

# 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

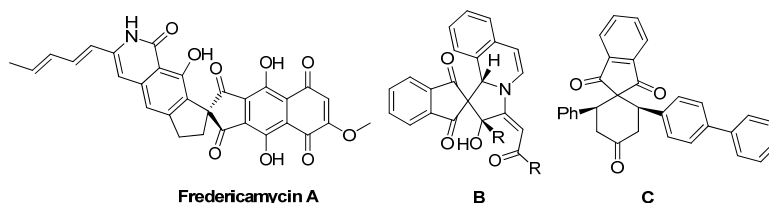
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## Introduction

2-Arylidene-1,3-indandiones are mostly attractive Michael acceptors<sup>1-5</sup> for the resulted substituted 1,3-indandiones had been widely found in many natural products with useful biological activities (Scheme 1).<sup>6-11</sup> 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.<sup>8</sup> Spiroheterocyclic dihydropyrrolo[2,1-*a*]isoquinolines **B** had potential pharmacological effects such as sedative, hypotensive and neuromuscular blocking activities.<sup>9</sup> Biphenyl-based spirocyclic ketones **C** was widely used as new anticancer agents.<sup>11</sup> 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.<sup>12-15</sup> 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.<sup>12</sup> Li and co-workers reported a cascade

reaction of 1,3-indanedione for the synthesis of tricyclic spiro-1,3-indandiones.<sup>13</sup> Ramachary and co-workers developed a cascade reaction of 2-Arylidene-indan-1,3-diones to synthesize drug-like cyclohexanes.<sup>14</sup> Other examples such as the Knoevenagel/Diels-Alder/ epimerization reaction of 1,3-indandione were also reported.<sup>15</sup>

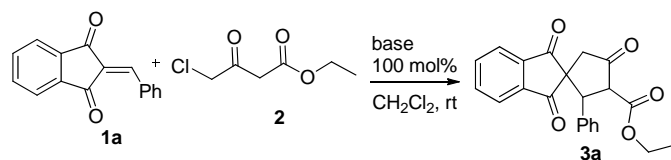
Despite the extensive efforts have been made, the synthesis of all carbon spiro-1,3-indandiones still presents a big challenge in organic synthesis.<sup>16-18</sup> Recently, we have been interested in the organocatalytic synthesis of cyclic products *via* cascade/domino reactions.<sup>19-27</sup> Herein, 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  $\text{CH}_2\text{Cl}_2$  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  $\text{Et}_3\text{N}$  was preferred in terms of the yield and diastereoselectivity (Table 1, entry 12). When the catalyst loading of  $\text{Et}_3\text{N}$  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**<sup>a</sup>

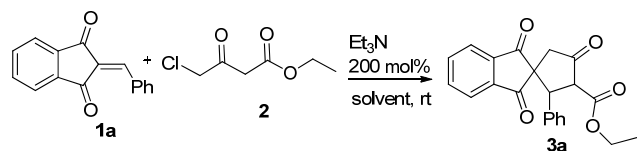
| Entry           | Base                            | Time (h) | Dr <sup>b</sup> | Yield (%) <sup>c</sup> |
|-----------------|---------------------------------|----------|-----------------|------------------------|
| 1               | KOH                             | 6        | 60:40           | 32                     |
| 2               | NaOH                            | 6        | 61:39           | 36                     |
| 3               | K <sub>2</sub> CO <sub>3</sub>  | 8        | 65:35           | 41                     |
| 4               | KHCO <sub>3</sub>               | 8        | 64:36           | 35                     |
| 5               | Na <sub>2</sub> CO <sub>3</sub> | 8        | 68:32           | 38                     |
| 6               | NaHCO <sub>3</sub>              | 8        | 65:35           | 31                     |
| 7               | LiOAc                           | 24       | 70:30           | 42                     |
| 8               | NaOAc                           | 24       | 70:30           | 33                     |
| 9               | DABCO                           | 24       | 86:14           | 85                     |
| 10              | DBU                             | 4        | 85:15           | 84                     |
| 11              | DMAP                            | 6        | 88:12           | 86                     |
| 12              | Et <sub>3</sub> N               | 4        | 95:5            | 91                     |
| 13 <sup>d</sup> | Et <sub>3</sub> N               | 2        | 95:5            | 96                     |

<sup>a</sup> Reactions were carried out with **1a** (0.1 mmol), **2** (0.12 mmol) and catalyst (0.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at room temperature.

