MICROWAVE-ASSISTED, Yb(OTf)₃/TfOH COCATALYZED SYNTHESIS OF XANTHONES AND THIOXANTHONES BY INTRAMOLECULAR FRIEDEL-CRAFTS REACTION UNDER SOLVENT-FREE CONDITIONS

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Abstract – An efficient method for the synthesis of biologically interesting xanthones and thioxanthones was achieved using Yb(OTf)₃/TfOH as co-catalysts by a microwave radiation-mediated reaction. Both electron-rich and electron-poor substrates could be cyclized in good yields.

Heterocyclic structural elements of the general formula (Figure 1) are common in natural products and molecules of pharmacological interest.¹ ² The compound of xanthone (9H-xanthen-9-one) exhibits a wide range of biological and pharmacological activities, e.g., antibacterial, anti-inflammatory, anticancer, antioxidant, antifulcer and antiviral activities.³ ⁵ Thioxanthone (9H-thioxanthen-9-one) derivatives also exhibit interesting anticancer activities.⁶

![Figure 1](image_url)

X=O xanthones
X=S thioxanthones

The preparation of such xanthone skeleton typically use benzophenones or diary ethers as intermediate under extremely harsh reaction conditions and/or employed strong acids or toxic metals.⁷ ⁹ Zhao and Larock have reported a facile one-pot coupling method to synthesize xanthones and thioxanthones from
arynes and benzoates in 35-81% yields. $^{10}$ η⁶-2-chloro-N,N-diethylbenzamide-η⁵-cyclo-pentadienyl iron hexafluorophosphate was also applied as a common building block for the synthesis of xanthones and thioxanthones. $^{11}$ Nevertheless, most of reported methods are multistep, under harsh reaction conditions or non-atomeconomic.

A number of reports have described catalytic Friedel-Crafts acylation reaction using carboxylic acids as acylating reagents. $^{12-15}$ We have recently described the synthesis of 1-azaxanthones and 1-azathioxanthones by Yb(OTf)$_3$/TfOH cocatalyzed intramolecular Friedel-Crafts reaction. $^{16}$ To extend the scope of the catalytic system and in an effort to prepare xanthones and thioxanthones, we turned our attention to the microwave-assisted Friedel-Crafts reaction. As is known, microwave heating has been widely applied in organic synthesis recently and its benefits have been well documented. $^{17,18}$ Here, we wish to report a new approach based on the microwave-assisted intramolecular Friedel-Crafts reaction for the preparation of xanthones and thioxanthones utilizing Yb(OTf)$_3$/TfOH as co-catalysts under solvent-free conditions.

We started our investigation using 2-phenoxybenzoic acid 1a as the model substrate. 1a (4 mmol) and Yb(OTf)$_3$ (0.2 mmol) were ground with silica gel (0.5 g) under microwave irradiation for 5 min (indicated by TLC), and isolated product 2a was afforded in 66% yield (entry 5). A blank experiment, in the absence of catalyst gave the unreacted starting material (entry 1). A series of metal triflates were evaluated due to their catalytic activities in Friedel-Crafts reaction. $^{16,19}$ Only 31% yield of 2a was obtained when using Zn(OTf)$_2$ (entry 2). Nevertheless, when Cu(OTf)$_2$ and Bi(OTf)$_3$ were employed, the product 2a was generated in 52% and 60% yields, respectively (entries 3 and 4). When 20 mol% of trifluoromethanesulfonic acid (TfOH) was used as the catalyst, the yield of 2a was slightly improved (entry 6). To our delight, 90% yield of 2a was obtained when combining 5 mol% of Yb(OTf)$_3$ and 20 mol% of TfOH (entry 7). Further optimization using 2 mol% of Yb(OTf)$_3$ and 10 mol% of TfOH showed that the yield of 2a was also in 90% (entry 8). We also compared this reaction with the traditional heating that took 10 h at 165 °C under solvent-free condition, and only 71% yield of 2a was afforded (entry 9). Effects of solvents on the yields in this reaction were examined and only trace amount of 2a was detected in the solvent of xylene (entry 11), while in DMF, no reaction was observed (entry 10). Therefore, 2 mol% of Yb(OTf)$_3$ and 10 mol% of TfOH as co-catalyst under microwave irradiation for 5 min was chosen as the standard reaction conditions.

