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# The first iodine improved 1,3-dipolar cycloaddition: facile and novel synthesis of 2-substituted benzo[*f*]isoindole-4,9-diones

Huan-Ming Huang [a], Jian-Rong Gao [a], Li-Fen Hou [b], Jian-Hong Jia [a], Liang Han [a], Qing Ye [a], Yu-Jin Li [a,*]

[a] State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou 310032, PR China
[b] College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou 450001, PR China

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ABSTRACT

The first novel protocol of the synthesis of 2-substituted benzo[*f*]isoindole-4,9-dione framework via the one-pot, 1,3-dipolar cycloaddition of quinones, paraformaldehyde and *N*-substituted amino ester hydrochlorides in the present of iodine at refluxing acetonitrile was reported. All these reactions proceed with good to excellent yields. The promising results obtained 1,3-dipolar cycloaddition will have the potential application in natural product exhibiting important biological activities.



## 1. Introduction

Pyrroles and their derivatives are one of the most important heterocyclic compounds, found in common structural scaffolds in natural products and bioactive molecules.[1] 2-Substituted benzo[*f*] isoindole-4,9-diones are the core structure of natural product exhibiting important biological activities.[1c] They exist in numerous bioactive molecules, such as *Azamonosporascone* in *Monosporascus cannonballus*,[2] *Reniera isoindole alkaloid* in antimicrobial activity,[3] *GR30921 X* for solid tumours,[4] *Bhimamycin C* and *Bhimamycin D* against human ovarian cancer cell lines[1c,5] in Fig. 1. Additionally, 2-substituted benzo[*f*]isoindole-4,9-diones have been found frequently in some anticancer compounds.[5b]

Interest in their chemistry continues unabated due to their wide usefulness as biologically active agents and key intermediates in the organic synthesis.[6] The 1,3-dipolar azomethine ylide cycloaddition is a powerful tool for the construction of five-membered heterocycles.[7] For instance, 2*H*-isoindole-4,7-diones,[8] β-substituted *meso*-tetraphenylporphyrins,[9] novel spirooxindoles.[10] In recent years, the metal (ion)-free catalysis of organic reactions are the challenge and get more and more attention.[3a,3c,11] For the last decade, the use of molecular iodine has become popular because of its high tolerance to air and moisture, low-cost, ready availability, high catalytic activity and so on.[12]

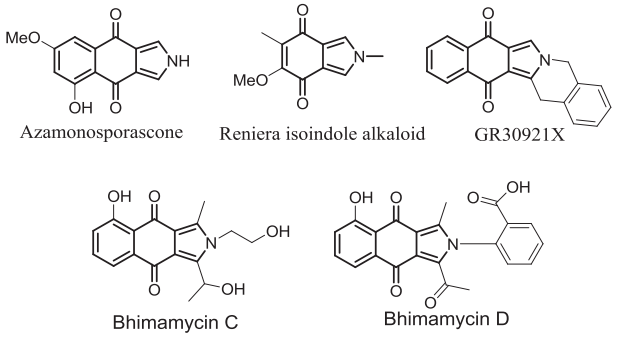


**Fig. 1.** Representative examples of natural products.

To the best of our knowledge, there is no report in the literature on the iodine participated in 1,3-dipolar cycloaddition of 1,4-naphthoquinone with azomethine ylides generated in situ from paraformaldehyde and *N*-substituted amino ester hydrochlorides. These products contain one ester group, which can be converted into useful building blocks. Interest in the functionalisation of quinone structures,[13] we herein reported the first efficient synthesis of novel 2-substituted benzo[*f*]isoindole-4,9-diones framework via

* Corresponding author. Tel.: +86 0571 88320891; fax: +86 0571 88320544; e-mail address: lyjzjut@zjut.edu.cn (Y.-J. Li).

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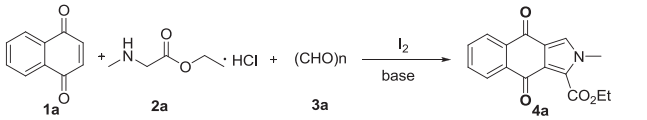
the one-pot, 1,3-dipolar cycloaddition of quinone, paraformaldehyde and *N*-substituted amino ester hydrochlorides.

