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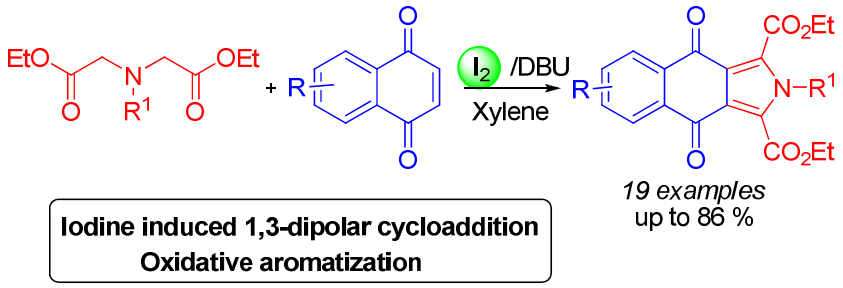
Huang-Ming Huang, Jian-Rong Gao, Qing Ye, Wu-Bin Yu, Wei-Jian Sheng, Yu-Jin Li*



Iodine induced 1,3-dipolar cycloaddition
Oxidative aromatization

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ARTICLE TYPE

Molecular iodine induced / 1,3-dipolar cycloaddition / oxidative aromatization sequence: an efficient strategy to construct 2-substituted benzo[*f*]isoindole-1,3-dicarboxylates

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A useful method for molecular iodine induced 1,3-dipolar cycloaddition / oxidative aromatization sequence to construct 2-substituted-benzo[*f*]isoindole-1,3-dicarboxylates is reported. This is the first report of a molecular iodine induced 1,3-dipolar cycloaddition between quinone structures and diethyl *N*-substituted iminodiacetates.

Introduction

Iminium ions are important reactive species in organic synthesis for the construction of carbon-carbon and carbon-heteroatom bonds.[1] Exploitation of these reactive intermediates by reacting with diverse nucleophiles to construct biologically relevant structural fragments has attracted great interest.[2] In the past few decades, the effective using of iminium ions as key intermediates has played -an important role in organic reactions, such as the Aza-Henry reactions,[3] Mannich reactions,[4] Diels-Alder reactions,[5] Cross dehydrogenative coupling (CDC) reactions,[6] Friedel-Crafts reactions,[7] *N*-acyl iminium ion cyclizations,[1b, 8] Ugi-Type processes,[8e, 9] Baylis-Hillman-Type reactions,[10] Pictet-Spengler reactions,[11] 1,3-Dipolar cycloadditions,[12] intramolecular cyclizations.[13] Since iodine is an inexpensive and environmentally benign reagent,[14] molecular iodine-mediated reaction for synthesis of heterocycles has been widely reported.[15] Moreover, molecular iodine catalyzed CDC reactions to produce iminium ions for the synthesizing a variety of functionalized tetrahydroisoquinolines have been illustrated by Itoh[6f] and Prabhu[6j].

The benzo[*f*]isoindole framework is the core structure in a large number of natural products exhibiting important biological activities. For example, Bhimamycin C and D,[16] which display bioactivities against human ovarian cancer cell lines, are EP4 receptor agonists in the treatment of pain, and inhibitors of HIV-1 integrase. (Figure 1). Furthermore, benzo[*f*]isoindole framework frequently appears in a number of other anticancer compounds.[16b]

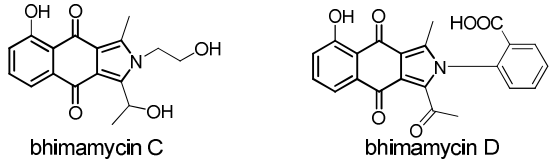


Figure 1 Representative examples of natural products.

Recently, Gong and co-workers[17] had reported the chiral azomethine ylide dipoles reacted with quinone derivatives, and after a subsequent base promoted isomerization to generate chiral isoindolines. From our ongoing study of quinones,[2c, 18] we herein reported a mechanism distinct method for the construction of 2-substituted benzo[*f*]isoindole-1,3-dicarboxylates **3** induced by molecular iodine.

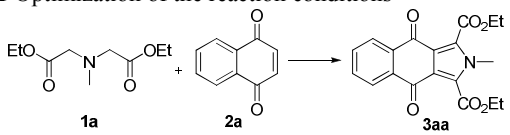
Results and discussion

Our initial investigations were focused on examining the feasibility of the reaction of diethyl *N*-methyliminodiacetate **1a** with 1,4-naphthoquinone **2a** and optimizing the reaction conditions for application to construct a variety of 2-substituted benzo[*f*]isoindole-1,3-dicarboxylates.

