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.¹³ Ramachary and co-workers developed a cascade reaction of 2-Arylidene-indan-1,3-diones to synthesize drug-like cyclohexanes.¹⁴ Other examples such as the Knoevenagel/Diels-Alder/ epimerization reaction of 1,3-indandione were also reported.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.¹⁶⁻¹⁸ Recently, we have been interested in the organocatalytic synthesis of cyclic products *via* cascade/domino reactions.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_2Cl_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_3N was preferred in terms of the yield and diastereoselectivity (Table 1, entry 12). When the catalyst loading of Et_3N 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**^a

Entry	Base	Time (h)	Dr ^b	Yield (%) ^c
1	KOH	6	60:40	32
2	NaOH	6	61:39	36
3	K ₂ CO ₃	8	65:35	41
4	KHCO ₃	8	64:36	35
5	Na ₂ CO ₃	8	68:32	38
6	NaHCO ₃	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 ₃ N	4	95:5	91
13 ^d	Et ₃ N	2	95:5	96

^a Reactions were carried out with **1a** (0.1 mmol), **2** (0.12 mmol) and catalyst (0.1 mmol) in CH₂Cl₂ (1 mL) at room temperature.

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

^c Isolated yields. ^d 200% mol Et₃N was added.

To get a better reaction conditions, we next screened the effects of solvents (Table 2, entries 1-8). Among the solvents tested, CHCl₃ 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 CH₂Cl₂ (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^a

Entry	Solvent	Time(h)	Dr ^b	Yield(%) ^c
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	CH ₂ Cl ₂	2	95:5	96
7	CHCl ₃	2	98:2	98
8 ^d	CHCl ₃	12	98:2	95

^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^a

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

^a Reactions were carried out with **1** (0.1 mmol), **2** (0.12 mmol) and Et₃N (0.2 mmol) in CHCl₃ (1 mL) at RT for 2 h.

^b Isolated yields. ^c Determined by ¹H NMR.

^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 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).¹⁸ 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 5.⁶ 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. ^1H 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_3N (56 μL) 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 $^\circ\text{C}$; ^1H NMR (400 MHz, CDCl_3) δ : 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) δ : 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) ν/cm^{-1} : 1706 (w), 1599 (s), 1562 (s), 1432 (m), 1384 (s), 1075 (m); HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{18}\text{NaO}_5$ ($\text{M}+\text{Na}$) $^+$: 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; ^1H NMR (400 MHz, CDCl_3) 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); ^{13}C NMR (100 MHz, CDCl_3) 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), 1561 (s), 1433 (m), 1384 (s), 1077 (m), 719 (m); HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{ClNaO}_5$ ($\text{M}+\text{Na}$) $^+$: 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; ^1H NMR (400 MHz, CDCl_3) 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); ^{13}C NMR (100 MHz, CDCl_3) 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) ν/cm^{-1} : 2926 (w), 1706(w), 1597(s), 1561 (s), 1434 (m), 1384 (s), 1076 (m); HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{ClNaO}_5$ ($\text{M}+\text{Na}$) $^+$: 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; ^1H NMR (400 MHz, CDCl_3) 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); ^{13}C NMR (100 MHz, CDCl_3) 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), 1353 (m), , 1088 (m), 996 (m), 862(m); HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{17}\text{ClNaO}_5$ ($\text{M}+\text{Na}$) $^+$: 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; ^1H NMR (400 MHz, CDCl_3) 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); ^{13}C NMR (100 MHz, CDCl_3) 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 $\text{C}_{23}\text{H}_{20}\text{NaO}_5$ ($\text{M}+\text{Na}$) $^+$: 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; ^1H NMR (400 MHz, CDCl_3) 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); ^{13}C NMR (100 MHz, CDCl_3) 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 $\text{C}_{23}\text{H}_{20}\text{NaO}_5$ ($\text{M}+\text{Na}$) $^+$: 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; ¹H NMR (400 MHz, CDCl₃) 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); 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, 128.8, 123.4, 123.2, 114.0, 112.4, 61.9, 60.0, 57.8, 52.0, 44.1, 14.1; IR (thin film) ν /cm⁻¹: 1704(w), 1599(s), 1562 (s), 1433(m), 1354 (m), 1075 (m), 863 (m); HRMS (ESI) calcd for C₂₂H₁₇FN₃O₅ (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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) ν /cm⁻¹: 1704(w), 1598(s), 1563 (s), 1433(m), 1354 (m), 1057 (m), 863 (m); HRMS (ESI) calcd for C₂₂H₁₇BrN₃O₅ (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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) ν /cm⁻¹: 1705(w), 1597(s), 1561 (s), 1433(m), 1384 (m), 1076 (m), 619(m); HRMS (ESI) calcd for C₂₂H₁₆SNaO₅ (M+Na)⁺: 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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) ν /cm⁻¹: 1704(w), 1587(s), 1563 (s), 1431(m), 1380 (m), 619(m); HRMS (ESI) calcd for C₁₉H₁₄NaO₃ (M+Na)⁺: 313.0835, found: 313.0845.

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