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An efficient synthesis of 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-*a*]isoquinolines by reaction of isoquinoline with electron-deficient acetylenes in the presence of benzoylcyanide

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Abstract Isoquinoline reacts with electron-deficient acetylenic compounds in the presence of benzoylcyanide to form 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-*a*]isoquinolines in good yields.

Keywords 1,3-Oxazine; Electron-deficient acetylenes; Isoquinoline; Benzoylcyanide; N-Heterocycles.

Introduction

Bridgehead nitrogen heterocycles are of interest because they constitute an important class of natural products, many of which exhibit useful biological activity [1, 2]. The reaction of nucleophiles, N-containing heterocycles in particular, with activated acetylenes has been the subject of significant research [3]. The isoquinoline derivatives are important structural components in naturally occurring alkaloids and synthetic analogues with interesting biological activities. Therefore, the development of a new and efficient synthesis route for the preparation of their analogues is of importance to both synthetic organic chemistry and medicinal chemistry [4]. As part of our current studies on the development of new routes in heterocyclic synthesis [5], we have employed this strategy to a novel three-component reaction leading to the diastereoselective synthesis of functionalized bridgehead nitrogen heterocycles.

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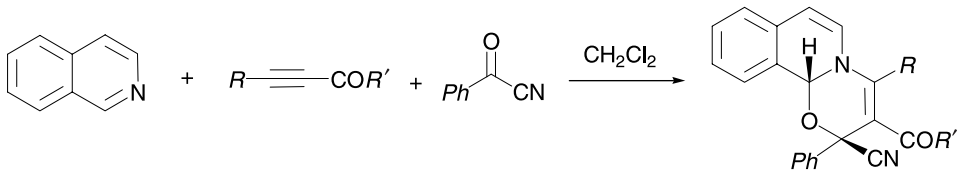
Results and discussion

The reaction of isoquinoline (**1**) with electron-deficient acetylenes **2** in the presence of benzoylcyanide (**3**) proceeded smoothly in CH_2Cl_2, and was completed within a few hours. The ^1H and ^{13}C NMR spectra of the crude products clearly indicated the formation of 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-*a*]isoquinolines **4a**–**4g** in 55–90% yields (Scheme 1).

The structures of **4a**–**4g** as 1:1:1 adducts were apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate m/z values. The ^1H and ^{13}C NMR spectroscopic data, as well as IR spectra, are in agreement with the proposed structures. Since **4** possess two stereogenic centers, two diastereoisomers, namely the (2*S*,11b*R*) and its enantiomer (2*R*,11b*S*), and (2*R*,11b*R*) and its enantiomer (2*S*,11b*S*) isomers, are possible. The NMR spectra of the mixtures are consistent with the presence of only a single diastereoisomer, except for **4a** and **4d**, which exhibit the second diastereoisomer in about 15% and 10%.

The ^1H NMR spectrum of the major isomer of **4a** showed three singlets for two *Me*O ($\delta = 3.59$ and 4.03 ppm) and one methine group ($\delta = 6.57$ ppm), along with multiplets for the aromatic and olefinic



1 2 3 4

2, 4	R	R′	Yield/% of 4
a	CO_2Me	O*Me*	90
b	CO_2Et	O*Et*	72
c	$CO_2{}^tBu$	O^t*Bu*	55
d	H	O*Me*	75
e	H	O*Et*	70
f	*Ph*CO	*Ph*	85
g	2,4-Me_2-C_6H_3CO	2,4-Me_2-C_6H_3	65