With the optimized reaction conditions in hand, we initiated our investigations into the scope of the microwave-assisted, Yb(OTf)$_3$/TfOH cocatalyzed intramolecular cyclization of various substituted 2-phenoxybenzoic acids and the results are summarized in Table 2. A wide range of 2-phenoxybenzoic acids with both electron-donating (entries 2-5 and 11-13) and electron-withdrawing groups (entries 6-7 and 14-15) afforded the corresponding cyclized products in good to excellent isolated yields. In the case
Table 1. Optimization of reaction conditions for the synthesis of 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Conditions</th>
<th>Yielda (%)</th>
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<tr>
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<td>none</td>
<td>MW 5min</td>
<td>N.R. b</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OTf)2(5)</td>
<td>none</td>
<td>MW 5min</td>
<td>31</td>
</tr>
<tr>
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</tr>
<tr>
<td>4</td>
<td>Bi(OTf)3(5)</td>
<td>none</td>
<td>MW 5min</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>Yb(OTf)3(5)</td>
<td>none</td>
<td>MW 5min</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>TfOH(20)</td>
<td>none</td>
<td>MW 5min</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>Yb(OTf)3/TfOH(5/20)</td>
<td>none</td>
<td>MW 5min</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>Yb(OTf)3/TfOH(2/10)</td>
<td>none</td>
<td>MW 5min</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>Yb(OTf)3/TfOH(2/10)</td>
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<td>165 °C 10 h</td>
<td>71</td>
</tr>
<tr>
<td>10</td>
<td>Yb(OTf)3/TfOH(2/10)</td>
<td>DMF</td>
<td>reflux 10 h</td>
<td>N.R.</td>
</tr>
<tr>
<td>11</td>
<td>Yb(OTf)3/TfOH(2/10)</td>
<td>xylene</td>
<td>reflux 10 h</td>
<td>trace</td>
</tr>
</tbody>
</table>

a yield of isolated product
b N.R. = no reaction

do meta-substituted substrate 1d, two regioisomeric xanthone products 2d and 2d' were obtained in 96% total yield (entry 4). Substrates 1h and 1i with a naphthyl moiety also worked well under the same reaction conditions affording 82% and 87% yields of the corresponding tetracyclic xanthone products, respectively (entries 8 and 9). It is important to note that fluoride and chloride groups are tolerated in this process (entries 6-7 and 10-15), which provided access to more structurally diverse xanthone skeletons via metal-catalyzed cross-coupling reactions.20 We were very excited to find that the deactivated substrate 1g bearing three fluorine atoms on aromatic ring was successfully transformed to 2g in 73% yield (entry 7).
Table 2. Extension of substrates for the synthesis of xanthones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
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<tbody>
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<td>98</td>
<td>9</td>
<td><img src="image" alt="2i" /></td>
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<td>91</td>
<td>10</td>
<td><img src="image" alt="2j" /></td>
<td>80</td>
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<tr>
<td>4</td>
<td><img src="image" alt="2d" /></td>
<td>33</td>
<td>11</td>
<td><img src="image" alt="2k" /></td>
<td>77</td>
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<td></td>
<td>![2d']](image)</td>
<td>63</td>
<td>12</td>
<td><img src="image" alt="2l" /></td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="2e" /></td>
<td>79</td>
<td>13</td>
<td><img src="image" alt="2m" /></td>
<td>90</td>
</tr>
<tr>
<td>6</td>
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<td>76</td>
<td>14</td>
<td><img src="image" alt="2n" /></td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="2g" /></td>
<td>73</td>
<td>15</td>
<td><img src="image" alt="2o" /></td>
<td>75</td>
</tr>
</tbody>
</table>

