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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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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 use 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,8c, 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 Itoh6d and Prabhur6f.

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

Recently, Gong and co-workers17 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 quinones2c, 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 CH2CN with NaHCO3 as a base to afford 3aa in 60% (Table 1, entry 1). Some other common iodine-addition initiation systems were also investigated, including I2/t-BuOCl and I2/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 NaHCO3 (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 °C 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 equivalents 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...
products was stirred for 5 h at reflux temperature under air condition. As the substituted group on NH atom increased, the yield of corresponding 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 employed because of some insoluble things and can not be identified by NMR or GC-MS (Table 2, entries 13-16).

Table 1 Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>iodine (equiv)</th>
<th>solvent</th>
<th>T (°C)</th>
<th>yield of 3aa (%)</th>
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<tr>
<td>1</td>
<td>NaHCO₃</td>
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<td>CH₃CN</td>
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<td>60</td>
</tr>
<tr>
<td>2</td>
<td>NaHCO₃</td>
<td>I₂ (3)</td>
<td>CH₃CN</td>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>NaHCO₃</td>
<td>I₂ (3)</td>
<td>CH₃CN</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>DBU</td>
<td>I₂ (3)</td>
<td>CH₃CN</td>
<td>80</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>DBU</td>
<td>I₂ (3)</td>
<td>CHCl₃</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>DBU</td>
<td>I₂ (3)</td>
<td>CHCl₃</td>
<td>60</td>
<td>49</td>
</tr>
<tr>
<td>7</td>
<td>DBU</td>
<td>I₂ (3)</td>
<td>toluene</td>
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<tr>
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<td>86</td>
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<tr>
<td>9</td>
<td>DBU</td>
<td>I₂ (3)</td>
<td>xylene</td>
<td>120</td>
<td>80</td>
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<tr>
<td>10</td>
<td>DBU</td>
<td>I₂ (2)</td>
<td>xylene</td>
<td>140</td>
<td>70</td>
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<tr>
<td>11</td>
<td>DBU</td>
<td>I₂ (2)</td>
<td>xylene</td>
<td>140</td>
<td>60</td>
</tr>
</tbody>
</table>

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As various ethyl N-alkyl iminodiacetates I 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'-azanediylidiacetate 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'-azanediylidiacetate 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. 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 O₂ and I₂. The GC-MS analysis of the reaction mixture of 1a with a stoichiometric amount of I₂ 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 I₂.

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 intermediate 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 ¹³C NMR spectra were recorded at 500 and 125 MHz, respectively, in CDCl₃ 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 (GC431HMS210) 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-substituted 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 in 8 mL saturated aqueous sodium thiosulfate and was extracted (3*10 mL) with CH₂Cl₂. The combined extracts were dried over MgSO₄. The solvent was removed under vacuum, and the resulting crude product was purified by chromatography on silica gel eluted with CH₂Cl₂ to obtain 3 as yellow solid.

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

Yield 86%; mp 122-123 °C. IR (KBr): 2985, 1728, 1668, 1594, 1548, 1517, 1474, 1466, 1147, 1025, 1008, 800, 744, 703 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.22 (dd, J₁ = 3.0 Hz, J₂ = 7.5 Hz, 2H), 7.73 (dd, J₁ = 3.5 Hz, J₂ = 7.5 Hz, 2H), 4.55 (q, J = 7.5 Hz, 2H), 3.93 (s, 3H), 1.50 (t, J = -7.5 Hz, 6H). ¹³C NMR (125 MHz, CDCl₃): 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 C₁₉H₁₄NO₆ [M+H⁺] 356.1129, found 356.1131.

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

Yield 70%; mp 109-110 °C. IR (KBr): 2985, 1716, 1678, 1594, 1546, 1505, 1436, 1280, 1145, 1044, 1014, 743, 709 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.18 (dd, J₁ = 3.5 Hz, J₂ = 7.5 Hz, 2H), 7.69 (dd, J₁ = 3.5 Hz, J₂ = 7.5 Hz, 2H), 4.52 (q, J = 6.5 Hz, 2H), 4.33 (q, J = 7.0 Hz, 2H), 1.48-1.44 (m, 9H). ¹³C NMR (125 MHz, CDCl₃): 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 C₁₉H₁₄NO₆Na [M+Na⁺] 392.1104, found 392.1112.