To our delight, the proposed reaction between **1a** and **2a** did indeed occur in the presence of iodine (3 equiv.) in CH_3CN with $NaHCO_3$ as a base to afford **3aa** in 60% (Table 1, entry 1). Some other common iodine-addition initiation systems were also investigated, including I_2/*t*-BuOCl and I_2/AgOAc, but these systems did not provide any improvement over molecular iodine only (Table 1, entries 2 and 3). Excitingly, the yield of **3aa** was up to 75% when DBU was used instead of $NaHCO_3$ (Table 1, entry 4). Solvent screening studies revealed that xylene was the most suitable solvent as other solvents furnished lower yield of **3aa** (Table 1, entries 4-8). When the temperature was dropped to 120 ^oC in xylene, the yield of **3aa** was decreased to 80% (Table 1, entry 9). As the iodine dropped to 2 equiv., the yield of **3aa** was decreased to 70% (Table 1, entry 10). The result showed that 3 equivlents of iodine was necessary in the reaction system. Finally, the best result was obtained in the presence of iodine (3 equiv.) in xylene with DBU as a base (Table 1, entry 8) and the isolated yield of **3aa** was 86%.Besides, the yield of **3aa** was decreased to 60% under nitrogen condition (Table 1, entry 11). Comparing to above result (Table 1, entry 8), which indicated oxygen played a role in the final aromatisation process. The structure of product **3ab** was unambiguously established by X-ray crystallographic

analysis.[19]

Table 1 Optimization of the reaction conditions [a]



entry	base	iodine (equiv)	solvent	T (°C)	yield of **3aa** (%) [b]
1	$NaHCO_3$	I_2 (3)	CH_3CN	80	60
2 [c]	$NaHCO_3$	I_2 (3)	CH_3CN	80	40
3 [d]	$NaHCO_3$	I_2 (3)	CH_3CN	80	20
4	DBU	I_2 (3)	CH_3CN	80	75
5	DBU	I_2 (3)	CH_2Cl_2	40	40
6	DBU	I_2 (3)	$CHCl_3$	60	49
7	DBU	I_2 (3)	toluene	110	70
8	DBU	I_2 (3)	xylene	140	86
9	DBU	I_2 (3)	xylene	120	80
10	DBU	I_2 (2)	xylene	140	70
11 [e]	DBU	I_2 (3)	xylene	140	60

[a] Reaction conditions: the mixture of **1a** (3.0 mmol), **2a** (1.0 mmol), base (3.0 mmol), iodine (3.0 mmol) in solvent (5.0 mL) was stirred for 5 h at reflux temperature under air condition. [b] isolated yield. [c] 3 equiv. *t*-BuOCl was added. [d] 3equiv. AgOAc was added. [e] under nitrogen condition.

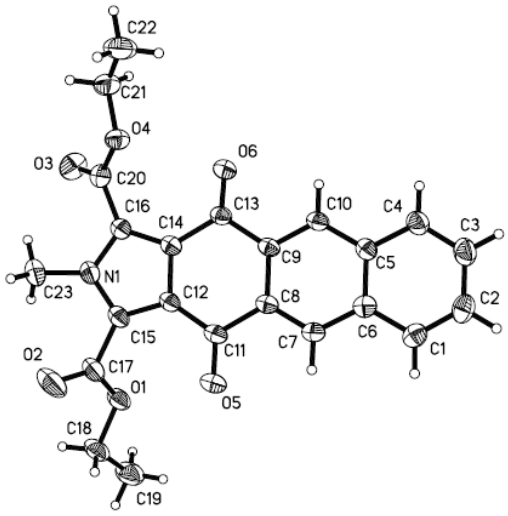
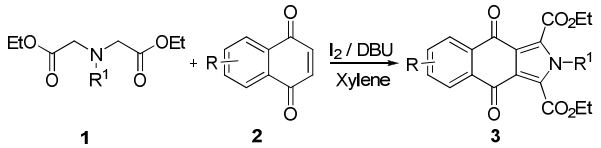
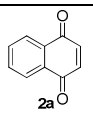
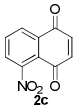
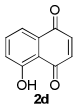


Figure 2 X-ray structure of **3ab**.

With the optimal reaction conditions established in hand, we then examined the substrate scope of this useful reaction. As highlighted in Table 2, a variety of ethyl N-substituted iminodiacetate **2** could react efficiently with **1a** to give the corresponding products in moderate to good yields upon isolation (Table 2, entries 1-4). As the substituted group on N-atom increased, the yield of **3** was reduced. It was also found that the reaction proceeded smoothly with different quinone structures (Table 2, entries 5-12). However, the yield of corresponding products **3ad-dd** were lower when 5-hydroxy-1,4-naphthoquinone **2d** was employ**ed** because of some insoluble things and can not be identified by NMR or GC-MS (Table 2, entries 13-16).

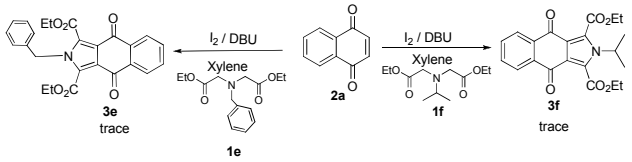
Table 2 Variation of the substrates



entry	**1**	R^1	**2**	**3**	yield of **3** (%) [a]
1	**1a**	Me		**3aa**	86
2	**1b**	Et		**3ba**	70
3	**1c**	n-Pr		**3ca**	64
4	**1d**	n-Bu		**3da**	40
5	**1a**	Me		**3ab**	81
6	**1b**	Et		**3bb**	73
7	**1c**	n-Pr		**3cb**	61
8	**1d**	n-Bu		**3db**	57
9	**1a**	Me		**3ac**	70
10	**1b**	Et		**3bc**	63
11	**1c**	n-Pr		**3cc**	60
12	**1d**	n-Bu		**3dc**	52
13	**1a**	Me		**3ad**	40
14	**1b**	Et		**3bd**	34
15	**1c**	n-Pr		**3cd**	23
16	**1d**	n-Bu		**3dd**	16

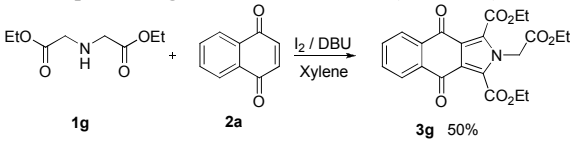
[a] isolated yield.

