JOC The Journal of Organic Chemistry

Article

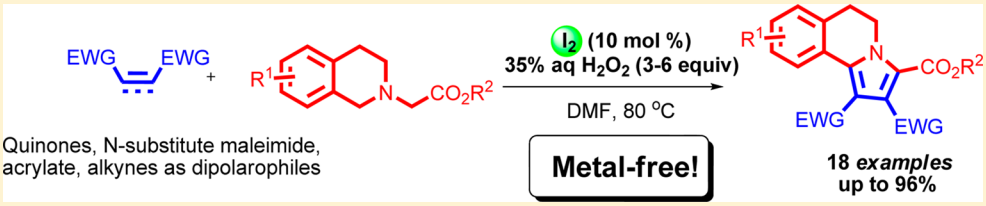
pubs.acs.org/joc

Iodine-Catalyzed 1,3-Dipolar Cycloaddition/Oxidation/Aromatization Cascade with Hydrogen Peroxide as the Terminal Oxidant: General Route to Pyrrolo[2,1-*a*]isoquinolines

Huan-Ming Huang, Yu-Jin Li,* Qing Ye, Wu-Bin Yu, Liang Han, Jian-Hong Jia, and Jian-Rong Gao*

State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China

Supporting Information



ABSTRACT: We report a novel molecular iodine-catalyzed 1,3-dipolar cycloaddition/oxidation/aromatization cascade process with hydrogen peroxide as the terminal oxidant for the construction of pyrrolo[2,1-*a*]isoquinolines. The product pyrrolo[2,1-*a*]-isoquinolines were obtained from reactions between simple, readily available dipolarophiles and tetrahydroisoquinolines in moderate to excellent yields without the need for a metal catalyst.

INTRODUCTION

Efficient transformations that do not require a metal catalyst are of great value, and organic transformations catalyzed by molecular iodine have attracted considerable attention because of this reagent's low toxicity, its low cost in comparison with that of transition-metal catalysts, its ready availability, and its utility for a large variety of reactions.[1] A novel class of iodine-based oxidation catalysts was introduced by Ishihara et al.,[2] and the most important features of this catalytic system are that the oxidation reactions require no metals and that water or *tert*-butyl alcohol is the only byproduct derived from the co-oxidant. This mild, efficient C−H oxidation method has been used to form C−C bonds,[3] C−O bonds,[1q,2,4] or both,[5] as well as C−N bonds.[6] Very recently, Itoh[7] reported a useful molecular iodine-catalyzed oxidative C−C bond formation reaction between tertiary amines and a carbon nucleophile with hydrogen peroxide as the terminal oxidant. In addition, a versatile aerobic catalytic system (I_2 and O_2/TBHP) for C−H functionalization was reported by Prabhu.[8] Despite these advances, catalysis by molecular iodine with hydrogen peroxide as the terminal oxidant has been largely unexplored, and the development of such a method for the efficient, practical synthesis of natural products and pharmaceuticals is highly desirable.

The pyrrolo[2,1-*a*]isoquinoline structure occurs in lamellarin alkaloids, a newly discovered family of marine natural products that exhibit a wide spectrum of biological activities,[9] and various approaches to the synthesis of this useful skeleton have been developed.[10] For example, pyrrolo[2,1-*a*]isoquinolines have been synthesized by 1,3-dipolar cycloadditions catalyzed by transition metals, such as Cu[10m] and Rh,[10q] or by photocatalysts, such as $[Ru(bpy)_3]^{2+}$,[10n] Ru polypyridine complexes,[10o] C_{60}-Bodipy hybrids,[10p] and porous material immobilized iodo-Bodipy.[10r] However, these methods require an extra oxidation step to convert the pyrrolidines to the pyrroles, except in the case of the version reported by Wang et al.[10m]

The 1,3-dipolar azomethine ylide cycloaddition is a powerful tool for the construction of five-membered heterocycles.[10m,n,11] Moreover, the 1,3-dipolar cycloaddition of stabilized isoquinolinium *N*-ylides with ketenes[12] and vinyl sulfonium salts[13] as dipolarophiles have been reported. To the best of our knowledge, there have been no reports of the iodine-catalyzed preparation of pyrrolo[2,1-*a*]isoquinolines. Iodine is less expensive than transition metals, and the use of iodine eliminates the need to remove traces of metal from the final products. Therefore, as part of our studies on the use of molecular iodine and the functionalization of quinone,[14] we developed a novel molecular iodine-catalyzed 1,3-dipolar cycloaddition/oxidation/aromatization cascade process using hydrogen peroxide as the terminal oxidant (Scheme 1, eq 2).

RESULTS AND DISCUSSION

We started by studying the 1,3-dipolar cycloaddition of 1,4-naphthoquinone (**1a**; 1 mmol), ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (**2a**; 1.2 mmol), molecular iodine (10 mol %), and 35% aqueous H_2O_2 (3 mmol) in CH_3CN under reflux conditions for 5 h (Table 1). To our delight, the reaction afforded dihydropyrrolo[2,1-*a*]isoquinoline **3a** in 56% yield (entry 1). The yield of **3a** could be increased to 78% or 71% when an equal volume of water or EtOH, respectively, was

Received: November 16, 2013

   dx.doi.org/10.1021/jo402540j | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Scheme 1. Methods for the Construction of Pyrrolo[2,1-*a*]isoquinolines

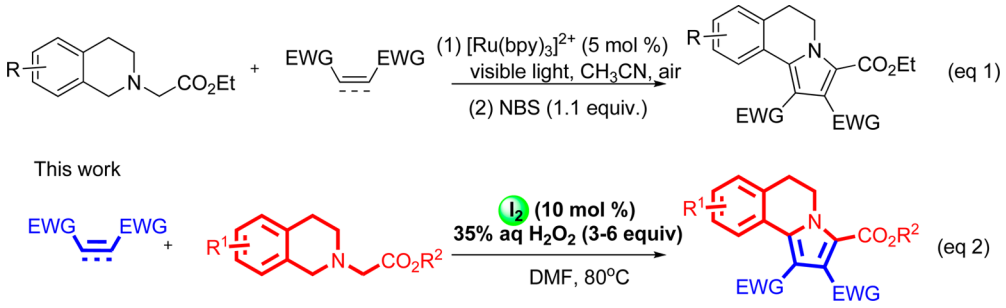
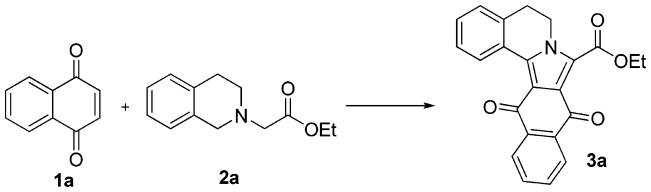


