Synthesis of Novel Dibenzo[3,4:7,8][1,5]diazocinoquinazolinones

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Abstract: A facile one step synthesis of dibenzo[3,4:7,8][1,5]diazocino[2,1-b:6,5-b]/c162diquinazolin-10,21-dione (4a) and N-methyl/ethyldibenzo[3,4:7,8][1,5]diazocino[6,5-b]quinazolin-5,16-diones (4b,c) is described. The mechanism involves a transannular reaction and the conformational structure of 4b was confirmed by X-ray crystallographic data.

Key words: diazocine, quinazolin-4(3H)-one, annelation, X-ray crystallographic analysis, microwave reaction.

During our search for bio-active heterocycles, we aimed to synthesise quinazolino[3,2-d][3,1,4]benzoxadiazepin-9-one (1) incorporating the structural features of both quinazolinone and benzoxadiazepine pharmacophores (Figure 1).1

The required synthon, 2-(2-aminophenyl)-3-hydroxyquinazolin-4(3H)-one (2, R = H), was prepared by known procedure from 2-amino-benzhydroxamic acid.2 Attempts to aroylate the amino group in 2 (R = H), with isatoic anhydride (3) in acetic acid yielded surprisingly, a diazocine, dibenzo[3,4:7,8][1,5]diazocino[2,1-b:6,5-b]/c162diquinazolin-10,21-dione (4a).3 A similar reaction with 2-(2-methyl/ethyl amino phenyl)-3-hydroxyquinazolin-4(3H)-one (2, R = CH₃/C₂H₅) yielded the corresponding N-methyl/ethyl dibenzo[3,4:7,8][1,5]diazocino[6,5-b]quinazolin-5,16-diones (4b,c), Scheme 1.

The structures of these novel dibenzocines were confirmed by their spectra and by a single crystal X-ray analysis of 4b (R = CH₃), Figure 2. The eight membered ring of 4b (R = CH₃) adopted in the crystal, a boat conformation (Figure 2), as expected for dibenzodiazocines.4

The mechanism of formation of 4 is proposed in Scheme 2. The amine 2 undergoes aroylation with isotoxic anhydride (3), and the quinazolinone ring then opens to an oxime that cyclises to 4b (R = CH₃)/4c (R = C₂H₅) by a transannular reaction. When R = H, the amide function undergoes cycloaddition to the iminoketene, generated in situ from 3, to yield 4a. Cycloaddition mechanisms with isatoic anhydride involving an iminoketene intermediate have been demonstrated.5

In an alternate synthesis, 4a was obtained in 60% yield by refluxing a mixture of 3 and methyl anthranilate (5) in diphenyl ether for 12 hours, Scheme 3. A plausible mechanism involves the initial formation of the dianthranilide (6),6 followed by condensation with the iminoketene. This route was proved by isolating 4a in the reaction of 6 and 3 in diphenyl ether.

We also discovered that isatoic anhydride (3) alone yielded 4a under microwave (and pyrolysis) conditions. The reaction obviously involves a thermal retro Diels–Alder fragmentation of 3, and the generated iminoketene will
dimerise to 6, followed by annelation, Scheme 4. In effect, four molecules of isatoic anhydride (3) are polymerized by pyrolysis to give 4a. The fact that an amide function of cyclic benzanilides such as 4 (R = H) or 6 can be condensed with isatoic anhydride (3) to give quinazolone compounds, has been demonstrated by obtaining 2,3-diphenylquinazolin-4(3H)-one in the reaction of 3 and benzanilide under microwave conditions. This is a novel self-polymerization reaction of isatoic anhydride, which is known to dimerize to 2(2-aminophenyl)-3,1-benzoxazin-4-one.5

Scheme 2

Scheme 3

Method 1
An equimolar mixture of 2(2-aminophenyl)-3-hydroxyquinazolin-4(3H)-one (2, R = H, 1.26 g, 5 mmol) and isatoic anhydride (3, 0.8 g, 5 mmol) was refluxed for 12 h in glacial HOAc (15 mL), containing a pinch of para-toluene sulfonic acid. The reaction mixture was brought to r.t., poured in ice cold H2O (200 mL) with vigorous stirring; the pale green solids separated were collected by filtration and dried. It was purified by column chromatography over neutral alumina (120 mesh) with petroleum ether–EtOAc (3:2) as eluent, gave 4a. Yield 1.35 g, 62%; mp >320 °C.