As various ethyl N-alkyl iminodiacetates **1** proceed with **2a-c** in moderate to good yields, ethyl N-benzyl iminodiacetate **1e** and ethyl N-isopropyl iminodiacetate **1f** were chose to expand the applicability of this reaction under the optimal reaction conditions. However, only trace desired product **3e** and **3f** were observed by GC-MS (Scheme 1). The reason may lie in that the steric hindrance of phenyl group or isopropyl group made it difficult to form the corresponding product.



Scheme 1 Reaction of **2a** with ethyl N-benzyl iminodiacetate **1e** and ethyl N-isopropyl iminodiacetate **1f**.

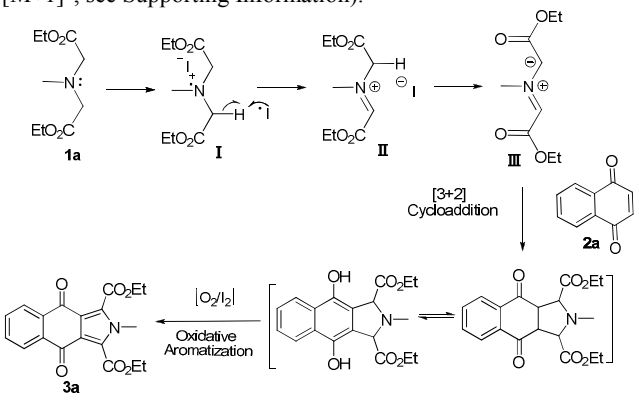
When 2,2'-azanediyldiacetate **1g** was employed to react with **2a**, a different product **3g** was obtained in 50% (Scheme 2).



Scheme 2 Reaction of **2a** with diethyl 2,2'-azanediyldiacetate **1g**.

A mechanism for the resulting product **3** was depicted in Scheme 3. Referred to the literature, the iminium ion **II** could be generated by the reaction of tertiaryamine **I** in the presence of molecular iodine.[6f, 6j] Subsequently, 1,3-dipole azomethine **III** was afforded through a deprotonation process of the iminium intermediate **II** and reacted with 1,4-naphthoquinone **2a** to

furnish the [3+2] cycloaddition product. Finally, the corresponding product **3a** was afforded by the co-oxidation of O_2 and I_2.[14b, 20] The GC-MS analysis of the reaction mixture of **1a** with a stoichiometric amount of I_2 had shown the formation of the 1,3-dipole azomethine **III** (molecular ion peak in 202.3 $[M+1]^+$, see Supporting Information).



Scheme 3 The possible mechanism for the cycloaddition / aromatization reaction induced by I_2.

Conclusions

In conclusion, we have developed a molecular iodine induced 1,3-dipolar cycloaddition / oxidative aromatization sequence to construct 2-substituted benzo[*f*]isoindole-1,3-dicarboxylates. This useful protocol provides a rapid and efficient strategy to construct biologically important compounds containing quinone structure. Moreover, we have developed a novel 1,3-dipolar cycloaddition reaction through using the intermedium of iminium ion induced by molecular iodine.

Experimental

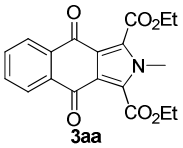
General

All chemicals were purchased from commercial vendors and were used as received without further purification; any exceptions are noted within the text and the vendors are noted within the context of use. The ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, in $CDCl_3$ using TMS as internal standard with a Bruker AM 500 spectrometer. Chemical shifts (δ) were reported as parts per million(ppm) and the following abbreviations were used to identify the multiplicities: s = singlet, d =doublet, t = triplet, q = quartet, m = multiplet, b = broad and all combinations thereof can be explained by their integral parts. The GC-MS was taken on Aglient (GC431-MS210) and elementary analysis was on Thermo Electron Corporation Flash EA 1112, HRMS were recorded on a Bruker MicroTOF-QII mass instrument (ESI).

General procedure for the preparation of 3

The mixture of diethyl *N*-substituented iminodiacetate (**1a**, 3.0 mmol, 3.0 equiv.), quinone (**2**, 1.0 mmol, 1.0 equiv.), DBU (3.0 mmol, 0.456 g, 3.0 equiv.), iodine (3.0 mmol, 0.762 g, 3.0 equiv.) and xylene (5.0 mL), was stirred for 5 h under refluxing temperature, determined by GC-MS and TLC. The reaction mixture was poured into 8 mL saturated aqueous sodium thiosulfate and was extracted (3*10 mL) with CH_2Cl_2. The combined extracts were dried over $MgSO_4$. The solvent was removed under vacuum, and the resulting crude product was purified by chromatography on silica gel eluted with CH_2Cl_2 to obtain **3** as yellow solid.