The new catalytic system was also successfully utilized for the synthesis of biologically interesting thioxanthones from corresponding 2-phenylthiobenzoic acids. All of the results are summarized in Table 3. The methyl-, methoxy- and chloro-substituted substrates 3b-3h have been allowed to react under our usual reaction conditions, and 70-85% yields of the substituted thioxanthones 4b-4h have been obtained (entries 2-8). It is noteworthy that chloride-containing thioxanthones were obtained (entries 4-8) and these products could be subject to facile functionalization via various Pd-catalyzed reactions.\textsuperscript{20} Para- and
meta-substituted 2-phenylthiobenzoic acids gave the corresponding products in good yield (entries 6 and 7) whereas a ortho-substituted 2-phenylthiobenzoic acid gave the product in a slightly lower yield probably due to the steric hindrance (entry 8).

Table 3. Extension of substrates for the synthesis of thixanthones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="4a" /></td>
<td>72</td>
<td>5</td>
<td><img src="image" alt="4e" /></td>
<td>73</td>
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<tr>
<td>2</td>
<td><img src="image" alt="4b" /></td>
<td>81</td>
<td>6</td>
<td><img src="image" alt="4f" /></td>
<td>85</td>
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<tr>
<td>3</td>
<td><img src="image" alt="4c" /></td>
<td>79</td>
<td>7(^b)</td>
<td><img src="image" alt="4g" /></td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="4d" /></td>
<td>70</td>
<td>8</td>
<td><img src="image" alt="4h" /></td>
<td>71</td>
</tr>
</tbody>
</table>

\(^a\) Reaction condition: Yb\((\text{OTf})_3\) (2 mol%), TfOH (10 mol%) and 3 (4 mmol) were ground together under microwave irradiation for 4 min.

\(^b\) This reaction produced a side product in trace which was not identified.

In summary, we have demonstrated a novel and efficient protocol for the preparation of biologically interesting xanthones and thioxanthones by a microwave radiation-mediated reaction using Yb\((\text{OTf})_3\)/TfOH as co-catalysts. Short reaction times, simple reagents, easy and clean work-up and solvent-free conditions are notable advantages of this method and these make this method an attractive and useful alternative to the existing methods for xanthones and thioxanthones. Further investigations using this methodology to construct biologically active xanthone containing molecules are underway.

**EXPERIMENTAL**

All the reactions were carried out in a domestic microwave oven: Galanz P70D20TL-D4 model.
(300W-700W) in closed Teflon container. Solid supports: Silica gel (mesh, 200-300). Melting points were determined by Büchi B-540 melting point apparatus and are uncorrected. The IR spectra (KBr pellet) were measured on a Nicolet Avatar-370 spectrometer. \(^1\)H NMR (400 MHz) and \(^{13}\)C NMR (100 MHz) spectra were recorded on a Varian 400-MHz spectrometer. Mass spectra were obtained on a Thermo Finnigan LCQ-Advantage spectrometer (ESI, APCI) or a Finnigan Trace DSQ spectrometer (EI, CI). HRMS was carried out on an APEX (Bruker) mass III spectrometer.

**General Procedure for Synthesis of xanthone 2a**

All reactions were performed using a Galanz P70D20TL-D4 microwave oven. A mixture of 2-phenoxybenzoic acid (4 mmol), Yb(OTf)$_3$ (0.08 mmol), TfOH(0.4 mmol) and dry silica gel (0.5 g) was mixed together in a crucible. Then the mixture was placed in the capped microwave reactor and the crucible was irradiated for 5 min. The reaction was monitored by TLC. At completion of the reaction, the resulting mixture was purified directly by column chromatography [eluent: petroleum/EtOAc (10:1)].