Table 1. Optimization of Reaction Conditions[a]



entry	solvent	temp (°C)	time (h)	iodine source (0.1 equiv)	yield of **3a** (%)[b]
1	CH_3CN	reflux	5	I_2	56
2	CH_3CN/H_2O (1/1 v/v)	80	10	I_2	78
3	CH_3CN/EtOH (1/1 v/v)	80	12	I_2	71
4	EtOH	reflux	5	I_2	46
5	EtOAc	reflux	18	I_2	36
6	$(CH_3)_2O$	reflux	23	I_2	20
7	CH_2Cl_2	reflux	23	I_2	10
8	THF	reflux	18	I_2	71
9	acetone	reflux	17	I_2	51
10	DMF	80	6	I_2	**94**
11[c]	DMF	80	8	I_2	83
12	DMF	80	10	NIS	79
13	DMF	80	8	I_2 (0.05 equiv)	91
14	DMF	120	5	I_2	89
15	DMF	80	25		20

[a]Compound **1a** (1.0 mmol), **2a** (1.2 mmol), the iodine source, and 35% aqueous H_2O_2 (3 equiv) in solvent (5 mL) were stirred for several hours at the specified temperature until **1a** was consumed. [b]Isolated yield. [c]The amount of 35% aqueous H_2O_2 was decreased to 2 equiv.

added to the CH_3CN (entries 2 and 3). To determine the ideal solvent for the transformation, we investigated the model reaction in EtOH (46% yield), ethyl acetate (36%), $(CH_3)_2O$ (20%), CH_2Cl_2 (10%), THF (71%), acetone (51%), and DMF (94%) (entries 4−10). The desired product **3a** was obtained in all the tested solvents, and the polar solvent DMF gave the best isolated yield (94%, entry 10). When the amount of 35% aqueous H_2O_2 was decreased to 2 equiv, the yield of **3a** was only 83% (entry 11). This result indicates that 3 equiv of 35% aqueous H_2O_2 was necessary because of its instability. We found that molecular iodine was the better of the two iodine sources tested for this 1,3-dipolar cycloaddition: when NIS was used as the iodine source, we obtained **3a** in only 79% yield (entry 12). When we decreased the amount of molecular iodine to 0.05 equiv, we obtained **3a** in 91% yield, but the reaction required 8 h (entry 13). When the reaction temperature was increased to 120 °C, the yield of **3a** dropped slightly, to 89% (entry 14). Notably, the yield of **3a** was only 20% in the absence of iodine (entry 15), indicating that iodine facilitated the cascade process. The best yield of **3a** (94%) was obtained from the reaction of **1a** (1 mmol), **2a** (1.2 mmol), molecular iodine (10 mol %), and 35% aqueous H_2O_2 (3 mmol) in DMF (5 mL) at 80 °C for 6 h (entry 10).

Using the optimized conditions, we evaluated the substrate scope of the reaction by using readily available starting materials (Table 2). 1,4-Anthroquinone (**1b**) and N-substituted maleimides (**1c−h**) reacted smoothly with **2a** to give the corresponding products (**3c−h**) in moderate to excellent yields (entries 2−8). More importantly, other dipolarophiles, such as activated alkynes and acrylates, also reacted smoothly with **2a** to afford the desired products in moderate yields (entries 9 and 10). To further evaluate the substrate scope, we examined various tetrahydroisoquinoline derivatives **2**. Excitingly, **3k** was obtained in 87% yield when **2b** was employed (entry 11). 1,4-Anthroquinone (**1b**) and *N*-phenylmaleimide (**1c**) reacted with **2b** to give the desired products in 83% and 78% yields, respectively (entries 12 and 13). Encouraged by these results, we prepared some tetrahydroisoquinoline derivatives containing various ester groups (methyl, ethyl, *tert*-butyl, and benzyl) and allowed them to react with 1,4-naphthoquinone or *N*-phenylmaleimide, and we obtained the corresponding products in moderate to good yields (entries 14−18).

To demonstrate the utility of the reaction, we also carried it out at larger scales, and the results indicated that the catalyst system may be suitable for scale-up chemistry. Specifically, we were pleased to find that 10 mol % molecular iodine catalyzed the reaction between 7.0 mmol of 1,4-naphthoquinone (**1a**) and 8.4 mmol of ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)-acetate (**2a**) at 80 °C in DMF and gave gram-scale quantities of **3a** in high yield (89%; Scheme 2).

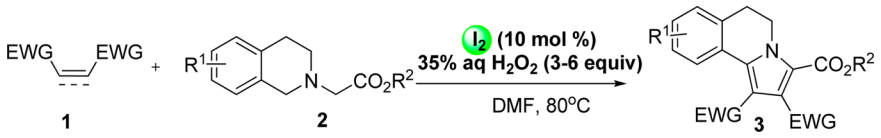
On the basis of the results described above, we propose a possible mechanism for the reaction of **1a** and **2a** (Scheme 3). Initially, tertiary amine (**2a**) was oxidized to isoquinolinium salt **A** by IOH,[7] which was generated from molecular iodine and hydrogen peroxide.[7,15] The 1,3-dipole **B** was formed by elimination of HI with tertiary amine (**2a**), and **B** then reacted with **1a** to afford the 1,3-dipolar addition product **D**. Finally, **3a** was formed through sequential oxidation. At the same time, the intermediate **C** was reoxidized to IOH and **2a** by hydrogen peroxide.[16]

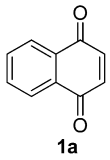
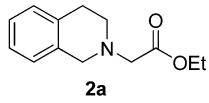
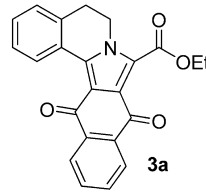
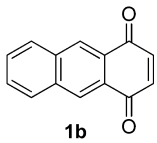
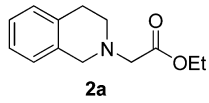
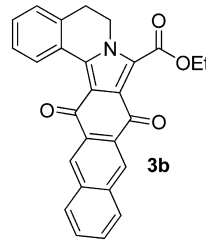
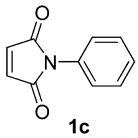
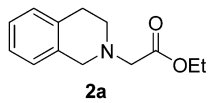
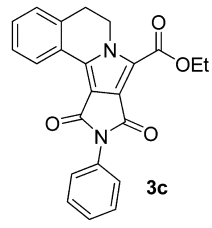
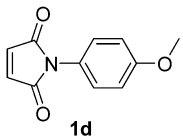
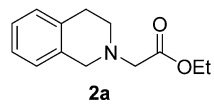
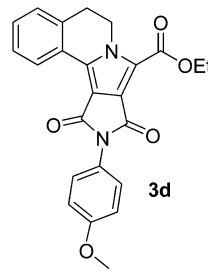
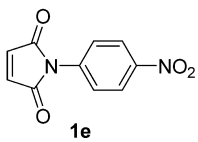
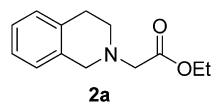
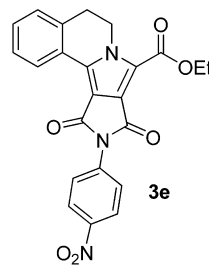
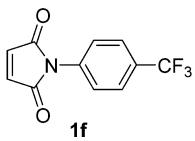
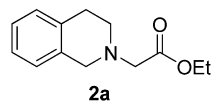
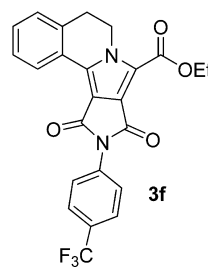
CONCLUSION

