclic lamellarin alkaloids, is a type of the N-bridgehead heterocyclic compound that possesses unique biological activities.[1] These types of alkaloids are often highly cytotoxic toward tumor cell lines and thus exhibit great potential as antitumor drugs. For example, lamellarin D has the ability to inhibit human topoisomerase I,[2a] and lamellarin α-20-sulfate is expected to be a selective HIV integrase inhibitor.[2b,c] The related lamellarin I and lamellarin K also exhibit anticancer activity.[2d,e] In the past, various methods for the construction of pyrrolo-[2,1-*a*]isoquinoline scaffolds have been reported, including dipolar[3] or azadiene Diels−Alder cycloaddition,[4] oxidative dimerization,[5] and double-barreled Heck cyclization.[6] However, these methods require multistep processes or suffer from limited substrate scope.

1,3-Dipolar cycloaddition is one strategy that may be used to efficiently construct the complex pyrrolo[2,1-*a*]isoquinoline scaffold (Scheme 1). Several strategies that use fewer steps and allow more flexible construction have been investigated: Cu,[7a] Rh,[7b] $[Ru(bpy)_3]^{2+}$,[7c] Ru polypyridine complexes,[7d] C_{60}-Bodipy hybrids,[7e] and iodo-Bodipy immobilized on porous material[7f] have all been employed. In addition, a method using an organo-photocatalyst has been reported.[8]

However, most of these methods require further oxidation by the addition of a stoichiometric oxidant, such as NBS, to aromatize the pyrrolidine ring. Thus, it is highly desirable to develop a more facile and atom economical method for the synthesis of pyrrolo[2,1-*a*]isoquinoline scaffolds. Many reports describing the use of tandem reactions for the synthesis of complex structures have appeared to date.[9−11] Wang et al.[7a] and Gao et al.[12a] have reported excellent methods for the one-step construction of pyrrolo[2,1-*a*]isoquinoline scaffolds (Scheme 2a). Wang et al. used catalytic $CuBr_2$ in combination with TBHP as a reoxidant, whereas Gao et al. used catalytic I_2 with H_2O_2. When we were preparing this paper, Shankaraiah's group reported a similar reaction employing the TBAI/TBHP system.[12b]

In the past, we have reported photo-oxidative reactions using molecular oxygen and fluorescent lamp irradiation.[13] In 2014, we reported a photo-oxidative cross-dehydrogenative coupling reaction, catalyzed by anthraquinone derivatives, in which the tetrahydroisoquinoline substrate was oxidized to an iminium intermediate.[13e] Iminium intermediates are known to be precursors in 1,3-dipolar cycloaddition reactions, and we envisioned that our photo-oxidative method could be a foothold to synthesize pyrrolo[2,1-*a*]isoquinolines. In this paper, we report the novel and straightforward photo-oxidative synthesis of the pyrrolo-[2,1-*a*]isoquinoline scaffold (Scheme 2b).

First, the reaction conditions were optimized (Table 1). 1,4-Naphthoquinone (**1a**) and ethyl 2-(3,4-dihydroisoquinolin-2-(1*H*)-yl)acetate (**2a**) were chosen as test substrates, and the reaction mixture containing **1a**, **2a**, and an organophotocatalyst was irradiated with a fluorescent lamp under an oxygen atmosphere for 20 h in order to yield the pyrrolo[2,1-*a*]isoquinoline product **3aa**. After extensive investigations, we found that various organophotocatalysts, including 2-*tert*-butylanthraquinone (2-^{t}Bu-AQN), 9,10-dicyanoanthracene (9,10-DCA), rose bengal (RB), eosin Y, and methylene blue (MB) catalyzed the reaction. In ^{i}PrOH, MB resulted in a product yield higher than that of the other organophotocatalysts tested (entries 1−5). During the study, we found the use of MeCN as the solvent prevented a side reaction, and **2a** was oxidized into **2a′**. Thus, we tried the mixed ^{i}PrOH/MeCN solvent system and determined their optimum ratio (entries 7 and 8). Thereafter, we confirmed that the reaction required visible light irradiation. Entries 9−11 show

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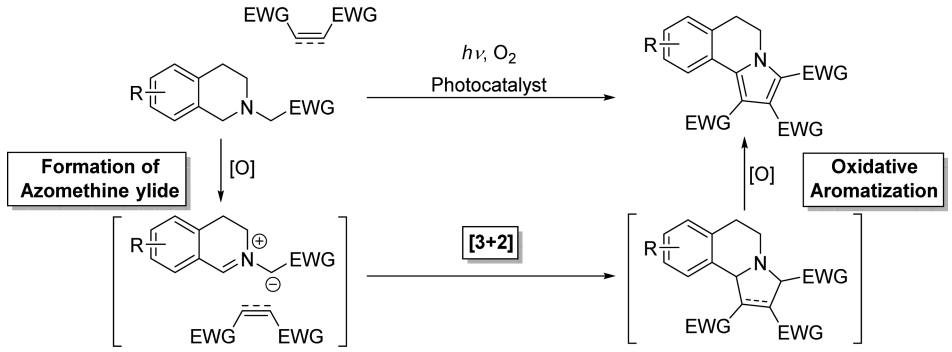
Scheme 1. Sequential 1,3-Dipolar Cycloaddition/Aromatization Reactions



Scheme 2. (a) Previous Reports of Sequential 1,3-Dipolar Cycloaddition/Aromatization Reactions and (b) Reaction Reported in This Work