**9H-Xanthen-9-one (2a)**

White solid. mp 175-176 °C (Lit.,\(^{21}\) mp 172-173 °C). IR (KBr): 1656, 1607, 1459, 1345, 1331, 758 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.33 (dd, J = 8.0, 1.6 Hz, 2H), 7.71-7.66 (m, 2H), 7.46 (d, J = 8.8 Hz, 1H), 7.35 (t, J = 7.2 Hz, 1H), 1.40 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 177.1, 156.1, 154.3, 136.1, 134.7, 133.7, 126.7, 125.8, 123.5, 122.2, 121.6, 120.9, 117.7, 117.4, 34.8, 31.4 (3C). MS (ESI): m/z = 323 (M\(^{+}\)+H).

**2-Methyl-9H-xanthen-9-one (2b)**

White solid. mp 122.7-123.2 °C (Lit.,\(^{22}\) mp 122 °C). IR (KBr): 3080, 2907, 1650, 1608, 1476, 1318, 760 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.32 (dd, J = 8.4, 2.4 Hz, 1H), 7.71-7.66 (m, 1H), 7.51 (dd, J = 8.0, 2.0 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.38-7.32 (m, 2H), 2.46 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 177.1, 156.1, 154.3, 136.1, 134.7, 133.7, 126.7, 125.8, 123.7, 121.8, 121.5, 118.0, 117.8, 21.2. MS (ESI): m/z = 241 (M\(^{+}\)+1).

**2-( tert-Butyl)-9H-xanthen-9-one (2c)**

White solid. mp 111.6-112.5 °C (Lit.,\(^{23}\) mp 114-115 °C). IR (KBr): 3068, 2970, 2953, 2867, 1658, 1614, 1467, 1320, 761 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.33 (dd, J = 8.0, 1.6 Hz, 1H), 8.30 (d, J = 2.4 Hz, 1H), 7.72 (dd, J = 8.8, 2.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 7.2 Hz, 1H), 1.40 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 177.1, 155.8, 154.0, 146.8, 134.6, 132.5, 126.5, 122.2, 121.6, 120.9, 117.7, 117.4, 34.8, 31.4 (3C). MS (ESI): m/z = 253 (M\(^{+}\)+H).
1-Methyl-9\(H\)-xanthen-9-one (2d)
White solid. mp 110.3-111 °C (Lit.,\(^{24}\) mp 109.5-110.5 °C) IR (KBr): 2963, 2922, 1655, 1600, 1344, 763 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.25 (dd, \(J = 8.0, 1.6\) Hz, 1H), 7.66-7.62 (m, 1H), 7.50 (t, \(J = 8.0\) Hz, 1H), 7.40 (d, \(J = 8.4\) Hz, 1H), 7.33-7.27 (m, 2H), 7.08 (d, \(J = 7.6\) Hz, 1H), 2.92 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 178.5, 157.2, 154.9, 141.7, 134.0, 133.4, 126.4, 123.4, 122.5, 119.8, 117.2, 115.8, 23.3. MS (ESI): m/z = 211 (M\(^++1\)).

3-Methyl-9\(H\)-xanthen-9-one (2d’)
White solid. mp 93-95 °C (Lit.,\(^{24}\) mp 98 °C). IR (KBr): 3064, 2923, 1657, 1605, 1464, 1325, 758 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.31 (d, \(J = 7.6\) Hz, 1H), 8.19 (d, \(J = 8.4\) Hz, 1H), 7.68 (t, \(J = 8.0\) Hz, 1H), 7.44 (d, \(J = 8.4\) Hz, 1H), 7.34 (t, \(J = 8.0\) Hz, 1H), 7.25 (s, 1H), 7.16 (d, \(J = 8.0\) Hz, 1H), 2.49 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 176.6, 155.9, 146.0, 134.3, 126.4, 126.2, 125.2, 123.5, 121.6, 119.3, 117.7, 117.5, 22.0. MS (ESI): m/z = 211 (M\(^++1\)).

