A FACILE AND EFFICIENT ENTRY TO NAPHTHO[2,3-*g*]INDOLE-6,11-DIONE DERIVATIVES

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Dedicated to Prof. E.C. Taylor in recognition of his contribution to Heterocyclic Chemistry

Abstract - Condensation of anthraquinone-2-carboxaldehyde with several α-azido carbonyl compounds leads to α-azido-β-antraquinonyl acrylates which under heating undergo ring-closure to give naphtho[2,3-*g*]indole-6,11-diones in a completely regioselective fashion.

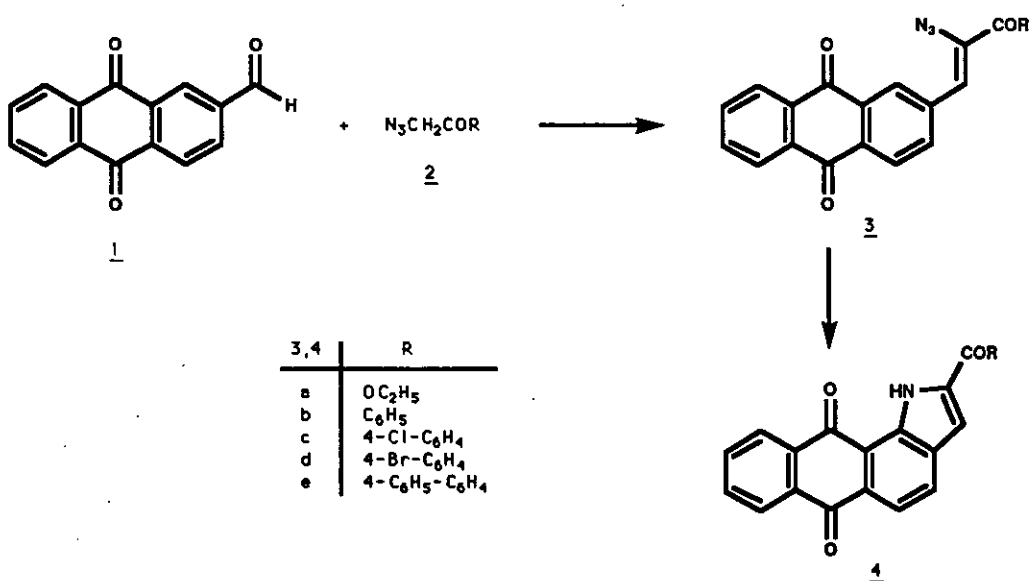
One of the most important goals in heterocyclic chemistry is the development of efficient synthetic methods for the preparation of heterocyclic quinones. This sort of compounds are involved in numerous biochemical processes because of their facile reduction-oxidation. They play an important role in electron transport processes as well as in oxidative phosphorylation processes.[1]

In spite of the amount of work involved with indolequinones (e.g. mitomycins) and carbazolequinones (e.g. murrayaquinones), a few studies dealing with the related system naphthoindole quinone have been reported.[1] In particular, the chemistry of the naphto[2,3-*g*]indole-6,11-dione ring system remains almost unexplored. Recently, its preparation by intramolecular addition of 2-alkynyl-1-aminoanthraquinones, available by coupling of 1-amino-2-iodoanthraquinone with aryl acetylenes in the presence of Pd compounds as catalysts, has been described.[2] However, the generality of this method is impaired by the availability of the not so simple starting material.

We report now a simple and apparently general method for the preparation of 2-substituted 1*H*-naphtho[2,3-*g*]indole-6,11-diones under mild reaction conditions. Our approach is based on the known thermal decomposition of α-azidoacrylates bearing a β-aryl or heteroaryl substituent to give fused pyrroles. Although this method has been applied for the annelation of a pyrrole ring into a preformed benzene,[3] thiophene,[4] furan,[5] indole[6] and quinoline ring,[7] no examples dealing with this kind of annelation into an anthraquinone ring have been reported, to the best of our knowledge.