## 2. Results and discussion

As indicated in Table 1, we started our novel methods for synthesis of 2-substituted benzo[*f*]isoindole-4,9-diones through 1,3-dipolar cycloaddition of 1,4-naphthoquinone **1a** with sarcosine ethyl ester hydrochloride **2a** and paraformaldehyde **3a** promoted by iodine.

**Table 1**
Optimization of the reaction conditions[a]




| Entry | **2a** (equiv) | Iodine (equiv) | Solvent | Base | Yield of **4a** (%)[b] |
|---|---|---|---|---|---|
| 1 | 3 | 0 | $CH_3CN$ | $NaHCO_3$ | 50.0 |
| 2 | 1 | 0 | $CH_3CN$ | $NaHCO_3$ | 18.1 |
| 3 | 3 | 0.1 | $CH_3CN$ | $NaHCO_3$ | 55.0 |
| 4 | 3 | 0.5 | $CH_3CN$ | $NaHCO_3$ | 70.0 |
| 5 | 3 | 0.7 | $CH_3CN$ | $NaHCO_3$ | 87.1 |
| 6 | 3 | 1 | $CH_3CN$ | $NaHCO_3$ | **93.4** |
| 7 | 2 | 1 | $CH_3CN$ | $NaHCO_3$ | 69.6 |
| 8 | 1 | 1 | $CH_3CN$ | $NaHCO_3$ | 35.1 |
| 9 | 3 | 1 | $CH_3CN$ | $K_2CO_3$ | 86.1 |
| 10 | 3 | 1 | $CH_3CN$ | DBU | 82.0 |
| 11 | 3 | 1 | $CHCl_3$ | $NaHCO_3$ | 71.5 |
| 12 | 3 | 1 | THF | $NaHCO_3$ | 87.7 |
| 13 | 3 | 1 | $C_2H_5OH$ | $NaHCO_3$ | 76.7 |
| 14 | 3 | 1 | 1,4-Dioxane | $NaHCO_3$ | 51.4 |
| 15 | 3 | 1 | Toluene | $NaHCO_3$ | 47.5 |
| 16 | 3 | 1 | DMF | $NaHCO_3$ | 92.0 |

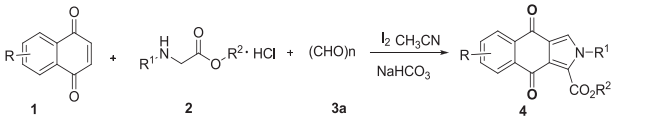
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0–3.0 mmol), **3a** (1.1 mmol), Iodine (0–1.0 mmol), base (3.0 mmol), and solvent (10.0 mL), was stirred for 8 h under refluxing temperature under air condition.
[b] Yield of the isolated product based on **1a**.

Initially, the corresponding product **4a** was obtained in 50% yield after refluxing for 8 h in acetonitrile in the absence of iodine, the yield of **4a** was obviously improved along with the increase of iodine (Table 1, entries 3–6). As the quantity of **2a** decreased, the yield of **4a** was also cut down correspondingly (Table 1, entries 6–8). Several bases were employed instead of Sodium bicarbonate, the yield of **4a** didn't obtain in better yield (Table 1, entries 9, 10). Then efforts were made to optimize other reaction parameters including solvents and reaction temperatures. Thus, the reaction was studied in different solvents, including $CHCl_3$, THF, −EtOH, 1,4-dioxane, toluene, DMF (Table 1, entries 10–16). Finally, to our satisfaction, the reaction in acetonitrile led to the desired product in excellent yield (93.4%, Table 1, entry 6).

With the optimal reaction conditions in hand, the scope of this iodine participated in 1,3-dipolar cycloaddition reaction was explored with a variety of *N*-substituted amino ester hydrochlorides, and the results were summarized in Table 2. To our delight, good yields were obtained in several cases (Table 2, entries 1–9, 11–19). Unfortunately, when *N*-phenylglycine ethyl ester hydrochloride **2j** took into the reaction, the corresponding product wasn't obtained because of its lower activity (Table 2, entry 10). The structure of product **4d** was unambiguously established by X-ray crystallographic analysis (Fig. 2).[14]

Considering many natural products and bioactive molecules have substituent groups on the structure of 1,4-naphthoquinone,[1c,5,15] we try to expand the reaction with several substituted