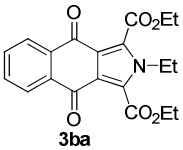
Diethyl 2-methyl-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3aa)



3aa

Yield 86%; mp 122-123 ℃. IR (KBr): 2985, 1720, 1706, 1667, 1594, 1548, 1517, 1474, 1466, 1147, 1025, 1008, 800, 744, 703 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ (ppm) 8.22 (dd, J_1= *3.0 Hz*, J_2= *7.5 Hz*, 2H), 7.73 (dd, J_1= *3.5 Hz*, J_2= *7.5 Hz*, 2H), 4.55 (q, *J= 7.5 Hz*，4H), 3.93 (s, 3H), 1.50 (t, *J= -7.5 Hz*, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 178.69 (2C), 160.84 (2C), 134.83 (2C), 133.44 (2C), 128.17 (2C), 127.05 (2C), 121.81 (2C), 62.70 (2C), 34.70, 14.01 (2C). GC-MS *m/z* 355.1 $[M]^+$, 356.0, 310.3, 296.6, 237.5, 210.5, 206.6. HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{18}NO_6$ $[M+H]^+$ 356.1129, found 356.1131.

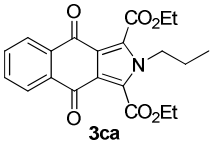
Diethyl 2-ethyl-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3ba)



3ba

Yield 70%; mp 109-110 ℃. IR (KBr): 2985, 1716, 1678, 1594, 1546, 1505, 1436, 1280, 1145, 1044, 1014, 743, 709 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ (ppm) 8.18 (dd, J_1= *3.5 Hz*, J_2= *7.5 Hz*, 2H), 7.69 (dd, J_1= *3.5 Hz*, J_2= *7.0 Hz*, 2H), 4.52 (q, *J= 6.5 Hz*，4H), 4.33 (q, *J= 7.0 Hz*，2H), 1.48-1.44 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 178.75 (2C), 160.98 (2C), 134.88 (2C), 133.33 (2C), 127.52 (2C), 126.93 (2C), 121.74 (2C), 62.49 (2C), 42.99, 16.54, 13.78 (2C). GC-MS *m/z* 370 $[M+H]^+$, 369.0 $[M]^+$, 342.2, 297.3, 296.2, 268.3, 197.3, 76.1. HRMS (ESI-TOF) m/z Calcd for $C_{20}H_{19}NO_6Na$ $[M+Na]^+$ 392.1104, found 392.1112.

Diethyl 2-propyl--2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3ca)

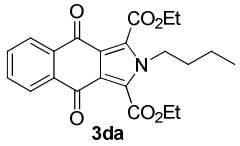


3ca

Yield 64%; mp 104-105 ℃. IR (KBr): 2968, 1728, 1668, 1594, 1512, 1471, 1421, 1317, 1264, 1225, 1143, 1005, 798, 743, 713 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ (ppm) 8.20 (dd, J_1= *4.0 Hz*, J_2= *7.0 Hz*, 2H), 7.71 (dd, J_1= *3.5 Hz*, J_2= *6.0 Hz*, 2H), 4.54 (q, *J= 7.5 Hz*, 4H), 4.28 (t, *J= 8.0 Hz*, 2H), 1.87-1.81 (m, 2H), 1.48 (t, *J= 7.5 Hz*, 6H), 0.94 (t, *J=7.5 Hz*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 178.79 (2C), 161.02 (2C), 134.89 (2C), 133.47 (2C), 127.72 (2C), 127.12 (2C), 121.83 (2C), 62.55 (2C), 48.96, 24.59, 13.81 (2C), 10.84. GC-MS *m/z* 384.1 $[M+H]^+$, 383.0 $[M]^+$, 325.3, 311.5, 211.3. HRMS (ESI-TOF) *m/z* Calcd for

$C_{21}H_{21}NO_6Na$ $[M+Na]^+$ 406.1261 , found 406.1265.

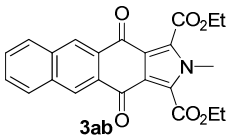
Diethyl 2-butyl-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3da)



3da

Yield 40.3%; mp 99-100 ℃. IR (KBr): 2927, 1728, 1673, 1467, 1368, 1261, 1227, 1201, 1097, 1017, 800 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ (ppm) 8.21 (dd, J_1= *3.0 Hz*, J_2= *6.0 Hz*, 2H), 7.72 (dd, J_1= *3.0 Hz*, J_2= *5.5 Hz*, 2H), 4.54 (q, *J= 6.5 Hz*, 4H), 4.31 (t, *J= 8.0 Hz*, 2H), 1.81-1.75 (m, 2H), 1.49 (t, *J= 6.5 Hz*, 6H), 1.38-1.32 (m, 2H), 0.94 (t, *J=7.0 Hz*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 178.86 (2C), 161.11 (2C), 134.89 (2C), 133.41 (2C), 127.72 (2C), 127.09 (2C), 121.74 (2C), 62.68 (2C), 47.56, 33.47, 19.79, 13.99 (2C), 13.54. GC-MS *m/z* 398.5 $[M+1]^+$, 397.4 $[M]^+$, 352.5, 325.5, 324.5 (100%), 296.8, 282.7, 254.7, 224.5. HRMS (ESI-TOF) *m/z* Calcd for $C_{22}H_{23}NO_6Na$ $[M+Na]^+$ 420.1423, found 420.1427.

