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# Stereoselective synthesis of dialkyl 3-spiroindanedione-1,2,3,3a-tetrahydropyrrolo[1,2-*a*]quinoline-1,2-dicarboxylates

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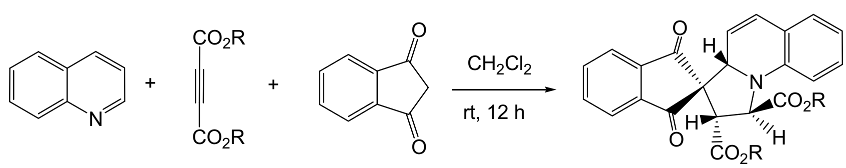
**Abstract**

The 1:1 intermediate generated by the addition of quinoline to dialkyl acetylenedicarboxylates is trapped by 1,3-indanedione to yield dialkyl 3-spiroindanedione-1,2,3,3a-tetrahydropyrrolo[1,2-*a*]quinoline-1,2-dicarboxylates in good yields. The structures of these products were confirmed by NMR and single-crystal X-ray diffraction studies.


*Keywords:* Quinoline; 4-Methylpyridine; *N*-Methylimidazole; Acetylenic esters; Spiro compound; 1,3-Indanedione

The quinoline moiety is present as a substructure in a broad range of biologically active compounds, most notably within anti-malaria agents.[1] Due to their biological importance, quinoline derivatives such as pyrroloquinolines have become synthetic targets of many organic and medicinal chemists.[2–7] The rich and fascinating chemistry that stems from the addition of nucleophiles to activated acetylenic compounds has evoked considerable interest. N-Heterocycles are known to form zwitterions with activated acetylene compounds such as dimethyl acetylenedicarboxylate.[8–10] These zwitterions can be trapped by a variety of electrophiles and proton donors, which is a novel protocol for the synthesis of heterocyclic compounds.[8–13]

In this Letter, we report the results of our studies involving the reactions of zwitterions derived from quinoline (**1**) and dialkyl acetylenedicarboxylates **2** in the presence of 1,3-indanedione (**3**), which constitutes a synthesis of dialkyl 3-spiroindanedion-1,2,3,3a-tetrahydropyrrolo[1,2-*a*]quinoline 1,2-dicarboxylates **4** (Scheme 1).[14]




**1** **2** **3** **4**

| **2, 4** | R | Yield/ % of **4** |
|---|---|---|
| **a** | Me | 90 |
| **b** | Et | 85 |
| **c** | $^t$Bu | 78 |

Scheme 1. Synthesis of compounds **4**.

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The structures of compounds **4a–c** were deduced from their elemental analyses and their IR, $^{1}H$ NMR and $^{13}C$ NMR spectra and a single-crystal X-ray analysis of one of them. For example, the $^{1}H$ NMR spectrum of **4a** exhibited five signals identified as methoxy ($\delta$ 3.50 and 3.88 ppm) and methine ($\delta$ 4.19, 4.87 and 5.03 ppm) protons, along with multiplets for the aromatic region. The $^{1}H$-decoupled $^{13}C$ NMR spectrum of **4a** showed 24 distinct resonances, which confirmed the proposed structure. The IR spectrum of **4a** displayed characteristic carbonyl bands (1752, 1725, 1720 and 1705 $cm^{-1}$). The $^{1}H$ NMR and $^{13}C$ NMR spectra of **4b** and **4c** were similar to those for **4a** except for the ester moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.