<sup>b</sup> Determined by <sup>1</sup>H NMR analysis of the crude product.

<sup>c</sup> Isolated yields. <sup>d</sup> 200% mol Et<sub>3</sub>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, CHCl<sub>3</sub> 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<sub>2</sub>Cl<sub>2</sub> (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<sup>a</sup>

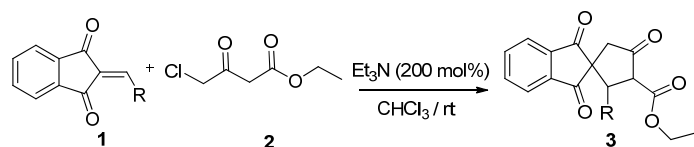
| Entry          | Solvent                  | Time(h) | Dr <sup>b</sup> | Yield(%) <sup>c</sup> |
|----------------|--------------------------|---------|-----------------|-----------------------|
| 1              | MeOH                     | 24      | 70:30           | 38                    |
| 2              | DMF                      | 24      | 68:32           | 29                    |
| 3              | Acetone                  | 12      | 82:18           | 76                    |
| 4              | THF                      | 12      | 80:20           | 69                    |
| 5              | Toluene                  | 12      | 85:15           | 90                    |
| 6              | $\text{CH}_2\text{Cl}_2$ | 2       | 95:5            | 96                    |
| 7              | $\text{CHCl}_3$          | 2       | 98:2            | 98                    |
| 8 <sup>d</sup> | $\text{CHCl}_3$          | 12      | 98:2            | 95                    |

<sup>a</sup> Reactions were carried out with **1a** (0.1 mmol), **2** (0.12 mmol) and  $\text{Et}_3\text{N}$  (0.2 mmol, 56  $\mu\text{L}$ ) in solvent (1 mL) at RT.

<sup>b</sup> Determined by  $^1\text{H}$  NMR analysis of the crude product.

<sup>c</sup> Isolated yields. <sup>d</sup> The reaction was carried out at 0 °C.

Under the optimized reaction condition, the  $\text{Et}_3\text{N}$  as base and  $\text{CHCl}_3$  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<sup>a</sup>

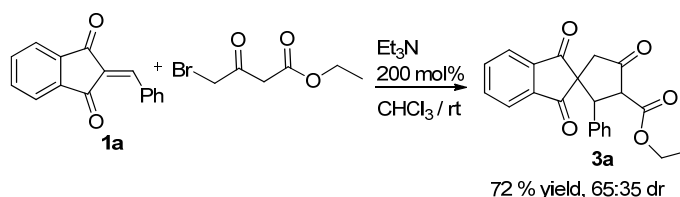
| Entry          | R   | Yield(%) <sup>b</sup> | Dr <sup>c</sup> |
|----------------|---|-----------------------|-----------------|
| 1              | Ph ( <b>1a</b> )                                  | 98                    | 98:2            |
| 2              | 2-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>1b</b> )  | 94                    | 96:4            |
| 3              | 3-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>1c</b> )  | 90                    | 95:5            |
| 4              | 4-Cl-C <sub>6</sub> H <sub>4</sub> ( <b>1d</b> )  | 98                    | 98:2            |
| 5              | 2-MeO-C <sub>6</sub> H <sub>4</sub> ( <b>1e</b> ) | 93                    | 96:4            |
| 6              | 4-MeO-C <sub>6</sub> H <sub>4</sub> ( <b>1f</b> ) | 97                    | 98:2            |
| 7              | 4-F-C <sub>6</sub> H <sub>4</sub> ( <b>1g</b> )   | 98                    | 98:2            |
| 8              | 4-Br-C <sub>6</sub> H <sub>4</sub> ( <b>1h</b> )  | 96                    | 97:3            |
| 9 <sup>d</sup> | 2-thionyl ( <b>1i</b> )                           | 91                    | 96:4            |
| 10             | 2-furyl   | -                     | -               |

<sup>a</sup> Reactions were carried out with **1** (0.1 mmol), **2** (0.12 mmol) and Et<sub>3</sub>N (0.2 mmol) in CHCl<sub>3</sub> (1 mL) at RT for 2 h.