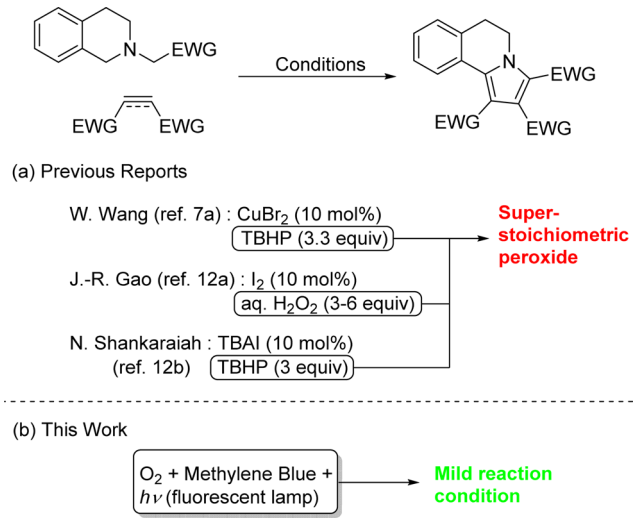
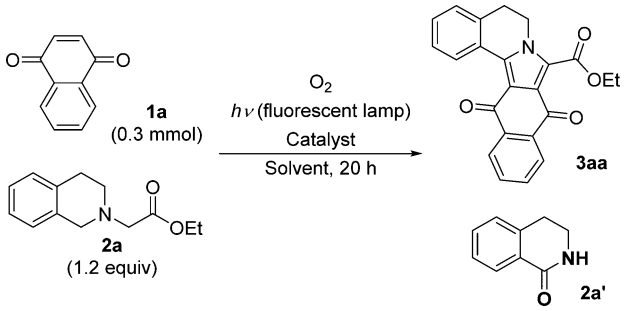


Table 1. Optimization of the Reaction Conditions



entry	catalyst (mol %)	solvent (mL)	yield of **3aa** (%)[a]
1	2-^{t}Bu-AQN (10)	^{i}PrOH (5)	35
2	9,10-DCA (10)	^{i}PrOH (5)	24
3	RB (10)	^{i}PrOH (5)	47
4	eosin Y (1)	^{i}PrOH (5)	28
5	MB (1)	^{i}PrOH (5)	62
6	MB (1)	MeCN (5)	34
7	MB (1)	^{i}PrOH/MeCN (4/1)	64
8	MB (1)	^{i}PrOH/MeCN (2/1)	69 (75)
9[b]	MB (1)	^{i}PrOH/MeCN (2/1)	14
10[c]	MB (1)	^{i}PrOH/MeCN (2/1)	17
11[d]	MB (1)	^{i}PrOH/MeCN (2/1)	54
12[e]	MB (1)	^{i}PrOH/MeCN (2/1)	trace
13		^{i}PrOH/MeCN (2/1)	38
14[f]	MB (1)	^{i}PrOH/MeCN (2/1)	0

[a]Yields were determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. The number in parentheses is the isolated yield. [b]Irradiation with a 300 W Xe lamp at 405 nm. [c]Irradiation with a 300 W Xe lamp at 610 nm. [d]Irradiation with a 300 W Xe lamp at 660 nm. [e]Under Ar atmosphere. [f]The reaction was conducted without irradiation of a fluorescent lamp (covered with aluminum foil).

the results of irradiation with a 300 W Xe lamp (irradiation at 350−800 nm) equipped with band-pass filters, allowing selective irradiation at λ = 405, 610, and 660 nm, respectively. Without a band-pass filter, no product was obtained, likely because of decomposition of substrates caused by the high-energy irradiation (the result is not shown). While the product was obtained with all the band-pass filters studied, the highest product yield was obtained with the irradiation at 660 nm (entry 11). Because the maximum absorption wavelength of MB is known to be around 660 nm,[14] this result suggests that the reaction is catalyzed by appropriately excited MB. We performed some additional experiments (entries 12−14) in order to elucidate the reaction mechanism. As the results show, the reaction requires molecular oxygen as a terminal oxidant and irradiation of the fluorescent lamp. On the other hand, we found that the reaction can proceed without a photocatalyst. This result implies that the substrates can act as sacrificial catalysts. Next, we added 0.3 mmol (1 equiv) of 1,4-diazabicyclo[2.2.2]octane (DABCO), which is known as a quencher of singlet oxygen, to the reaction mixture (0.1 M of DABCO solution). When DABCO was added, we confirmed that the reaction rate was inhibited partially (see Supporting Information for details). Thus, we assume that singlet oxygen is involved in the reaction mechanism.

With the optimized reaction conditions in hand, we examined the scope and limitations of the reaction. As shown in Table 2, naphthoquinone-type substrates reacted smoothly. We found that alternation of the ester moieties in the tetrahydroisoquinoline derivatives (**3aa**−**3ac**) and the inclusion of substituents on the aromatic rings, both in the naphthoquinone-type substrates and tetrahydroisoquinoline derivatives (**3ba**−**3ca**, **3ad**, and **3bd**), did not inhibit the reaction. The reason why the yield of **3ad** is lower than that of the other products has not been known.

Tables 3 and 4 show the results for other dipolarophiles such as alkynes, maleimides, and alkenes. Using previously optimized conditions, the yields of the products were found to be low. In most cases, however, substitution of ^{i}PrOH in the solvent mixture allowed the yield of the corresponding products to improve. When we employed ethyl acrylate, alkyne with amide,

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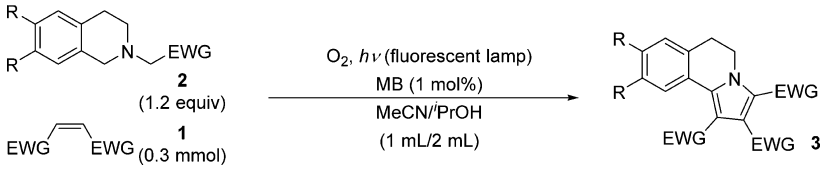
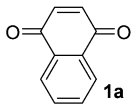
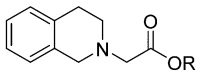
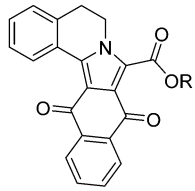
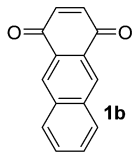
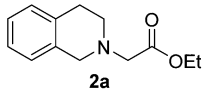
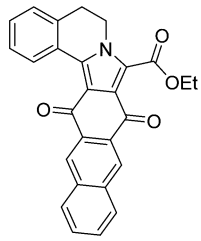
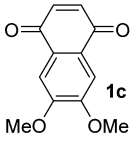
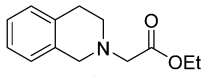
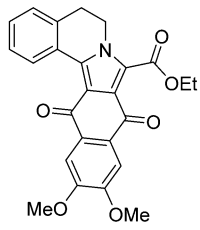
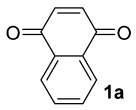
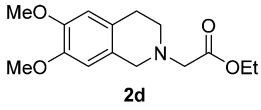
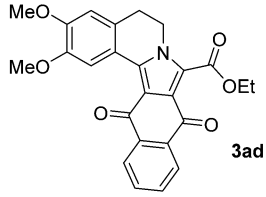
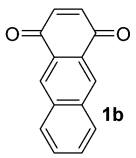
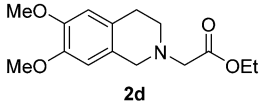
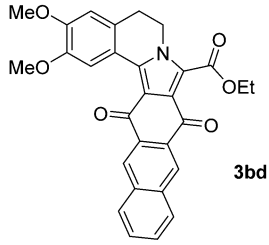
Table 2. Substrate Scope 1[a]



