Synthesis of activated spirocyclopentanes via a cascade Michael/alkylation reaction of ethyl-4-chloro-3-oxobutanoate and 2-arylidene-1,3-indandiones

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Abstract
A cascade Michael/alkylation reaction of ethyl-4-chloro-3-oxobutanoate and 2-Arylidene-1,3-indandiones had been studied, providing a number of activated spirocyclopentanes in excellent yields (up to 96%) and diastereoselectivities (up to dr > 20:1). Different bases were evaluated and triethylamine was found to be the most efficient for this transformation under mild reaction.

Keywords: Cascade reaction, spirocyclopentanes, bases

Introduction
2-Arylidene-1,3-indandiones are mostly attractive Michael acceptors1-5 for the resulted substituted 1,3-indandiones had been widely found in many natural products with useful biological activities (Scheme 1).6-11 Among various 1,3-indandiones and their derivatives, multicyclic spiro-1,3-indandiones are especially valuable. For example, fredericamycin A was reported as an antitumor compound with antibiotic properties.8 Spiroheterocyclic dihydropyrrolo[2,1-a]isoquinolines B had potential pharmacological effects such as sedative, hypotensive and neuromuscular blocking activities.9 Biphenyl-based spirocyclic ketones C was widely used as new anticancer agents.11 Among the chemical synthesis methods of these useful bioactive compounds, the cascade reactions based on 1,3-indandione and its derivatives are extremely attractive in terms of efficiency and atomic economy.12-15 For example, Barbas III and co-workers developed a multicomponent reaction through combinations of Aldol, Wittig, Knoevenagel, Michael, Diels-Alder and Huisgen cycloaddition reactions, providing polycyclic spirotriones in good yields and diastereoselectivities.12 Li and co-workers reported a cascade
reaction of 1,3-indanedione for the synthesis of tricyclic spiro-1,3-indandiones.\textsuperscript{13} Ramachary and co-workers developed a cascade reaction of 2-Arylidene-indan-1,3-diones to synthesize drug-like cyclohexanes.\textsuperscript{14} Other examples such as the Knoevenagel/Diels-Alder/epimerization reaction of 1,3-indandione were also reported.\textsuperscript{15}

Despite the extensive efforts have been made, the synthesis of all carbon spiro-1,3-indandiones still presents a big challenge in organic synthesis.\textsuperscript{16-18} Recently, we have been interested in the organocatalytic synthesis of cyclic products via cascade/domino reactions.\textsuperscript{19-27} Herein, we report the cascade Michael/Alkylation reaction of ethyl-4-chloro-3-oxobutanoate and 2-Arylidene-1,3-indandiones, which provided activated spirocyclopentanes in excellent yields and diastereoselectivities.

Scheme 1. Multicyclic spiro-1,3-indandiones.

**Results and Discussion**

Firstly, the cascade Michael/Alkylation reactions of 2-Arylidene-1,3-indandiones 1a and ethyl-4-chloro-3-oxobutanoate 2 were examined in CH\textsubscript{2}Cl\textsubscript{2} at room temperature with different bases as the catalysts (Table 1). Initial screening of the reaction conditions demonstrated that the organic and inorganic base had a significant role to play in both reactivity and selectivity. Using the inorganic bases as the catalysts, the cascade Michael/Alkylation product 3a was obtained in low yields and diastereoselectivities (Table 1, entries 1-8). The spirocyclopentane 3a was achieved in good yields and diastereoselectivities by using the organic bases as the catalysts (Table 1, entries 9-12). Further investigation demonstrated that the Et\textsubscript{3}N was preferred in terms of the yield and diastereoselectivity (Table 1, entry 12). When the catalyst loading of Et\textsubscript{3}N was used to be 200 mol %, the highest yield (96%) and diastereoselectivity (95:5) was obtained (Table 1, entry 13).
Table 1. Base-catalyzed cascade Michael/Alkylation reaction of 1a with 2