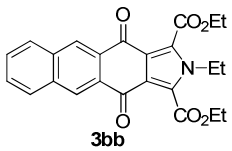
Diethyl 2-methyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1,3-dicarboxylate (3ab)



3ab

Yield 81%; mp 176-177 ℃. IR (KBr): 2927, 1720, 1705, 1674, 1621, 1513, 1472, 1293, 1242, 1208, 1186, 1107, 1038, 1022, 762, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): 8.73 (s, 2H), 8.04 (dd, J_1 *= 3.0 Hz*, J_2 *= 6.5 Hz* 2H), 7.65 (dd, J_1 *=3.5 Hz*, J_2 *= 6.0 Hz*, 2H), 4.57 (q, *J = 7.0 Hz*,4H), 3.93 (s, 3H), 1.52 (t, *J= 7.5 Hz*, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) 178.60 (2C), 160.97 (2C), 134.81 (2C), 131.26 (2C), 129.97 (2C), 129.25 (2C), 129.17 (2C), 128.29 (2C), 122.63 (2C), 62.73 (2C), 34.72 (1C), 14.05 (2C). GC-MS *m/z* 405.9 $[M+1]^+$, 361.2, 333.2, 289.3, 288.4, 262.3, 261.3. Anal. Calcd for $C_{18}H_{17}NO_4S_2$: C, 68.14; H, 4.72; N, 3.46. Found: C, 68.04; H, 4.88; N, 3.26.

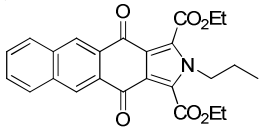
Diethyl 2-ethyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1,3-dicarboxylate (3bb)



3bb

Yield 73%; mp 134-135 ℃. IR (KBr): 2978, 1725, 1674, 1619, 1437, 1281, 1234, 1185, 1038, 1015, 862, 759 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ (ppm) 8.73 (s, 2H), 8.03 (dd, J_1= *3.5 Hz*, J_2= *6.0 Hz*, 2H), 7.64 (dd, J_1= *3.5 Hz*, J_2= *6.5 Hz*, 2H), 4.57 (q, *J= 6.5 Hz*, 4H), 4.36 (q, *J= 7.5 Hz*, 2H), 1.53-1.49 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 178.72 (2C), 161.16 (2C), 134.81 (2C), 131.34 (2C), 129.96 (2C), 129.19 (2C), 129.13 (2C), 127.53 (2C), 122.64 (2C), 62.55 (2C), 43.12, 16.79, 14.01 (2C). GC-MS *m/z* 419.9 $[M+H]^+$, 419.0 $[M]^+$, 390.2, 375.1, 346.2, 318.3, 300.2, 274.4. HRMS(ESI-TOF) m/z Calcd for $C_{24}H_{22}NO_6$ $[M+H]^+$ 420.1442, found 420.1449.

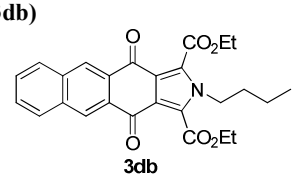
Diethyl 2-propyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1,3-dicarboxylate (3cb)



3cb

Yield 61%; mp 110-111 ℃. IR (KBr): 2965, 1736, 1670, 1602, 1501, 1440, 1282, 1187, 1041, 1011, 917, 761 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ (ppm) 8.67 (s, 2H), 7.99 (dd, J_1= *3.0 Hz*, J_2= *6.5 Hz*, 2H), 7.60 (dd, J_1= *3.0 Hz*, J_2= *6.5 Hz*, 2H), 4.56 (q, *J= 7.0 Hz*, 4H), 4.28 (q, *J= 7.5 Hz*, 2H), 1.88-1.81 (m, 2H), 1.50 (q, *J= 7.5 Hz*, 6H), 0.95 (q, *J= 7.5 Hz*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 178.58 (2C), 161.13 (2C), 134.71 (2C), 131.23 (2C), 129.91 (2C), 129.21 (2C), 129.14 (4C), 127.81 (2C), 122.49 (2C), 62.71 (2C), 49.20, 24.74, 14.02 (2C), 10.90. GC-MS: *m/z* 433.8 $[M+H]^+$, 432.9$[M]^+$, 404.2, 388.3, 347.2, 346.3, 300.2, 41.0. HRMS (ESI-TOF) m/z Calcd for $C_{25}H_{24}NO_6$ $[M+H]^+$ 434.1598, found 434.1606.