2-Methoxy-9\(H\)-xanthen-9-one (2e)
White solid. mp 131.8-132.6 °C (Lit.,\(^{25}\) mp 132-139 °C). IR (KBr): 3033, 2958, 2834, 1649, 1615, 1466, 1317, 758 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.33 (dd, \(J = 8.0, 1.2\) Hz, 1H), 7.72-7.67 (m, 1H), 7.47 (d, \(J = 8.4\) Hz, 1H), 7.42 (d, \(J = 9.2\) Hz, 1H), 7.35 (t, \(J = 8.0\) Hz, 1H), 7.31 (dd, \(J = 3.2, 9.2\) Hz, 1H), 3.91 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 177.0, 156.1, 156.0, 151.0, 134.6 (2C), 126.7, 125.0, 123.8, 122.2, 121.3, 119.5, 118.1, 56.2. MS (ESI): m/z = 227 (M\(^++1\)).

2-Chloro-9\(H\)-xanthen-9-one (2f)
White solid. mp 170.3-171.7 °C (Lit.,\(^{25}\) mp 173-173 °C). IR (KBr): 3079, 2958, 2834, 1649, 1615, 1466, 1317, 758 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.31 (dd, \(J = 8.0, 1.2\) Hz, 1H), 8.28 (d, \(J = 2.8\) Hz, 1H), 7.65 (dd, \(J = 8.8, 2.8\) Hz, 1H), 7.49-7.43 (m, 2H), 7.39 (t, \(J = 7.2\) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 175.7, 155.7, 154.1, 134.9, 134.3, 129.4, 126.5, 125.7, 124.0, 122.3, 121.2, 119.5, 117.8. MS (EI): m/z (%) = 232 ([M\(^++2\)], 32), 230 (M\(^+\), 100), 202 (21), 139 (22).

1,2,3-Trifluoro-9\(H\)-xanthen-9-one (2g)
White solid. mp 179-180 °C. IR (KBr): 3081, 1660, 1646, 1615, 1511, 1469, 1312, 1130, 1066, 761 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.26 (dd, \(J = 8.0, 1.6\) Hz, 1H), 7.75-7.70 (m, 1H), 7.44-7.37 (m, 2H), 7.14-7.09 (m, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 175.7, 155.3, 154.1, 134.9, 134.3, 129.4, 126.5, 125.7, 124.0, 122.3, 121.2, 119.5, 117.8. MS (EI): m/z (%) = 232 ([M\(^++2\)], 32), 230 (M\(^+\), 100), 202 (21), 139 (22).
HRMS (ESI): calcd for C\textsubscript{13}H\textsubscript{6}F\textsubscript{3}O\textsubscript{2} [M+H]\textsuperscript{+}: 251.0320, found: 251.0316.

12\textit{H}-Benzo[\textit{a}]xanthen-12-one (2h)
White solid. mp 141-141.7 °C (Lit.,\textsuperscript{26} mp 143-144 °C). IR (KBr): 3047, 2921, 1643, 1611, 1588, 1467, 1299, 1240, 767, 750 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 10.06 (d, \(J = 8.8\) Hz, 1H), 8.41 (d, \(J = 7.6\) Hz, 1H), 8.08 (d, \(J = 9.2\) Hz, 1H), 7.86 (d, \(J = 8.0\) Hz, 1H), 7.75 (t, \(J = 8.0\) Hz, 1H), 7.69 (t, \(J = 8.0\) Hz, 1H), 7.57 (t, \(J = 7.6\) Hz, 1H), 7.51 (d, \(J = 8.8\) Hz, 2H), 7.41 (t, \(J = 8.0\) Hz, 1H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\): 178.0, 157.2, 154.3, 136.3, 133.6, 130.9, 129.9, 129.2, 128.1, 126.7, 126.4, 125.8, 124.0, 123.4, 117.8, 117.3, 114.3. MS (ESI): m/z = 247 (M\textsuperscript{+}+1).