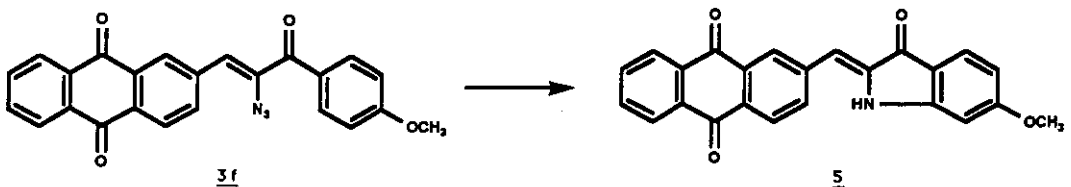
Condensation of anthraquinone-2-carboxaldehyde (1), prepared from the commercially available 2-hydroxymethyl-anthraquinone by oxidation with chromium trioxide-pyridine,[8] with ethyl azidoacetate (2) (R=OEt) in the presence of sodium ethoxide at -30°C, leads to the corresponding α-azido-β-anthraquinonyl acrylate (3a), which decomposes at room temperature to give the 1*H*-naphtho[2,3-*g*]indole-6,11-dione (4a) (R=OEt), as crystalline solid in 58% yield after crystallization, in a completely regioselective fashion. The isomeric linear naphtho[2,3-*f*]indole-5,10-dione could not be detected neither by thin layer chromatography nor ^{13}C-nmr analysis of the crude product. Attempts to isolate the intermediate azide (3a), failed.

Similar results are obtained from the reaction of (1) with several α-azidoacetophenones (2) (R = aryl), available from α-bromoacetophenones and polymeric quaternary ammonium azide.[9] Thus, when the reaction is carried out in THF at room temperature in the presence of acetic acid and piperidine, the corresponding azides (3) are isolated as crystalline solids, which are used without purification for the next step. Treatment of compounds (3) with triphenylphosphine in dry dichloromethane at room temperature lead to a complex mixture in which neither the expected iminophosphorane nor the tetracyclic naphtho[2,3-*g*]indole-6,11-dione could be detected. However, heating in toluene at reflux temperature for 5 h leads to naphtho[2,3-*g*]indole-6,11-dione (4b-e) (32-78%) in a completely regioselective fashion.



3,4	R
a	OC_2H_5
b	C_6H_5
c	$4\text{-}Cl\text{-}C_6H_4$
d	$4\text{-}Br\text{-}C_6H_4$
e	$4\text{-}C_6H_5\text{-}C_6H_4$

In the thermal treatment of the azide (3f) (Ar = $4\text{-}CH_3OC_6H_4$) the pyrrole annelation takes place onto the aromatic ring belonging to the acyl group, instead of the aromatic ring of the anthraquinone moiety, to give (5). This fact can be ascribed to the higher nucleophilic character of the electron donating substituted ring with respect to the anthraquinone ring.



3f 5

The identity of compounds (4) was accomplished by COSY, HCCOR and DEPT experiments. In the ^{1}H nmr spectra the 3-H proton appears as a singlet at δ = 8.56-8.87 ppm and the 4-H and 5-H protons appear as doublets (J= 8.60-8.80 Hz) at δ = 8.11-8.30 and δ = 7.93-8.03 ppm, respectively. The mass spectra show the expected molecular ion peaks and the fragmentation pattern is in agreement with the proposed structure.

EXPERIMENTAL

Melting points were obtained in a Kofler hot-stage apparatus and are uncorrected. Ir spectra were run using NaCl plates on a Nicolet FT-5DX spectrophotometer in Nujol emulsions. ^{1}H Nmr spectra were recorded using a Bruker AC-200 (200 MHz) and tetramethylsilane as internal reference. ^{13}C Nmr spectra, were determined on a Bruker AC-200 (50.3 MHz) spectrometer. The EI-mass spectra were obtained with a Hewlett-Packard 5993 C spectrometer at 70 eV. Elemental analyses were performed with an Eager 200 instrument.