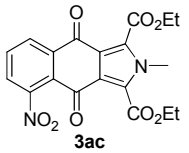
Diethyl 2-butyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1,3-dicarboxylate (3db)



3db

Yield 57%; mp 100-101 ℃. IR (KBr): 2961, 1735, 1705, 1677, 1619, 1435, 1305, 1273, 1236, 1182, 1033, 1020, 753 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ(ppm) 8.69 (s, 2H), 8.00 (dd, J_1= *3.0 Hz*, J_2= *6.0 Hz*, 2H), 7.61 (dd, J_1= *3.0 Hz*, J_2= *6.5 Hz*, 2H), 4.56 (q, *J= 7.5 Hz*, 4H), 4.30 (q, *J= 8.0 Hz*, 2H), 1.82-1.76 (m, 2H), 1.51 (q, *J= 7.0 Hz*, 6H), 1.38-1.31 (m, 2H), 0.94 (q, *J= 7.5 Hz*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 178.55 (2C), 161.08 (2C), 134.69 (2C), 131.20 (2C), 129.87 (2C), 129.11 (2C), 129.08 (2C), 127.74 (2C), 122.46 (2C), 62.66 (2C), 47.54, 33.42, 19.74, 13.98 (2C), 13.51. GC-MS *m/z* 448.0 $[M+H]^+$, 446.9 $[M]^+$, 418.0, 402.1, 375.1, 374.3 (100%), 304.3, 41.0. HRMS (ESI-TOF) *m/z* Calcd for $C_{26}H_{26}NO_6$ $[M+H]^+$ 448.1755, found 448.1750.

Diethyl 2-methyl-5-nitro-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3ac)

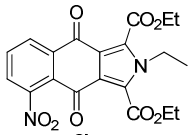


3ac

Yield 70%; mp 85-86 ℃. IR (KBr): 2983, 1723, 1676, 1593, 1544, 1509, 1375, 1306, 1252, 1226, 1144, 1026, 912, 798, 712 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ (ppm) 8.40 (dd, J_1= *1.0 Hz*, J_2= *7.5 Hz*, 1H), 7.83 (t, *J= 7.5 Hz*, 1H), 7.70 (dd, J_1= *1.0 Hz*, J_2= *8.0 Hz*, 1H), 4.54 (q, *J= 7.0 Hz*, 2H), 4.47 (q, *J= 7.0 Hz*, 2H), 3.96 (s, 3H), 1.49 (t, *J= 7.0 Hz*, 3H) ,1.43 (t, *J= 6.5 Hz*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 176.18, 175.21, 160.25, 160.08, 149.43, 135.97, 133.77, 129.58, 128.65, 128.51, 127.35,

126.75, 121.63, 120.67, 62.91, 62.87, 34.95, 13.96, 13.73. GC-MS *m/z* 400.8 $[M]^+$, 399.8, 384.2, 356.2, 339.3, 309.1, 284.1, 256.1. HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{16}N_2O_8Na$ $[M+Na]^+$ 423.0799, found 423.0807.

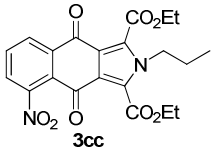
Diethyl 2-ethyl-5-nitro-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3bc)



3bc

Yield 63%; mp 75-76 ℃. IR (KBr): 2982, 1730, 1681, 1531, 1440, 1309, 1233, 1141, 1018, 798, 711 cm^{-1}. ^1H NMR(500 MH_Z, $CDCl_3$): δ (ppm) 8.39 (dd, J_1=*0.5 Hz*, J_2= *7.0 Hz*, 1H), 7.82 (t, *J= 8.0 Hz*, 1H), 7.70 (dd, J_1= *1.5 Hz*, J_2= *8.5 Hz*, 1H), 4.54 (q, *J= 7.5 Hz*, 2H), 4.47 (q, *J= 7.5 Hz*, 2H), 4.40 (q, *J= 7.0 Hz*, 2H), 3.96 (s, 3H), 1.48 (t, *J= 7.0 Hz*, 6H) ,1.43 (t, *J= 7.0 Hz*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 176.24, 175.26, 160.38, 160.16, 149.38, 136.00, 133.77, 129.54, 128.04, 127.79, 127.32, 126.79, 121.75, 120.71, 62.90, 62.89, 43.44, 16.75, 13.93, 13.71. GC-MS *m/z* 414.8 $[M]^+$, 413.8, 396.0, 386.0, 369.2, 342.3, 325.3, 295.1. HRMS (ESI-TOF) *m/z* Calcd for $C_{20}H_{18}N_2O_8Na$ $[M+Na]^+$ 437.0955, found 437.0958.

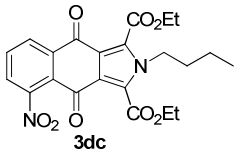
Diethyl 2-propyl-5-nitro-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3cc)