1	2	3
 1a	 2a or 2b or 2c	 R = Et (**3aa**): 20 h, 75% R = Me (**3ab**): 20 h, 74% R = *t*-Bu (**3ac**): 20 h, 58%
 1b	 2a	 **3ba**: 30 h, 61%
 1c	 2a	 **3ca**: 50 h, 73%
 1a	 2d	 **3ad**: 20 h, 34%
 1b	 2d	 **3bd**: 20 h, 61%

[a]Yields shown in the table are all pure, isolated yields.

alkyne with ketone, *N*-methylmaleimide, acrylonitrile, or maleic anhydride as the reaction substrate, products were either obtained in low yield (**3e′a**, **3ga**, **3gd**, **3ha**, **3ja**, **3ka**, and **3kd**) or not obtained at all (**3la**), perhaps because of in situ decomposition of the substrates. We also tried to apply this reaction to a tetrahydroisoquinoline derivative bearing a nitrile substituent. Surprisingly, the desired product was obtained cleanly, albeit in a relatively low yield (**3ae**).

Based on the results obtained above and previous reports demonstrating that MB can oxidize tertiary amines via a single electron transfer (SET),[15] we propose that the reaction occurs via the mechanism shown in Scheme 3. In the first step, irradiation from the fluorescent lamp excites a molecule of MB, which oxidizes the tetrahydroisiquinoline derivative to a radical cation; this assumption is consistent with the redox potentials of MB ($^3MB^+/MB^\bullet$: +1.21 V)[16] and the tetrahydroisoquinoline derivative (**2a**) (**2a**/**2a**$^{\bullet+}$: +0.75 V).[17] Then, after involvement of singlet oxygen and a peroxy anion, an azomethine ylide was formed, generating up to 1 equiv of hydrogen peroxide. Iodometry results[18] and some reports[19] employing singlet oxygen to abstract hydrogen atoms also support this step of the mechanism. Next, 1,3-dipolar cycloaddition occurs between the azomethine ylide and the dipolarophile to yield a pyrrolidine-type cycloadduct. Finally, the cycloadduct is oxidized again, and the corresponding product bearing the pyrrolo[2,1-*a*]-isoquinoline scaffold is formed. Although this oxidative aromatization may be preceded by the secondary photoinduced electron transfer process, we cannot deny the involvement of singlet oxygen or peroxide in situ generated under photo-oxidative conditions.

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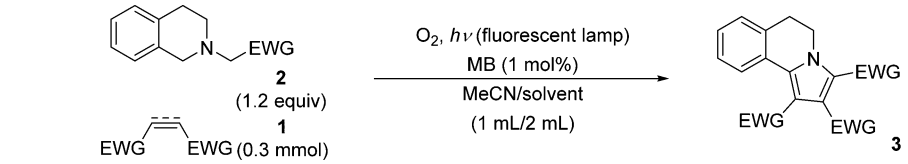
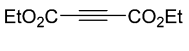
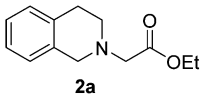
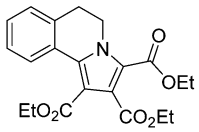
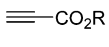
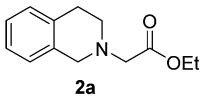
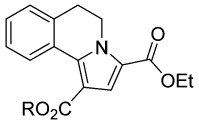
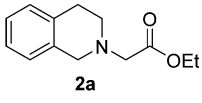
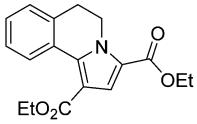
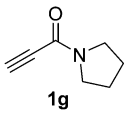
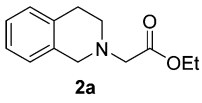
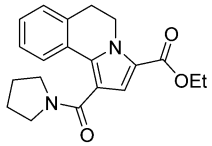
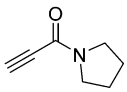
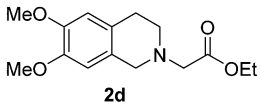
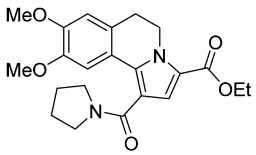
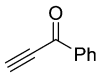
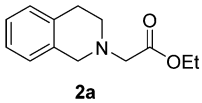
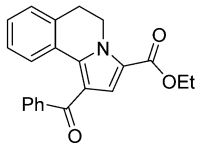
Table 3. Substrate Scope 2[a]



1	2	3
 1d	 2a	 **3da**: THF, 100 h, 48%
 1e or 1f	 2a	 R = Et (**3ea**): $^{i}Pr_2O$, 20 h, 69% R = Me (**3fa**): $^{i}Pr_2O$, 20 h, 66%
 1e'	 2a	 **3e'a**: THF, 20 h, 21%
 1g	 2a	 **3ga**: THF, 70 h, 18%
 1g	 2d	 **3gd**: THF, 70 h, 12%
 1h	 2a	 **3ha**: THF, 50 h, 10%

[a]Yields shown in the table are all pure, isolated yields.