In conclusion, we developed a novel molecular iodine-catalyzed 1,3-dipolar cycloaddition/oxidation/aromatization cascade process with hydrogen peroxide as the terminal oxidant to construct pyrrolo[2,1-*a*]isoquinolines. In comparison with various reported methods using heavy metals, this approach is less expensive and thus more practical. This novel catalyst system

dx.doi.org/10.1021/jo402540j | J. Org. Chem. XXXX, XXX, XXX−XXX

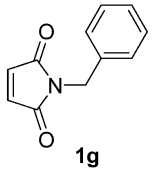
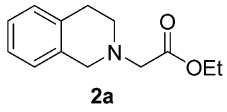
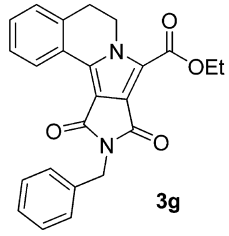
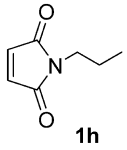
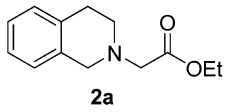
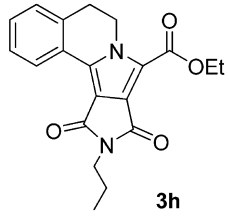
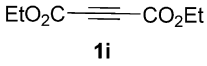
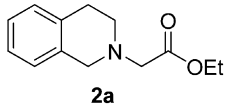
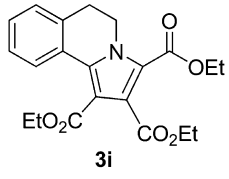
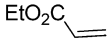
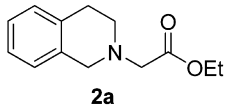
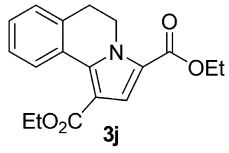
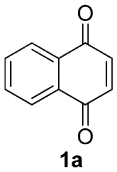
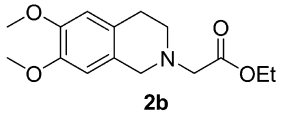
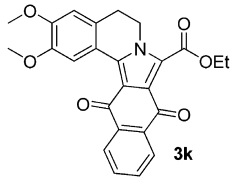
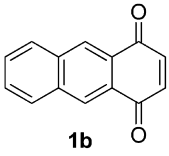
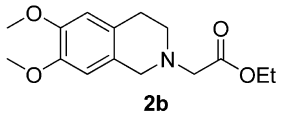
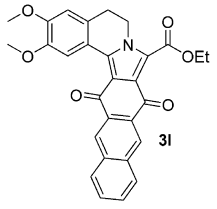
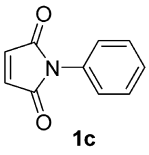
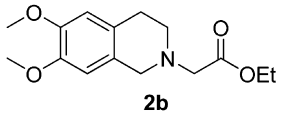
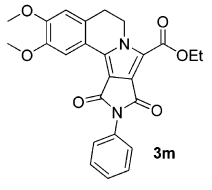
Table 2. Reactions of Different Dipolarophiles with Tetrahydroisoquinolines



entry	dipolarophile **1**	tetrahydroisoquinoline **2**	product **3**	yield (%) [a]
1	 **1a**	 **2a**	 **3a**	94
2	 **1b**	 **2a**	 **3b**	83
3 [b]	 **1c**	 **2a**	 **3c**	93
4 [b]	 **1d**	 **2a**	 **3d**	87
5 [b]	 **1e**	 **2a**	 **3e**	81
6 [b]	 **1f**	 **2a**	 **3f**	88

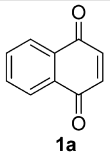
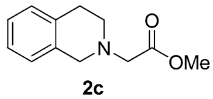
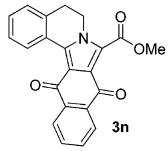
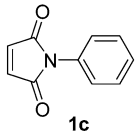
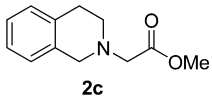
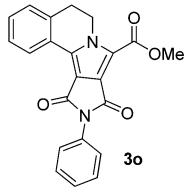
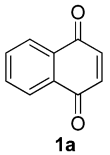
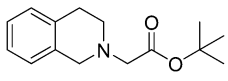
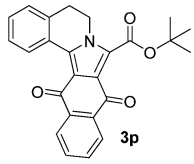
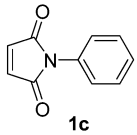
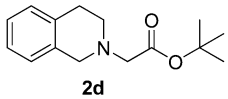
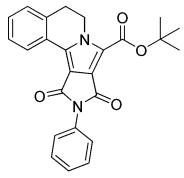
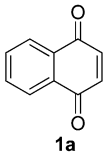
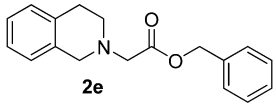
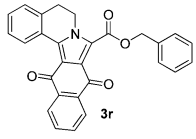
dx.doi.org/10.1021/jo402540j | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 2. continued

entry	dipolarophile **1**	tetrahydroisoquinoline **2**	product **3**	yield (%) [a]
7 [b]	 **1g**	 **2a**	 **3g**	83
8 [b]	 **1h**	 **2a**	 **3h**	96
9 [b]	 **1i**	 **2a**	 **3i**	62
10 [b]	 **1j**	 **2a**	 **3j**	42
11	 **1a**	 **2b**	 **3k**	87
12	 **1b**	 **2b**	 **3l**	83
13 [b]	 **1c**	 **2b**	 **3m**	78

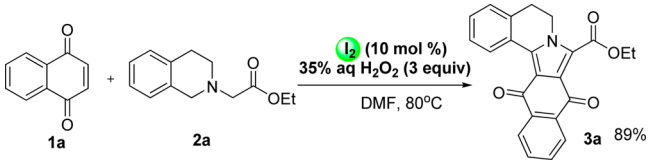
dx.doi.org/10.1021/jo402540j | *J. Org. Chem.* XXXX, XXX, XXX−XXX

Table 2. continued

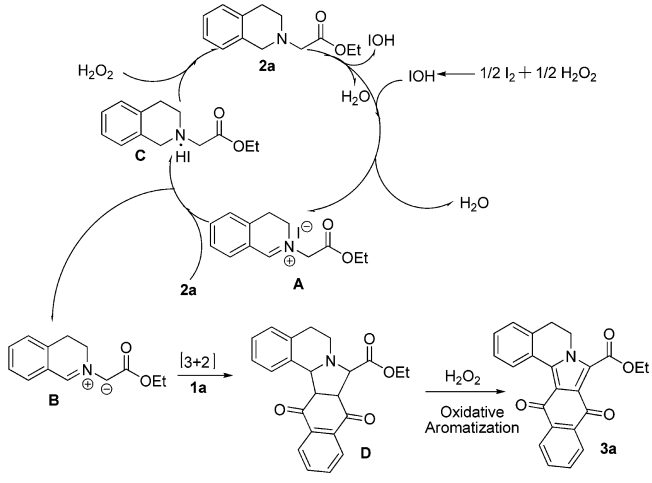
entry	dipolarophile **1**	tetrahydroisoquinoline **2**	product **3**	yield (%) [a]
14	 **1a**	 **2c**	 **3n**	89
15 [b]	 **1c**	 **2c**	 **3o**	90
16	 **1a**	 **2d**	 **3p**	78
17 [b]	 **1c**	 **2d**		65
18	 **1a**	 **2e**	 **3r**	60

[a]Yield of the isolated product. [b]6 equiv of 35% aqueous H_2O_2 was added.