**Table 2**
Study of the reaction scope by variation of *N*-substituted amino esters




| Entry | **1** | **2** | | **4** | Yield of **4** (%)[a] |
|---|---|---|---|---|---|
| | | $R^1$ | $R^2$ | | |
| 1 | | Me | Et | **4a** | 93.4 |
| 2 | | Et | Et | **4b** | 95.1 |
| 3 | | *n*-Pr | Et | **4c** | 98.1 |
| 4 | | *n*-Bu | Et | **4d** | 92.3 |
| 5 | | $PhCH_2$ | Et | **4g** | 91.8 |
| 6 | | Me | *n*-Pr | **4e** | 61.5 |
| 7 | | Me | *n*-Bu | **4f** | 53.9 |
| 8 | 1a | Me | Isoamyl | **4h** | 58.7 |
| 9 | | Me | *i*-Pr | **4i** | 50.6 |
| 10 | | Ph | Et | **4j** | N.R. |
| 11 | | Me | Et | **4k** | 78.0 |
| 12 | | Et | Et | **4l** | 70.3 |
| 13 | | *n*-Pr | Et | **4m** | 68.2 |
| 14 | | *n*-Bu | Et | **4n** | 51.7 |
| 15 | | $PhCH_2$ | Et | **4o** | 88.5 |
| 16 | | Me | *n*-Pr | **4p** | 51.8 |
| 17 | 1b | Me | *n*-Bu | **4q** | 55.3 |
| 18 | | Me | Isoamyl | **4r** | 36.6 |
| 19 | | Me | *i*-Pr | **4s** | 47.4 |
| 20 | 1c | Me | Et | **4t**+**4t′** | 50.1 |
| 21 | 1d | Me | Et | **4u**+**4u′** | 52.6 |

[a] Isolated yield.

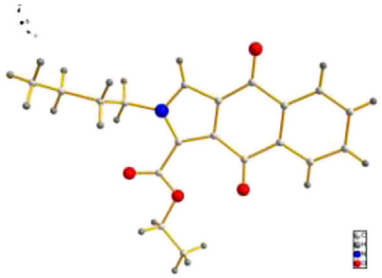
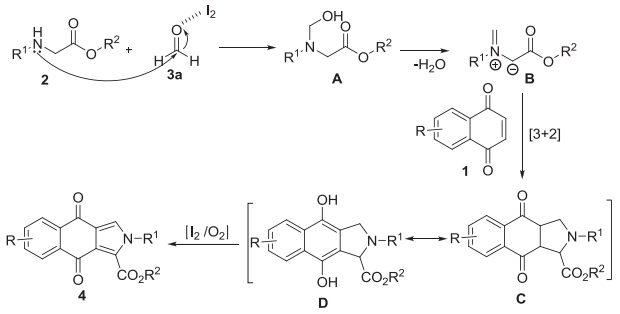


**Fig. 2.** X-ray structure of **4d**.

1,4-naphthoquinones. Unfortunately, product **4t** was afforded in 50.1% total yield with two isomers and the ratio of **4t** and **4t′** was 1:1 determined by $^1H$ NMR when 5-hydroxy-1,4-naphthoquinone **1c** was employed (Table 2, entry 20). Similar result was obtained in 52.6% total yield in the case of 5-nitro-1,4-naphthoquinone **1d** (Table 2, entry 21).

On the basis of the above results, a possible mechanism of the present reaction is depicted in Scheme 1. Firstly, with molecular iodine activated the carbonyl group,[16] paraformaldehyde **3a** was attacked by *N*-substituted amino ester to give the initial addition product **A**. Then the 1,3-dipole **B** was formed by removal of $H_2O$ and reacted with quinones **1** to product intermediate **C** together with its isomer **D** through aromatization. The final product **4** was obtained by co-oxidation of molecular iodine and oxygen.[17]



**Scheme 1.** Proposed mechanism.

## 3. Conclusion

In summary, we have reported a novel protocol of the synthesis of 2-substituted benzo[*f*]isoindole-4,9-diones framework via the one-pot, 1,3-dipolar cycloaddition 1,4-naphthoquinone, paraformaldehyde and *N*-substituted amino ester hydrochlorides in the present of iodine at refluxing acetonitrile, which to the best of our knowledge has no precedents. We have shown that these reactions proceed with good yields and the promising results obtained 1,3-dipolar cycloaddition will have the potential application in natural product exhibiting important biological activities. These products contain one ester group, which can be converted into useful building blocks. Further work aimed at the optimization, functionalization of these exciting molecular scaffolds and will be published in due course.