In summary, we demonstrated a sequential [3 + 2] cycloaddition/oxidative aromatization to efficiently construct the pyrrolo-[2,1-*a*]isoquinoline scaffold. In this method, a tetrahydroisoquinoline derivative seems to be oxidized to an iminium intermediate under photo-oxidative conditions through a SET. This hypothesis is consistent with previous reports suggesting that methylene blue can oxidize tertiary amine via a SET process. Subsequently, reaction with a dipolarophile bearing an activated multiple bond followed by further oxidation yields the desired aromatized product. This method allows the construction of complex molecular architecture in a safe and facile way.

EXPERIMENTAL SECTION

General Information. Substrates **1b**,[20] **1c**,[21] **1g**,[22] **1h**,[23] **2a**,[7d] and **2e**[24] were synthesized according to a reported procedure. Because of their similarity to **2a**, **2b**−**2d** were synthesized by the method that provided **2a** with minor changes. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts (δ) are expressed in parts per million and are internally referenced [0.00 ppm (tetramethylsilane) for ^{1}H NMR and 77.0 ppm ($CDCl_3$) for ^{13}C NMR], and coupling constants (J) are reported in hertz. The pure product was separated by flash column chromatography performed on silica gel. High-resolution mass spectra (HRMS) were measured in DART mode, and the mass analyzer of the HRMS was TOF. Melting points are uncorrected. Known compounds are confirmed by the comparison of their ^{1}H and ^{13}C spectra to that in the literature.

Electrochemical Measurements. Cyclic voltammetry was performed with a three-electrode system consisting of a glassy carbon working electrode, a coiled platinum counter electrode, and a $Ag/AgNO_3$ reference electrode. The voltammograms were recorded at a scan rate of 100 mV/s at 25 °C. Temperature was controlled during the measurements by circulating constant-temperature ethanol throughout the cell compartment. The solvent used for the electrochemical measurements was MeCN containing 0.1 M tetrapropylammonium perchlorate (TPAP) as a supporting electrolyte for MeCN. TPAP was dried well under high vacuum just before use. The sample solutions were prepared in a drybox completely filled with N_2 gas to prevent contamination by moisture. The solutions were purged with N_2 gas to remove oxygen, and N_2 gas was passed over the solution during the measurements. The ferrocene (Fc)/Fc^+ redox couple was employed for potential-scale calibration in aprotic solvents according to IUPAC recommendations. Typical voltammograms are shown in Figure S1. The redox potentials for reversible waves were obtained as the midpoint

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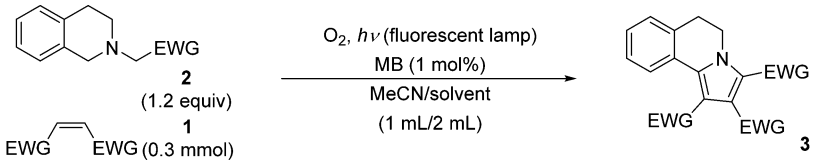
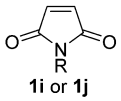
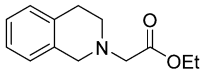
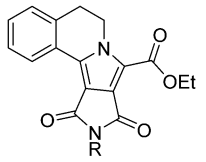
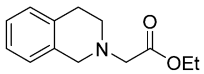
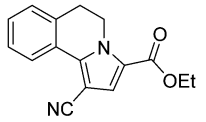
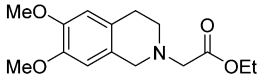
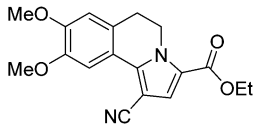
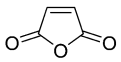
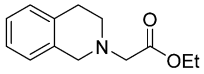
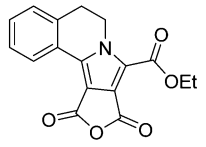
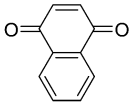
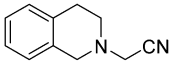
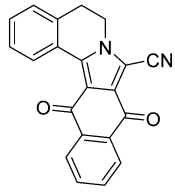
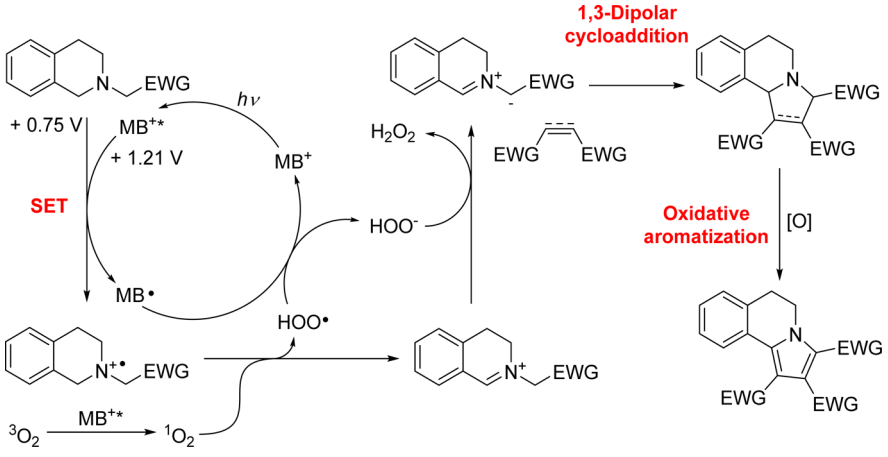
Table 4. Substrate Scope 3[a]



1	2	3
 1i or 1j	 2a		R = Ph (**3ia**): $CHCl_3$, 120 h, 49% R = Me (**3ja**): $CHCl_3$, 40 h, 17%
 1k	 2a		**3ka**: $CHCl_3$, 20 h, 24%
 1k	 2d		**3kd**: $CHCl_3$, 20 h, 19%
 1l	 2a		**3la**: ^{i}PrOH, 20 h, 0%
 1a	 2e		**3ae**: THF, 120 h, 30%

[a]Yields shown in the table are all pure, isolated yields.

Scheme 3. Plausible Mechanistic Pathway for the Reaction



potentials and were calculated from the average of the cathodic and anodic peak positions in the voltammograms of redox couples. In the case of irreversible waves, the oxidation and reduction potentials were obtained as anodic and cathodic peak potentials, respectively.