2-Ethoxycarbonyl-1*H*-naphtho[2,3-*g*]indole-6,11-dione, (4a). To a well stirred solution containing sodium (0.25 g, 11 mmol) in dry ethanol (10 ml), a solution of ethyl azidoacetate (1.42 g, 11 mmol) and anthraquinone-2-carboxaldehyde (0.67 g, 2.84 mmol) in dry THF (10 ml) was added dropwise at -30°C under nitrogen. The reaction mixture was allowed to warm to room temperature and was then stirred for 8 h. After this, it was poured into aqueous 30% ammonium chloride (30 ml) and then extracted with ether (3 x 40 ml). The combined extracts were washed with water (3 x 40 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The resulting material was chromatographed over silica gel with ethyl acetate-petroleum ether (3:7) as eluent to afford the compound with R_f = 0.84 which was crystallized from ethanol. Yield: 0.52 g (58%), yellow needles; mp 129-132°C. Anal. Calcd for $C_{19}H_{13}NO_4$: C, 71.47; H, 4.10; N, 4.39. Found C, 71.55; H, 3.98; N, 4.19. $\nu_{max.}$ (cm^{-1}) 3330, 1724, 1680, 1591, 1434, 1333, 1296, 1271, 1246, 1111, 974, 932, 872, 799, 706, 633; δ (^{1}H, 200 MHz) ($CDCl_3$) 8.87 (1H, s, H-3), 8.38 (1H, d, J = 7.20 Hz), 8.32 (1H, d, J = 7.20 Hz), 8.29-8.25 (2H, m, H-7 + H-10), 7.90-7.80 (2H, m, H-8 + H-9), 4.46 (2H, q, J = 7.00 Hz), 1.46 (3H, t, J = 7.00 Hz); δ (^{13}C) 182.34 (C=O), 182.04 (C=O), 164.86 (COOEt), 136.01 (q), 135.54 (q), 134.39, 134.31, 134.25, 133.55 (q), 133.46 (q), 133.39 (q), 132.24 (q), 132.05 (q), 128.41, 127.36,

127.30, 127.24, 61.78, 14.21; m/z (%) 319 (M^+, 3), 235 (26), 208 (10), 207 (20), 152 (21), 151 (96), 150 (61), 99 (12), 98 (10), 75 (100), 74 (50).

General Procedure for the Preparation of 2-Aroyl-1*H*-naphtho[2,3-*g*]indole-6,11-dione, (4b-e). - To a solution of anthraquinone-2-carboxaldehyde (0.67 g, 2.84 mmol) in dry THF (10 ml), acetic acid (0.05 ml) and piperidine (0.033 ml), an equimolecular amount of the corresponding α-azidoacetophenone in dry THF (15 ml) was slowly added. The reaction mixture was stirred at room temperature under nitrogen for 72 h and the resulting precipitate was washed with cold ethanol (2x20 ml) and characterized as the corresponding azido derivative (3b-e) which, without further purification, was solved in toluene and heated at reflux temperature for 5 h. On cooling compounds (4b-e) were isolated and recrystallized from toluene.

2-Benzoyl-1*H*-naphtho[2,3-*g*]indole-6,11-dione, (4b).- Yield: 0.54 g (54%), orange prisms; mp 213-216°C. Anal. Calcd for $C_{23}H_{13}NO_3$: C, 78.62; H, 3.73; N, 3.99 %. Found: C, 78.46; H, 3.58; N, 3.82. ν_{max} (cm^{-1}) 3233, 1653, 1585, 1568, 1551, 1444, 1359, 1336, 1296, 1268, 1149, 934, 854, 775, 730, 713; δ (^1H, 200 MHz) (DMSO-d_6) 8.61 (1H, s, H-3), 8.40-8.25 (2H, m), 8.19 (1H, d, J = 8.80 Hz), 7.93 (1H, d, J = 8.80 Hz), 7.90-7.80 (2H, m), 7.75-7.68 (2H, m), 7.64-7.56 (3H, m); δ (^{13}C) 182.37 (C=O), 181.65 (C=O), 171.98 (PhC=O), 139.45 (q), 135.50 (q), 134.54, 134.36, 133.09 (q), 132.99 (q), 131.90, 131.83 (q), 130.97, 130.41 (q), 128.90 (q), 128.58, 128.50, 128.19 (q), 127.25, 126.73, 126.65, 124.61; m/z (%) 351 (M^+, 8), 338 (6), 319 (17), 318 (25), 262 (10), 252 (17), 251 (16), 248 (13), 247 (6), 235 (62), 208 (5), 207 (24), 152 (11), 151 (29), 150 (15), 105 (100), 77 (63).