## 4. Experimental section

### 4.1. 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 $^1$H 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 ($\delta$) 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 Agilent (GC431–MS210) and elementary analysis was on Thermo Electron Corporation Flash EA 1112, HRMS were recorded on a Bruker MicroTOF-QII mass instrument (ESI).

*4.1.1. Typical procedure for the preparation of ethyl 2-methyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4a**).* Typically, a mixture of 1,4-naphthoquinone (**1a**, 1.0 mmol, 0.158 g, 1.0 equiv), sarcosine ethyl ester hydrochloride (**2a**, 3.0 mmol, 0.4605 g, 3.0 equiv), paraformaldehyde (**3a**, 1.1 mmol, 0.0330 g, 1.1 equiv), Iodine (1.0 mmol, 0.2540 g, 1.0 equiv), sodium bicarbonate (3.0 mmol, 0.2520 g, 3.0 equiv) in acetonitrile (10.0 mL), was stirred at refluxing temperature under air condition until the staring material was consumed, as 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 afford the desired product **4a** as yellow solid (0.2643 g, yield 93.4%, mp 149–150 °C).

Yield 93.4%, mp 152–153 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 8.26–8.24 (m, 1H), 8.23–8.21 (m, 1H), 7.74–7.69 (m, 2H), 7.48 (s, 1H), 4.52 (q, *J*=8.0 Hz, 2H), 3.95 (s, 3H), 1.50 (t, *J*=7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ (ppm) 180.1, 178.7, 160.9, 135.9, 134.3, 133.4, 133.1, 128.0, 127.4, 126.6, 125.8, 123.6, 122.6, 62.1, 37.5, 14.2; GC–MS *m*/*z* 283.9 $[M+H]^+$, 283.0, 239.2, 211.2, 183.0, 170.1, 113.2, 50.0; Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.71; H, 4.73; N, 4.75.

*4.1.2. Ethyl 2-ethy-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4b**).* Yield 95.1%, mp 143–144 °C; $^1$H NMR (500 MHz, $CDCl_3$): 8.26–8.21 (m, 2H), 7.73–7.71 (m, 2H), 7.55 (s, 1H), 4.52 (q, *J*=6.5 Hz, 2H), 4.31 (q, *J*=7.0 Hz, 2H), 1.53–1.49 (m, 6H); $^{13}$C NMR ($CDCl_3$, 125 MHz): 180.3, 178.9, 161.1, 136.0, 134.4, 133.4, 133.0, 127.4(2C), 126.6, 126.0, 123.3, 122.7, 62.2, 45.1, 16.5, 14.1; GC–MS: *m*/*z* 298.2 (M+1), 297.2 (M, 100%), 268.3, 253.3, 225.3, 197.2, 140.2, 113.2; Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68, H, 5.09, N, 4.71. Found: C, 68.41; H, 5.18, N, 4.48.

*4.1.3. Ethyl 2-propy-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4c**).* Yield 98.1%, mp 115–116 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 8.25–8.21 (m, 2H), 7.74–7.69 (m, 2H), 7.52 (s, 1H), 4.52 (q, *J*=8.0 Hz, 2H), 4.23 (q, *J*=7.5 Hz, 2H), 1.91–1.84 (m, 2H), 1.50 (t, *J*=6.5 Hz, 3H), 0.97 (t, *J*=7.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ (ppm) 180.2, 178.9, 161.0, 135.9, 134.4, 133.4, 133.1, 127.4, 126.8, 126.6, 125.6, 123.3, 122.5, 62.2, 51.6, 24.5, 14.1, 11.0; GC–MS *m*/*z* 311.8 $[M+H]^+$, 310.8, 281.8, 265.9, 264.0, 250.0, 238.2, 224.0, 211.1; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{18}H_{17}NO_4Na$ $[M+Na]^+$ 334.1050, found 334.1052.

*4.1.4. Ethyl 2-butyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4d**).* Yield 92.3%, mp 162–163 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 8.26–8.22 (m, 2H), 7.74–7.69 (m, 2H), 7.52 (s, 1H), 4.52 (q, *J*=7.0 Hz, 2H), 4.26 (t, *J*=7.5 Hz, 2H), 1.85–1.79 (m, 2H), 1.50 (t, *J*=7.0 Hz, 3H), 1.41–1.33 (m, 2H), 0.97 (t, *J*=7.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ (ppm) 180.2, 178.9, 161.1, 136.0, 134.4, 133.4, 133.1, 127.4, 126.66 (2C), 125.7, 123.3, 122.5, 62.2, 49.8, 33.2, 19.8, 14.1, 13.6; GC–MS *m*/*z* 326.6 $[M+H]^+$, 325.7, 279.8, 251.8 (100%), 210.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$ 348.1206, found 348.1209.