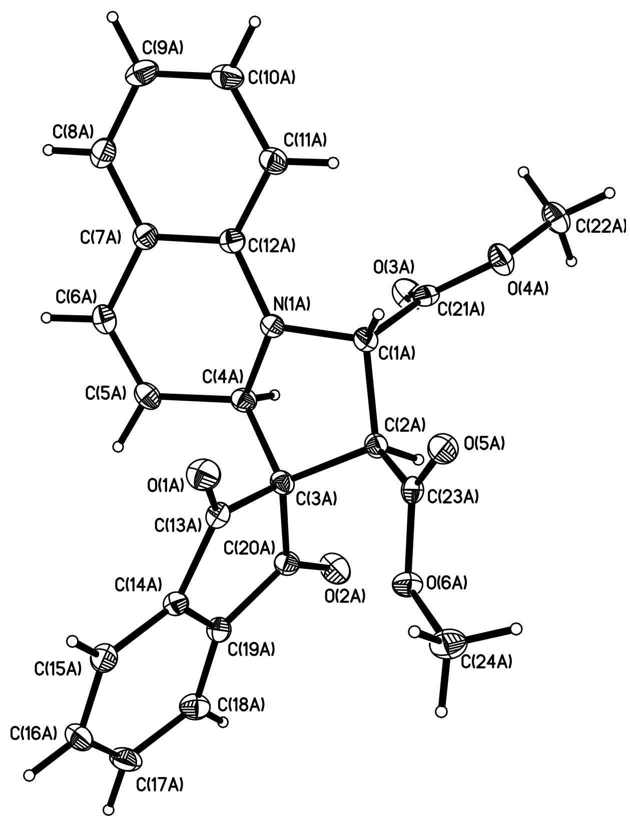



Fig. 1. X-ray crystal structure of **4a**. ORTEP-III plot;[15] arbitrary atom numbering.

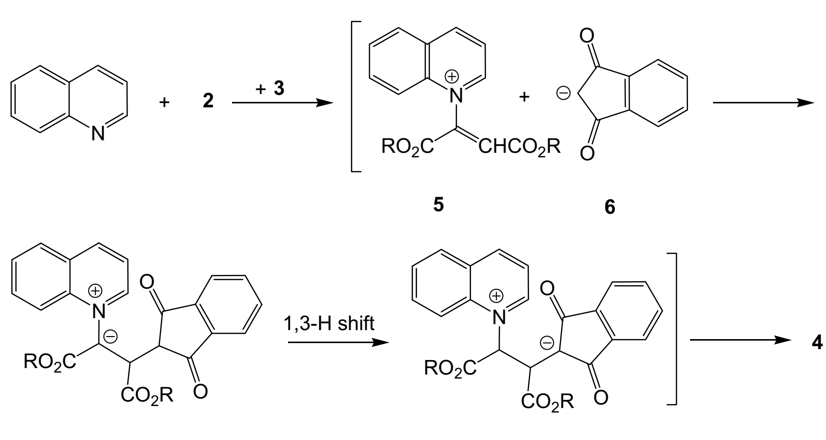
Unambiguous evidence for the structure and stereochemistry of **4a** was obtained from a single-crystal X-ray analysis. An ORTEP[15] diagram of **4a** is shown in Figure 1. There are four molecules of **4a** in the unit cell. The stereochemistry was deduced from the crystallographic data and the same configuration was assumed for the other derivatives on account of their NMR spectroscopic similarities.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation (Scheme 2). Presumably, the zwitterionic intermediate[8–10] formed from quinoline and the dialkyl acetylenedicarboxylates is protonated by **3** to furnish intermediate **5**, which is attacked by carbanion **6** to produce **7**. This intermediate is converted to product **4** via a 1,3-proton shift and cyclization.

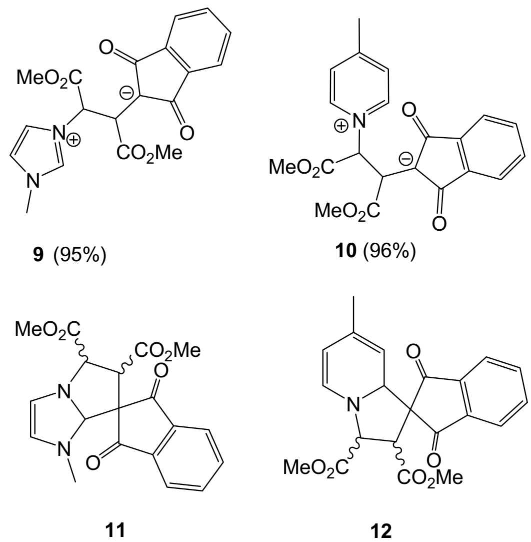
Under similar reaction conditions, *N*-methylimidazole and 4-methylpyridine produced 1,4-zwitterionic[16,17] compounds **9** and **10**, respectively (Scheme 3).[18]

The $^{1}H$ NMR spectrum of **9** exhibited four singlets identified as *N*-methyl ($\delta$ 2.50 ppm), methoxy ($\delta$ 3.53 and 3.73 ppm) and N–CH=N ($\delta$ 9.11 ppm) protons, along with two doublets ($\delta$ 4.26 and 5.92 ppm, $^{3}J = 8.9$ Hz) for the vicinal aliphatic methine protons. The $^{1}H$ NMR and $^{13}C$ NMR spectra of **10** were similar to those for **9** except for the heterocyclic moiety, which exhibited characteristic resonances in appropriate regions of the spectrum. Observation of a single resonance for the two keto groups of the 1,3-indanedione residue supports the open-chain structures for **9** and **10**. The keto groups in the corresponding cyclic structures **11** and **12** (Scheme 3) are diastereotopic and would exhibit two different resonances in the $^{13}C$ spectrum.