Scheme 2. Gram-Scale Reaction



Scheme 3. Proposed Mechanism



can be expected to be effective for the preparation of biologically important pyrrolo[2,1-*a*]isoquinolines and is compatible with a wide range of dipolarophiles. Further studies on the applications of this strategy will be reported in due course.

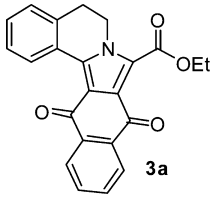
EXPERIMENTAL SECTION

General Information. All solvents were purified and dried using standard methods prior to use. Commercially available reagents were used without further purification. ^{1}H NMR spectra were recorded on an NMR instrument operated at 500 MHz. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$, δ 7.26 ppm). ^{13}C NMR spectra were recorded on an NMR instrument operated at 125 MHz with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$, δ 77.1 ppm). MS and HRMS were measured in EI or ESI mode and the mass analyzer of the HRMS was TOF. Thin-layer chromatography was performed on precoated glass-backed plates and visualized with UV light at 254 nm. Flash column chromatography was performed on silica gel.

dx.doi.org/10.1021/jo402540j | J. Org. Chem. XXXX, XXX, XXX−XXX

General Procedure for the Synthesis of 3. The dipolarophile **1** (1.0 mmol) was added to a mixture of the tetrahydroisoquinoline **2** (1.2 mmol), 35% aqueous H_2O_2 (3−6 mmol), and iodine (0.1 mmol) in DMF (5.0 mL). The solution was stirred for 6 h at 80 °C. After **1** was completely consumed (as indicated by TLC and GC-MS), the reaction mixture was washed with aqueous $Na_2S_2O_3$, dried over magnesium sulfate, and concentrated in vacuo. Purification of the crude product by flash chromatography on silica gel with CH_2Cl_2 as the eluent provided desired products **3**.

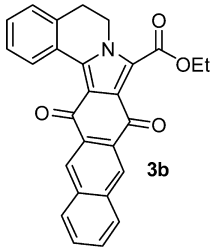
*Ethyl 9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-a]-isoquinoline-8-carboxylate (**3a**):*[10m]



3a

yellow solid, yield 94% (0.349 g), mp 144−145 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.01 (d, J = 8.0 Hz, 1H), 8.31−8.30 (m, 1H), 8.23−8.21 (m, 1H), 7.75−7.69 (m, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.39 (t, J = 6.5 Hz, 1H), 7.29−7.27 (m, 1H), 4.56 (q, J = 7.0 Hz, 2H), 4.30 (t, J = 6.5 Hz, 2H), 3.12 (t, J = 6.5 Hz, 2H), 1.51 (t, J = 7.0 Hz, 3H); IR ν/cm^{-1} (KBr) 1704, 1660, 1524, 1465, 1413, 1384, 1311, 1268, 1227, 1141, 1108, 1047, 1010, 984, 790, 729, 711; GC-MS m/z 372.0 $[M + 1]^+$, 326.7, 301.0, 243.6, 77.8, 51.0.

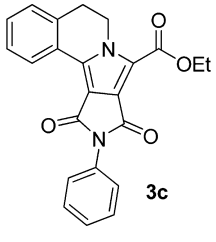
*Ethyl 9,16-dioxo-5,6,9,16-tetrahydronaphtho[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (**3b**).*



3b

orange solid, yield 83% (0.349 g), mp 234−235 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.00 (d, J = 8.0 Hz, 1H), 8.71 (s, 1H), 8.63 (s, 1H), 7.95−7.94 (m, 2H), 7.55−7.54 (m, 2H), 7.41 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 4.57 (q, J = 7.0 Hz, 2H), 4.22 (t, J = 6.5 Hz, 2H), 3.06 (t, J = 6.5 Hz, 2H), 1.54 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 179.4, 179.2, 161.6, 135.5, 134.8, 134.6, 133.5, 132.1, 131.2, 129.9, 129.8, 129.7, 129.2, 129.0, 128.8, 128.7, 128.5, 127.3, 127.3, 126.4, 126.1, 124.0, 118.2, 62.5, 43.1, 29.1, 14.1; IR ν/cm^{-1} (KBr) 1665, 1461, 1267, 1016, 751; HRMS (ESI-TOF) m/z calcd for $C_{27}H_{20}NO_4$ $[M + H]^+$ 422.1392, found 422.1388.

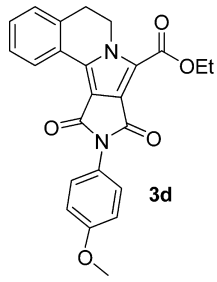
*Ethyl 9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5H-pyrrolo-[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3c**):*[10m] white



3c

solid, yield 93% (0.359 g), mp 190−191 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.59 (d, J = 8.5 Hz, 1H), 7.50 (t, J = 7.0 Hz, 2H), 7.43−7.36 (m, 5H), 7.29 (d, J = 7.5 Hz, 1H), 4.77 (q, J = 8.0 Hz, 2H), 4.44 (q, J = 7.0 Hz, 2H), 3.18 (t, J = 7.0 Hz, 2H), 1.48 (t, J = 8.0 Hz, 3H); IR ν/cm^{-1} (KBr) 1759, 1709, 1551, 1482, 1421, 1384, 1341, 1301, 1279, 1198, 1155, 1111, 1090, 1051, 945, 895, 862, 823, 759; GC-MS m/z 386.8 $[M + 1]^+$, 385.8, 339.9, 314.0, 270.1, 139.1.

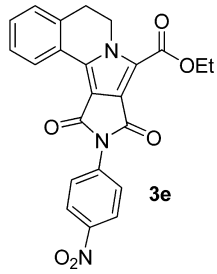
*Ethyl 10-(4-methoxyphenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3d**):*[10m]



3d

white solid, yield 87% (0.362 g), mp 168−169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.57 (d, J = 7.5 Hz, 1H), 7.41−7.35 (m, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.28−7.27 (m, 1H), 7.00 (d, J = 9.0 Hz, 2H), 4.75 (t, J = 7.0 Hz, 2H), 4.42 (q, J = 7.5 Hz, 2H), 3.84 (s, 3H), 3.17 (t, J = 7.0 Hz, 2H), 1.47 (t, J = 7.5 Hz, 3H); IR ν/cm^{-1} (KBr) 1761, 1707, 1514, 1385, 1280, 1250, 1194, 1159, 1111, 1031, 809, 743; GC-MS m/z 417.3 $[M + 1]^+$, 385.1, 325.6, 288.2, 236.1, 156.7, 71.1.