*4.1.5. Ethyl 2-benzyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4e**).* Yield 91.8%, mp 100–101 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 8.25–8.21 (m, 2H), 7.74–7.69 (m, 2H), 7.53 (s, 1H), 7.38–7.32 (m, 3H), 7.21 (d, *J*=6.5 Hz, 2H), 5.45 (s, 2H), 4.43 (q, *J*=7.0 Hz, 2H), 1.37 (t, *J*=8.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ (ppm) 180.1, 178.8, 161.0, 135.9, 135.1, 134.4, 133.5 (2C), 129.1, 128.6 (2C), 127.7, 127.3 (2C), 127.0, 126.7, 125.9, 123.4, 122.6, 62.2, 53.2, 13.9; GC–MS *m*/*z* 360.2 $[M+H]^+$, 359.2 $[M]^+$, 330.2, 314.3, 313.2, 135.2, 91.2, 65.1; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{22}H_{17}NO_4Na$ $[M+Na]^+$ 382.1050, found 382.1059.

*4.1.6. Propyl 2-methy-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4f**).* Yield 61.5%, mp 121–122 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 8.26–8.24 (m, 1H), 8.23–8.21 (m, 1H), 7.74–7.69 (m, 2H), 7.49 (s, 1H), 4.41 (t, *J*=7.0 Hz, 2H), 4.00 (s, 3H), 1.94–1.86 (m, 2H), 1.09 (t, *J*=8.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ (ppm) 180.1, 178.7, 161.0, 136.0, 134.3, 133.5, 133.1, 128.0, 127.5, 126.6, 125.8, 123.6, 122.7, 67.7, 37.6, 22.0, 10.5; GC–MS *m*/*z* 298.1 $[M+H]^+$, 297.1, 255.1, 239.3, 238.3, 211.2, 170.2, 41.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{17}H_{15}NO_4Na$ $[M+Na]^+$ 320.0893, found 320.0898.

*4.1.7. Butyl 2-methyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4g**).* Yield 53.9%, mp 120–121 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ (ppm) 8.25–8.23 (m, 1H), 8.21–8.20 (m, 1H), 7.73–7.68 (m, 2H), 7.48 (s, 1H), 4.44 (t, *J*=7.0 Hz, 2H), 3.94 (s, 3H), 1.87–1.82 (m, 2H), 1.56–1.48 (m, 2H), 1.01 (t, *J*=7.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ (ppm) 180.0, 178.6, 160.9, 135.9, 134.3, 133.4, 133.0, 128.0, 127.4,

126.6, 125.8, 123.5, 122.6, 65.9, 37.5, 30.6, 19.2, 13.7; GC–MS *m*/*z* 312.4 $[M+H]^+$, 311.5, 239.5, 238.5, 211.5, 170.5, 113.5, 41.2; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{18}H_{17}NO_4Na$ $[M+Na]^+$ 334.1050, found 334.1052.

*4.1.8. Isopentyl 2-methyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4h**).* Yield 58.7%, mp 119–120 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.26–8.24 (m, 1H), 8.23–8.21 (m, 1H), 7.75–7.69 (m, 2H), 7.49 (s, 1H), 4.48 (t, *J*=7.0 Hz, 2H), 3.95 (s, 3H), 1.87–1.81 (m, 1H), 1.79–1.75 (m, 2H), 1.01 (d, *J*=6.5 Hz, 6H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 178.0, 178.5, 160.9, 135.9, 134.2, 133.4, 133.0, 128.0, 127.4, 126.5, 125.7, 123.5, 122.5, 64.7, 37.5, 37.1, 25.1, 22.5 (2C); GC–MS *m*/*z* 326.2 $[M+H]^+$, 325.3, 256.2, 238.3, 170.3, 113.2, 41.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$ 348.1206, found 348.1216.