*Synthesis of Ethyl 9,14-Dioxo-5,6,9,14-tetrahydrobenzo[5,6]-isoindolo[1,2-a]-isoquinoline-8-carboxylate (**3aa**).* A solution of 1,4-naphthoquinone (**1a**, 47.4 mg, 0.3 mmol), ethyl 2-(3,4-dihydroisoquinolin-2-(1*H*)-yl)acetate (**2a**, 78.9 mg, 0.36 mmol), methylene blue solution in MeCN (0.003 mmol/mL, 1 mL), and ^{i}PrOH (2 mL) was stirred under oxygen atmosphere (balloon) with irradiation of a fluorescent lamp (Philips mini Decorative T2 Twister EL/mdT2, 23 W, 120 V, 60 Hz, 360 mA, 2700 K, 1600 lumens) for 20 h.

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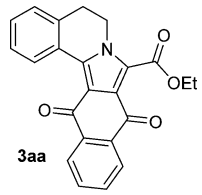
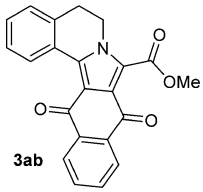
The reaction mixture was concentrated in vacuo. Purification of the crude by flash column chromatography ($CHCl_3$) provided **3aa**. Other products were also provided in the same way in which the solvent, the reaction time, and the eluent of flash column chromatography depend on products.

*Ethyl 9,14-Dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-a]-isoquinoline-8-carboxylate (**3aa**):*[12a]



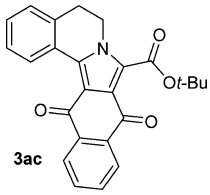
Yellow solid, yield 75% (83.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, J = 7.5 Hz, 1H), 8.32−8.30 (m, 1H), 8.24−8.22 (m, 1H), 7.74−7.70 (m, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.29−7.26 (m, 1H), 4.55 (q, J = 7.5 Hz, 2H), 4.30 (t, J = 6.3 Hz, 2H), 3.12 (t, J = 6.3 Hz, 2H), 1.51 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 179.7, 179.5, 161.4, 135.6, 134.6, 133.6, 133.3, 132.9, 130.0, 128.8, 127.40 (2C), 127.38, 127.2, 126.6, 126.3, 123.2, 117.4, 62.5, 43.1, 29.1, 14.0 (the peak of 127.40 seems to be overlapped); R_f = 0.66 ($CHCl_3$); IR ν/cm^{-1} (ATR) 1702, 1658, 1511, 1464, 1413, 1383, 1309, 1263, 1225, 1140, 1107, 1047, 1009, 984, 790, 728, 710.

*Methyl 9,14-Dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-a]-isoquinoline-8-carboxylate (**3ab**):*[12a]



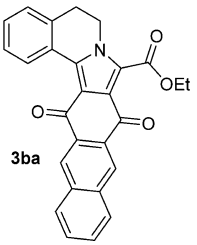
Orange solid, yield 74% (79.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, J = 8.1 Hz, 1H), 8.32−8.31 (m, 1H), 8.24−8.22 (m, 1H), 7.75−7.72 (m, 2H), 7.47 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.30−7.28 (m, 1H), 4.32 (t, J = 6.9 Hz, 2H), 4.09 (s, 3H), 3.13 (t, J = 6.6 Hz, 2H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 179.6 (2C), 161.9, 135.8, 135.6, 134.6, 133.6, 133.4, 133.0, 130.1, 128.8, 127.4 (2C), 127.2, 126.6, 126.6, 125.4, 123.4, 117.5, 53.1, 43.2, 29.1 (both of the peaks of 179.6 and 127.4 seem to be overlapped); R_f = 0.57 ($CHCl_3$); IR ν/cm^{-1} (ATR) 1710, 1655, 1465, 1412, 1386, 1313, 1263, 1216, 1139, 1113, 1060, 1011, 799, 730.

*tert-Butyl 9,14-Dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo-[1,2-a]-isoquinoline-8-carboxylate (**3ac**):*[12a]



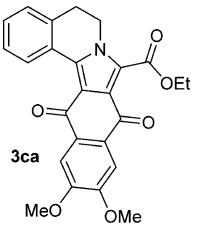
Orange solid, yield 58% (69.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, J = 8.0 Hz, 1H), 8.31−8.29 (m, 1H), 8.24−8.22 (m, 1H), 7.73−7.70 (m, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.38 (t, J = 6.9 Hz, 1H), 7.38−7.26 (m, 1H), 4.27 (t, J = 6.6 Hz, 2H), 3.12 (t, J = 6.9 Hz, 2H), 1.71 (s, 9H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 179.8, 179.4, 160.6, 135.7, 135.0, 134.8, 133.5, 133.2, 132.9, 129.9, 128.7, 127.7, 127.7, 127.43, 127.40, 126.2, 126.5 (2C), 122.4, 117.1, 84.1, 43.0, 29.1, 28.0 (the peak of 126.5 seems to be overlapped); R_f = 0.74 ($CHCl_3$); IR ν/cm^{-1} (ATR) 1719, 1668, 1467, 1421, 1369, 1266, 1228, 1140, 1010, 982, 712.

*Ethyl 9,16-Dioxo-5,6,9,16-tetrahydronaphtho[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (**3ba**):*[12a]



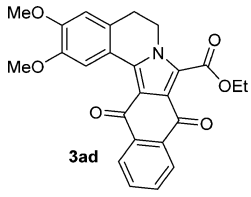
Orange solid, yield 61% (77.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (d, J = 8.1 Hz, 1H), 8.80 (s, 1H), 8.71 (s, 1H), 8.04−8.02 (m, 2H), 7.63−7.61 (m, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 6.9 Hz, 1H), 4.58 (q, J = 6.9 Hz, 2H), 4.29 (t, J = 6.3 Hz, 2H), 3.11 (t, J = 6.9 Hz, 2H), 1.54 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 179.6, 179.4, 161.6, 135.6, 134.9, 134.6, 133.6, 132.1, 131.2, 130.0, 129.9, 129.8, 129.3, 128.9 (2C), 128.6, 127.4, 127.40, 127.36, 126.4, 126.1, 124.0, 118.2, 62.5, 43.2, 29.1, 14.0 (the peak of 128.9 seems to be overlapped); R_f = 0.66 ($CHCl_3$); IR ν/cm^{-1} (ATR) 1706, 1666, 1619, 1464, 1262, 1185, 1158, 1029, 915, 758.