IR (KBr): 3042, 1684.1, 1604.6, 1490.6, 1471.0, 1348.7, 1273.5, 1138.4, 955.5, 768.1, 649.0 cm−1. 1H NMR (CDCl3): δ = 7.17–7.76 (m, 14 H), 8.25 (d, 2 H, J = 10 Hz).

13C NMR (CDCl3): δ = 121.1, 127.2, 127.7, 128.2, 128.5, 129.1, 129.8, 131.2, 133.9, 134.8, 135.9, 147.2, 151.8, 161.1.

EI-MS: m/z (%) = 440 (100) [M+], 411 (17.2), 295 (18.5), 220 (11.9).

Method 2
Isatoic anhydride (3, 0.4 g, 2.5 mmol) was doped over Montmorillonite clay and subjected to microwave irradiation (BPL-Sanyo-700T; at an output 600 Watts), for 7 min at a pulse of 2 min. The progress of reaction was monitored by TLC. The reaction mixture was subjected to column chromatography over neutral alumina (120 mesh) with petroleum ether–EtOAc (3:2) as eluent, gave 4a. Yield 0.5 g, 46%; mp >320 °C.

N-Alkyldibenzo[3,4:7,8][1,5]diazocino[6,5-b]quinazolin-5,16-dione (4b, R = CH3; 4c, R = C2H5)
Synthetic procedure same as in Method 1.

4b Yield 72%; mp 300 °C. IR (KBr): 3043, 1693, 1653, 1601, 1586, 1473, 890, 585 cm−1. 1H NMR (CDCl3): δ = 3.24 (s, 3 H), 7.02–7.71 (m, 11 H), 8.25 (d, 1 H, J = 10 Hz).

13C NMR (CDCl3): δ = 164.0, 161.0, 146.9, 142.2, 135.0, 134.6, 133.8, 131.3, 130.6, 129.8, 126.1, 127.1, 121.3, 36.5.

EI-MS: m/z (%) = 353 (46.15) [M+], 324 (30.7), 296 (7.7), 276 (12.3), 241 (30.7), 43 (100).


X-ray data of 4b (R = CH3) recrystallized in petroleum ether–EtOAc mixture. All measurements were made on Nonius Cads4 diffractometer. The data were collected at a temperature 293 K using omega two theta diffraction measurement method. C22H15N3O2, formula M = 353.37, monoclinic, space group P21/n. Unit cell dimensions a = 8.9036(6), b = 13.7731(18), c = 14.3244(19), α = 90.00; β = 97.950; γ = 90.00; volume = 1739.7(3); Z = 4; density = 1.349 gcm−3; absorption co-efficient = 0.716 mm−1, θ range for data collection 4.47 to 67–95. Further details on the crystal structure investigation have been deposited with the Cambridge crystallographic data centre with the deposition number CCDC 175034. Any required information could be obtained at e-mail: deposit@ccdc.cam.ac.uk.

4c Yield 73%; mp 286 °C. IR (KBr): 3034, 1687, 1649, 1605, 1566, 1453, 951, 883 cm−1.

1H NMR (CDCl3): δ = 3.97 (t, 3 H, J = 7.2 Hz), 3.36 (q, 1 H, J = 7.2 Hz), 4.40 (q, 1 H, J = 7.2 Hz), 7.15–7.80 (m, 11 H), 8.34 (d, 1 H, J = 10 Hz).

13C NMR (CDCl3): δ = 166.7, 161.1, 147.2, 140.6, 135.8, 134.9, 134.8, 131.3, 131.0, 129.7, 129.1, 128.6, 128.4, 127.1, 121.1, 43.7, 12.9.

EI-MS: m/z (%) = 367 (24.67), 338 (15.58), 297 (6.49), 44 (100).
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References