Scheme 1

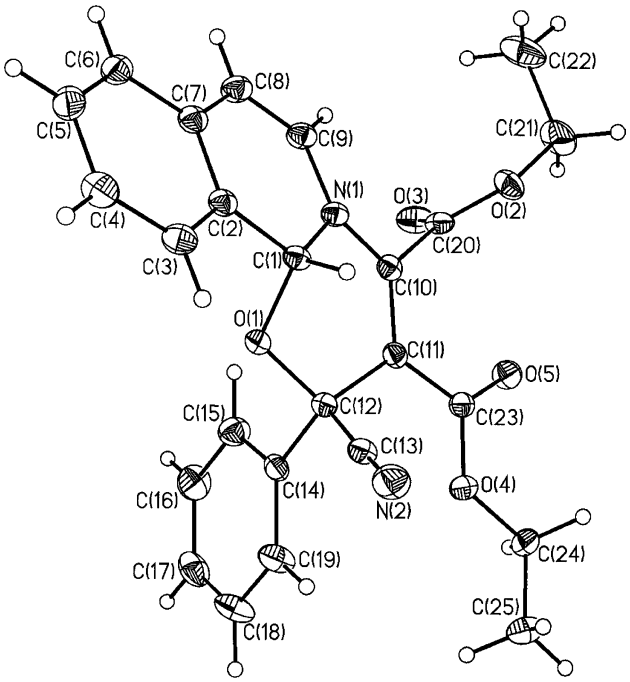
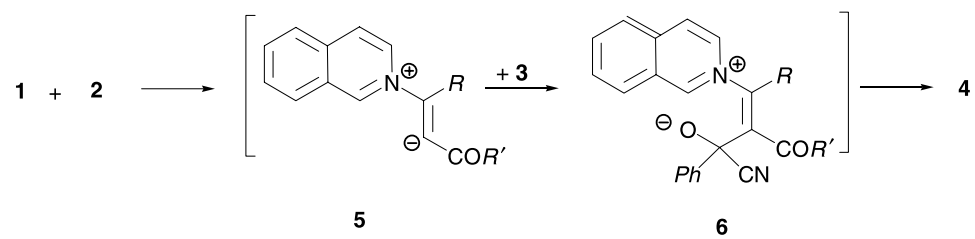


Fig. 1 X-Ray crystal structure of **4b**. ORTEP-III plot [6]; arbitrary atom numbering

moieties. The ^{1}H-decoupled ^{13}C NMR spectrum of this isomer showed 21 distinct signals in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **4b**–**4g** are similar to those for **4a** except for the substituents on the enamine moiety of the oxazine ring system, which exhibited characteristic resonances in appropriate regions of the spectrum.

Unambiguous evidence for the structure and stereochemistry (2*R*,11b*R*)/(2*S*,11b*S*) of **4b** was obtained from a single-crystal X-ray analysis. An ORTEP [6] diagram of **4b** is shown in Fig. 1. There are 2 molecules of **4b** in the unit cell. The stereochemistry deduced from the crystallographic experiment was applied to the other derivatives on account of their NMR-spectroscopic similarity.

A tentative mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of the 1,3-dipolar intermediate **5** from isoquinoline and the acetylenic compound [7–9]. Subsequent nucleophilic attack of the adduct **5** to benzoylcyanide affords **6**, which undergoes a cyclization reaction to give **4**.



5 6

Scheme 2

In conclusion, we described a convenient diastereoselective synthesis of 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-*a*]isoquinolines using isoquinoline, acetylenic compounds, and benzoylcyanide. The advantage of the present procedure is that the reaction is performed under neutral conditions by simple mixing of the starting materials.

Experimental

Isoquinoline, benzoylcyanide, and acetylenic compounds were obtained from Fluka and were used without further purification. Diaroylacetylenes were prepared according to Ref. [10]. Mp Electrothermal-9100 apparatus. IR spectra: Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, respectively; δ in ppm, J in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in m/z. Elemental analyses (C, H, and N) were performed with a Heraeus CHN–O-Rapid analyzer; the results were found to be in good agreement with the calculated values.

General procedure for the preparation of compounds ***4***

To a stirred solution of 0.131 g **3** (1 mmol) and 1 mmol **2** in 10 cm^3 dry CH_2Cl_2, 0.129 g **1** (1 mmol) was added at rt. The mixture was then stirred for 24 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography (SiO_2, *Merck* 230–400 mesh) using an *n*-hexane-*Et*O*Ac* mixture as eluent.

Dimethyl 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate (**4a**, $C_{23}H_{18}N_2O_5$)

