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Diastereoselective synthesis of spiro-functionalized tetraalkyl benzoisoquinopyrrolonaphthyridine-tetracarboxylates from isoquinoline, dialkyl acetylenedicarboxylates, and indane-1,3-dione

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ABSTRACT

An effective route to spiro-functionalized fused polycyclic derivatives of isoquinoline is described via tandem reaction of isoquinoline, dialkyl acetylenedicarboxylates, and indane-1,3-dione.

Tandem reactions (TRs) are of paramount importance in the context of green chemistry as they offer a convenient strategy for the rapid, elegant, and convergent construction of complex organic molecules without isolating and purifying the intermediates, resulting in substantial minimization of waste, labor, time, and cost.[1] Tandem processes lead to skeletal changes rather than merely functional group transformations. Important classes of TRs are the Mannich reaction, Diels–Alder reactions of benzyne, cycloaddition of ketenes, and carbene/nitrene insertion.[2–8] Therefore, TRs have become an increasingly active area of research, yielding novel chemical scaffolds for drug discovery efforts.

We recently[9] reported the formation of novel spiro tetrahydropyrroloquinoline derivatives via the reaction of indane-1,3-dione with Huisgen zwitterions formed in situ from quinoline and activated acetylenes via cyclization. As part of our continuing interest in the construction of novel heterocycles,[10–12] we now report the results of our studies involving the reactions of zwitterions derived from isoquinoline (**1**) and dialkyl acetylenedicarboxylates **2** in the presence of indane-1,3-dione (**3**), which constitutes a synthesis of spiro-functionalized tetraalkyl benzoisoquinopyrrolonaphthyridine-tetracarboxylates **4** (Scheme 1).[13]

The structures of compounds **4a–d** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR, and single-crystal X-ray analyses. For example, the ^{1}H NMR spectrum of **4a** exhibited four singlets (δ 3.60, 3.75, 3.83, and 3.90) identified as methoxy protons, along with multiplets for the remaining aliphatic and aromatic protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 39 distinct resonances which further confirmed the proposed structure. The IR spectrum of **4a** displayed characteristic ketone and ester carbonyl bands. The ^{1}H NMR and ^{13}C NMR spectra of **4b–d** were similar to those for **4a** except for the ester moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.

Unambiguous evidence for the structure and stereochemistry of **4a** was obtained from a single-crystal X-ray analysis. An ORTEP[14] diagram of **4a** is shown in Figure 1. There are two molecules of **4a** in the unit cell. The stereochemistry deduced from the crystallographic experiment, by analogy can be applied to the other products **4b–d** on account of their NMR-spectroscopic similarities.

Although the mechanistic details of the reaction are not known, a plausible rationalization can be advanced to explain the product formation (Scheme 2). Presumably, the zwitterionic intermediate[15–17] **5** formed from isoquinoline and the dialkyl acetylenedicarboxylate, is protonated by **3** to furnish intermediate **6**, which is attacked by carbanion **7**, to produce **8**. This intermediate is converted into **10** via a 1,3-proton shift and cyclization, which then undergoes a [2+4] cycloaddition reaction with **5** to produce product **4**.

In summary, we report a tandem transformation involving isoquinoline and dialkyl acetylenedicarboxylates in the presence of indane-1,3-dione, which affords a new route to the stereoselective

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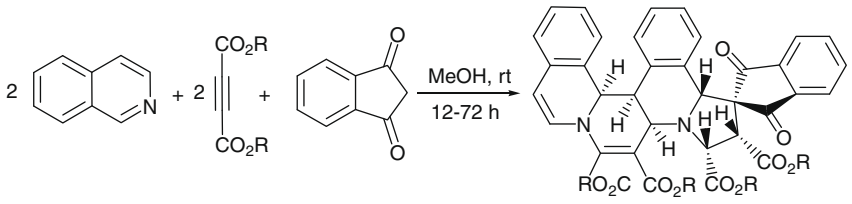