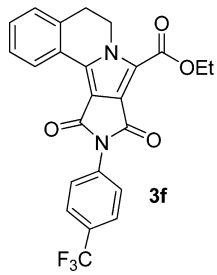
*Ethyl 10-(4-nitrophenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo-[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3e**):*[10n]



3e

yellow solid, yield 81% (0.349 g), mp 206−207 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.55 (d, J = 8.5 Hz, 1H), 8.35 (d, J = 9.0 Hz, 2H), 7.72 (d, J = 9.5 Hz, 2H), 7.46−7.40 (m, 2H), 7.32 (d, J = 7.0 Hz, 1H), 4.80 (t, J = 6.5 Hz, 2H), 4.46 (q, J = 7.5 Hz, 2H), 3.21 (t, J = 6.5 Hz, 2H), 1.49 (t, J = 7.5 Hz, 3H); IR ν/cm^{-1} (KBr) 1761, 1713, 1524, 1384, 1321, 1277, 1194, 1138, 1109, 1040, 1011, 893, 853, 817, 777; GC-MS m/z 432.5 $[M + 1]^+$, 400.2, 333.8, 263.9, 200.9, 184.5, 85.1.

*Ethyl 10-(4-trifluoromethylphenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3f**):*

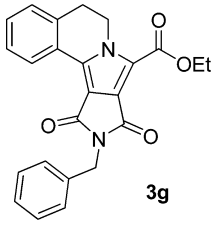


3f

white solid, yield 88% (0.400 g), mp 203−204 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.49−8.47 (m, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.36−7.34 (m, 2H), 7.25 (t, J = 4.5 Hz, 1H), 4.70 (t, J = 7.0 Hz, 2H), 4.39 (q, J = 7.0 Hz, 2H), 3.13 (t, J = 7.0 Hz, 2H), 1.47 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 162.2, 160.6, 159.1, 135.8, 134.2, 133.5, 132.3, 130.3, 127.7, 127.6, 127.5, 126.8, 125.7, 125.6, 125.5, 125.1, 124.5, 122.8, 118.8, 115.6, 61.5, 43.2, 27.9, 13.9; IR ν/cm^{-1} (KBr) 1762, 1712, 1477, 1417, 1385, 1325, 1277, 1196, 1162, 1117, 1068, 1019, 947, 895, 845, 815; GC-MS m/z 454.7 $[M + 1]^+$, 453.8, 371.0, 408.8, 381.8, 338.0, 139.0; HRMS (ESI-TOF) m/z calcd for $C_{24}H_{18}F_3N_2O_4$ $[M + H]^+$ 455.1219, found 455.1216.

dx.doi.org/10.1021/jo402540j | J. Org. Chem. XXXX, XXX, XXX−XXX

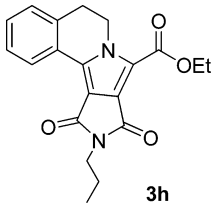
*Ethyl 10-benzyl-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo-[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3g**):*[10n]



3g

white solid, yield 83% (0.332 g), mp 200−201 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.49 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.0 Hz, 2H), 7.38−7.30 (m, 3H), 7.27−7.23 (m, 1H), 7.20 (d, J = 7.0 Hz, 1H), 4.77 (s, 2H), 4.68 (t, J = 7.0 Hz, 2H), 4.43 (q, J = 7.0 Hz, 2H), 3.10 (t, J = 7.0 Hz, 2H), 1.49 (t, J = 7.0 Hz, 3H); GC-MS m/z 401.0 $[M + 1]^+$, 400.0, 371.0, 353.9, 325.9, 224.2, 195.1.

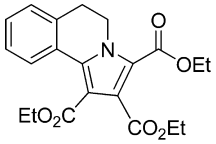
*Ethyl 10-propyl-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo-[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3h**):*



3h

white solid, yield 96% (0.338 g), mp 188−189 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.53 (d, J = 8.5 Hz, 1H), 7.42−7.39 (m, 1H), 7.38−7.34 (m, 1H), 7.27 (d, J = 8.5 Hz, 1H), 4.72 (t, J = 7.0 Hz, 2H), 4.43 (q, J = 7.0 Hz, 2H), 3.59 (t, J = 7.0 Hz, 2H), 3.15 (t, J = 7.0 Hz, 2H), 1.72−1.67 (m, 2H), 1.49 (t, J = 7.0 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 164.2, 162.7, 159.7, 132.8, 132.4, 130.1, 127.9, 127.9, 127.6, 125.9, 125.7, 118.1, 116.7, 61.5, 43.3, 39.9, 28.4, 22.0, 14.2, 11.4; IR ν/cm^{-1} (KBr) 1752, 1700, 1471, 1385, 1330, 1280, 1199, 1123, 1012, 779, 746; GC-MS m/z 353.0 $[M + 1]^+$, 352.0, 323.1, 278.1, 266.2, 222.2, 139.2, 103.0; HRMS (ESI-TOF) m/z calcd for $C_{20}H_{21}N_2O_4$ $[M + H]^+$ 353.1501, found 353.1498.

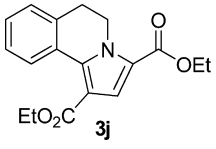
*3-Ethyl 1,2-diethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,2,3-tricarboxylate (**3i**):*



3i

white solid, yield 62% (0.239 g), mp 112−113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.20−8.18 (m, 1H), 7.32−7.30 (m, 2H), 7.25−7.24 (m, 1H), 4.54 (t, J = 7.0 Hz, 2H), 4.38 (q, J = 7.0 Hz, 2H), 4.34−4.30 (m, 4H), 3.00 (t, J = 7.0 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H), 1.37−1.32 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 166.0, 163.4, 159.9, 136.6, 134.3, 129.2, 128.5, 127.3, 126.9, 126.9, 126.5, 119.0, 110.8, 61.4, 61.0, 60.7, 42.6, 29.4, 14.12, 14.09, 14.05; IR ν/cm^{-1} (KBr) 1673, 1581, 1431, 1366, 1155, 1043, 886; GC-MS m/z 385.5 $[M]^+$, 384.7, 339.7, 312.8, 265.7, 221.9, 139.0, 129.9; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{24}NO_6$ $[M + H]^+$ 386.1604, found 386.1598.

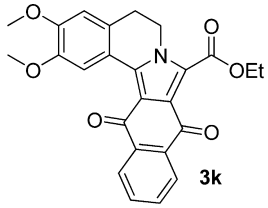
*Diethyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (**3j**):*[10n]*:*



3j

yellow solid, yield 42% (0.131 g), mp 100−101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.45 (d, J = 8.5 Hz, 1H), 7.50 (s, 1H), 7.36−7.30 (m, 2H), 7.25 (d, J = 6.0 Hz, 1H), 4.61 (t, J = 6.5 Hz, 2H), 4.37−4.32 (m, 4H), 3.03 (t, J = 6.5 Hz, 2H), 1.41−1.38 (m, 6H); GC-MS m/z 314.2 $[M + 1]^+$, 312.9, 283.5, 155.9,73.5.