In summary, we have reported a transformation involving N-heterocycles and dialkyl acetylenedicarboxylates in




Scheme 2. Proposed mechanism for the formation of the compounds **4**.




Scheme 3. Structures of compounds **9** and **10**.

the presence of 1,3-indanedione, which affords a new route to the stereoselective synthesis of spiro compounds. The present procedure has the advantage that not only is the reaction performed under neutral conditions, but also the reactants can be mixed without any prior activation or modification.

## References and notes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14. *General procedure for the synthesis of compounds* **4**: A solution of 0.26 g of quinoline (2 mmol) in 5 mL of dry $CH_2Cl_2$ was added to a stirred solution of the dialkyl acetylenedicarboxylate (2 mmol) and 0.29 g of 1,3-indanedione (2 mmol) in 10 mL of dry $CH_2Cl_2$ at room temperature. The reaction mixture was then allowed to stir for 12 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using 4:1 *n*-hexane–EtOAc mixture as eluent to afford the pure product. Compound **4a**: red crystals, mp 216–218 °C, yield: 0.74 g (90%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 1752, 1725, 1720, 1705, 1634, 1592, 1250, 1229. MS (EI, 70 eV): $m/z$ (%) = 417 ($M^+$, 8), 358 (10), 326 (9), 298 (8), 273 (24), 241 (6), 201 (54), 170 (28), 149 (40), 143 (94), 129 (80), 128 (42), 77 (44), 76 (52), 59 (85), 43 (100). Anal. Calcd for $C_{24}H_{19}NO_6$ (417.41): C, 69.06; H, 4.59; N, 3.36. Found: C, 68.62; H, 4.43; N, 3.45. $^1$H NMR: $\delta$ 3.50 (3H, s, OMe), 3.88 (3H, s, OMe), 4.19 (1H, d, $^3J$ = 7.6 Hz, CH), 4.87 (1H, dd, $^3J$ = 10.0, 3.2 Hz, CH), 5.03 (1H, d, $^3J$ = 7.6 Hz, CH), 5.32–5.33 (1H, m, CH), 6.19 (1H, d, $^3J$ = 10.0 Hz, CH), 6.60–6.64 (2H, m, CH), 6.74 (1H, d, $^3J$ = 7.2 Hz, CH), 7.08–7.11 (1H, m, CH), 7.84–786 (2H, m CH), 7.92–7.93 (1H, m, CH), 8.03–8.05 (1H, m, CH). $^{13}$C NMR: $\delta$ 51.2 (OMe), 52.6 (OMe), 52.9 (N–CH), 64.0 (CH), 69.0 (CH), 67.4 (C), 110.1 (CH), 110.2 (CH), 115.5 (CH), 118.4 (CH), 118.6 (CH), 123.2 (C),123.3 (C), 127.6 (CH), 129.7 (CH), 130.3 (CH), 135.4 (C), 136.0 (C), 142.4 (CH), 143.0 (CH), 169.2 (C=O), 172.6 (C=O), 196.2 (C=O), 198.9 (C=O). X-ray crystal-structure determination of **4a**: structure-determination and refinement data: formula, $C_{24}H_{19}NO_6$, $M_r$ 417.40; crystal size, $0.30 \times 0.25 \times 0.16$ mm$^3$, crystal system, triclinic, $a = 12.3824(7)$, $b = 13.3569(7)$, $c = 13.4178(13)$ Å, $\alpha = 101.9490(10)°$, $\beta = 99.344(2)°$, $\gamma = 112.3360(10)°$, space group $P1$; $Z = 4$, $V = 1935.6(2)$ Å$^3$, $D_{calc} = 1.432$ g cm$^{-3}$; $R = 0.0456$ (for 6901 reflections), $R_w = 0.0789$; $-16 \leqslant h \leqslant 16$; $-18 \leqslant k \leqslant 18$;$-16 \leqslant l \leqslant 16$; Mo K$\alpha$ radiation ($\lambda = 0.71073$ Å); $T = 100(2)$ K. The crystallographic data of **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-628361. Copies of the data can be obtained, free of charge, via the internet (http://www.ccdc.cam.ac.uk/data_request/cif), e-mail (data_request@ccdc.cam.ac.uk), or fax (+44–1223–336033). Compound **4b**: red crystals, mp 225–227 °C, yield: 0.76 g (85%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 2930, 1731, 1708 1700, 1687, 1651, 1457, 1213, 1020. MS (EI, 70 eV): $m/z$ (%) = 445 ($M^+$, 6), 372 (12), 354 (9), 326 (6), 301 (28), 256 (8), 215 (50), 170 (25), 164 (40), 143 (96), 129 (75), 128 (44), 77 (48), 76 (46), 73 (65), 57 (100). Anal. Calcd for $C_{26}H_{23}NO_6$ (445.47): C, 70.10; H, 5.20; N, 3.14. Found: C, 69.93; H, 5.35; N, 3.32. $^1$H NMR: $\delta$ 0.83 (3H, t, $^3J$ = 6.9 Hz, Me), 1.35 (3H, t, $^3J$ = 6.9 Hz, Me), 3.86 (1H, dt, $^3J$ = 17.5, 6.9 Hz, CH), 3.97 (1H, dt, $^3J$ = 17.5, 6.9 Hz, CH), 4.13 (1H, d, $^3J$ = 7.4 Hz, CH), 4.32 (2H, d, $^3J$ = 7.3 Hz, CH), 4.88 (1H, br d, $^3J$ = 10.0 Hz, CH), 4.98 (1H, d, $^3J$ = 7.4 Hz, CH), 5.34 (1H, s, CH), 6.17 (1H, d, $^3J$ = 10.0 Hz, CH), 6.57–6.64 (2H, m, 2CH), 6.71 (1H, d, $^3J$ = 7.0 Hz, CH), 7.06 (1H, t, $^3J$ = 7.5 Hz, CH), 7.83 (2H, br s, 2CH), 7.90–8.07 (2H, m, 2CH). $^{13}$C NMR: $\delta$ 13.4 (Me), 14.1 (Me), 51.4 (CH), 61.7 (O–$CH_2$), 61.9 (O–$CH_2$), 64.2 (CH), 67.3 (C), 69.0 (CH), 110.1 (2 CH), 115.7 (CH), 118.3 (CH), 118.7 (CH), 123.1 (C), 123.3 (C), 127.6 (CH), 129.6 (CH), 130.3 (CH), 135.4 (C), 136.0 (C), 142.5 (CH), 143.1 (CH), 168.6 (C=O), 172.2 (C=O), 196.4 (C=O), 199.0 (C=O). Compound **4c**: red crystals, mp 203–206 °C, yield: 0.78 g (78%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 2900, 1725, 1710 1700, 1690, 1651, 1457, 1213, 1020. MS (EI, 70 eV): $m/z$ (%) = 501 ($M^+$, 4), 410 (10), 400 (12), 382 (11), 357 (20), 308 (10), 255 (50), 216 (40), 182 (20), 143 (95), 129 (76), 128 (40), 101 (70), 85 (100), 77 (40), 76 (52). Anal. Calcd for $C_{30}H_{31}NO_6$ (501.58): C, 71.84; H, 6.23; N, 2.79. Found: C, 72.41; H, 6.37; N, 2.95. $^1$H NMR: $\delta$ 1.37 (9H, s, C*Me*$_3$), 1.48 (9H, s, C*Me*$_3$), 3.99 (1H, d, $^3J$ = 5.0 Hz, CH), 4.77 (1H, t, $^3J$ = 5.0 Hz, CH), 4.82 (1H, dt, $^3J$ = 10.0, 5.0 Hz, CH), 5.20 (1H, s, CH), 6.09 (1H, d, $^3J$ = 10.0 Hz, CH), 6.47–6.50 (2H, m, 2CH), 6.60–6.62 (1H, m, CH), 6.96–6.99 (1H, m, 1CH), 7.87–7.90 (2H, m, 2CH), 7.85–8.00 (1H, m, 1CH), 8.08–8.10 (1H, m, 1CH). $^{13}$C NMR: $\delta$ 27.9 (C*Me*$_3$), 28.0 (C*Me*$_3$), 52.1 (CH), 65.1 (CH), 67.0 (C), 69.0 (CH), 77.3 (*C*Me$_3$), 82.6 (*C*Me$_3$), 110.2 (2CH), 115.9 (CH), 118.0 (CH), 118.6 (CH), 123.0 (C), 123.2 (C), 127.3 (CH), 130.7 (CH), 131.0 (CH), 135.4 (C), 136.0 (C), 142.0 (CH), 142.7 (CH), 170.8 (C=O), 171.5 (C=O), 193.3 (C=O), 195.0 (C=O).
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18. *General procedure for the synthesis of compounds* **9** *and* **10**: A solution of *N*-methylimidazole or 4-methylpyridine (2 mmol) in 5 mL of dry