*4.1.9. Isopropyl 2-methyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4i**).* Yield 50.6%, mp 133–134 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.26–8.24 (m, 1H), 8.22–8.20 (m, 1H), 7.74–7.69 (m, 2H), 7.46 (s, 1H), 5.39–5.34 (m, 1H), 3.94 (s, 3H), 1.49 (d, *J*=6.0 Hz, 6H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 180.2, 178.7, 160.4, 136.0, 134.8, 134.4, 133.5, 133.1, 127.7, 127.5, 126.7, 125.5, 123.4, 122.6, 70.3, 37.4, 21.8; GC–MS *m*/*z* 298.1 $[M+H]^+$, 297.1, 239.2, 211.2, 183.2, 170.3, 154.2, 43.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{17}H_{18}NO_4$ $[M+H]^+$ 298.1074, found 298.1080.

*4.1.10. Ethyl 2-methyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1-carboxylate (**4k**).* Yield 78.0%, mp 202–203 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.73 (d, *J*=13.5 Hz, 2H), 8.04–8.02 (m, 2H), 7.65–7.63 (m, 2H), 7.52 (s, 1H), 4.53 (q, *J*=7.0 Hz, 2H), 3.95 (s, 3H), 1.52 (t, *J*=7.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 179.9, 178.6, 160.9, 134.9, 134.6, 132.3, 139.9, 129.9 (2C), 129.5, 129.0 (2C), 128.7, 128.0, 125.9, 124.3, 123.5, 62.1, 37.5, 14.1; GC–MS *m*/*z* 333.1 $[M]^+$, 289.2, 262.2, 261.3 (100%), 220.2, 163.3, 42.1; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{20}H_{15}NO_4Na$ $[M+Na]^+$ 356.0893, found 356.0900.

*4.1.11. Ethyl 2-ethyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1-carboxylate (**4l**).* Yield 70.3%, mp 187–188 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.77 (d, *J*=7.5 Hz, 2H), 8.07–8.05 (m, 2H), 7.68–7.64 (m, 2H), 7.61 (s, 1H), 4.55 (q, *J*=7.0 Hz, 2H), 4.33 (q, *J*=7.0 Hz, 2H), 1.55–1.52 (m, 6H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 179.8, 178.5, 161.0, 134.8, 134.5, 132.2, 130.9, 129.8, 129.8, 129.3, 128.9, 128.9, 128.6, 126.1, 125.5, 123.9, 123.4, 62.0, 44.8, 16.3, 14.0; GC–MS *m*/*z* 348.0 $[M+H]^+$, 347.1, 303.3, 286.3, 275.3, 247.3, 190.3, 163.3, 120.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{21}H_{17}NO_4Na$ $[M+Na]^+$ 370.1050, found 370.1058.

*4.1.12. Ethyl 2-propyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1-carboxylate (**4m**).* Yield 68.2%, mp 176–177 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.78 (d, *J*=6.5 Hz, 2H), 8.08–8.05 (m, 2H), 7.68–7.65 (m, 2H), 7.58 (s, 1H), 4.55 (q, *J*=7.0 Hz, 2H), 4.25 (t, *J*=6.5 Hz, 2H), 1.94–1.86 (m, 2H), 1.53 (t, *J*=7.0 Hz, 3H), 0.99 (t, *J*=7.5 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 180.2, 178.8, 161.2, 135.0, 134.7, 132.4, 131.1, 130.0 (2C), 129.5, 129.1, 129.0, 128.8, 126.8, 125.9, 124.1, 123.4, 62.2, 51.6, 24.5, 14.1, 11.0; GC–MS *m*/*z* 362.5 $[M+H]^+$, 361.5, 317.7, 290.5, 289.8, 261.8, 190.5, 163.5, 126.5; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{22}H_{19}NO_4Na$ $[M+Na]^+$ 384.1206, found 384.1208.

*4.1.13. Ethyl 2-butyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1-carboxylate (**4n**).* Yield 51.7%, mp 156–157 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.74 (d, *J*=7.0 Hz, 2H), 8.05–8.04 (m, 2H), 7.65–7.63 (m, 2H), 7.56 (s, 1H), 4.54 (q, *J*=7.0 Hz, 2H), 4.26 (t, *J*=7.5 Hz, 2H), 1.90–1.80 (m, 2H), 1.52 (t, *J*=7.0 Hz, 3H), 1.41–1.34 (m, 2H), 0.97 (t, *J*=3.5 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 183.9, 180.2, 161.3, 135.0, 134.8, 132.4, 131.2, 130.0 (2C), 129.5, 129.1 (2C), 128.8, 126.8, 126.0, 124.1, 123.5, 62.2, 49.8, 33.2, 19.8, 14.2, 13.6; GC–MS *m*/*z* 376.0 $[M+H]^+$, 375.1, 304.2, 302.2 (100%), 274.2, 190.2, 155.2, 126.3; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{23}H_{21}NO_4Na$ $[M+Na]^+$ 398.1363, found 398.1371.