Yellow powder; yield: 0.36 g (90%); mp 68–70°C; IR (KBr): $\bar{\nu}$ = 1737 (C=O), 1699 (C=O), 1582, 1556, 1420, 1277, 1232 cm^{-1}; major isomer [(2*R*,11*R*)/(2*S*,11*S*)] (85%): ^{1}H NMR: δ = 3.59 (s, O*Me*), 4.03 (s, O*Me*), 5.88 (d, ^3J = 7.8 Hz, CH), 6.40 (d, ^3J = 7.8 Hz, CH), 6.57 (s, CH), 7.13 (d, ^3J = 7.5 Hz, CH), 7.29 (t, ^3J = 7.1 Hz, CH), 7.34 (d, ^3J = 7.4 Hz, CH), 7.38–7.40 (m, 3CH), 7.48 (d,^3J = 7.7 Hz, CH), 7.65–7.67 (m, 2CH) ppm; ^{13}C NMR: δ = 51.9 (O*Me*), 53.7 (O*Me*), 78.1 (C), 82.1 (CH), 106.1 (CH), 118.1 (CN), 122.8 (CH), 125.1 (C), 125.5 (CH), 126.6 (2CH), 127.7 (CH), 128.1 (CH), 128.7 (2CH), 128.9 (C), 129.4 (C), 129.6 (CH), 130.1 (CH), 136.0 (C), 145.3 (C), 163.0 (C=O), 163.1 (C=O) ppm; minor isomer [(2*S*,11*R*)/(2*R*,11*S*)] (15%): ^{1}H NMR: δ = 3.70 (s, O*Me*), 4.06 (s, O*Me*), 5.81 (d, ^3J = 7.8 Hz, CH), 6.32 (d, ^3J = 7.8 Hz, CH), 6.90 (d, ^3J = 7.7 Hz, CH), 7.07 (d, ^3J = 7.5 Hz, CH) ppm; ^{13}C NMR: δ = 52.1 (O*Me*), 53.7 (O*Me*), 76.5 (CH), 78.1 (CH), 106.0 (CH), 118.2 (CN), 122.9 (CH), 125.2 (C), 125.4 (CH), 127.1 (CH), 127.5 (CH), 129.9 (CH), 123.0 (CH), 130.0 (C), 138.8 (C) ppm; MS (EI, 70 eV): m/z (%) = 401 (2), 149 (64), 129 (44), 105 (90), 77 (100), 59 (86).

[(2R,11bR)/(2S,11bS)]-Diethyl 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate (**4b**, $C_{25}H_{22}N_2O_5$)

White powder; yield: 0.31 g (72%); mp 148–150°C; IR (KBr): $\bar{\nu}$ = 1730 (C=O), 1695 (C=O), 1583, 1557, 1273, 1222, 764 cm^{-1}. ^{1}H NMR: δ = 1.03 (t, ^3J = 7.1 Hz, *Me*), 1.46 (t, ^3J = 7.1 Hz, *Me*), 4.05 (q, ^3J = 7.1 Hz, CH_2), 4.45–4.56 (m, CH_2), 5.88 (d, ^3J = 7.8 Hz, CH), 6.43 (d, ^3J = 7.8 Hz, CH), 6.58 (s, CH), 7.13 (d, ^3J = 7.5 Hz, CH), 7.29 (t, ^3J = 7.5 Hz, CH), 7.34 (t, ^3J = 7.4 Hz, CH), 7.38–7.40 (m, 3CH), 7.48 (d,^3J = 7.6 Hz, CH), 7.68 (d,^3J = 7.6 Hz, 2CH) ppm; ^{13}C NMR: δ = 13.6 (*Me*), 13.9 (*Me*), 61.0 (OCH_2), 63.2 (OCH_2), 76.6 (C), 82.1 (CH), 105.8 (CH), 105.9 (C), 118.2 (CN), 122.8 (CH), 125.1 (C), 125.5 (CH), 126.7 (2CH), 127.7 (CH), 128.1 (CH), 128.6 (2CH), 129.5 (C), 129.6 (CH), 130.1 (CH), 136.3 (C), 145.4 (C), 162.4 (C=O) 162.5 (C=O) ppm; MS (EI, 70 eV): m/z (%) = 258 (16), 105 (80), 77 (100).

X-Ray crystal structure of ***4b***

Structure-determination and refinement of data: formula, ($C_{25}H_{22}N_2O_5$): F_w = 430.45, crystal size 0.25 × 0.20 × 0.20 mm, triclinic, space group $P-1$, Z = 2, a = 8.6587(5) Å, b = 11.5873(5) Å, c = 11.6619 (7) Å, α = 89.9290(10)°, β = 77.572(2)°, γ = 71.6430(10)°, V = 1081.69(11) Å^3, D_{calcd} = 1.322 g cm^{-3}, R = 0.0441, R_w = 0.0867 (for 5009 reflections), $-12 \le h \le 12$; $-15 \le k \le 16$; $-16 \le l \le 16$° Mo (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-647815. 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).