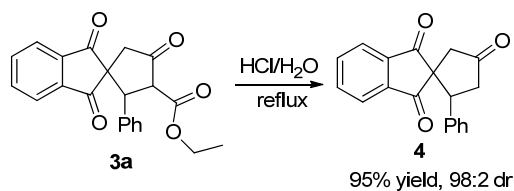
<sup>b</sup> Isolated yields. <sup>c</sup> Determined by <sup>1</sup>H NMR.

<sup>d</sup> 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.

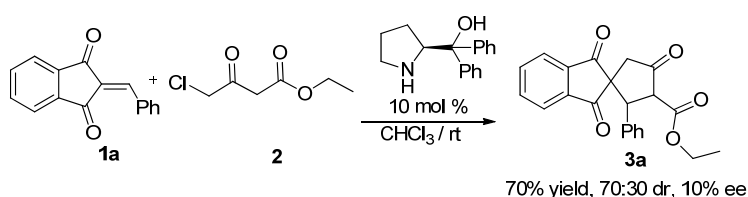
**Scheme 2.** Reaction of ethyl-4-bromo-3-oxobutanoate and 2-Arylidene-1,3-indandione **1a**.

The product **3a** could be readily decarboxylated 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).



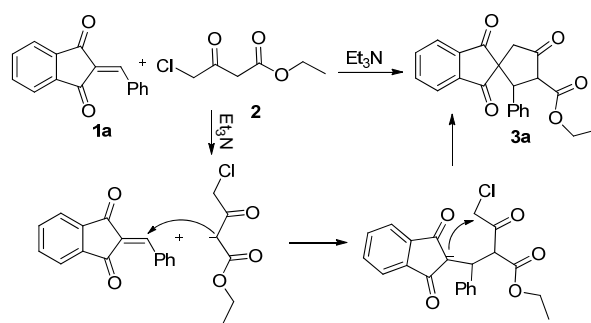
**Scheme 3.** Transformation of **3a** to spirocyclopentane **4**.

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).<sup>18</sup> 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.<sup>6</sup> 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.**  $^1\text{H}$  NMR and  $^{13}\text{C}$  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 ( $\text{CDCl}_3$ ,  $\delta = 77.0$ ). 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 ( $\text{cm}^{-1}$ ), 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.<sup>28</sup>

### 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  $\text{CHCl}_3$  (1 mL) was stirred at room temperature for 10 min. Then,  $\text{Et}_3\text{N}$  (56  $\mu\text{L}$ ) 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  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 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)  $\nu/\text{cm}^{-1}$ : 1706 (w), 1599 (s), 1562 (s), 1432 (m), 1384 (s), 1075 (m); HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{18}\text{NaO}_5$  ( $\text{M}+\text{Na}$ )<sup>+</sup>: 385.1046, found: 385.1041.

**Ethyl-2-(2-chlorophenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-**

**carboxylate (3b).** White solid, mp 132.9-134.7 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.93 (d, *J* 7.6 Hz, 1H), 7.76-7.62 (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), 4.18-4.11 (m, 2H), 3.12 (d, *J* 18.8 Hz, 1H), 2.76 (d, *J* 18.4 Hz, 1H), 1.21 (t, *J* 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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)  $\nu$ /cm<sup>-1</sup>: 2925 (w), 1598(s), 1561 (s), 1433 (m), 1384 (s), 1077 (m), 719 (m); HRMS (ESI) calcd for C<sub>22</sub>H<sub>17</sub>ClNaO<sub>5</sub> (M+Na)<sup>+</sup>: 419.0657, found: 419.0661.

**Ethyl-2-(3-chlorophenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carboxylate (3c).** White solid, mp 139.2-140.8 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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, 125.7, 123.3, 123.2, 61.9, 59.7, 57.6, 52.2, 43.9, 41.1; IR (thin film)  $\nu$ /cm<sup>-1</sup>: 2926 (w), 1706(w), 1597(s), 1561 (s), 1434 (m), 1384 (s), 1076 (m); HRMS (ESI) calcd for C<sub>22</sub>H<sub>17</sub>ClNaO<sub>5</sub> (M+Na)<sup>+</sup>: 419.0657, found: 419.0648.