7\textit{H}-Benzo[c]xanthen-7-one (2i)
Red solid. mp 159-160 °C (Lit.,\textsuperscript{26} mp 160 °C). IR (KBr): 3060, 1656, 1608, 1468, 1385, 831, 757 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 8.66 (dd, \(J = 7.2, 2.4\) Hz, 1H), 8.39 (dd, \(J = 8.0, 2.0\) Hz, 1H), 8.26 (d, \(J = 8.8\) Hz, 1H), 7.92 (dd, \(J = 7.2, 2.4\) Hz, 1H), 7.78-7.74 (m, 1H), 7.74-7.65 (m, 4H), 7.46-7.41 (m, 1H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\): 176.5, 155.4, 153.3, 136.2, 134.1, 129.3, 127.8, 126.6, 126.3, 124.2, 123.8, 122.6, 122.2, 121.2, 117.8, 117.3. MS (ESI): m/z = 247 (M\textsuperscript{+}+1).

3-Chloro-9\textit{H}-xanthen-9-one (2j)
White solid. mp 128.2-129.6 °C (Lit.,\textsuperscript{27} mp 127-128 °C). IR (KBr): 3083, 1677, 1598, 1463, 1424, 938, 754 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 8.31 (dd, \(J = 8.0, 1.6\) Hz, 1H), 8.26 (d, \(J = 8.8\) Hz, 1H), 7.74-7.70 (m, 1H), 7.51 (d, \(J = 2.0\) Hz, 1H), 7.47 (d, \(J = 8.4\) Hz, 1H), 7.39 (t, \(J = 8.0\) Hz, 1H), 7.33 (dd, \(J = 8.4, 1.6\) Hz, 1H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\): 176.0, 156.0, 155.7, 140.6, 134.8, 127.9, 126.5, 124.6, 124.1, 121.5, 120.2, 117.9, 117.8. MS (ESI): m/z = 230 (M\textsuperscript{+}).

6-Chloro-2-methoxy-9\textit{H}-xanthen-9-one (2k)
White solid. mp 165.4-166.4 °C. IR (KBr): 3068, 2974, 2843, 1658, 1596, 1488, 1435, 820, 773 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 8.25 (d, \(J = 8.4\) Hz, 1H), 7.65 (d, \(J = 3.2\) Hz, 1H), 7.48 (d, \(J = 2.0\) Hz, 1H), 7.40 (d, \(J = 9.2\) Hz, 1H), 7.32-7.29 (m, 2H), 3.91 (s, 3H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\): 175.8, 155.9, 155.8, 150.5, 140.3, 127.8, 124.8, 124.4, 121.8, 119.5, 119.1, 117.7, 105.6, 56.0. HRMS (ESI): calcd for C\textsubscript{14}H\textsubscript{10}ClO\textsubscript{3} [M+H]\textsuperscript{+}: 261.0318, found: 261.0316.

6-Chloro-2-methyl-9\textit{H}-xanthen-9-one (2l)
White solid. mp 149-150 °C (Lit.,\textsuperscript{28} mp 148-148.5 °C). IR (KBr): 3086, 2917, 1660, 1606, 1437, 814, 774 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 8.24 (d, \(J = 8.8\) Hz, 1H), 8.07 (s, 1H), 7.52 (dd, \(J = 8.4, 2.4\) Hz, 1H),
7.47 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 8.8, 2.0 Hz, 1H), 2.47 (s, 3H). 13C NMR (100 MHz, CDCl3) δ: 175.8, 155.8, 153.8, 140.2, 135.9, 133.8, 127.7, 125.74, 124.2, 121.0, 120.0, 117.6, 117.4, 20.8. MS (ESI): m/z = 245 (M+1).

6-Chloro-2,4-dimethyl-9H-xanthen-9-one (2m)
Pale yellow solid. mp 140-142 °C. IR (KBr): 3056, 3007, 2958, 2917, 1657, 1600, 1429, 919, 776 cm\(^{-1}\). 1H NMR (400 MHz, CDCl3) δ: 8.23 (d, J = 8.8 Hz, 1H), 7.91 (s, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.37 (s, 1H), 7.30 (dd, J = 8.4, 2.0 Hz, 1H), 2.49 (s, 3H), 2.42 (s, 3H). 13C NMR (100 MHz, CDCl3) δ: 176.0, 155.8, 152.3, 140.2, 137.0, 133.3, 127.8, 126.7, 124.2, 123.4, 121.0, 119.9, 118.2. MS (EI): m/z (%) = 266 ([M+2], 66), 264 (M+, 100), 236 (26), 173 (12).