3cc

Yield 60%; mp 70-71 ℃. IR (KBr): 2977, 1734, 1682, 1532, 1438, 1367, 1315, 1227, 1142, 1018, 797, 712 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ (ppm) 8.40 (dd, J_1= *1.0 Hz*, J_2= *8.0 Hz*, 1H), 7.83 (t, *J= 8.0 Hz*, 1H), 7.70 (dd, J_1= *0.5 Hz*, J_2= *7.5 Hz*, 1H), 4.54 (q, *J= 7.5 Hz*, 2H), 4.48 (q, *J= 7.0 Hz*, 2H), 4.37 (t, *J= 7.5 Hz*, 2H), 4.31-4.26 (m, 2H), 1.80-1.74 (m, 2H), 1.48 (t, *J= 7.5 Hz*, 3H), 1.43 (t, *J= 7.0 Hz*, 3H), 0.94 (t,*J=7.5Hz*,3H). ^{13}C NMR (125MHz,$CDCl_3$): δ (ppm) 176.30, 175.34, 160.48, 160.26, 149.47, 136.06, 133.77, 129.58,128.33, 128.11, 127.34, 126.85, 121.73, 120.70, 62.94, 62.89, 49.34, 24.82, 13.95, 13.74, 10.90. GC-MS *m/z* 429.1 $[M+H]^+$, 428.1, 400.2, 383.3, 342.3, 341.3, 295.4, 206.4. HRMS (ESI-TOF) *m/z* Calcd for $C_{21}H_{21}N_2O_8$ $[M+H]^+$ 429.1293, found 429.1321 .

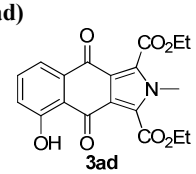
Diethyl 2-butyl-5-nitro-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3dc)



3dc

Yield 52%; mp 65-66 ℃. IR (KBr): 2966, 1740, 1620, 1544, 1445, 1373, 1220, 1018, 800, 711 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ(ppm) 8.40 (dd, J_1= *1.0 Hz*, J_2= *7.5 Hz*, 1H), 7.83 (t, *J= 7.5 Hz*, 1H), 7.70 (dd, J_1= *1.5 Hz*, J_2= *8.0 Hz*, 1H), 4.54 (q, *J= 7.0 Hz*, 2H), 4.48 (q, *J= 7.0 Hz*, 2H), 4.34 (t, *J= 7.5 Hz*, 2H) , 1.85-1.79 (m, 2H) ,1.49 (t, *J= 7.5 Hz*, 3H), 1.43 (t, *J= 7.0 Hz*, 3H), 0.94 (t, *J= 7.0 Hz*, 3H). ^{13}C NMR(125MHz,$CDCl_3$): δ (ppm) 176.27, 175.28, 160.45, 160.24, 149.46, 136.05, 133.71, 129.53, 128.26, 128.05, 127.30, 126.84, 121.68, 120.65, 62.88, 62.83, 47.69, 33.45, 19.72, 13.93,13.71,13.49. GC-MS *m/z* 443.1 $[M+H]^+$, 412.3, 397.2, 370.2, 369.2 (100%), 297.5, 269.3. HRMS (ESI-TOF) m/z Calcd for $C_{22}H_{23}N_2O_8$ $[M+H]^+$ 443.1449, found 443.1461.

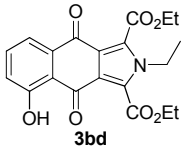
Diethyl 2-methyl-5-hydroxy-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3ad)



3ad

Yield 40%; mp 133-134 ℃. IR (KBr): 2964, 1705, 1669, 1634, 1455, 1262, 1082, 1021, 802, 695 cm^{-1}. ^1H NMR(500 MH_Z, $CDCl_3$): δ (ppm) 12.65 (s, 1H), 7.73 (dd, J_1= *1.0 Hz*, J_2= *7.5 Hz*, 1H), 7.59 (t, *J= 8.0 Hz*, 1H), 7.22 (dd, J_1= *1.0 Hz*, J_2= *8.5 Hz*, 1H), 4.56-4.51 (m, 4H), 3.91 (s, 3H), 1.50-1.47 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 184.77, 177.87, 162.73, 160.62, 160.60, 135.99, 135.16, 128.72, 128.22, 123.95, 121.77, 120.90, 119.35, 116.95, 62.84, 62.73, 34.75, 13.99, 13.98. GC-MS *m/z* 372.2 $[M+H]^+$, 371.3, 326.4, 325.5, 299.5, 253.5, 225.5, 63.1. HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{17}NO_7Na$ $[M+Na]^+$ 394.0907, found 394.0897.

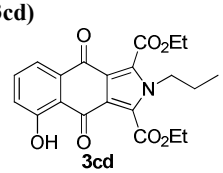
Diethyl 2-ethyl-5-hydroxy-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3bd)



3bd

Yield 34%; mp 100-101 ℃. IR (KBr): 2977, 1735, 1705, 1674, 1633, 1555, 1365, 1350, 1263, 1226, 1075, 801, 715 cm^{-1}. ^1H NMR (500 MH_Z, $CDCl_3$): δ (ppm) 12.67 (s, 1H), 7.73 (dd, J_1=*1.5 Hz*, J_2= *7.5 Hz*, 1H), 7.59 (t, *J= 8.5 Hz*, 1H), 7.22 (dd, J_1= *1.0 Hz*, J_2= *8.5 Hz*, 1H), 4.56-4.52 (m, 4H), 4.34 (q, *J= 6.5 Hz*, 2H), 1.50-1.46 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 184.86, 177.98, 162.74, 160.81, 160.75, 135.98, 135.22, 128.05, 127.55, 123.96, 62.87, 62.76, 43.32, 16.73, 13.97 (2C). GC-MS *m/z* 386.3 $[M+H]^+$, 385.5 (100%), 339.6, 312.5, 266.5, 239.3, 183.2, 155.5. HRMS (ESI-TOF) m/z Calcd for $C_{20}H_{20}NO_7$ $[M+H]^+$ 386.1235, found 386.1250.