**Ethyl-2-(4-chlorophenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carboxylate (3d).** White solid, mp 127.5-129.1 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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)  $\nu$ /cm<sup>-1</sup>: 2925 (w), 1704(w), 1596(s), 1561 (s), 1353 (m), , 1088 (m), 996 (m), 862(m); HRMS (ESI) calcd for C<sub>22</sub>H<sub>17</sub>ClNaO<sub>5</sub> (M+Na)<sup>+</sup>: 419.0657, found: 419.0653.

**Ethyl-2-(2-methoxyphenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carboxylate (3e).** Light yellow solid, mp 124.1-125.8 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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)  $\nu$ /cm<sup>-1</sup>: 1705(w), 1598(s), 1562 (s), 1432(m), 1354 (m), 1075 (m); HRMS (ESI) calcd for C<sub>23</sub>H<sub>20</sub>NaO<sub>5</sub> (M+Na)<sup>+</sup>: 415.1152, found: 415,1146

**Ethyl-2-(4-methoxyphenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carboxylate (3f).** Light yellow solid, mp 112.8-114.2 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) 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)  $\nu$ /cm<sup>-1</sup>: 1704(w), 1562(s), 1515 (s), 1354 (m), 1076 (m), 862 (m); HRMS (ESI) calcd for C<sub>23</sub>H<sub>20</sub>NaO<sub>5</sub> (M+Na)<sup>+</sup>: 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; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 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, 2H), 2.97 (d, *J* 18.4 Hz, 1H), 2.68 (d, *J* 18.4 Hz, 1H), 1.23 (t, *J* 7.2 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 204.3, 201.8, 199.7, 167.2, 142.2, 141.4, 136.4, 136.3, 134.0, 132.4, 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)  $\nu/\text{cm}^{-1}$ : 1704(w), 1599(s), 1562 (s), 1433(m), 1354 (m), 1075 (m), 863 (m); HRMS (ESI) calcd for C<sub>22</sub>H<sub>17</sub>FN<sub>3</sub>O<sub>5</sub> (M+Na)<sup>+</sup>: 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; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 204.3, 201.7, 199.7, 167.2, 142.2, 141.4, 136.4, 136.3, 132.9, 131.8, 129.3, 123.4, 123.3, 122.2, 61.9, 59.6, 57.7, 52.0, 44.2, 14.1; IR (thin film)  $\nu/\text{cm}^{-1}$ : 1704(w), 1598(s), 1563 (s), 1433(m), 1354 (m), 1057 (m), 863 (m); HRMS (ESI) calcd for C<sub>22</sub>H<sub>17</sub>BrN<sub>3</sub>O<sub>5</sub> (M+Na)<sup>+</sup>: 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; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 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), 1.26 (t, *J* 6.8 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 204.0, 201.7, 199.5, 167.1, 142.5, 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)  $\nu/\text{cm}^{-1}$ : 1705(w), 1597(s), 1561 (s), 1433(m), 1384 (m), 1076 (m), 619(m); HRMS (ESI) calcd for C<sub>22</sub>H<sub>16</sub>SN<sub>3</sub>O<sub>5</sub> (M+Na)<sup>+</sup>: 391.0611, found: 391.0605.

**Ethyl-1',3',4-trioxo-2-(thiophen-2-yl)-1',3'-dihydrospirocyclopentane-1,2'-indene (4).** White solid, mp 122.4-123.6 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.81 (d, *J* 7.2 Hz, 1H), 7.65-7.60 (m, 3H), 6.99-6.95 (m, 5H), 3.94 (q, *J* 13.6 Hz, *J* 8.0 Hz, 1H), 3.27-3.24 (br, 1H), 2.82 (d, *J* 18.4 Hz, 1H), 2.78-2.66 (br, 1H), 2.56 (d, *J* 18.4 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 201.1, 200.0, 197.0, 141.2, 140.6, 135.0, 134.8, 134.2, 127.5, 126.9, 126.5, 122.1, 122.0, 61.1, 49.3, 43.2, 40.7; IR (thin film)  $\nu/\text{cm}^{-1}$ : 1704(w), 1587(s), 1563 (s), 1431(m), 1380 (m), 619(m); HRMS (ESI) calcd for C<sub>19</sub>H<sub>14</sub>N<sub>3</sub>O<sub>3</sub> (M+Na)<sup>+</sup>: 313.0835, found: 313.0845.

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