\[
\begin{array}{cccc}
\text{Entry} & \text{Base} & \text{Time (h)} & \text{Dr}^b & \text{Yield}^c \\
1 & \text{KOH} & 6 & 60:40 & 32 \\
2 & \text{NaOH} & 6 & 61:39 & 36 \\
3 & \text{K}_2\text{CO}_3 & 8 & 65:35 & 41 \\
4 & \text{KHCO}_3 & 8 & 64:36 & 35 \\
5 & \text{Na}_2\text{CO}_3 & 8 & 68:32 & 38 \\
6 & \text{NaHCO}_3 & 8 & 65:35 & 31 \\
7 & \text{LiOAc} & 24 & 70:30 & 42 \\
8 & \text{NaOAc} & 24 & 70:30 & 33 \\
9 & \text{DABCO} & 24 & 86:14 & 85 \\
10 & \text{DBU} & 4 & 85:15 & 84 \\
11 & \text{DMAP} & 6 & 88:12 & 86 \\
12 & \text{Et}_3\text{N} & 4 & 95:5 & 91 \\
13^d & \text{Et}_3\text{N} & 2 & 95:5 & 96 \\
\end{array}
\]

\(^a\) Reactions were carried out with 1a (0.1 mmol), 2 (0.12 mmol) and catalyst (0.1 mmol) in CH\(_2\)Cl\(_2\) (1 mL) at room temperature.

\(^b\) Determined by \(^1\)H NMR analysis of the crude product.

\(^c\) Isolated yields. \(^d\) 200% mol Et\(_3\)N was added.

To get a better reaction conditions, we next screened the effects of solvents (Table 2, entries 1-8). Among the solvents tested, CH\(_2\)Cl\(_2\) was found to be the best solvent to give the best yield and selectivity (Table 2, entries 7 and 8). A slightly lower yields but also excellent diastereoselectivity were observed with the solvents of CH\(_2\)Cl\(_2\) (Table 2, entry 6). Almost the same selectivities were obtained when reactions were performed at the solvents of acetone, THF and toluene (Table 2, entries 3-5). Reactions in MeOH or DMF afforded the desired product 3a in only low yield and selectivity (Table 2, entries 1 and 2).
Table 2. Screening of the solvent and temperature

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time(h)</th>
<th>Dr</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>24</td>
<td>70:30</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>24</td>
<td>68:32</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>Acetone</td>
<td>12</td>
<td>82:18</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>12</td>
<td>80:20</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>12</td>
<td>85:15</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>2</td>
<td>95:5</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>CHCl₃</td>
<td>2</td>
<td>98:2</td>
<td>98</td>
</tr>
<tr>
<td>8d</td>
<td>CHCl₃</td>
<td>12</td>
<td>98:2</td>
<td>95</td>
</tr>
</tbody>
</table>

a Reactions were carried out with 1a (0.1 mmol), 2 (0.12 mmol) and Et₃N (0.2 mmol, 56 uL) in solvent (1 mL) at RT.

b Determined by ¹H NMR analysis of the crude product.

c Isolated yields. d The reaction was carried out at 0 °C.