1

2	R
a	Me
b	Et
c	^{i}Pr
d	^{t}Bu

3

4	R	Yield %
a	Me	85
b	Et	76
c	^{i}Pr	70
d	^{t}Bu	67

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

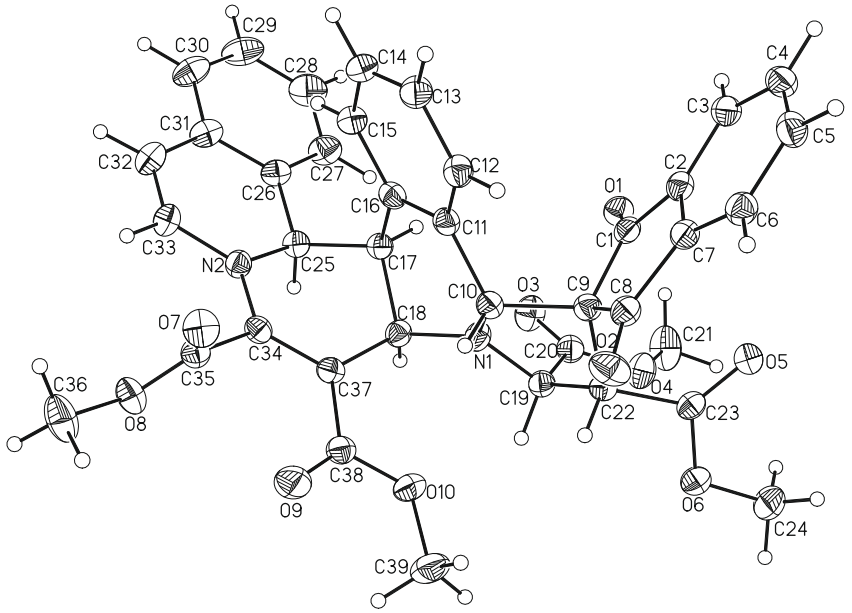
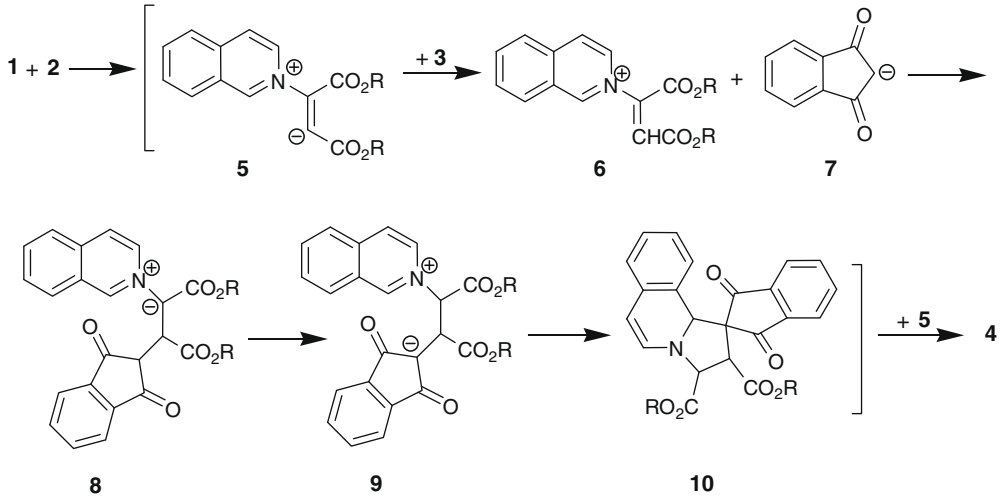


Figure 1. X-ray crystal structure of **4a**. ORTEP-III plot;[14] arbitrary atom numbering.



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

synthesis of complex 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.

