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Tandem synthesis of functionalized tetrahydro-4a*H*-benzo[*c*]isoquino-[1,2-*t*]pyrrolo[1,2-*a*][1,6]naphthyridines

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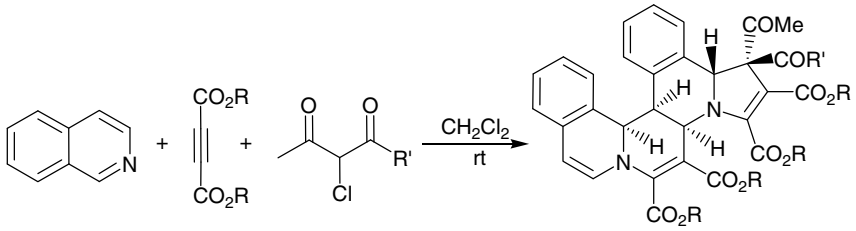
ABSTRACT

An effective route to fused hexacyclic derivatives of isoquinoline is described via tandem reaction of isoquinoline, dialkyl acetylenedicarboxylates, and 3-chloropentane-2,4-dione or alkyl 3-chloroacetoacetates.

Tandem reactions (TRs) that require in situ generation of reactive species, are special types of organic reactions in which the product is formed by successive reactions. Numerous organic transformations are the result of TRs. In fact, tandem processes lead to skeletal changes rather than merely functional group transformations. The secondary reaction for which the structural prerequisite is absent in the initial substrate must be triggered by the first reaction. Important classes of TRs are the Mannich reaction, the Diels–Alder reaction of benzyne, cycloaddition of ketenes, and carbene/nitrene insertions.[1–7] TRs have become an increasingly active area of research, yielding novel chemical scaffolds for drug discovery efforts.

As part of our current studies on the development of new routes to heterocyclic systems,[8–11] we now report the reaction between isoquinoline (**1**) and electron-deficient acetylenic esters **2** in the presence of 3-chloropentane-2,4-dione (**3a**) or alkyl 3-chloroacetoacetates (**3b–c**) in CH_2Cl_2, which led to compounds **4a–d** in 67–91% yields (based on **1**, Scheme 1).[12]

The structures of compounds **4a–d** were deduced from their elemental analyses and their IR, ^1H NMR and ^{13}C NMR spectra,



1

2	R
a	Me
b	Et

3	R'
a	Me
b	OMe
c	OEt

4	R	R'	Yield/ %
a	Me	Me	89
b	Me	OMe	91
c	Me	OEt	88
d	Et	Me	67

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

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and by single-crystal X-ray analysis of **4b**. For example, the ^{1}H NMR spectrum of **4a** exhibited seven singlets identified as methyl (δ 1.43 and 2.44), methoxy (δ 3.67, 3.71, 3.79, and 4.04), and methine (δ 5.91) protons, along with characteristic multiplets for other protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** showed 35 distinct resonances, which confirmed the proposed structure. The IR spectrum of **4a** displayed characteristic carbonyl bands (1730, 1731, 1720, 1698, 1656, and 1637 cm^{-1}). The ^{1}H NMR and