*Ethyl 11,12-Dimethoxy-9,16-dioxo-5,6,9,16-tetrahydrobenzo-[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (**3ca**):*



Yellow solid, yield 73% (94.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 7.76 (s, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.29−7.27 (m, 1H), 4.55 (q, J = 7.5 Hz, 2H), 4.28 (t, J = 6.3 Hz, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 3.12 (t, J = 6.9 Hz, 2H), 1.51 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 179.3, 179.0, 161.6, 153.0, 152.8, 135.5, 133.7, 130.4, 130.0, 129.4, 128.8, 127.4, 127.3, 126.4, 126.0, 123.2, 117.4, 108.6, 108.0, 62.5, 56.4, 43.1, 29.1, 14.1; R_f = 0.51 ($CHCl_3$); IR ν/cm^{-1} (ATR) 1695, 1662, 1582, 1506, 1464, 1421, 1364, 1276, 1207, 1189, 1086, 1015, 886, 803, 773, 743; HRMS (DART) m/z calcd for $C_{25}H_{22}NO_6$ $[M + H]^+$ 432.1447, found 432.1435; mp 212−213 °C.

*Ethyl 2,3-Dimethoxy-9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]-isoindolo[1,2-a]isoquinoline-8-carboxylate (**3ad**):*[12a]



Orange solid, yield 34% (44.0 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.30 (d, J = 6.9 Hz, 1H), 8.19 (d, J = 6.9 Hz, 1H), 7.71−7.68 (m, 2H), 6.75 (s, 1H), 4.55 (q, J = 7.5 Hz, 2H), 4.27 (t, J = 6.3 Hz, 2H), 4.1 (s, 3H), 3.94 (s, 3H), 3.06 (t, J = 6.3 Hz, 2H), 1.50 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 179.6, 161.6, 150.2, 147.7, 136.3, 135.9, 134.7, 133.2, 132.8, 127.3, 127.0, 126.6, 126.0, 123.0, 119.1, 116.4, 112.4, 110.2, 62.5, 56.3, 56.0, 43.3, 28.6, 14.0; R_f = 0.23 ($CHCl_3$); IR ν/cm^{-1} (ATR) 1717, 1654, 1531, 1470, 1385, 1280, 1253, 1204, 1152, 1127, 1043, 1015, 995, 722, 702.

DOI: 10.1021/acs.joc.6b00439
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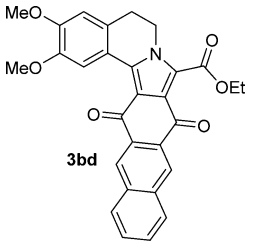
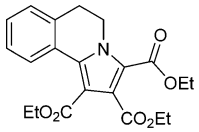
*Ethyl 2,3-Dimethoxy-9,16-dioxo-5,6,9,16-tetrahydronaphtho-[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (**3bd**):*[12a]



3bd

Orange solid, yield 61% (87.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.86 (s, 1H), 8.76 (s,1H), 8.09−8.05 (m, 2H), 7.66−7.64 (m, 2H), 6.78 (s, 1H), 4.57 (q, J = 6.9 Hz, 1H), 4.30 (t, J = 6.3 Hz, 2H), 4.15 (s, 3H), 3.96 (s, 3H), 3.09 (t, J = 6.9 Hz, 2H), 1.53 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 179.5, 161.8, 150.1, 147.7, 136.3, 134.9, 134.6, 132.3, 131.3, 129.8 (2C), 129.3, 128.9, 128.8, 128.5, 126.9, 126.1, 123.8, 119.2, 117.2, 112.4, 110.1, 62.5, 56.3, 55.9, 43.3, 28.6, 14.0 (the peak of 129.8 seems to be overlapped); R_f = 0.37 ($CHCl_3$); IR ν/cm^{-1} (ATR) 1717, 1660, 1530, 1482, 1382, 1256, 1238, 1234, 1184, 1132, 1036, 915, 761.

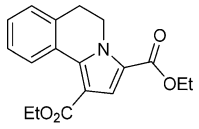
*Triethyl 5,6-Dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3da**):*[7b]



3da

White solid, yield 48% (55.5 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19−8.17 (m, 1H), 7.32−7.31 (m, 2H), 7.26−7.25 (m, 1H), 4.54 (t, J = 6.3 Hz, 2H), 4.37 (q, J = 7.5 Hz, 2H), 4.34−4.29 (m, 4H), 3.00 (t, J = 6.9 Hz, 2H), 1.41 (t, J = 6.9 Hz, 3H), 1.36−1.32 (m, 6H). ^{13}C NMR (125 Hz, $CDCl_3$) δ 166.1, 163.4, 159.9, 136.7, 134.3, 129.2, 128.5, 127.3, 126.9 (2C), 126.4, 118.9, 110.7, 61.5, 61.0, 60.7, 42.5, 29.3, 14.10, 14.08, 14.03 (the peak of 126.9 seems to be overlapped); R_f = 0.29 (hexane/EtOAc = 4:1); IR ν/cm^{-1} (ATR) 1704, 1661, 1532, 1464, 1426, 1384, 1253, 1186, 1109, 1028, 760.

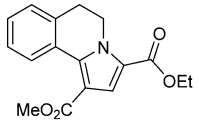
*Diethyl 2,3-Dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (**3ea**):*[12a]



3ea

Yellow solid, yield 69% (64.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1H), 7.49 (s, 1H), 7.35−7.27 (m, 2H), 7.25 (d, J = 8.6 Hz, 1H), 4.59 (t, J = 6.3 Hz, 2H), 4.35−4.30 (m, 4H), 3.01 (t, J = 6.9 Hz, 2H), 1.40−1.37 (m, 6H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 164.5, 160.9, 137.7, 134.0, 128.8, 128.5, 127.2, 127.0, 126.8, 121.3, 121.0, 112.3, 60.3, 60.2, 42.3, 42.2, 29.4, 14.4; R_f = 0.66 (hexane/EtOAc = 4:1); IR ν/cm^{-1} (ATR) 1702, 1538, 1452, 1417, 1252, 1206, 1156, 1078, 1028, 768, 753, 744.