[(2R,11bR)/(2S,11bS)]-Di(tert-butyl) 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate (**4c**, $C_{29}H_{30}N_2O_5$)

Yellow powder; yield: 0.26 g (55%); mp 69–71°C; IR (KBr): $\bar{\nu}$ = 1726, 1696 (2C=O), 1280, 1230, 1138, 763 cm^{-1}. ^{1}H NMR: δ = 1.29 (s, C*Me*$_3$), 1.67 (s, C*Me*$_3$), 5.78 (d, ^3J = 7.4 Hz, CH), 5.80 (s, CH), 6.43 (d, ^3J = 7.0 Hz, CH), 6.82 (d, ^3J = 6.7 Hz, CH), 7.05 (d, ^3J = 6.7 Hz, CH), 7.12 (t, ^3J = 6.7 Hz, CH), 7.25–7.26 (m, CH), 7.35–7.36 (m, CH), 7.48–7.50 (m, 3CH), 7.71–7.72 (m, CH) ppm; ^{13}C NMR: δ = 27.7 (C*Me*$_3$), 27.8 (C*Me*$_3$), 75.1 (C), 78.0 (CH), 82.5 (*CMe*$_3$), 84.9 (*CMe*$_3$), 103.3 (C), 105.0 (CH), 119.0 (CN), 122.8 (CH), 125.1 (C), 125.2 (CH), 126.6 (C), 127.1 (CH), 127.4 (CH), 128.2 (2CH), 128.7 (2CH), 129.6 (CH), 129.7 (CH), 139.4 (C), 146.2 (C), 161.5 (C=O), 162.2 (C=O) ppm.

Methyl 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-a]isoquinoline-3-carboxylate (**4d**, $C_{21}H_{16}N_2O_3$)

Pale yellow powder; yield: 0.25 g (75%); mp 151–153°C; IR (KBr): $\bar{\nu}$ = 1688 (C=O), 1604, 1209, 769 cm^{-1}. major isomer [(2*R*,11*R*)/(2*S*,11*S*)] (90%): ^{1}H NMR: δ = 3.60 (s, O*Me*), 5.79 (d, ^3J = 7.6 Hz, CH), 6.43 (d, ^3J = 7.6 Hz, CH), 6.69 (s, CH), 7.09 (d, ^3J = 7.5 Hz, CH), 7.24 (d, ^3J = 7.3 Hz, CH), 7.31 (t, ^3J = 7.2 Hz, CH), 7.36–7.39 (m, 3CH), 7.47 (d,^3J = 7.7 Hz, CH), 7.66–7.68 (m, 2CH), 7.88 (s, CH) ppm; ^{13}C NMR: δ = 51.3 (O*Me*), 76.4 (C), 81.9 (CH), 104.9 (CH), 105.9 (C), 118.2 (CN), 125.3 (CH), 125.4 (C), 126.3 (CH), 126.6 (2CH), 127.3 (CH), 127.4 (CH), 128.4 (2CH), 129.4 (CH), 129.8 (CH), 130.0 (C), 136.3 (C), 141.6 (CH), 163.8 (C=O) ppm; minor isomer [(2*S*,11*R*)/(2*R*,11*S*)] (10%): ^{1}H NMR: δ = 3.78

(s, O*Me*), 5.72 (d, $^3J = 7.6$ Hz, CH), 5.84 (s, CH), 6.37 (d, $^3J = 7.6$ Hz, CH), 7.95 (s, CH) ppm; ^{13}C NMR: $\delta = 51.6$ (O*Me*), 77.9 (CH), 105.1 (CH), 125.2 (CH), 126.4 (CH), 128.8 (2CH), 138.7 (C), 142.4 (CH), 164.4 (C=O) ppm.

[(2R,11bR)/(2S,11bS)]-Ethyl 2-cyano-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-a]isoquinoline-3-carboxylate
(**4e**, $C_{22}H_{18}N_2O_3$)
Yellow powder; yield: 0.25 g (70%); mp 127–129°C; IR (KBr): $\bar{\nu} = 1688$ (C=O), 1604, 1205, 759 cm^{-1}. ^{1}H NMR: $\delta = 1.28$ (t, $^3J = 7.2$ Hz, *Me*), 4.03–4.05 (m, OCH_2), 5.79 (d, $^3J = 6.1$ Hz, CH), 6.45 (d, $^3J = 6.1$ Hz, CH), 6.71 (s, CH), 7.95–7.10 (m, CH), 7.25 (d, $^3J = 6.6$ Hz, 2CH), 7.36–7.37 (m, 3CH), 7.48 (d, $^3J = 5.9$ Hz, CH), 7.66–7.67 (m, 2CH), 7.89 (s, CH) ppm; ^{13}C NMR: $\delta = 13.9$ (*Me*), 76.6 (C), 60.4 (OCH_2), 82.0 (CH), 104.8 (CH), 106.1 (C), 118.3 (CN), 125.3 (CH), 125.4 (C), 126.4 (CH), 126.7 (2CH), 127.4 (CH), 127.5 (CH), 128.4 (2CH), 129.5 (CH), 129.9 (CH), 130.1 (C), 136.5 (C), 141.5 (CH), 163.5 (C=O) ppm.