Under the optimized reaction condition, the Et₃N as base and CHCl₃ as the solvent were proved to be efficient for the synthesis of spirocyclopentanes (Table 3). For example, spirocyclopentanes 3 were obtained in excellent yields and diastereoselectivities by using different substrates such as aryl and heteroaryl-1,3-indandiones. The position of the substituents at the phenyl ring seems to have slightly effect on the yields and diastereoselectivities. As can be seen in table 3, the para-substitution generally resulted in better yields and diastereoselectivities, no matter electron-withdrawing or electron-donating groups were introduced (Table 3, entries 4, 6-8). In comparison, ortho-chloro and meta-chloro substituted 2-Arylidene-1,3-indandiones 1b and 1c afforded lower yields and diastereoselectivities (Table 3, entries 2-3). Similarly, ortho-methoxy substituted 2-arylidene-1,3-indandione 1e gave lower yields and diastereoselectivities than its para-substituted analog 1f (Table 3, entries 5 and 6). The 2-thiophenyl-1,3-indandione 1i provided the product in lower yield (91%, Table 3, entry 9). Disappointedly, no Michael/Alkylation product was obtained when the 2-furyl-1,3-indandione was used in the reaction.
Table 3  Synthesis of spirocyclopentanes 3 from a variety of 1,3-indandiones\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield(%)\textsuperscript{b}</th>
<th>Dr\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (1a)</td>
<td>98</td>
<td>98:2</td>
</tr>
<tr>
<td>2</td>
<td>2-Cl-C\textsubscript{6}H\textsubscript{4} (1b)</td>
<td>94</td>
<td>96:4</td>
</tr>
<tr>
<td>3</td>
<td>3-Cl-C\textsubscript{6}H\textsubscript{4} (1c)</td>
<td>90</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl-C\textsubscript{6}H\textsubscript{4} (1d)</td>
<td>98</td>
<td>98:2</td>
</tr>
<tr>
<td>5</td>
<td>2-MeO-C\textsubscript{6}H\textsubscript{4} (1e)</td>
<td>93</td>
<td>96:4</td>
</tr>
<tr>
<td>6</td>
<td>4-MeO-C\textsubscript{6}H\textsubscript{4} (1f)</td>
<td>97</td>
<td>98:2</td>
</tr>
<tr>
<td>7</td>
<td>4-F-C\textsubscript{6}H\textsubscript{4} (1g)</td>
<td>98</td>
<td>98:2</td>
</tr>
<tr>
<td>8</td>
<td>4-Br-C\textsubscript{6}H\textsubscript{4} (1h)</td>
<td>96</td>
<td>97:3</td>
</tr>
<tr>
<td>9\textsuperscript{d}</td>
<td>2-thionyl (1i)</td>
<td>91</td>
<td>96:4</td>
</tr>
<tr>
<td>10</td>
<td>2-furyl</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions were carried out with 1 (0.1 mmol), 2 (0.12 mmol) and Et\textsubscript{3}N (0.2 mmol) in CHCl\textsubscript{3} (1 mL) at RT for 2 h.

\textsuperscript{b} Isolated yields. \textsuperscript{c} Determined by \textsuperscript{1}H NMR.

\textsuperscript{d} The reaction was carried out at room temperature for 8 h.

After the success of Michael/Alkylation reaction of ethyl-4-chloro-3-oxobutanoate, the reaction of ethyl-4-bromo-3-oxobutanoate with 2-Arylidene-1,3-indandione 1a was also studied. Disappointedly, only moderate yield and diastereoselectivity were obtained in comparison with ethyl-4-chloro-3-oxobutanoate (Scheme 2). Further studies are in progress in our group.

Scheme 2. Reaction of ethyl-4-bromo-3-oxobutanoate and 2-Arylidene-1,3-indandione 1a.

The product 3a could be readily decarboxylationed by concentrated hydrochloric acid. The treatment of 3a with concentrated hydrochloric acid in water provided activated spirocyclopentane 4 in excellent yield and diastereoselectivity (Scheme 3).
Scheme 3. Transformation of 3a to spirocyclopentane 4.

An asymmetric version of this reaction was also studied by using diphenyl-L-prolinol as the catalyst, but only moderate yield and low enantioselectivity were achieved (Scheme 4). Further studies are also in progress in our group.

Scheme 4. Asymmetric reaction of Ethyl-4-chloro-3-oxobutanoate and 2-Arylidene-1,3-indandione.

A proposed mechanism for the cascade Michael/Alkylation reaction is illustrated in Scheme 5. The possible catalytic Michael/Alkylation reaction may go through three main steps: (a) the deprotonation of ethyl-4-chloro-3-oxobutanoate by triethylamine gives the alpha-carbon anion; (b) the Michael addition of the ethyl-4-chloro-3-oxobutanoate to 2-Arylidene-1,3-indandiones; (c) intramolecular cyclization afforded spirocyclopentanes 3a in excellent yield.

Scheme 5. Possible mechanism for the cascade Michael/alkylation reaction.
Conclusions

We have developed a cascade Michael/Alkylation reaction of ethyl-4-chloro-3-oxobutanoate and 2-Arylidene-1,3-indandiones, providing a number of activated spirocyclopentanes in excellent yields (up to 96%) and diastereoselectivities (up to dr > 20:1).