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

Yield 64%; mp 104-105 °C. IR (KBr): 2968, 1728, 1668, 1594, 1512, 1471, 1421, 1317, 1264, 1225, 1143, 1005, 798, 743, 713 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.20 (dd, J₁ = 4.0 Hz, J₂ = 7.0 Hz, 2H), 7.71 (dd, J₁ = 3.5 Hz, J₂ = 6.0 Hz, 2H), 4.54 (q, J = 7.5 Hz, 2H), 4.28 (t, J = 8.0 Hz, 2H), 1.87-1.81 (m, 2H), 1.48 (t, J = 7.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 178.79 (2C), 161.02 (2C), 134.89 (2C), 133.47 (2C), 127.70 (2C), 126.93 (2C), 121.83 (2C), 62.55 (2C), 48.96, 24.59, 13.81 (2C). GC-MS m/z 384.1 [M⁺+H⁺], 383.0 [M⁺], 325.3, 311.5, 211.3. HRMS (ESI-TOF) m/z Calcd for C₁₉H₁₄NO₆Na [M+Na⁺] 392.1104, found 392.1112.
C_{21}H_{22}NO_3Na [M+Na]^+ 406.1261, found 406.1265.

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

Yield 40.3%; mp 99-100 °C. IR (KBr): 2927, 1728, 1673, 1467, 1368, 1261, 1227, 1201, 1097, 1017, 800 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.21 (dd, J = 3.0 Hz, J = 6.0 Hz, 2H), 7.72 (dd, J = 3.0 Hz, J = 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). ¹³C NMR (125 MHz, CDCl₃): 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+H]^+ , 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_4Na [M+Na]^+ 420.1423, found 420.1427.

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

Yield 81%; mp 176-177 °C. IR (KBr): 2927, 1720, 1705, 1674, 1621, 1513, 1472, 1293, 1242, 1208, 1186, 1107, 1038, 1022, 762, 747 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): 8.73 (s, 2H), 8.04 (dd, J = 3.0 Hz, J = 6.5 Hz, 2H), 7.65 (dd, J = 3.5 Hz, J = 6.0 Hz, 2H), 4.57 (q, J = 7.0 Hz, 4H), 3.93 (s, 3H), 1.52 (t, J = 7.5 Hz, 2H), 1.34, 1.21, 1.19, 1.17, 1.15, 0.96-0.92 (m, 2H), 0.84-0.82 (m, 2H). ¹³C NMR (CDCl₃, 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+H]^+, 361.2, 333.2, 289.3, 288.4, 262.3, 261.3. Anal. Calcd for C_{18}H_{17}NO_3S_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)**

Yield 73%; mp 134-135 °C. IR (KBr): 2978, 1725, 1674, 1619, 1437, 1281, 1234, 1185, 1038, 1015, 862, 759 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.73 (s, 2H), 8.03 (dd, J = 3.5 Hz, 2H), 7.64 (dd, J = 3.5 Hz, J = 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). ¹³C NMR (125 MHz, CDCl₃): 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_{23}H_{24}NO_4 448.1750, found 448.1755.

**Diethyl 2-butyl-2H-naphtho[2,3-f]isoindole-4,9-dione-1,3-dicarboxylate (3ac)**

Yield 70%; mp 85-86 °C. IR (KBr): 2983, 1723, 1676, 1593, 1544, 1509, 1375, 1306, 1252, 1226, 1144, 1026, 912, 798, 712 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.40 (dd, J = 1.0 Hz, J = 7.5 Hz, 1H), 7.83 (t, J = 7.5 Hz, 1H), 7.70 (dd, J = 1.0 Hz, J = 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). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 176.18, 175.21, 160.25, 160.08, 149.43, 135.97, 133.77, 129.58, 128.65, 128.51, 127.55, 100.06, 99.87, 98.42, 92.33, 61.45, 30.32, 28.51, 28.39, 22.97, 22.94, 21.91, 21.90.
Diethyl 2-ethyl-5-nitro-2H-benzo[f]isoindole-4,9-dione-1,3-dicarboxylate (3bc)