[(2R,11bR)/(2S,11bS)]-3,4-Dibenzoyl-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-a]isoquinoline-2-carbonitrile
(**4f**, $C_{33}H_{22}N_2O_3$)
Orange powder; yield: 0.41 g (85%); mp 208–210°C; IR (KBr): $\bar{\nu} = 1753$, 1615 (2C=O), 1530, 1366, 1332, 1280, 1233 cm^{-1}. ^{1}H NMR: $\delta = 5.84$ (t, $^3J = 7.7$ Hz, CH), 6.33 (d, $^3J = 7.7$ Hz, CH), 6.88 (s, CH), 7.03 (t, $^3J = 7.5$ Hz, 2CH), 7.09 (d, $^3J = 7.5$ Hz, 2CH), 7.15 (d, $^3J = 7.2$ Hz, CH), 7.23 (d, $^3J = 7.2$ Hz, CH), 7.33–7.39 (m, 7CH), 7.54–7.63 (m, 4CH), 7.71 (d, $^3J = 6.6$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 76.7$ (C), 82.3 (CH), 106.6 (CH), 118.8 (CN), 123.9 (CH), 125.5 (CH), 125.6 (CH), 126.9 (2CH), 127.7 (2CH), 127.9 (CH), 128.0 (C), 128.6 (2CH), 128.7 (2CH), 128.9 (2CH), 129.0 (2CH), 129.1 (C), 129.5 (CH), 129.6 (C), 130.2 (CH), 131.6 (CH), 134.6 (CH), 135.8 (C), 136.2 (C), 139.4 (C), 148.0 (C), 189.3 (C=O), 192.1 (C=O) ppm.

[(2R,11bR)/(2S,11bS)]-3,4-Bis(2,4-dimethybenzoyl)-2-phenyl-2,11b-dihydro-[1,3]oxazino[2,3-a]isoquinoline-2-carbonitrile (**4g**, $C_{37}H_{30}N_2O_3$)
Orange powder; yield: 0.35 g (65%); mp 193–195°C (decomp); IR (KBr): $\bar{\nu} = 1642$, 1617 (2C=O), 1534, 763 cm^{-1}. ^{1}H NMR: $\delta = 1.72$ (s, *Me*), 2.01 (s, *Me*), 2.25 (s, *Me*), 2.32 (s, *Me*), 5.82 (d, $^3J = 7.8$ Hz, CH), 6.31 (d, $^3J = 7.8$ Hz, CH), 6.72 (d, $^3J = 7.7$ Hz, CH), 6.80 (s, CH), 6.83 (d, $^3J = 7.7$ Hz, CH), 7.06 (d, $^3J = 7.9$ Hz, CH), 7.13 (d, $^3J = 7.5$ Hz, CH), 7.21 (d,^{3} $J = 7.5$ Hz, CH), 7.31–7.44 (m, 5CH), 7.47 (s, 2CH), 7.58 (d, $^3J = 7.2$ Hz, CH), 7.73 (d, $^3J = 7.8$ Hz, 2CH) ppm; ^{13}C NMR: $\delta = 18.2$ (*Me*), 20.4 (*Me*), 20.7 (*Me*), 21.3 (*Me*), 77.5 (C), 81.9 (CH), 106.7 (CH), 118.5 (CN), 123.4 (CH), 125.4 (CH), 125.7 (C), 127.0 (2CH), 127.7 (CH), 127.8 (C), 128.1 (CH), 128.3 (C), 128.4 (2CH), 128.9 (C), 129.0 (C), 129.2 (CH), 129.4 (C), 130.0 (CH), 130.1 (CH), 130.6 (CH), 132.5 (CH), 132.6 (CH), 133.7 (C), 134.1 (C), 134.4 (CH), 135.4 (CH), 136.7 (C), 138.6 (C), 139.3 (C), 190.1 (C=O), 192.8 (C=O) ppm.

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