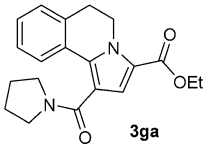
*3-Ethyl 1-Methyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (**3fa**):*[7a]



3fa

Yellow solid, yield 66% (59.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (d, J = 7.5 Hz, 1H), 7.49 (s, 1H), 7.35−7.28 (m, 2H), 7.25 (d, J = 8.6 Hz, 1H), 4.59 (t, J = 6.3 Hz, 2H), 4.31 (q, 7.5 Hz, 2H), 3.85 (s, 3H), 3.01 (t, J = 6.9 Hz, 2H), 1.38 (t, 7.2 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 164.9, 160.9, 137.8, 134.0, 128.9, 128.4, 127.2, 127.0, 126.9, 121.3, 121.1, 111.8, 60.3, 51.4, 42.2, 29.4, 14.3; R_f = 0.57 (hexane/EtOAc = 4:1); IR ν/cm^{-1} (ATR) 1698, 1540, 1458, 1407, 1252, 1205, 1164, 1079, 1015, 771, 755, 741.

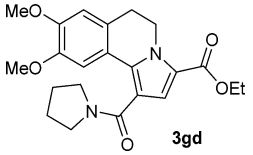
*Ethyl 1-(1-Pyrrolidinylcarbonyl)-5,6-dihydropyrrolo[2,1-a]-isoquinoline-3-carboxylate (**3ga**):*



3ga

Yellow gum, yield 18% (18.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65−7.63 (m, 1H), 7.25−7.22 (m, 3H), 7.07 (s, 1H), 4.61 (t, J = 3.2 Hz, 2H), 4.30 (q, J = 7.5 Hz, 2H), 3.67 (t, J = 7.5 Hz, 2H), 3.26 (t, J = 6.9 Hz, 2H), 3.06 (t, J = 6.9 Hz, 2H), 1.93 (quint, J = 7.3 Hz, 2H), 1.80 (quint, J = 6.9 Hz, 2H), 1.36 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 166.5, 161.1, 132.6, 132.2, 128.0, 127.8, 127.6, 127.4, 124.8, 121.2, 117.2 (2C), 60.1, 48.5, 45.8, 42.2, 29.1, 25.9, 24.6, 14.4 (the peak of 117.2 seems to be overlapped); R_f = 0.31 (hexane/EtOAc = 1:1); IR ν/cm^{-1} (ATR) 1696, 1615, 1549, 1455, 1401, 1241, 1185, 1082, 846, 757; HRMS (DART) m/z calcd for $C_{20}H_{23}N_2O_3$ $[M + H]^+$ 339.1709, found 339.1698.

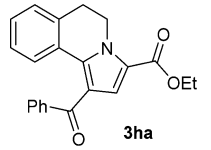
*Ethyl 1-(1-Pyrrolidinylcarbonyl)-2,3-dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (**3gd**):*



3gd

Yellow gum, yield 12% (14.3 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.07 (s, 1H), 6.74 (s, 1H), 4.58 (t, J = 6.6 Hz, 2H), 4.29 (q, J = 7.5 Hz, 2H), 3.91 (s, 3H), 3.84 (s, 3H), 3.65 (t, J = 7.4 Hz, 2H), 3.25 (t, J = 6.9 Hz, 2H), 2.99 (t, J = 7.2 Hz, 2H), 1.92 (quint, J = 7.5 Hz, 2H), 1.80 (quint, J = 6.9 Hz, 2H), 1.35 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 166.8, 161.1, 148.8, 148.0, 132.5, 125.6, 120.8, 120.4, 117.4, 116.2, 110.7, 108.0, 60.1, 55.93, 55.88, 48.6, 45.9, 42.3, 28.8, 26.0, 24.7, 14.4; R_f = 0.23 (hexane/EtOAc = 1:2); IR ν/cm^{-1} (ATR) 1691, 1609, 1463, 1399, 1241, 1215, 1190, 1145, 1077, 859, 759; HRMS (DART) m/z calcd for $C_{22}H_{27}N_2O_5$ $[M + H]^+$ 399.1920, found 399.1908.

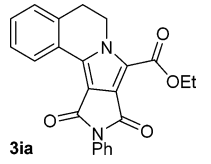
*Ethyl 1-Benzoyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (**3ha**):*



3ha

White gum, yield 10% (10.4 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 7.4 Hz, 2H), 7.87 (d, J = 8.0 Hz, 1H), 7.56 (m, 1H), 7.47 (t, J = 7.5 Hz, 2H), 7.25−7.24 (m, 2H), 7.19−7.17 (m, 2H), 4.66 (t, J = 6.9 Hz, 2H), 4.30 (q, J = 7.4 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H), 1.34 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 192.3, 161.0, 139.1, 137.5, 133.6, 132.4, 129.9, 128.8, 128.3, 127.5 (2C), 127.0 (2C), 122.2, 120.9, 120.0, 60.4, 42.4, 29.3, 14.4 (both of the peaks of 127.5 and 127.0 seem to be overlapped); R_f = 0.32 (hexane/EtOAc = 5:1); IR ν/cm^{-1} (ATR) 1698, 1645, 1449, 1410, 1247, 1214, 1184, 1082, 888, 731; HRMS (DART) m/z calcd for $C_{22}H_{20}NO_3$ $[M + H]^+$ 346.1443, found 346.1445.