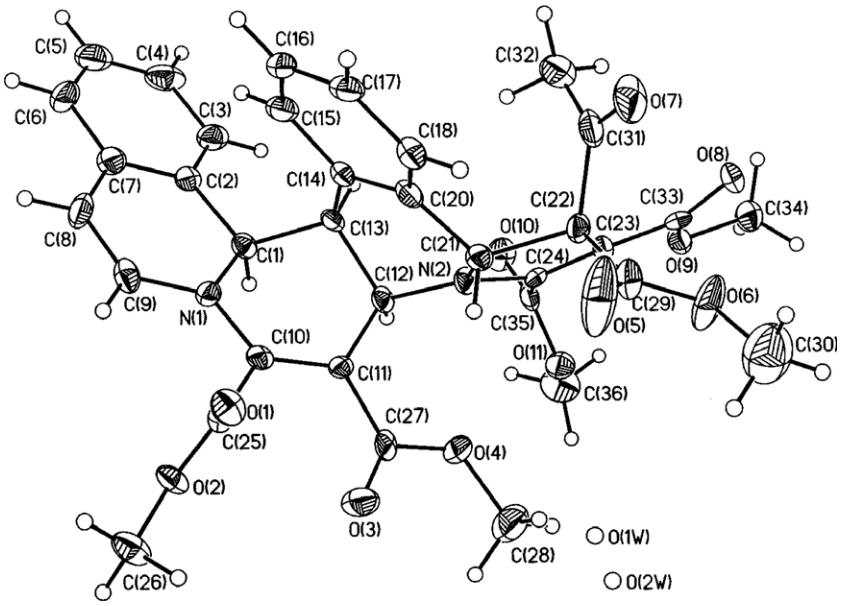
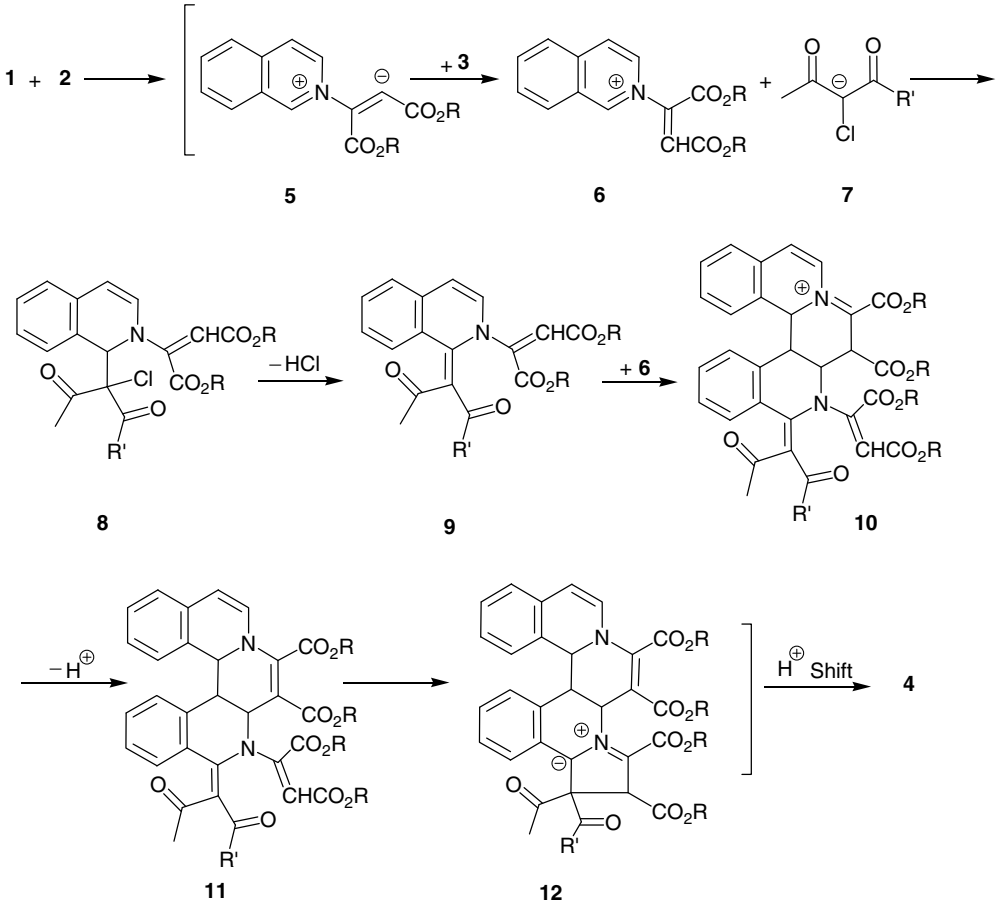
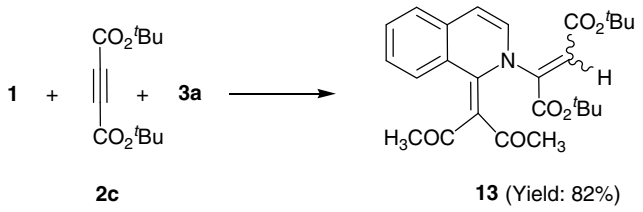


Figure 1. X-ray crystal structure of **4b**. ORTEP-III plot;[13] arbitrary atom numbering.



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



Scheme 3. Synthesis of compound **13**.

^{13}C NMR spectra of **4b–d** were similar to those of **4a** except for the ester moieties, which exhibited characteristic resonances in appropriate regions of the spectra.