*4.1.14. Ethyl 2-benzyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1-carboxylate (**4o**).* Yield 88.5%, mp 149–150 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.74 (d, *J*=8.5 Hz, 2H), 8.05–8.03 (m, 2H), 7.65–7.63 (m, 2H), 7.58 (s, 1H), 7.38–7.24 (m, 3H), 7.23 (d, *J*=7.5 Hz, 2H), 5.46 (s, 2H), 4.45 (q, *J*=7.0 Hz, 2H), 1.40 (t, *J*=7.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 18.0, 178.7, 161.1, 135.1, 134.9, 134.6, 132.2, 131.0, 130.0 (2C), 129.5, 129.1 (3C), 129.0, 128.9, 128.6, 127.8 (2C), 127.1, 126.1, 124.1, 123.5, 62.2, 53.2, 13.9; GC–MS *m*/*z* 410.1 $[M+H]^+$, 409.2 $[M]^+$, 380.2, 364.2, 363.3, 274.3, 91.0, 65.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{26}H_{19}NO_4Na$ $[M+Na]^+$ 432.1206, found 432.121.

*4.1.15. Propyl 2-methyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1-carboxylate (**4p**).* Yield 51.8%, mp 127–128 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.71 (d, *J*=3.5 Hz, 2H), 8.02 (dd, $J_1$=3.5 Hz, $J_2$=6.0 Hz, 2H), 7.63 (dd, $J_1$=3.5 Hz, $J_2$=6.5 Hz, 2H), 7.51 (s, 1H), 4.42 (t, *J*=7.0 Hz, 2H), 3.94 (s, 3H), 1.92 (q, *J*=7.5 Hz, 2H), 1.12 (t, *J*=8.0 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 179.9, 178.5, 161.1, 134.9, 134.6, 132.3, 130.9, 129.9 (2C), 129.5, 129.0 (2C), 128.6, 128.1, 125.9, 124.3, 123.5, 67.7, 37.5, 22.0, 10.5; GC–MS *m*/*z* 348.0 $[M+H]^+$, 347.1, 289.2, 275.3, 262.2, 261.3, 163.3, 41.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{21}H_{17}NO_4Na$ $[M+Na]^+$ 370.1050, found 370.1058.

*4.1.16. Butyl 2-methyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1-carboxylate (**4q**).* Yield 55.3%, mp 147–148 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.74 (s, *J*=13.5 Hz, 2H), 8.05 (dd, $J_1$=3.5 Hz, $J_2$=6.5 Hz, 2H), 7.65 (dd, $J_1$=3.5 Hz, $J_2$=6.5 Hz, 2H), 7.53 (s, 1H), 4.47 (t, *J*=7.5 Hz, 2H), 3.96 (s, 3H), 1.91–1.85 (m, 2H), 1.59–1.51 (m, 2H), 1.03 (t, *J*=7.5 Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 180.0, 178.5, 161.1, 134.9, 134.6, 132.3, 130.9, 129.9 (2C), 129.5, 129.0 (2C), 128.7, 128.0, 126.0, 124.3, 123.5, 66.0, 37.5, 30.6, 19.2, 13.8; GC–MS *m*/*z* 362.0 $[M+H]^+$, 361.0, 289.0, 262.2, 261.2, 220.2, 207.2, 73.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{22}H_{19}NO_4Na$ $[M+Na]^+$ 384.1206, found 384.1215.

*4.1.17. Isopentyl 2-methyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1-carboxylate (**4r**).* Yield 36.6%, mp 100–101 °C; δ (ppm) 8.75 (d, *J*=12.5 Hz, 2H), 8.06–8.05 (m, 2H), 7.66 (dd, $J_1$=3.0 Hz, $J_2$=6.0 Hz, 2H), 7.55 (s, 1H), 4.50 (t, *J*=7.5 Hz, 2H), 3.97 (s, 3H), 1.88–1.83 (m, 1H), 1.82–1.77 (m, 2H), 1.02 (d, *J*=6.5 Hz, 6H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 180.1, 178.6, 161.2, 135.0, 134.7, 132.4, 131.0, 130.0 (2C), 129.6, 129.1 (2C), 128.8, 128.1, 126.1, 124.4, 123.6, 65.0, 37.6, 30.3, 25.3, 22.6 (2C); GC–MS: *m*/*z* 376.5 $[M+H]^+$, 375.5, 306.5, 289.7, 288.7, 261.8, 163.6, 41.3; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{23}H_{21}NO_4Na$ $[M+Na]^+$ 398.1363, found 398.137.