Experimental Section

General. $^1$H NMR and $^{13}$C NMR spectra were recorded on Bruker AVANCE 400 spectrometer. Chemical shifts of protons are reported in parts per million downfield from tetramethylsilane ($\delta = 0$). Chemical shifts of carbon are referenced to the central peak of the solvent (CDCl$_3$, $\delta = 77.0$). Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). Optical rotations were measured on a Perkin-Elmer 341 digital polarimeter. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. The high resolution mass spectroscopic data were obtained with Shimadzu LCMS-IT-TOF spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as follows: frequency of absorption (cm$^{-1}$), intensity of absorption (s = strong, m = medium, w = weak). Enantiomeric excesses were determined by HPLC using a Daicel Chiralpak OD-H column and eluting with a hexane/i-PrOH solution. Flash chromatography was performed over silica gel (230-400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Commercially available reagents and analytical grade solvents were used without further purification. 2-Arylidene-1,3-indandiones were prepared according to reported procedures.$^{28}$

Typical procedure for asymmetric synthesis of spirocyclopentanes

A solution of 1a (23.4 mg, 0.1 mmol) and 2 (16.4 mg, 0.12 mmol) in CHCl$_3$ (1 mL) was stirred at room temperature for 10 min. Then, Et$_3$N (56 uL) was added. The reaction solution was stirred at room temperature for 2 h. Then, the solvent was evaporated under vacuum, and the residue was purified by flash column chromatography over silica gel (petroleum ether/EtOAc 3/1) to give product 3a as a white solid.

Ethyl 1',3',4-trioxo-2-phenyl-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carboxylate (3a). White solid, mp 134.5-135.6 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.89-7.88 (m, 1H), 7.73-7.70 (m, 3H), 7.06-7.03 (m, 5H), 4.46 (d, $J$ 13.6 Hz, 1H), 4.40 (d, $J$ 13.6 Hz, 1H), 4.21-4.11 (m, 2H), 2.99 (d, $J$ 18.4 Hz, 1H), 2.69 (d, $J$ 18.4 Hz, 1H), 1.23-1.20 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 205.0, 201.9, 199.9, 167.4, 142.3, 141.5, 136.1, 136.0, 133.7, 128.6, 128.1, 127.5, 123.2, 123.1, 61.8, 60.0, 57.7, 53.0, 43.8, 14.1; IR (thin film) $\nu$/cm$^{-1}$: 1706 (w), 1599 (s), 1562 (s), 1432 (m), 1384 (s), 1075 (m); HRMS (ESI) calcd for C$_{22}$H$_{18}$NaO$_5$ (M+Na)$^+$: 385.1046, found: 385.1041.
carboxylate (3b). White solid, mp 132.9-134.7 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.93 (d, J 7.6 Hz, 1H), 7.76-7.67 (m, 3H), 7.24-7.20 (m, 1H), 7.08-7.05 (m, 2H), 6.96 (t, J 7.6 Hz, 1H), 5.07 (d, J 13.6 Hz, 1H), 4.30 (d, J 13.2 Hz, 1H), 4.17-4.14 (m, 2H), 2.69 (d, J 7.8 Hz, 1H), 1.24 (t, J 7.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 204.4, 201.9, 198.4, 166.7, 142.3, 141.3, 136.1, 136.0, 134.8, 131.8, 130.0, 129.1, 128.0, 126.9, 123.4, 122.9, 61.9, 59.8, 59.2, 47.9, 42.9, 14.0; IR (thin film) ν/cm⁻¹: 2925 (w), 1598(s), 1581 (s), 1434 (m), 1384 (s), 1077 (m), 719 (m); HRMS (ESI) calcd for C₂₂H₁₇ClNaO₅ (M+Na)⁺: 419.0657, found: 419.0661.

Ethyl-2-(3-chlorophenyl)-1',3',4-trioxo-1,3'-dihydropyro[cyclopentane-1,2'-indene]-3-carboxylate (3c). White solid, mp 139.2-140.8 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.92 (d, J 7.6 Hz, 1H), 7.78-7.74 (m, 3H), 7.05-6.96 (m, 4H), 4.41 (d, J 13.6 Hz, 1H), 4.36 (d, J 13.6 Hz, 1H), 4.20-4.15 (m, 2H), 2.98 (d, J 18.4 Hz, 1H), 2.69 (d, J 18.4 Hz, 1H), 1.24 (t, J 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 204.2, 201.6, 199.5, 167.1, 142.2, 141.4, 136.4, 136.3, 135.9, 134.6, 129.9, 128.4, 127.8, 123.3, 123.2, 61.9, 57.9, 57.6, 52.2, 43.9, 41.1; IR (thin film) ν/cm⁻¹: 2926 (w), 1706(w), 1597(s), 1561 (s), 1434 (m), 1384 (s), 1076 (m); HRMS (ESI) calcd for C₂₂H₁₇ClNaO₅ (M+Na)⁺: 419.0657, found: 419.0648.