Unambiguous evidence for the structure and stereochemistry of **4b** was obtained from a single-crystal X-ray analysis. An ORTEP[13] diagram of **4b** is shown in Figure 1. There are two molecules of **4b** and two molecules of H_2O 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 maybe advanced to explain the product formation (Scheme 2). Presumably, the zwitterionic intermediate[14–16] formed from isoquinoline and **2** is protonated by **3** to furnish intermediate **6**, which is attacked by carbanion **7** to produce **8**. This intermediate is converted to **9**, which undergoes a [2+4] cycloaddition reaction with **6** to produce **10**. Intermediate **10** then undergoes a series of proton-transfer reactions to generate product **4**.

Under similar reaction conditions, di-*tert*-butyl acetylenedicarboxylate (**2c**) reacts with **1** and **3a** to produce compound **13** in 82% yield (Scheme 3). The ^{1}H NMR spectrum of **13** exhibited five singlets for the *tert*-butyl (δ 1.62 and 1.65), methyl (δ 2.18 and 2.68), and alkene (δ 5.32) protons, along with characteristic signals for the isoquinoline residue. Due to the steric hindrance induced by the *tert*-butyl groups, compound **13**, unlike **9** (see Scheme 2), does not undergo a cycloaddition reaction.

In summary, we have reported a transformation involving isoquinoline, dialkyl acetylenedicarboxylates, and 1,3-dicarbonyl compounds, which leads to the diastereoselective synthesis of functionalized hexacyclic derivatives of isoquinoline. 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.