Diethyl 2-propyl-5-hydroxy-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3cd)

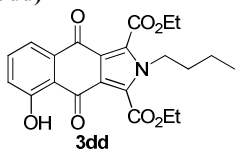


3cd

Yield 23%; mp 100-101 ℃. IR (KBr): 2974, 1732, 1637, 1618, 1557, 1509, 1444, 1356, 1342, 1268, 1218, 1081, 1010, 834, 748

cm^{-1}. ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ (ppm) 12.67 (s, 1H), 7.73 (dd, J_1= *1.5 Hz*, J_2= *7.5 Hz*, 1H), 7.59 (t, *J= 8.5 Hz*, 1H), 7.22 (dd, J_1= *1.0 Hz*, J_2= *8.5 Hz*, 1H),4.56-4.51 (m, 4H), 4.26 (q, *J= 8.5 Hz*, 2H),1.92-1.80 (m, 2H) ,1.48 (t, *J= 7.0 Hz*, 3H), 0.95 (t, *J= 7.5 Hz*, 3H), 0.94 (t,*J=7.5Hz*,3H). ^{13}C NMR (125MHz,CDCl$_3$): δ (ppm) 184.89, 178.05, 162.75, 160.86, 160.82, 136.00, 135.23, 128.32, 127.82, 123.97, 121.72, 120.81, 119.36, 116.99, 62.87, 62.78, 49.34, 24.76, 13.98, 13.96, 10.93. GC-MS *m/z* 400.1 [M+H]$^+$, 399.3, 370.3, 353.5, 312.3, 266.2, 254.3, 41.1. HRMS (ESI-TOF) m/z Calcd for $C_{21}H_{21}NO_7Na$ [M+Na]$^+$ 422.1210, found 422.1218.

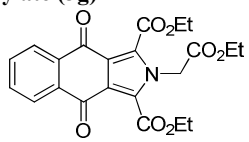
Diethyl 2-butyl-5-hydroxy-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3dd)



3dd

Yield 16%; mp 85-86 ℃. IR (KBr): 2964, 1712, 1671, 1632, 1560, 1511, 1439, 1367, 1349, 1262, 1204, 1079, 1019, 801 cm^{-1}. ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ (ppm) 12.67 (s, 1H), 7.73 (dd, J_1= *1.0 Hz*, J_2= *7.5 Hz*, 1H), 7.59 (t, *J= 7.5 Hz*, 1H), 7.22 (dd, J_1= *1.5 Hz*, J_2= *8.0 Hz*, 1H), 4.56-4.51 (m, 4H), 4.29 (t, *J= 7.5 Hz*, 2H), 1.81-1.75 (m, 2H) ,1.48 (t, *J= 7.0 Hz*, 6H), 1.40-1.32 (m, 2H), 0.95 (t, *J= 7.5 Hz*, 3H). ^{13}C NMR (125MHz, CDCl$_3$): δ (ppm) 183.85, 177.00, 161.72, 159.83, 159.78, 134.95, 134.21, 127.25, 126.77, 122.94, 120.67, 119.78, 118.32, 115.97, 61.82, 61.73, 46.67, 32.40, 18.75, 12.95(2C), 12.51. GC-MS *m/z* 414.1 [M+H]$^+$, 413.2, 384.2, 368.2, 340.2, 312.2, 298.2, 270.2. HRMS (ESI-TOF) m/z Calcd for $C_{22}H_{23}NO_7Na$ [M+Na]$^+$ 436.1367, found 436.1376.

Diethyl 2-(2-ethoxy-2-oxoethyl)-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3g)



3g

Yield 50%; mp 137-138 ℃. ^{1}H NMR (500 MH$_Z$, CDCl$_3$): δ (ppm) 8.23 (dd, J_1= *3.0 Hz*, J_2= *5.5 Hz*, 2H), 7.74 (dd, J_1= *3.5 Hz*, J_2= *6.5 Hz*, 2H), 5.23 (s, 2H), 4.51 (q, *J= 7.0 Hz*, 4H), 4.27 (q, *J= 7.5 Hz*, 2H), 1.48 (t, *J= 7.0 Hz*, 6H), 1.30 (t, *J= 7.5 Hz*, 3H). ^{13}C NMR (125MHz, CDCl$_3$): δ (ppm) ; 178.47 (2C), 166.69, 160.59 (2C), 134.80(2C), 133.47(2C), 127.83(2C), 127.03 (2C), 122.60 (2C), 62.70 (2C), 62.26, 48.52, 14.03, 13.88 (2C). HRMS (ESI-TOF) m/z Calcd for $C_{22}H_{21}NO_8Na$ [M+Na]$^+$ 450.1165, found 450.1167.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [X-ray crystallographic data (CIF files) of **3ab**, spectral data of all compounds and copies of ^{1}H and ^{13}C NMR spectra of products **3**]. See DOI: 10.1039/b000000x/

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19 CDCC 915883 (**3ab**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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