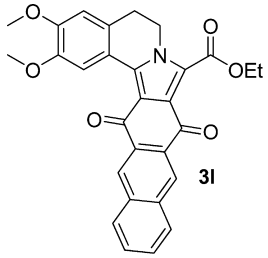
*Ethyl 2,3-dimethoxy-9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]-isoindolo[1,2-a]isoquinoline-8-carboxylate (**3k**):*



3k

orange solid, yield 87% (0.375 g), mp 194−195 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.88 (s, 1H), 8.23 (t, J = 2.0 Hz, 1H), 8.12−8.10 (m, 1H), 7.66−7.60 (m, 2H), 6.67 (s, 1H), 4.51 (q, J = 7.0 Hz, 2H), 4.21 (t, J = 7.0 Hz, 2H), 4.06 (s, 3H), 3.89 (s, 3H), 3.01 (t, J = 7.0 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 179.5, 179.4, 161.5, 150.2, 147.6, 136.2, 135.8, 134.6, 133.1, 132.7, 127.3, 126.9, 126.4, 125.9, 122.9, 119.1, 116.3, 112.4, 110.2, 62.4, 54.3, 55.9, 43.3, 28.5, 14.0; IR ν/cm^{-1} (KBr) 1718, 1657, 1479, 1385, 1282, 1257, 1217, 1152, 1132, 1045, 1015, 705; HRMS (ESI-TOF) m/z calcd for $C_{25}H_{22}NO_6$ $[M + H]^+$ 432.1447, found 432.1444.

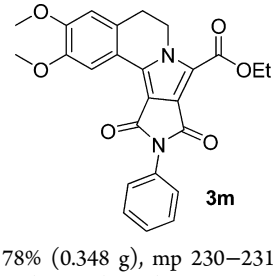
*Ethyl 2,3-dimethoxy-9,16-dioxo-5,6,9,16-tetrahydronaphtho-[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (**3l**):*



3l

orange solid, yield 83% (0.399 g), mp 271−272 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.98 (s, 1H), 8.80 (s, 1H), 8.68 (s, 1H), 8.04−8.00 (m, 2H), 7.63−7.61 (m, 2H), 6.73 (s, 1H), 4.57 (q, J = 7.5 Hz, 2H), 4.26 (t, J = 7.0 Hz, 2H), 4.13 (s, 3H), 3.93 (s, 3H), 3.06 (t, J = 7.0 Hz, 2H), 1.54 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 179.6, 179.4, 161.8, 150.2, 147.7, 136.3, 134.9, 134.6, 132.4, 131.3, 129.83, 129.77, 129.3, 128.82, 128.76, 128.4, 127.0, 126.1, 123.8, 119.3, 117.2, 112.6, 110.2, 62.5, 56.3, 56.0, 43.3, 28.6, 14.1; IR ν/cm^{-1} (KBr) 1719, 1659, 1479, 1384, 1271, 1240, 1222, 1186, 1133, 1038, 914, 763; HRMS (ESI-TOF) m/z calcd for $C_{29}H_{24}NO_6$ $[M + H]^+$ 482.1604, found 482.1600.

*Ethyl 2,3-dimethoxy-9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3m**):*[10n]

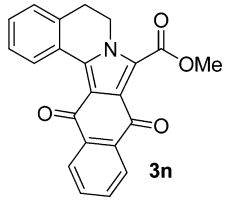


3m

orange solid, yield 78% (0.348 g), mp 230−231 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.24 (s, 1H), 7.49−7.47 (m, 2H), 7.40−7.36 (m, 3H), 6.75 (s, 1H), 4.73 (t, J = 7.0 Hz, 2H), 4.41 (q, J = 7.0 Hz, 2H), 3.97 (s, 3H), 3.93 (s, 3H), 3.11 (t, J = 7.0 Hz, 2H), 1.46 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 163.46, 161.59, 159.59, 150.67, 148.57, 134.01, 132.60128.97 (2C), 127.84, 127.28 (2C), 125.55, 125.03, 118.29, 118.08, 114.75, 110.48, 110.26, 61.48, 56.14, 55.97, 43.42, 27.81, 14.12; GC-MS m/z 447.1 $[M + 1]^+$, 445.0, 411.3, 385.4, 301.9, 254.3, 100.1, 56.4.

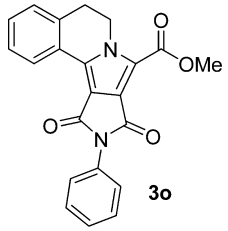
dx.doi.org/10.1021/jo402540j | J. Org. Chem. XXXX, XXX, XXX−XXX

*Methyl 2,3-dimethoxy-9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]-isoindolo[1,2-a]isoquinoline-8-carboxylate (**3n**):*



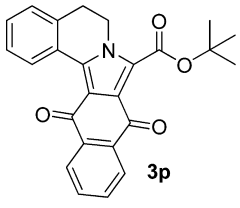
orange solid, yield 89% (0.318 g), mp 205−206 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.95 (s, J = 8.0 Hz, 1H), 8.27−8.25 (m, 1H), 8.17−8.16 (m, 1H), 7.71−7.65 (m, 2H), 7.42 (t, J = 6.5 Hz, 1H), 7.36−7.33 (m, 1H), 7.23 (s, J = 7.0 Hz, 1H), 4.26 (t, J = 6.5 Hz, 2H), 4.06 (s, 3H), 3.08 (t, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 179.51, 179.47, 161.8, 135.8, 135.6, 134.6, 133.7, 133.3, 132.9, 130.1, 128.9, 127.4 (2C), 127.2, 126.5, 126.3, 125.4, 123.4, 117.5, 53.0, 43.2, 29.0; IR ν/cm^{-1} (KBr) 1712, 1656, 1466, 1412, 1385, 1314, 1269, 1224, 1140, 1113, 1060, 1012, 799, 734; GC-MS m/z 358.1 $[M + 1]^+$, 356.8, 333.6, 276.5, 139.8, 73.9; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{16}NO_4$ $[M + H]^+$ 358.1079, found 358.1077.

*Methyl 2,3-dimethoxy-9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3o**):*



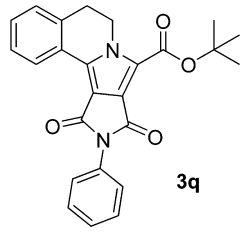
orange solid, yield 90% (0.335 g), mp 217−218 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.58−8.57 (m, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.43−7.36 (m, 5H), 7.29−7.28 (m, 1H), 4.77 (t, J = 7.0 Hz, 2H), 3.98 (s, 3H), 3.18 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 163.0, 161.5, 160.0, 133.6, 132.6, 132.4, 130.4, 128.8 (2C), 128.0, 127.9, 127.70, 127.65, 127.0 (2C), 125.5, 125.3, 118.2, 116.3, 52.3, 43.4, 28.3; IR ν/cm^{-1} (KBr) 1497, 1385, 1199, 756, 694, 620; GC-MS m/z 373.6 $[M + 1]^+$, 372.1, 348.6, 303.2, 256.4, 202.1, 154.1, 54.6; HRMS (ESI-TOF) m/z calcd for $C_{22}H_{17}N_2O_4$ $[M + H]^+$ 373.1188, found 373.1184.