2,6-Dichloro-9H-xanthen-9-one (2n)
White solid. mp 219-220 °C (Lit., mp 219-220 °C). IR (KBr): 3092, 1664, 1600, 1437, 1291, 920, 820, 774 cm\(^{-1}\). 1H NMR (400 MHz, CDCl3) δ: 8.26-8.22 (m, 2H), 7.66 (dd, J = 8.8, 2.4 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.35 (dd, J = 8.4, 2.0 Hz, 1H). 13C NMR (100 MHz, CDCl3) δ: 175.3, 156.2, 154.4, 141.4, 135.3, 130.3, 128.3, 126.2, 125.3, 122.7, 120.1, 119.9, 118.2. MS (EI): m/z (%) = 266 ([M+2], 66), 264 (M+, 100), 236 (26), 173 (12).

6-Chloro-2-fluoro-9H-xanthen-9-one (2o)
White solid. mp 212-212.7 °C. IR (KBr): 3084, 1665, 1604, 1446, 1294, 1075, 819, 773 cm\(^{-1}\). 1H NMR (400 MHz, CDCl3) δ: 8.60 (dd, J = 8.0, 1.2 Hz, 2H), 7.63-7.60 (m, 4H), 7.57-7.54 (m, 2H), 7.49-7.46 (m, 2H). 13C NMR (100 MHz, CDCl3) δ: 179.6, 137.10 (2C), 132.1 (2C), 129.7 (2C), 126.1 (2C), 125.8 (2C). MS (EI): m/z (%) = 212 (50), 184 (M+, 100), 152 (18), 139 (24).

9H-Thioxanthen-9-one (4a)
Yellow solid. mp 219-220 °C (Lit., mp 219-220 °C). IR (KBr): 1644, 1591, 1435, 1320, 731 cm\(^{-1}\). 1H NMR (400 MHz, CDCl3) δ: 8.60 (d, J = 8.8 Hz, 1H), 8.41 (s, 1H), 7.60-7.54 (m, 4H). 13C NMR (100 MHz, CDCl3) δ: 179.6, 137.10 (2C), 132.1 (2C), 129.7 (2C), 129.0 (2C), 126.1 (2C), 125.8 (2C). MS (EI): m/z (%) = 212 (50), 184 (M+, 100), 152 (18), 139 (24).

2-Methyl-9H-thioxanthen-9-one (4b)
Yellow solid. mp 124-124.8 °C (Lit., mp 124-124 °C). IR (KBr): 3059, 2971, 2909, 1633, 1602, 1588, 1438, 1318, 748 cm\(^{-1}\). 1H NMR (400 MHz, CDCl3) δ: 8.60 (d, J = 8.8 Hz, 1H), 8.41 (s, 1H), 7.60-7.54 (m,
2H), 7.48-7.42 (m, 3H), 2.49 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 180.0, 137.5, 136.5, 134.2, 133.8, 132.2, 129.9, 129.7, 129.7, 129.3, 129.1, 126.2, 126.0, 21.6. MS (EI): m/z (%) = 226 (M$^+$, 100), 197 (24).

4-Methoxy-9$H$-thioxanthen-9-one (4c)

Yellow solid. mp 164.8-165.8 °C (Lit.,$^{31}$ mp 167-169 °C). IR (KBr): 3066, 3000, 2836, 1633, 1595, 1424, 1339, 1265, 735 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.59 (d, $J = 8.0$ Hz, 1H), 8.25 (d, $J = 8.0$ Hz, 1H), 7.66-7.58 (m, 2H), 7.49-7.41 (m, 2H), 7.13 (d, $J = 8.0$ Hz, 1H), 4.04 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 180.0, 154.5, 137.4, 132.3, 130.4, 129.8, 129.1, 127.7, 126.9, 126.4, 126.1, 121.9, 112.4, 56.8. MS (ESI): m/z = 242 (11), 226 (M$^+$, 100), 197 (35), 165 (14).