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13. *General procedure for the synthesis of compounds* **4**: A solution of isoquinoline (0.26 g, 2 mmol) in dry MeOH (5 mL) was added to a stirred solution of the dialkyl acetylenedicarboxylate (2 mmol) and indane-1,3-dione (0.15 g, 1 mmol) in dry MeOH (10 mL) at rt. After completion of the reaction (12–72 h), as indicated by TLC (EtOAc/hexane, 2:1), the obtained precipitate was filtered and washed with cold Et_2O (4 mL) to afford pure title compound.*Compound* **4a**: White powder, mp 195–198 °C (dec.), yield: 0.58 g (85%). IR (KBr) (ν_{max}/cm^{-1}): 1739, 1738, 1707, 1435, 1252, 1225, 1060, 1024, 775, 770, 725. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.60 (3H, s, MeO), 3.75 (3H, s, MeO), 3.83 (3H, s, MeO), 3.90 (3H, s, MeO), 4.05 (1H, d, ^3J = 8.7 Hz, CH), 4.27 (1H, d, ^3J = 6.7 Hz, CH), 4.71 (1H, s, CH), 5.03 (1H, d, ^3J = 8.7 Hz, CH), 5.15 (1H, d, ^3J = 6.6 Hz, CH), 5.28 (1H, d, ^3J = 7.8 Hz, CH), 5.49 (1H, s, CH), 5.70 (1H, d, ^3J = 7.8 Hz, CH), 6.10 (1H, d, ^3J = 7.7 Hz, CH), 6.47 (1H, t, ^3J = 7.4 Hz, CH), 6.70 (1H, t, ^3J = 7.5 Hz, CH), 6.93–6.95 (1H, m, CH), 7.03 (1H, d, ^3J = 8 Hz, CH), 7.18–7.23 (2H, m, 2 CH), 7.27–7.29 (1H, m, 1 CH), 7.61 (1H, d, ^3J = 7.5 Hz, CH), 7.71 (1H, dd, ^3J = 8.2, 6.7 Hz, CH), 7.79 (1H, dd, ^3J = 7.4, 6.6 Hz, CH), 8.03 (1H, d, ^3J = 7.5 Hz, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 42.4 (CH), 51.9 (CH), 52.1 (CH), 52.2 (N–CH), 52.8 (N–CH), 53.0 (N–CH), 54.7 (N–CH), 61.1 (OMe), 61.8 (OMe), 62.2 (OMe), 62.1 (OMe), 102.1 (C), 104.0 (CH), 122.7 (CH), 123.3 (CH), 124.3 (CH), 125.1 (CH), 125.4 (CH), 125.5 (CH), 126 (CH), 126.5 (CH), 127.5 (CH), 128.1 (CH), 128.5 (CH), 129.7 (C), 131.2 (C), 133.8 (C), 134.1 (C), 134.8 (C), 135.7 (CH), 142.2 (CH), 144.3 (C), 147.1 (C), 164.6 (C=O), 166.9 (C=O), 169.5 (C=O), 172.5 (C=O), 197.7 (C=O), 200.3 (C=O). MS (EI, 70 eV): *m/z* (%) = 339 (25), 281 (20), 255 (24), 145 (24), 129 (25), 104 (72), 76 (60), 44 (100). Anal. Calcd for $C_{39}H_{32}N_2O_{10}$ (688.67): C, 68.02; H, 4.68; N, 4.07. Found: C, 68.15; H, 4.63; N, 4.12. X-ray crystal-structure determination of **4a**: Structure-determination and refinement data: formula, $C_{39}H_{32}N_2O_{10}$, M_r 688.67; crystal system, triclinic, a = 10.0341(5) Å, b = 11.5551(5) Å, c = 15.1664(7) Å, α = 79.8720(10)°, β = 77.0240(10)°, γ = 74.1180(10)°, space group $P\bar{1}$; Z = 2, V = 1635.83(13) Å^3, D_{calcd} = 1.398 g cm^{-3}, crystal size, 0.25 × 0.25 × 0.20 mm^3, R = 0.0519 (for 7873 reflections), R_w = 0.1139; $-13 \le h \le 13$; $-15 \le k \le 15$; $-20 \le l \le 20$°; Mo Kα radiation (λ = 0.71073 Å); T = 120(2) K. The crystallographic data of **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-737928. 