Acknowledgment

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12. *General procedure for the preparation of compounds* **4**: To a stirred solution of **2** (2 mmol) and **3** (2 mmol) in 10 mL of CH_2Cl_2 was added 0.24 ml of isoquinoline (2 mmol) dropwise at −10 °C over 5 min. The reaction mixture was then allowed to warm up to room temperature and stand for 2 h. The solvent was removed under reduced pressure, and the residue was purified 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:** yield: 0.57 g (89%); red powder, mp: 143–145 °C. IR (KBr) (ν_{max}/cm^{-1}): 3420 (CH), 1732, 1730, 1720, 1698, 1656, 1637 (C=O), 1248 (C–O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.43 (3H, s, Me), 2.44 (3H, s, Me), 3.67 (3H, s, OMe), 3.71 (3H, s, OMe), 3.79 (3H, s, OMe), 4.04 (3H, s, OMe), 4.09 (1H, *dd*, ^3J = 6.7 Hz, ^3J = 6.6 Hz, CH), 5.14 (1H, *d*, ^3J = 6.7 Hz, CH), 5.40 (1H, *d*, ^3J = 7.8 Hz, CH), 5.47 (1H, *d*, ^3J = 6.6 Hz, CH), 5.91 (1H, *s*, CH), 5.79 (1H, *d*, ^3J = 7.8 Hz, CH), 6.90–7.11 (4 H, *m*, 4 CH), 7.23–7.26 (4H, *m*, 4CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 27.2 (Me), 29.4 (Me), 41.9 (CH), 51.2 (CH), 51.8 (CH), 52.6 (C), 53.2 (CH), 53.3 (OMe), 53.4 (OMe), 61.2 (OMe), 61.8 (OMe), 98.0 (C), 98.5 (C), 116.5 (C), 120.9 (C), 129.3 (C), 129.4 (C), 129.2 (C), 128.6 (C), 125.3 (CH), 125.6 (CH), 126.0 (CH), 126.5 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 128.0 (CH), 128.6 (CH), 130.1 (CH), 162.9, 163.9, 164.7, and 165.4 (4 C=O, ester), 204.4 and 206.1 (2 C=O). MS (EI, 70 eV): *m*/*z* (%) = 640 (M^+, 3), 609 (28), 597 (38), 581 (49), 384 (75), 325 (63), 266 (83), 256 (41), 197 (34), 59 (100), 43 (78). Anal. Calcd for $C_{35}H_{32}N_2O_{10}$ (640.64): C, 65.62; H, 5.03; N, 4.37. Found: C, 65.86; H, 5.12; N, 4.43.
Compound **4b:** yield: 0.60 g (91%); yellow powder. Mp: 186–188 °C, IR (KBr) (ν_{max}/cm^{-1}): 3440 (CH), 1738, 1731, 1729, 1706, 1639, 1667 (C=O), 1249 (C–O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (3 H, s, Me), 3.64 (3H, s, OMe), 3.73 (3H, s, OMe), 3.79 (3H, s, OMe), 3.86 (3H, s, OMe), 4.04 (3H, s, OMe), 4.06 (1H, *dd*, ^3J = 6.8, ^3J = 6.7, CH), 5.12 (1H, *d*, ^3J = 6.8, CH), 5.39 (1H, *d*, ^3J = 7.9, CH), 5.46 (1H, *d*, ^3J = 6.7, CH), 5.58 (1H, *s*, CH), 5.78 (1H, *d*, ^3J = 7.9 Hz, CH), 6.90–7.11 (4H, *m*, 4 CH), 7.23–7.35 (4H, *m*, 4CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 27.2 (Me), 41.9 (CH), 51.1 (C), 51.2 (CH), 51.8 (CH), 52.6 (CH), 53.3 (OMe), 61.2 (OMe), 61.3 (OMe), 61.8 (OMe), 53.3 (OMe), 98.0 (C), 98.5 (C), 116.5 (C), 120.9 (C), 129.3 (C), 129.4 (C), 129.2 (C), 128.6 (C), 125.3 (CH), 125.6 (CH), 126.0 (CH), 126.5 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 128.0 (CH), 128.6 (CH), 130.1 (CH), 162.9, 163.9, 164.7, 165.4, 172.2 (5C=O, ester), 201.5 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 656 (M^+, 2), 625 (30), 613 (35), 597 (52), 591 (38), 384 (69), 325 (71), 272 (68), 239 (48), 59 (100), 43 (70). Anal. Calcd for $C_{35}H_{32}N_2O_{11}$ (656.64): C, 64.02; H, 4.91, N, 4.27. Found: C, 64.32; H, 4.98; N, 4.32. *X-ray crystal-structure determination of* **4b:** Structure-determination and refinement data: formula, $C_{35}H_{32}N_2O_{11}\cdot H_2O$, M_r 672.63; crystal size, 0.24 × 0.22 × 0.18 mm^3, crystal system, triclinic, a = 9.7206(11) Å, b = 12.6246(14) Å, c = 13.7483(15) Å, α = 82.850(5)°, β = 85.766(5)°, γ = 74.816(5)°, space group *P*1; Z = 2, V = 1614.1(5) Å^3, D_{calcd} = 1.384 g cm^{-3}, crystal size 0.24 × 0.22 × 0.18 mm^3; R = 0.0580 (for 2848 relections), R_w = 0.1561; $-11 \leqslant h \leqslant 11$; $-15 \leqslant k \leqslant 15$; $-16 \leqslant l \leqslant 16$°; Mo K$\alpha$ radiation (λ = 0.71073 Å); T = 100(2) K. The crystallographic data of **4b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC-647814. 