Ethyl-2-(4-chlorophenyl)-1',3',4-trioxo-1,3'-dihydropyro[cyclopentane-1,2'-indene]-3-carboxylate (3d). White solid, mp 127.5-129.1 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.90 (d, J 7.2 Hz, 1H), 7.78-7.50 (m, 3H), 7.06-7.00 (m, 4H), 4.42 (d, J 13.6 Hz, 1H), 4.37 (d, J 14.0 Hz, 1H), 4.19-4.14 (m, 2H), 2.97 (d, J 18.4 Hz, 1H), 2.68 (d, J 18.4 Hz, 1H), 1.23 (t, J 7.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 204.3, 201.8, 199.7, 167.2, 142.2, 141.4, 136.4, 136.3, 134.0, 132.4, 129.0, 128.9, 123.4, 123.2, 61.9, 60.0, 57.8, 52.0, 44.1, 14.1; IR (thin film) ν/cm⁻¹: 2925 (w), 1704(w), 1596(s), 1561 (s), 1434 (m), 1384 (s), 1076 (m); HRMS (ESI) calcd for C₂₂H₁₇ClNaO₅ (M+Na)⁺: 419.0657, found: 419.0653.

Ethyl-2-(2-methoxyphenyl)-1',3',4-trioxo-1,3'-dihydropyro[cyclopentane-1,2'-indene]-3-carboxylate (3e). Light yellow solid, mp 124.1-125.8 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.91 (d, J 7.6 Hz, 1H), 7.72 (br, 1H), 7.61 (br, 1H), 7.54 (d, J 7.6 Hz, 1H), 7.10 (d, J 7.6 Hz, 1H), 6.99 (br, 1H), 6.79 (br, 1H), 6.36 (d, J 8.0 Hz, 1H), 4.73 (d, J 14.0 Hz, 1H), 4.45 (d, J 13.6 Hz, 1H), 4.17-4.14 (m, 2H), 3.49 (s, 3H), 3.10 (d, J 18.8 Hz, 1H), 2.73 (d, J 18.8 Hz, 1H), 1.22 (t, J 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 205.9, 201.7, 198.3, 167.4, 156.7, 142.8, 140.7, 135.5, 135.4, 129.0, 127.0, 122.7, 122.3, 121.9, 120.5, 109.5, 61.7, 59.5, 57.4, 54.1, 46.4, 42.4, 14.1; IR (thin film) ν/cm⁻¹: 1705(w), 1598(s), 1562 (s), 1432(m), 1354 (m), 1075 (m); HRMS (ESI) calcd for C₂₃H₂₀NaO₅ (M+Na)⁺: 415.1152, found: 415.1146.