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**: White powder, mp 170–174 °C (dec.), yield: 0.57 g (76%). IR (KBr) (ν_{max}/cm^{-1}): 1738, 1737, 1594, 1252, 1228, 1178, 1054, 1031, 756. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70 (3H, t, ^3J = 7.0 Hz, Me), 0.79 (3H, t, ^3J = 7.0 Hz, Me), 0.99 (3H, t, ^3J = 7.1 Hz, Me), 1.43 (3H, t, ^3J = 7.1 Hz, Me), 3.65 (1H, d, ^3J = 7.1 Hz, CH), 3.74 (1H, d, ^3J = 8.7 Hz, CH), 3.80 (2H, m, 2 CH), 3.91 (1H, s, CH), 4.01 (1H, d, ^3J = 8.7 Hz, CH), 4.08–4.17 (3H, m, 3 CH), 4.21 (1H, d, ^3J = 10 Hz, CH), 4.28–4.38 (3H, m, 3 CH), 4.41–4.45 (1H, m, CH), 6.16 (1H, d, ^3J = 7.5 Hz, CH), 6.42 (1H, dd, ^3J = 7.4, 7.1 Hz, CH), 6.51 (1H, d, ^3J = 6.8 Hz, CH), 6.82 (1H, d, ^3J = 6.5 Hz, CH), 6.89 (1H, dd, ^3J = 7.7, 7.3 Hz, CH), 7.01–7.06 (3H, m, 3 CH), 7.18 (1H, d, ^3J = 8 Hz, CH), 7.46 (1H, d, ^3J = 7.5 Hz, CH), 7.56 (1H, t, ^3J = 7.3 Hz, CH), 7.63–7.69 (2H, m, 2 CH), 8.11 (1H, d, ^3J = 7.5 Hz, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.2 (Me), 13.3 (Me), 14.0 (Me), 14.4 (Me), 43.1 (CH), 43.2 (N–CH), 50.7 (N–CH), 54.3 (N–CH), 60.8 (N–CH), 60.9 (CH), 61.2 (CH), 61.5 (CH), 62.9 (CH_2O), 64.3 (CH_2O), 64.5 (CH_2O), 69.3 (CH_2O), 70.4 (C), 122.2 (CH), 122.7 (CH), 123.4 (CH), 123.5 (CH), 124.9 (CH), 125.5 (CH), 125.9 (CH), 126.5 (CH), 127.1 (CH), 127.6 (CH), 128.5 (CH), 132.7 (C), 134.9 (C), 135.1 (C), 135.2 (C), 135.6 (C), 136.3 (C), 141.6 (CH), 142.3 (C), 142.5 (CH), 168.4 (C=O), 169.4 (C=O), 171.3 (C=O), 172.3 (C=O), 196.7 (C=O), 197.7 (C=O). MS (EI, 70 eV): *m/z* (%) = 395 (28), 323 (20), 297 (23), 145 (26), 129 (25), 104 (68), 76 (50), 44 (100). Anal. Calcd for $C_{43}H_{40}N_2O_{10}$ (744.79): C, 69.34; H, 5.41; N, 3.76. Found: C, 69.52; H, 5.46; N, 3.68.
   Compound **4c**: White powder, mp 180–183 °C (dec.), yield: 0.56 g (70%). IR (KBr) (ν_{max}/cm^{-1}): 1739, 1736, 1589, 1254, 1230, 1175, 1052, 1032, 758. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 (6H, d, ^3J = 7.2 Hz, 2 Me), 0.81 (6H, d, ^3J = 7.2 Hz, 2 Me), 1.25 (6H, d, ^3J = 7.1 Hz, 2 Me), 1.45 (6H, d, ^3J = 7.1 Hz, 2 Me), 3.68 (1H, d, ^3J = 7.0 Hz, CH), 3.75 (1H, d, ^3J = 8.8 Hz, CH), 3.95 (1H, m, CH), 3.97 (1H, s, CH), 4.01 (1H, d, ^3J = 8.8 Hz, CH), 4.08–4.17 (2H, m, 4 CH), 4.21 (1H, d, ^3J = 8.9 Hz, CH), 4.28–4.38 (2H, m, 2 CH), 4.40–4.46 (1H, m, CH), 6.15 (1H, d, ^3J = 7.6 Hz, CH), 6.42 (1H, d, ^3J = 7.5 Hz, CH), 6.54 (1H, d, ^3J = 6.8 Hz, CH), 6.82 (1H, d, ^3J = 6.6 Hz, CH), 6.89 (1H, d, ^3J = 7.8 Hz, CH), 7.01–7.05 (2H, m, 2 CH), 