*tert-Butyl 2,3-dimethoxy-9,14-dioxo-5,6,9,14-tetrahydrobenzo-[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (**3p**):*



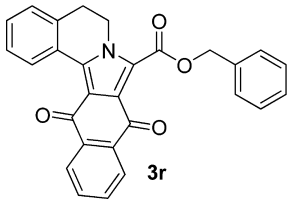
orange solid, yield 78% (0.311 g), mp 170−171 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.02 (d, J = 7.5 Hz, 1H), 8.30 (dd, J_1 = 2.0 Hz, J_2 = 6.5 Hz, 1H), 8.23 (dd, J_1 = 2.0 Hz, J_2 = 6.5 Hz, 1H), 7.72−7.69 (m, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 1H), 4.27 (t, J = 7.0 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H), 1.72 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 179.8, 179.3, 160.6, 135.8, 135.0, 134.9, 133.5, 133.1, 132.9 (2C), 129.9, 128.8, 127.7, 127.4, 127.4, 127.2, 126.5, 122.4, 117.2, 84.1, 43.0, 29.1, 28.1 (3C); IR ν/cm^{-1} (KBr) 1660, 1467, 1385, 1266, 1229, 1141, 1010, 714; HRMS (ESI-TOF) m/z calcd for $C_{25}H_{21}NO_4Na$ $[M + Na]^+$ 422.1369, found 422.1365.

*tert-Butyl 2,3-dimethoxy-9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3q**):*



orange solid, yield 65% (0.269 g), mp 234−235 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.59 (dd, J_1 = 1.5 Hz, J_2 = 8.0 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 7.43−7.35 (m, 5H), 7.28 (t, J = 6.5 Hz, 1H), 4.75 (t, J = 6.5 Hz, 2H), 3.16 (t, J = 6.5 Hz, 2H), 1.68 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 163.2, 161.6, 159.0, 133.0, 132.8, 132.4, 130.1, 128.9 (2C), 127.9, 127.9, 127.7, 127.6, 127.3 (2C), 125.7, 124.7, 120.2, 116.0, 83.4, 43.3, 28.4, 28.3 (3C); IR ν/cm^{-1} (KBr) 1759, 1703, 1481, 1415, 1385, 1349, 1305, 1289, 1154, 1135, 1112, 1089, 1051, 950, 889, 843, 762; HRMS (ESI-TOF) m/z calcd for $C_{25}H_{22}N_2O_4Na$ $[M + Na]^+$ 437.1478, found 437.1475.

*Benzyl 2,3-dimethoxy-9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5H-pyrrolo[3′,4′:3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (**3r**):*



orange solid, yield 60% (0.260 g), mp 198−199 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 9.00 (d, J = 7.5 Hz, 1H), 8.30 (dd, J_1 = 2.5 Hz, J_2 = 6.0 Hz, 1H), 8.24 (dd, J_1 = 3.0 Hz, J_2 = 6.5 Hz, 1H), 7.74−7.70 (m, 2H), 7.57 (d, J = 6.5 Hz, 2H), 7.47−7.36 (m, 5H), 7.27 (d, J = 8.5 Hz, 1H), 5.53 (s, 2H), 4.26 (t, J = 6.5 Hz, 2H), 3.08 (t, J = 6.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 179.8, 179.5, 161.4, 135.9, 135.8, 135.2, 134.9, 133.7, 133.4, 133.1, 130.2, 129.0, 128.8 (2C), 128.7 (2C), 128.7, 127.5, 127.5, 127.3, 126.7, 126.4, 125.5, 123.7, 117.7, 68.4, 43.3, 29.2; IR ν/cm^{-1} (KBr) 1642, 1384, 1262, 1097, 802; HRMS (ESI-TOF) m/z calcd for $C_{28}H_{20}NO_4$ $[M + H]^+$ 434.1392, found 434.1390.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving NMR spectra for compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lyjzjut@zjut.edu.cn (Y.-J.L.); gdgjr@zjut.edu.cn (J.-R.G.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of China (Grant No. 21176223), the National Natural Science Foundation of Zhejiang (Grant No. LY13B020016), and the Key Innovation Team of Science and Technology in Zhejiang Province (Grant No. 2010R50018).

■ REFERENCES

(1) (a) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Chem. Eur. J.* **2012**, *18*, 5460−5489. (b) Togo, H.; Iida, S. *Synlett* **2006**, *2006*, 2159−2175. (c) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.;

Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 15720−15725. (d) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4764−4766. (e) Huo, Z.; Tomeba, H.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 5531−5533. (f) Küpper, F. C.; Feiters, M. C.; Olofsson, B.; Kaiho, T.; Yanagida, S.; Zimmermann, M. B.; Carpenter, L. J.; Luther, G. W.; Lu, Z.; Jonsson, M.; Kloo, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 11598−11620. (g) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668−1669. (h) Fei, N.; Hou, Q.; Wang, S.; Wang, H.; Yao, Z.-J. *Org. Biomol. Chem.* **2010**, *8*, 4096−4103. (i) Ali, S.; Zhu, H.-T.; Xia, X.-F.; Ji, K.-G.; Yang, Y.-F.; Song, X.-R.; Liang, Y.-M. *Org. Lett.* **2011**, *13*, 2598−2601. (j) Batchu, H.; Bhattacharyya, S.; Batra, S. *Org. Lett.* **2012**, *14*, 6330−6333. (k) Alcaide, B.; Almendros, P.; Cabrero, G.; Callejo, R.; Ruiz, M. P.; Arnó, M.; Domingo, L. R. *Adv. Synth. Catal.* **2010**, *352*, 1688−1700. (l) Wu, W.-B.; Huang, J.-M. *Org. Lett.* **2012**, *14*, 5832−5835. (m) Lee, W.-C.; Shen, H.-C.; Hu, W.-P.; Lo, W.-S.; Murali, C.; Vandavasi, J. K.; Wang, J.-J. *Adv. Synth. Catal.* **2012**, *354*, 2218−2228. (n) Li, Y.-X.; Ji, K.-G.; Wang, H.-X.; Ali, S.; Liang, Y.-M. *J. Org. Chem.* **2011**, *76*, 744−747. (o) Li, Y.-X.; Wang, H.-X.; Ali, S.; Xia, X.-F.; Liang, Y.-M. *Chem. Commun.* **2012**, *48*, 2343−2345. (p) Zhu, Y.-p.; Liu, M.-c.; Jia, F.-c.; Yuan, J.-j.; Gao, Q.-h.; Lian, M.; Wu, A.-x. *Org. Lett.* **2012**, *14*, 3392−3395. (q) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Adv. Synth. Catal.* **2013**, *355*, 170−180. (r) Sashidhara, K. V.; Kumar, A.; Agarwal, S.; Kumar, M.; Kumar, B.; Sridhar, B. *Adv. Synth. Catal.* **2012**, *354*, 1129−1140. (s) Zhang, X.; Zhou, Y.; Wang, H.; Guo, D.; Ye, D.; Xu, Y.; Jiang, H.; Liu, H. *Adv. Synth. Catal.* **2011**, *353*, 1429−1437.