Ethyl-2-(4-methoxyphenyl)-1',3',4-trioxo-1,3'-dihydropyro[cyclopentane-1,2'-indene]-3-carboxylate (3f). Light yellow solid, mp 112.8-114.2 °C; ¹H NMR (400 MHz, CDCl₃) δ: 7.88 (d, J 1.6 Hz, 1H), 7.75-7.72 (m, 3H), 6.98 (d, J 8.8 Hz, 2H), 6.58 (d, J 8.8 Hz, 2H), 4.41 (d, J 13.6 Hz, 1H), 4.35 (d, J 13.6 Hz, 1H), 4.18-4.13 (m, 2H), 3.62 (s, 3H), 2.97 (d, J 18.4 Hz, 1H), 2.67 (d, J 18.4 Hz, 1H), 1.22 (t, J 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ: 205.1, 202.2, 200.1, 167.5, 159.2, 142.3, 141.6, 136.1, 136.0, 128.7, 125.6, 123.2, 123.1, 113.9, 61.7, 60.1, 58.0, 55.0, 52.4, 43.9, 14.1; IR (thin film) ν/cm⁻¹: 1704(w), 1562(s), 1515 (s), 1354 (m), 1076 (m), 862 (m); HRMS (ESI) calcd for C₂₃H₂₀NaO₅ (M+Na)⁺: 415.1152, found: 415.1145.
Ethyl-2-(4-fluorophenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carboxylate (3g). Light yellow solid, mp 154.7-156.5 °C; \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.91 (d, \(J = 6.8\) Hz, 1H), 7.80-7.75 (m, 3H), 7.06-7.00 (m, 4H), 4.42 (d, \(J = 13.6\) Hz, 1H), 4.37 (d, \(J = 14.0\) Hz, 1H), 4.19-4.14 (m, 1H), 2.97 (d, \(J = 18.4\) Hz, 1H); \(^{13}^C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\): 204.3, 201.8, 199.7, 167.2, 142.2, 141.4, 136.4, 136.3, 134.0, 132.9, 129.0, 128.8, 123.4, 123.2, 114.0, 112.4, 61.9, 60.0, 57.8, 52.0, 44.1, 14.1; IR (thin film) \(\nu/cm^-1\): 1704(w), 1599(s), 1562 (s), 1433(m), 1354 (m), 1075 (m), 863 (m); HRMS (ESI) calcd for C\(_{22}\)H\(_{17}\)FNaO\(_5\) (M+Na)\(^+\): 403.0952, found: 403.0963.

Ethyl-2-(4-bromophenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carboxylate (3h). White solid, mp 144.9-146.5 °C; \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.83 (d, \(J = 6.4\) Hz, 1H), 7.71-7.68 (m, 3H), 7.13 (d, \(J = 8.4\) Hz, 2H), 6.88 (d, \(J = 8.4\) Hz, 2H), 4.34 (d, \(J = 13.6\) Hz, 1H), 4.29 (d, \(J = 14.0\) Hz, 1H), 4.12-4.07 (m, 2H), 2.89 (d, \(J = 18.4\) Hz, 1H), 2.61 (d, \(J = 18.4\) Hz, 1H), 1.16 (t, \(J = 6.8\) Hz, 3H); \(^{13}^C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\): 204.3, 201.7, 199.7, 167.2, 142.2, 141.4, 136.4, 136.3, 132.9, 129.3, 123.4, 123.3, 122.2, 61.9, 59.6, 57.7, 52.0, 44.2, 14.1; IR (thin film) \(\nu/cm^-1\): 1704(w), 1598(s), 1563 (s), 1433(m), 1354 (m), 1057 (m), 863 (m); HRMS (ESI) calcd for C\(_{22}\)H\(_{17}\)BrNaO\(_5\) (M+Na)\(^+\): 463.0152, found: 463.0144, 465.0134.

Ethyl-1',3',4-trioxo-2-(thiophen-2-yl)-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carboxylate (3i). Yellow solid, mp 112.4-113.8 °C; \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.96 (d, \(J = 7.2\) Hz, 1H), 7.83-7.77 (m, 3H), 6.94 (d, \(J = 4.8\) Hz, 1H), 6.76 (d, \(J = 3.2\) Hz, 1H), 6.69 (t, \(J = 4.8\) Hz, 1H), 4.66 (d, \(J = 13.2\) Hz, 1H), 4.35 (d, \(J = 13.2\) Hz, 1H), 4.25-4.16 (m, 2H), 2.97 (d, \(J = 18.4\) Hz, 1H), 2.68 (d, \(J = 18.4\) Hz, 1H), 2.33 (t, \(J = 6.8\) Hz, 3H); \(^{13}^C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\): 204.0, 201.7, 199.7, 167.1, 141.6, 136.6, 136.2, 136.1, 126.8, 126.3, 125.0, 123.4, 123.3, 61.9, 59.7, 59.6, 48.0, 44.1, 14.1; IR (thin film) \(\nu/cm^-1\): 1705(w), 1597(s), 1561 (s), 1433(m), 1384 (m), 1076 (m), 619(m); HRMS (ESI) calcd for C\(_{22}\)H\(_{16}\)SNaO\(_5\) (M+Na)\(^+\): 391.0611, found: 391.0605.

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