$CH_2Cl_2$ was added to a stirred solution of 0.28 g of DMAD (2 mmol) and 0.29 g of 1,3-indanedione (2 mmol) in 10 mL of dry $CH_2Cl_2$ at room temperature. The reaction mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure, and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using a 4:1 hexane–EtOAc mixture as eluent to afford the pure product. Compound **9**: Yellow crystals, 190–192 °C (decomp.), yield: 0.70 g (95%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 2930, 1725, 1715, 1705, 1695, 1537, 1415, 1116. MS (EI, 70 eV): $m/z$ (%) = 370 (3), 354 (6), 323 (10), 288 (12), 257 (18), 256 (50), 228 (30), 197 (32), 170 (36), 115 (14), 113 (36), 82 (100), 76 (44), 59 (54), 42 (26). Anal. Calcd for $C_{19}H_{18}N_2O_6$ (370.30): C, 61.62; H, 4.90; N, 7.56. Found: C, 61.75; H, 5.02; N, 7.70. $^1$H NMR: $\delta$ 2.50 (3H, s, N–Me), 3.53 (3H, s, OMe), 3.73 (3H, s, OMe), 4.26 (1H, d, $^3J$ = 8.9 Hz, CH), 5.92 (1H, d, $^3J$ = 8.9 Hz, CH), 6.97–6.99 (2H, m, CH), 7.15–7.17 (2H, m, CH), 7.50 (1H, s, CH), 7.55 (1H, s, CH), 9.11 (1H, s, CH). $^{13}$C NMR: $\delta$ 35.6 (N–Me), 41.7 (CH), 51.6 (OMe), 53.0 (OMe), 60.3 (CH), 95.4 (C–), 116.8 (2CH), 122.4 (CH), 122.7 (CH), 129.0 (2CH), 137.3 (CH), 139.9 (2C), 168.2 (C=O), 172.0 (C=O), 187.7 (2C=O). Compound **10**: Yellow crystals; 160–162 °C (decomp.), yield: 0.73 g (96%). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 2930, 1730, 1725, 1700, 1695, 1635, 1417, 1171. MS (EI, 70 eV): $m/z$ (%) = 381 (4), 365 (9), 334 (12), 288 (14), 256 (40), 228 (32), 197 (30), 170 (35), 113 (28), 93 (100), 76 (50), 59 (60), 42 (20). Anal. Calcd for $C_{21}H_{19}NO_6$ (381.39): C, 66.14; H, 5.02; N, 3.67. Found: C, 66.01; H, 5.18; N, 3.78. $^1$H NMR: $\delta$ 2.48 (3H, s, Me), 3.56 (3H, s, OMe), 3.72 (3H, s, OMe), 4.47 (1H, d, $^3J$ = 10.0 Hz, CH), 5.46 (1H, d, $^3J$ = 10.0 Hz, CH), 6.92–6.94 (2H, m, CH), 7.13–7.15 (2H, m, CH), 7.79 (2H, d, $^3J$ = 5.0 Hz, CH), 7.77 (2H, d, $^3J$ = 5.0 Hz, CH). $^{13}$C NMR: $\delta$ 21.4 (Me), 41.8 (CH), 51.7 (OMe), 53.4 (OMe), 60.2 (CH), 95.0 (C$^-$), 116.9 (2CH), 127.0 (2CH), 129.0 (2CH), 139.6 (2C), 144.7 (2CH), 160.0 (C), 167.6 (C=O), 171.3 (C=O), 187.6 (2 C=O).