Yield 63%; mp 75-76 °C. IR (KBr): 2982, 1730, 1681, 1531, 1440, 1309, 1233, 1141, 1018, 798, 711 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.39 (dd, J₁ = 0.5 Hz, J₂ = 7.0 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 7.70 (dd, J₁ = 1.5 Hz, J₂ = 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). HRMS (ESI-TOF) m/z Calcd for C₂₉H₂₂N₂O₈Na [M+Na⁺]⁺ 423.0799, found 423.0807.

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

Yield 60%; mp 70-71 °C. IR (KBr): 2977, 1734, 1682, 1532, 1438, 1367, 1315, 1227, 1142, 1018, 797, 712 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 8.40 (dd, J₁ = 1.0 Hz, J₂ = 8.0 Hz, 1H), 7.83 (t, J = 8.0 Hz, 1H), 7.70 (dd, J₁ = 0.5 Hz, J₂ = 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 = 7.5 Hz, 3H). ¹³C NMR (125 MHz, CDCl₃): 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 414.8 [M⁺], 413.8, 396.0, 386.0, 369.2, 342.3, 325.3, 295.1. HRMS (ESI-TOF) m/z Calcd for C₂₉H₂₂N₂O₈Na [M+Na⁺]⁺ 437.0955, found 437.0958.

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

Yield 34%; mp 100-101 °C. IR (KBr): 2977, 1735, 1705, 1674, 1633, 1555, 1365, 1350, 1263, 1226, 1075, 801, 715 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 12.67 (s, 1H), 7.73 (dd, J₁ = 1.0 Hz, J₂ = 7.5 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.22 (dd, J₁ = 1.0 Hz, J₂ = 8.5 Hz, 1H), 4.56-4.51 (m, 4H), 3.91 (s, 3H), 1.50-1.47 (m, 4H). ¹³C NMR (125 MHz, CDCl₃): δ (ppm) 176.77, 177.87, 162.73, 160.62, 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 C₂₀H₁₆NO₆Na [M+Na⁺]⁺ 394.0907, found 394.0897.

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

Yield 40%; mp 133-134 °C. IR (KBr): 2964, 1705, 1669, 1634, 1455, 1262, 1082, 1021, 802, 695 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ (ppm) 12.65 (s, 1H), 7.73 (dd, J₁ = 1.0 Hz, J₂ = 7.5 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.22 (dd, J₁ = 1.0 Hz, J₂ = 8.5 Hz, 1H), 4.54-4.51 (m, 4H), 3.91 (s, 3H), 1.50-1.47 (m, 4H). ¹³C NMR (125 MHz, CDCl₃): 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 C₂₀H₁₆NO₆ [M+H⁺]⁺ 386.1235, found 386.1250.
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Notes and references

1. H NMR (500 MHz, CDCl3): δ (ppm) 12.67 (s, 1H), 7.73 (dd, J1 = 1.5 Hz, J2 = 7.5 Hz, 1H), 7.59 (t, J = 8.5 Hz, 1H), 7.22 (dd, J1 = 1.0 Hz, J2 = 8.5 Hz, 1H), 4.56-4.51 (m, 2H), 4.27 (q, J = 7.5 Hz, 2H), 1.48 (t, J = 7.0 Hz, 3H), 0.95 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H). 13C NMR (125MHz, CDCl3): 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 C23H26NO8Na [M+Na]+ 436.1367, found 436.1376.

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

Yield 50%; mp 137-138 °C. 1H NMR (500 MHz, DMSO-d6): δ (ppm) 8.23 (dd, J1 = 3.0 Hz, J2 = 5.5 Hz, 2H), 7.74 (dd, J1 = 3.5 Hz, J2 = 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). 13C NMR (125MHz, DMSO-d6): 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 C23H23NO8Na [M+Na]+ 450.1165, found 450.1167.

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