*Ethyl 9,11-Dioxo-10-phenyl-6,9,10,11-tetrahydro-5H-pyrrolo-[3′,4′: 3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3ia**):*[7a]



3ia

White solid, yield 49% (56.7 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J = 7.5 Hz, 1H), 7.49 (t, J = 8.1 Hz, 2H), 7.42−7.37 (m, 5H), 7.29 (d, J = 6.9 Hz, 1H), 4.79 (t, J = 6.6 Hz, 2H), 4.44 (q, J = 6.9 Hz, 2H),

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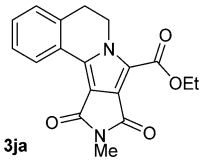
3.20 (t, J = 6.9 Hz, 2H), 1.47 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 163.1, 161.6, 159.7, 133.5, 132.5, 132.5, 132.4, 130.3, 128.9, 128.0, 127.8, 127.7, 127.1, 125.5, 125.2, 118.6, 116.2, 61.7, 43.4, 28.3, 24.2, 14.2; R_f = 0.37 (hexane/EtOAc = 3:1); IR ν/cm^{-1} (ATR) 1756, 1699, 1547, 1472, 1418, 1383, 1345, 1276, 1196, 1155, 1111, 1089, 1049, 945, 894, 861, 822, 755, 724.

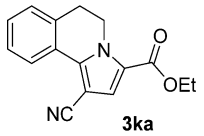
*Ethyl 9,11-Dioxo-10-methyl-6,9,10,11-tetrahydro-5H-pyrrolo-[3′,4′: 3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3ja**):*[7b]



3ja

White solid, yield 17% (16.8 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, J = 8.0 Hz, 1H), 7.41−7.39 (m, 1H), 7.38−7.36 (m, 1H), 7.26 (d, J = 7.5 Hz, 1H), 4.71 (t, J = 7.2 Hz, 2H), 4.41 (q, J = 6.9 Hz, 2H), 3.15 (t, J = 6.9 Hz, 2H), 3.10 (s, 3H), 1.48 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 164.1, 162.8, 159.6, 132.8, 132.3, 130.1, 127.9, 127.8, 127.6, 125.8, 125.6, 118.1, 116.6, 61.5, 43.2, 28.3, 24.2, 14.1; R_f = 0.34 (hexane/EtOAc = 3:1); IR ν/cm^{-1} (ATR) 1753, 1690, 1546, 1475, 1380, 1349, 1270, 1192, 980, 774, 738; HRMS (DART) m/z calcd for $C_{18}H_{17}N_2O_4$ $[M + H]^+$ 325.1189, found 325.1217.

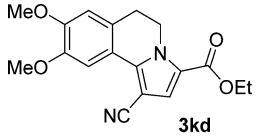
*Ethyl 1-Cyano-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (**3ka**):*



3ka

White solid, yield 24% (19.2 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 7.5 Hz, 1H), 7.39−7.33 (m, 2H), 7.29−7.28 (1H, m), 4.66 (t, J = 7.2 Hz, 2H), 4.33 (q, J = 7.5 Hz, 2H), 3.10 (t, J = 6.9 Hz, 2H), 1.38 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 160.2, 139.3, 132.6, 129.6, 128.0, 127.8, 126.0, 124.8, 122.5, 121.5, 116.7, 88.8, 60.7, 42.6, 28.6, 14.3; R_f = 0.31 (hexane/EtOAc = 5:1); IR ν/cm^{-1} (ATR) 2224, 1706, 1457, 1410, 1251, 1190, 1101, 836, 768, 722, 689; HRMS (DART) m/z calcd for $C_{16}H_{15}N_2O_2$ $[M + H]^+$ 267.1134, found 267.1130; mp 105−106 °C.

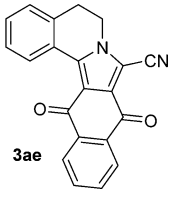
*Ethyl 1-Cyano-2,3-dimethoxy-5,6-dihydropyrrolo[2,1-a]-isoquinoline-3-carboxylate (**3kd**):*



3kd

White solid, yield 19% (18.6 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.24 (s, 1H), 6.77 (s, 1H), 4.63 (t, J = 7.2 Hz, 2H), 4.31 (q, J = 7.5 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 3.03 (t, J = 6.9 Hz, 2H), 1.38 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 160.3, 150.0, 148.4, 140.0, 125.8, 122.1, 121.3, 118.5, 117.2, 110.7, 107.5, 87.6, 60.6, 56.1, 56.0, 42.7, 28.2, 14.3; R_f = 0.31 (hexane/EtOAc = 1:1); IR ν/cm^{-1} (ATR) 2213, 1697, 1612, 1546, 1466, 1251, 1217, 1196, 1151, 1015, 850, 721; HRMS (DART) m/z calcd for $C_{18}H_{19}N_2O_4$ $[M + H]^+$ 327.1345, found 327.1352; mp 133−134 °C.

*9,14-Dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-a]-isoquinoline-8-carbonitrile (**3ae**):*



3ae

Yellow solid, yield 30% (28.9 mg); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.01 (d, J = 8.1 Hz, 1H), 8.33 (dd, 7.4 Hz, 1H), 8.28 (dd, 6.9 Hz, 1H), 7.80−7.77 (m, 2H), 7.50 (m, 1H), 7.46 (m, 1H), 7.35−7.33 (m, 1H), 4.37 (t, J = 6.9 Hz, 2H), 3.24 (t, J = 6.9 Hz, 2H); ^{13}C NMR (125 Hz, $CDCl_3$) δ 178.7 (2C), 137.9, 135.7, 134.1, 133.6, 133.4, 133.3, 131.1, 129.8, 129.1, 127.9 (2C), 127.7, 126.8, 125.7, 117.9, 111.1, 104.7, 43.8, 28.7 (both of the peaks of 178.7 and 127.9 seem to be overlapped) ; R_f = 0.51 ($CHCl_3$); IR ν/cm^{-1} (ATR) 2222, 1657, 1588, 1546, 1504, 1463, 1420, 1267, 1245, 1197, 1186, 1156, 1061, 1008, 985, 745, 730, 717, 689; HRMS (DART) m/z calcd for $C_{21}H_{13}N_2O_2$ $[M + H]^+$ 325.0977, found 325.0982; mp >295 °C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00439.

Cyclic voltammogram of **2a**, ^{1}H NMR and ^{13}C NMR for all compounds except **3e′a** and **3ia**, and emission spectrum of the fluorescent lamp (PDF)

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Notes

The authors declare no competing financial interest.

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