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 **4c:** yield: 0.59 g (88%); yellow powder. mp: 100–102 °C. IR (KBr) (ν_{max}/cm^{-1}): 3410 (CH), 1748, 1725, 1720, 1644, 1612, 1637 (C=O), 1248 (C–O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (3H, *t*, ^3J = 7.1, Me), 1.50 (3H, s, Me), 3.62 (3H, s, OMe), 3.73 (3H, s, OMe), 3.82 (3H, s, OMe), 4.03 (3H, s, OMe), 4.06 (1H, *dd*, ^3J = 6.7, ^3J = 6.6, CH), 4.27 (2H, *q*, ^3J = 7.1, OCH_2), 5.16 (1H, *d*, ^3J = 6.7, CH), 5.39 (1H, *d*, ^3J = 7.9, CH), 5.48 (1H, *d*, ^3J = 6.6, CH), 5.58 (1H, *s*, CH), 5.79 (1H, *d*, ^3J = 7.9, CH), 6.92–6.96 (4H, *m*, 4CH), 7.23–7.26 (4H, *m*, 4CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.9 (Me), 26.9 (Me), 41.7 (CH), 50.8 (CH), 51.7 (CH), 52.9 (CH), 53.0 (C), 53.1 (OMe), 53.3 (OMe), 61.1 (OMe), 61.8 (OMe), 63.4 (OCH_2), 98.0 (C), 98.5 (C), 116.5 (C), 120.9 (C), 129.3 (C), 129.4 (C), 129.2 (C), 128.6 (C), 125.2 (CH), 125.5 (CH), 126.1 (CH), 126.5 (CH), 127.3 (CH), 127.4 (CH), 127.5 (CH), 128.0 (CH), 129.9 (CH), 131.1 (CH), 162.7, 163.8, 164.4, 165.6, 171.5 (5C=O, ester), 201.5 (C=O). MS (EI, 70 eV): *m*/*z* (%) = 670 (M^+, 3), 655 (38), 639 (46), 627 (57), 621 (31), 607 (42), 384 (62), 325 (64), 286 (58), 243 (51), 213 (40), 73 (76), 59 (100), 43 (68). Anal. Calcd for $C_{36}H_{34}N_2O_{11}$ (670.67): C, 64.47; H, 5.11; N, 4.18. Found: C, 64.69; H, 5.31; N, 4.24.
Compound **4d:** yield: 0.65 g (67%); yellow powder; mp: 101–103 °C. IR (KBr) (ν_{max}/ cm^{-1}): 3405 (CH), 1741, 1721, 1720, 1698, 1619, 1637 (C=O), 1248 (C–O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (3H, *t*, ^3J = 7.2, Me), 1.25 (3H, s, Me), 1.28 (3H, *t*, ^3J = 7.2, Me), 1.32 (3H, *t*, ^3J = 7.1, Me), 1.41 (3H, *s*, Me), 1.47 (3H, *t*, ^3J = 7.3, Me), 4.18 (2H, *q*, ^3J = 7.2, OCH_2), 4.23 (2H, *q*, ^3J = 7.1, OCH_2), 4.32 (2H, *q*, ^3J = 7.2, OCH_2), 4.50 (2H, *q*, ^3J = 7.1, OCH_2), 3.88 (1H, *dd*, ^3J = 6.8, ^3J = 6.5, CH), 4.05 (1H, *d*, ^3J = 6.8, CH), 5.10 (1H, *d*, ^3J = 6.5, CH), 5.49 (1H, s, CH), 5.39 (1H, *d*, ^3J = 7.9, CH), 5.82 (1H, *d*, ^3J = 7.9, CH), 6.88–6.92 (4H, *m*, 4 CH), 7.23–7.27 (4H, m, 4 CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 14.0 (Me), 14.1 (Me), 18.4 (Me), 22.7 (Me), 29.6 (Me), 31.4 (Me), 42.5 (CH), 51.0 (C), 52.8 (CH), 52.9 (CH), 53.1 (CH), 56.1 (OCH_2), 56.3 (OCH_2), 61.1 (OCH_2), 62.0 (OCH_2), 98.0 (C), 98.5 (C), 113.9 (C), 118.9 (C), 123.9 (C), 126.9 (C), 127.2 (C), 131.9 (C), 115.7 (CH), 123.9 (CH), 124.4 (CH), 126.7 (CH), 127.1 (CH), 127.2 (CH), 128.0 (CH), 128.9 (CH), 129.5 (CH), 133.3 (CH), 160.2, 165.9, 164.0, 169.4 (4C=O, ester), 197.5, 204.0 (2C=O). MS (EI, 70 eV): *m*/*z* (%) = 696 (M^+, 4), 651 (28), 623 (51), 608 (52), 550 (36), 477 (47), 412 (16), 339 (72), 284 (60), 245 (53), 202 (21), 73 (100), 43 (74). Anal. Calcd for $C_{39}H_{40}N_2O_{10}$ (696.75): C, 67.23; H, 5.79; N, 4.02. Found: C, 67.30; H, 5.83; N, 4.10.
Compound **13:** yield: 0.74 g (82%); yellow powder; mp: 210–212 °C; IR (KBr) (ν_{max}/cm^{-1}): 3420 (CH), 1736, 1720, 1681, 1637 (C=O), 1278 (C–O). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (9H, s, Me_3C), 1.65 (9H, s, Me_3C), 2.18 (3H, s, Me), 2.68

(3H, s, Me), 5.32 (1H, s, CH), 7.10 (1H, d, ^{3}J = 12.7, CH), 7.95–8.15 (4H, m, 4 CH), 9.00 (1H, d, ^{3}J = 12.7, CH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 28.1 (Me_3C), 28.3 (Me_3C), 30.9 (Me), 32.7 (Me), 82.6 (Me_3C), 82.9 (Me_3C), 114.7 (C), 119.5 (C), 125.6 (C), 128.9 (C), 129.3 (C), 124.0 (CH), 124.3 (CH), 124.7 (CH), 127.2 (CH), 128.0 (CH), 128.3 (CH), 124.0 (CH), 159.9 and 163.4 (2C=O, ester), 201.1, 201.2 (2C=O). MS (EI, 70 eV): m/z (%) = 453 (M^+, 5), 410 (32), 409 (41), 351 (39), 297 (62), 139 (28), 88 (58), 57 (100). Anal. Calcd for $C_{26}H_{31}NO_6$ (453.53): C, 68.86; H, 6.89; N, 3.09. Found: C, 69.13; H, 6.98; N, 3.15.

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