(2) (a) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376−1379. (b) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331−5334. (c) Uyanik, M.; Ishihara, K. *ChemCatChem.* **2012**, *4*, 177−185.

(3) Kumar, R. A.; Saidulu, G.; Prasad, K. R.; Kumar, G. S.; Sridhar, B.; Reddy, K. R. *Adv. Synth. Catal.* **2012**, *354*, 2985−2991.

(4) (a) Chen, L.; Shi, E.; Liu, Z.; Chen, S.; Wei, W.; Li, H.; Xu, K.; Wan, X. *Chem. Eur. J.* **2011**, *17*, 4085−4089. (b) Wei, W.; Zhang, C.; Xu, Y.; Wan, X. *Chem. Commun.* **2011**, *47*, 10827−10829. (c) Kumar, R. A.; Maheswari, C. U.; Ghantasala, S.; Jyothi, C.; Reddy, K. R. *Adv. Synth. Catal.* **2011**, *353*, 401−410.

(5) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979−981.

(6) (a) Froehr, T.; Sindlinger, C. P.; Kloeckner, U.; Finkbeiner, P.; Nachtsheim, B. J. *Org. Lett.* **2011**, *13*, 3754−3757. (b) Liu, Z.; Zhang, J.; Chen, S.; Shi, E.; Xu, Y.; Wan, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 3231−3235. (c) Ma, L.; Wang, X.; Yu, W.; Han, B. *Chem. Commun.* **2011**, *47*, 11333−11335.

(7) Nobuta, T.; Tada, N.; Fujiya, A.; Kariya, A.; Miura, T.; Itoh, A. *Org. Lett.* **2013**, *15*, 574−577.

(8) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092−1095.

(9) (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2007**, *108*, 264−287. (b) Pla, D.; Albericio, F.; Alvarez, M. *MedChemComm* **2011**, *2*, 689−697. (c) Fukuda, T.; Ishibashi, F.; Iwaob, M. *Heterocycles* **2011**, *83*, 491−529. (d) Handy, S. T.; Zhang, Y. *Org. Prep. Proced. Int.* **2005**, *37*, 411−445. (e) Bailly, C. *Curr. Med. Chem. Anti-Cancer Agents* **2004**, *4*, 363−378. (f) Pla, D.; A, F. A. M. *Anti-Cancer Agents Med. Chem.* **2008**, *2008*, 746−760.

(10) (a) Banwell, M.; Hockless, D. *Chem. Commun.* **1997**, *33*, 2259−2260. (b) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed.* **1997**, *36*, 155−156. (c) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *121*, 54−62. (d) Ridley, C. P.; Reddy, M. V. R.; Rocha, G.; Bushman, F. D.; Faulkner, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 3285−3290. (e) Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 866−868. (f) Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959−2962. (g) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362−2366. (h) Ploypradith, P.; Kagan, R. K.; Ruchirawat, S. *J. Org. Chem.* **2005**, *70*, 5119−5125. (i) Su, S.; Porco, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 7744−7745. (j) Ohta, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *J. Org. Chem.* **2009**, *74*, 8143−8153. (k) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. *Org. Lett.* **2010**, *13*, 312−315. (l) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177−180. (m) Yu, C.; Zhang, Y.; Zhang, S.; Li, H.; Wang, W. *Chem. Commun.* **2011**, *47*, 1036−1038. (n) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171−7175. (o) Rueping, M.; Leonori, D.; Poisson, T. *Chem. Commun.* **2011**, *47*, 9615−9617. (p) Huang, L.; Zhao, J. *Chem. Commun.* **2013**, *49*, 3751−3753. (q) Wang, H.-T.; Lu, C.-D. *Tetrahedron Lett.* **2013**, *54*, 3015−3018. (r) Guo, S.; Zhang, H.; Huang, L.; Guo, Z.; Xiong, G.; Zhao, J. *Chem. Commun.* **2013**, *49*, 8689−8691.

(11) (a) Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 346−355. (b) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207−4220. (c) Candelon, N.; Lastecoueres, D.; Diallo, A. K.; Ruiz Aranzaes, J.; Astruc, D.; Vincent, J.-M. *Chem. Commun.* **2008**, *44*, 741−743. (d) Demko, Z. P.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2110−2113. (e) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604−637. (f) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(12) Kobayashi, M.; Tanabe, M.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2006**, *47*, 1469−1471.

(13) An, J.; Yang, Q.-Q.; Wang, Q.; Xiao, W.-J. *Tetrahedron Lett.* **2013**, *54*, 3834−3837.

(14) (a) Huang, H.-M.; Han, J.; Xu, F.-S.; Li, Y.-J.; Dong, H.-Q.; Yu, W.-B.; Gao, J.-R. *Chem. Lett.* **2013**, *42*, 921−923. (b) Huang, H.-M.; Gao, J.-R.; Hou, L.-F.; Jia, J.-H.; Han, L.; Ye, Q.; Li, Y.-J. *Tetrahedron* **2013**, *69*, 9033−9037. (c) Huang, H.-M.; Li, Y.-J.; Dai, Y.-P.; Yu, W.-B.; Ye, Q.; Gao, J.-R. *J. Chem. Res.* **2013**, *37*, 34−37. (d) Huang, H.-M.; Li, Y.-J.; Yang, J.-R.; Jia, J.-H.; Ye, Q.; Han, L.; Gao, J.-R. *Tetrahedron* **2013**, *69*, 5221−5226. (e) Li, Y.-J.; Huang, H.-M.; Dong, H.-Q.; Jia, J.-H.; Han, L.; Ye, Q.; Gao, J.-R. *J. Org. Chem.* **2013**, *78*, 9424−9430. (f) Li, Y.-J.; Huang, H.-M.; Ju, J.; Jia, J.-H.; Han, L.; Ye, Q.; Yu, W.-B.; Gao, J.-R. *RSC Adv.* **2013**, *3*, 25840−25848.

(15) (a) Leere Øiestad, Å. M.; Petersen, A. C.; Bakken, V.; Vedde, J.; Uggerud, E. *Angew. Chem., Int. Ed.* **2001**, *40*, 1305−1309. (b) Barluenga, J.; Marco-Arias, M.; González-Bobes, F.; Ballesteros, A.; González, J. M. *Chem. Eur. J.* **2004**, *10*, 1677−1682.

(16) For several examples of in situ generated hypoiodite with hydrogen peroxide, see refs 2a and 2b.