*4.1.18. Isopropyl 2-methyl-2H-naphtho[2,3-f]isoindole-4,11-dione-1-carboxylate (**4s**).* Yield 47.4%, mp 192–193 °C; $^1H$ NMR (500 MHz, $CDCl_3$): $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.79 (s, 1H), 8.76 (s, 1H), 8.07 (dd, $J_1$=3.5 Hz, $J_2$=6.0 Hz, 2H), 7.66 (dd, $J_1$=3.5 Hz, $J_2$=6.0 Hz, 2H), 7.54 (s, 1H), 1.52 (d, *J*=6.5 Hz, 6H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 179.9, 178.4, 160.5, 134.9, 134.6, 132.2, 130.9, 129.9 (2C), 129.4, 129.0, 128.9, 128.6, 127.8, 126.5, 124.0, 123.3, 70.2, 37.3, 21.7 (2C); GC–MS *m*/*z*, 348.0 $[M+H]^+$, 346.9, 289.0, 261.2 (100%), 220.2, 41.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{21}H_{17}NO_4Na$ $[M+Na]^+$ 370.1050, found 370.1057.

*4.1.19. Ethyl 8-hydroxy-2-methyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4t**) and ethyl 5-hydroxy-2-methyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4t′**).* Yield 50.1%; $^1H$ NMR (500 MHz,

$CDCl_3$): δ (ppm) 12.94 (s, 1H), 12.67 (s, 1H), 7.77–7.74 (m, 2H), 7.61–7.57 (m, 2H), 7.48–7.46 (m, 2H), 7.25–7.20 (m, 2H), 4.54–4.49 (m, 4H), 3.96 (s, 3H), 3.94 (s, 3H), 1.51–1.48 (m, 6H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 185.7, 185.0, 179.1, 177.9, 162.9, 162.4, 160.5, 160.5, 136.0, 135.9, 135.6, 134.5, 128.1, 128.0, 126.3, 126.1, 124.1, 123.4 (2C), 122.5, 122.4, 121.8, 119.6, 118.8, 117.6, 116.5, 62.2, 62.1, 37.5, 37.4, 14.1, 14.0; GC–MS *m*/*z*, 300.0 $[M+H]^+$, 299.0, 253.1, 227.3, 225.3, 170.2, 142.2, 63.0; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{21}H_{17}NO_4Na$ $[M+Na]^+$ 322.0686, found 322.0689.

*4.1.20. Ethyl 8-nitro-2-methyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4u**) and ethyl 5-nitro-2-methyl-2H-benzo[f]isoindole-4,9-dione-1-carboxylate (**4u′**).* Yield 52.6%; $^1H$ NMR (500 MHz, $CDCl_3$): δ (ppm) 8.45–8.39 (m, 2H), 7.85–7.80 (m, 2H), 7.77–7.64 (m, 2H), 7.64–7.51 (m, 2H), 4.54–4.49 (m, 2H), 4.47–4.43 (m, 2H), 1.52–1.49 (m, 3H), 1.45–1.42 (m, 3H); $^{13}C$ NMR ($CDCl_3$, 125 MHz): δ (ppm) 177.4, 176.2, 176.0, 175.3, 160.2, 160.1, 149.8, 149.1, 137.0, 135.5, 134.0, 133.5, 129.8, 129.2, 128.6, 127.8, 127.4, 126.7, 126.3, 125.1, 123.1, 122.6, 122.2, 121.7, 121.3, 62.3, 62.2, 37.8, 37.6, 14.1, 13.8; GC–MS *m*/*z*, 328.0 $[M]^+$, 298.1, 284.1, 267.1, 256.1, 253.2, 226.2, 198.2, 127.2; HRMS (ESI-TOF) *m*/*z* Calcd for $C_{21}H_{17}NO_4Na$ $[M+Na]^+$ 351.0587, found 351.0596.

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## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.08.029.

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