7.19 (1H, d, ^3J = 8 Hz, CH), 7.46 (1H, d, ^3J = 7.6 Hz, CH), 7.56 (1H, t, ^3J = 7.3 Hz, CH), 7.63–7.70 (2H, m, 2 CH), 8.12 (1H, d, ^3J = 7.6 Hz, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3 (2 Me), 14.6 (2 Me), 14.8 (2 Me), 15.2 (2 Me), 43.3 (CH), 43.5 (N–CH), 51.1 (N–CH), 54.6 (N–CH), 60.4 (N–CH), 61.2 (CH), 61.4 (CH), 61.6 (CH), 63.5 (O–CH), 65.2 (O–CH), 67.5 (O–CH), 70.3 (O-CH), 70.9 (C), 122.8 (CH), 122.9 (CH), 123.6 (CH), 123.8 (CH), 125.1 (CH), 125.3 (CH), 125.7 (CH), 126.4 (CH), 127.3 (CH), 127.4 (CH), 128.6 (CH), 132.4 (C), 134.7 (C), 135.2 (C), 135.5 (C), 135.7 (C), 136.1 (C), 141.8 (CH), 142.4 (C), 142.6 (CH), 168.3 (C=O), 169.8 (C=O), 171.6 (C=O), 172.4 (C=O), 196.8 (C=O), 197.9 (C=O). MS (EI, 70 eV): *m/z* (%) = 451 (30), 365 (19), 339 (28), 145 (25), 129 (21), 104 (65), 76 (62), 44 (100). Anal. Calcd for $C_{47}H_{48}N_2O_{10}$ (800.90): C, 70.49; H, 6.04; N, 3.50. Found: C, 70.52; H, 6.08; N, 3.55.
   Compound **4d**: White powder, mp 200–203 °C (dec.), yield: 0.57 g (67%). IR (KBr) (ν_{max}/cm^{-1}): 1732, 1731, 1595, 1455, 1366, 1249, 1150, 837, 761. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (9H, s, Me_3C), 1.02 (9H, s, Me_3C), 1.26 (9H, s, Me_3C), 1.65 (9H, s, Me_3C), 3.72 (1H, d, ^3J = 9.0 Hz, CH), 3.98 (1H, s, CH), 4.06 (1H, d, ^3J = 9.0 Hz, CH), 4.18 (1H, d, ^3J = 6.8 Hz, CH), 4.21 (1H, d, ^3J = 6.8 Hz, CH), 4.34 (1H, d, ^3J = 7.5 Hz, CH), 4.38 (1H, s, CH), 4.47 (1H, d, ^3J = 3.0 Hz, CH), 6.18 (1H, d, ^3J = 7.7 Hz, CH), 6.41 (1H, d, ^3J = 7.6 Hz, CH), 6.64 (1H, d, ^3J = 7.0 Hz, CH), 6.77 (1H, d, ^3J = 6.8 Hz, CH), 6.88 (1H, t, ^3J = 7.5 Hz, CH), 7.00–7.06 (2H, m, 2 CH), 7.16 (1H, d, ^3J = 7.8 Hz, CH), 7.50 (1H, d, ^3J = 7.6 Hz, CH), 7.56 (1H, t, ^3J = 7.4 Hz, CH), 7.62–7.65 (1H, m, CH), 7.69–7.70 (1H, m, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 27.2 (Me_3C), 27.3 (Me_3C), 27.9 (Me_3C), 28.3 (Me_3C), 43.1 (N–CH), 43.6 (N–CH), 51.6 (N–CH), 55.8 (N–CH), 60.9 (CH), 63.3 (CH), 64.2 (C), 65.9 (CH), 81.1 (CMe_3), 81.2 (CMe_3), 81.6 (CMe_3), 82.3 (CMe_3), 123.3 (CH), 123.5 (CH), 124.8 (CH), 125.5 (CH), 125.8 (CH), 126.3 (CH), 126.9 (CH), 127.0 (CH), 127.4 (C), 128.1 (C), 128.4 (CH), 133.1 (C), 134.8 (CH), 135.0 (CH), 135.3 (C), 135.6 (CH), 135.7 (C), 141.8 (CH), 142.4 (C), 142.7 (CH), 143.7 (C), 167.4 (C=O), 168.5 (C=O), 170.5 (C=O), 172.0 (C=O), 196.9 (C=O), 198.2 (C=O). MS (EI, 70 eV): *m/z* (%) = 507 (30), 407 (23), 381 (19), 145(33), 129 (26), 104 (59), 76 (63), 44 (100). Anal. Calcd for $C_{51}H_{56}N_2O_{10}$ (857.00): C, 71.48; H, 6.59; N, 3.27. Found: C, 71.35; H, 6.65; N, 3.38.
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