4-Chloro-9$H$-thioxanthen-9-one (4d)

Yellow solid. mp 169-172 °C (Lit.,$^{32}$ mp 175 °C). IR (KBr): 1650, 1459, 1403, 1318, 735 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.58-8.57 (m, 1H), 7.71 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.66-7.64 (m, 2H), 7.53-7.49 (m, 1H), 7.44 (t, $J = 8.0$ Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 179.7, 136.8, 136.7, 132.8, 131.2, 130.4, 130.0, 128.6, 128.5, 127.0, 126.7, 126.4. MS (ESI): m/z = 247 (M$^{+}$+1).

3-Chloro-5-methyl-9$H$-thioxanthen-9-one (4e)

Pale yellow solid. mp 183.5-184.8 °C. IR (KBr): 3073, 3053, 3013, 1632, 1582, 1380, 1317, 748 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.50 (d, $J = 8.4$ Hz, 1H), 8.47 (d, $J = 8.0$ Hz, 1H), 7.60 (d, $J = 2.0$ Hz, 1H), 7.49 (d, $J = 7.2$ Hz, 1H), 7.42-7.37 (m, 2H), 2.52 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 179.4, 138.7, 137.9, 135.8, 133.8, 133.4, 131.0, 129.1, 127.5, 127.0, 126.8, 125.7, 125.4, 19.4. HRMS (ESI): calcd for C$_{14}$H$_{10}$ClOS [M+H$^+$]: 261.0141, found: 261.0139.

6-Chloro-2-methyl-9$H$-thioxanthen-9-one (4f)

Pale yellow solid. mp 221-222 °C. IR (KBr): 3074, 3056, 3017, 2912, 1634, 1581, 1401, 1124, 769 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.52 (d, $J = 8.8$ Hz, 1H), 8.39 (s, 1H), 7.54 (d, $J = 2.0$ Hz, 1H), 7.45 (d, $J = 1.2$ Hz, 2H), 7.39 (dd, $J = 8.8$, 2.0 Hz, 1H), 2.49 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 178.9, 138.6, 136.6, 133.7, 133.3, 131.2, 129.4, 128.6, 127.4, 126.6, 125.6, 125.0, 21.3. HRMS (ESI): calcd for C$_{14}$H$_{10}$ClOS [M+H$^+$]: 261.0141, found: 261.0139.

3-Chloro-6-methoxy-9$H$-thioxanthen-9-one (4g)

Yellow solid. mp 182.5-183.8 °C. IR (KBr): 3073, 3053, 3013, 1632, 1582, 1317, 1102, 748 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.49 (d, $J = 8.8$ Hz, 1H), 8.46 (d, $J = 7.2$ Hz, 1H), 7.59 (d, $J = 2.0$ Hz, 1H), 7.48 (d, $J = 7.6$ Hz, 1H), 7.48-7.37 (m, 2H), 2.52 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 179.0, 138.6,
3,5-Dichloro-9H-thioxanthen-9-one (4h)

Pale yellow solid. mp 219-221 °C (Lit.,33 mp 255 °C). IR (KBr): 3081, 1638, 1583, 1402, 1311, 752 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.54 (dd, J = 8.0, 1.2 Hz, 1H), 8.50 (d, J = 8.8 Hz, 1H), 7.72 (dd, J = 7.6, 1.2 Hz, 1H), 7.64 (d, J = 1.2 Hz, 1H), 7.47-7.43 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ: 178.9, 139.6, 138.2, 136.1, 132.9, 131.5, 131.3, 130.5, 128.5, 127.6, 127.0, 126.6, 125.9. MS (ESI): m/z = 280 (M⁺).

ACKNOWLEDGEMENTS

We are grateful to the National Natural Science Foundation of China (No 20876147) and Natural Science Foundation of Zhejiang Province (No Y4090346) for financial support.

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