2-p-Chlorobenzoyl-1*H*-naphtho[2,3-*g*]indole-6,11-dione, (4c).- Yield: 0.65 g (59%), yellow needles; mp 225-226°C. Anal. Calcd for $C_{23}H_{12}ClNO_3$: C, 71.60; H, 3.14; N, 3.63. Found: C, 71.49; H, 3.08; N, 3.39. ν_{max} (cm^{-1}) 3250, 1676, 1647, 1591, 1574, 1495, 1466, 1342, 1296, 1245, 1149, 1098, 1013, 934, 832, 724, 707; δ (^1H, 200 MHz) (DMSO-d_6) 8.56 (1H, s, H-3), 8.25-8.15 (2H, m), 8.11 (1H, d, J = 8.80 Hz), 7.96 (1H, d, J = 8.80 Hz), 7.92-7.86 (2H, m), 7.72 (2H, d, J = 8.10 Hz), 7.56 (2H, d, J = 8.10 Hz); δ (^{13}C) 182.30 (C=O), 181.56 (C=O), 171.02 (ArC=O), 139.47 (q), 135.54 (q), 134.47, 134.28, 133.07 (q), 132.95 (q), 131.75 (q), 130.48, 130.33, 128.82 (q), 128.50, 128.44, 128.12 (q), 127.95 (q), 127.20, 126.66, 126.59, 124.47 (q); m/z (%) 387 (M^++2, 1), 385 (M^+, 3), 247 (1), 208 (17), 207 (26), 167 (2), 165 (5), 152 (3), 151 (5), 141 (34), 139 (100), 113 (8), 111 (22).

2-p-Bromobenzoyl-1*H*-naphtho[2,3-*g*]indole-6,11-dione, (4d).- Yield: 0.95 g (78%), yellow prisms; mp 218-220°C. Anal. Calcd for $C_{23}H_{12}BrNO_3$: C, 64.21; H, 2.81; N, 3.26. Found: C, 64.18; H, 2.70; N, 3.15 . ν_{max} (cm^{-1}) 3233 1676, 1647, 1585, 1574, 1342, 1296, 1149, 1075, 1013, 934, 832, 707; δ (^1H, 200 MHz) (DMSO-d_6) 8.64 (1H, s, H-3), 8.29 (1H, d, J = 8.60 Hz), 8.22-8.10 (2H, m), 7.94 (1H, d, J = 8.60 Hz), 7.91-7.80 (2H, m), 7.75 (2H, d, J = 8.20 Hz), 7.62 (2H, d, J = 8.20 Hz); δ (^{13}C) 182.40 (C=O), 181.57 (C=O), 171.58 (ArC=O), 139.67 (q), 135.13 (q), 134.49 , 134.29, 133.11 (q), 132.91 (q), 131.66 (q), 131.41, 130.64, 130.21 (q), 128.84 (q), 128.14 (q), 127.24, 126.69, 126.61, 124.49 (q), 124.36, 124.21; m/z (%) 431 (M^++2, 8), 429 (M^+, 8), 247 (4), 221 (3), 220 (8), 219 (3), 218 (9), 185 (100), 183 (100), 157 (23), 155 (19).

2-p-Phenylbenzoyl-1*H*-naphtho[2,3-*g*]indole-6,11-dione, (4e).- Yield: 0.39 g (32%), brown prisms; mp 189-

191°C. Anal. Calcd for $C_{29}H_{17}NO_3$: C, 81.49; H, 4.01; N, 3.28. Found C, 81.65; H, 3.98; N, 3.34. ν_{max} (cm^{-1}) 3267, 1676, 1591, 1325, 1296, 1155, 1098, 934, 843, 707; δ (^1H, 200 MHz) (DMSO-d_6) 8.87 (1H, s, H-3), 8.30 (1H, d, J = 8.70 Hz), 8.25-8.15 (2H, m), 8.03 (1H, d, J = 8.70 Hz), 7.90-7.80 (2H, m), 7.70-7.60 (2H, m), 7.51-7.40 (3H, m), 7.25 (2H, d, J = 7.30 Hz), 7.14 (2H, d, J = 7.30 Hz); δ (^{13}C) 182.36 (C=O), 181.58 (C=O), 171.49 (ArC=O), 144.12 (q), 140.62 (q), 138.86 (q), 135.20 (q), 134.60, 134.37, 133.14 (q), 132.90 (q), 131.86, 131.60 (q), 131.04, 128.91 (q), 128.70, 128.54, 128.46, 128.23 (q), 128.12 (q), 127.90, 127.60, 127.30, 126.81, 126.59; m/z (%) 427 (M^+, 2), 247 (4), 208 (3), 207 (6), 181 (100), 153 (33), 152 (64), 151 (22), 77 (12).

2-(2-Antraquinolyl)-6-methoxybenzopyrrol-3-one, (5).- This compound was obtained following the procedure previously described for the preparation of 1*H*-naphtho[2,3-*g*]indole-6,11-diones (4b-e). Yield: 0.57 g (53%), brown prisms; mp 173-175°C. Anal. Calcd for $C_{24}H_{15}NO_4$: C, 75.58; H, 3.96; N, 3.67. Found: C, 75.39; H, 3.80; N, 3.80. ν_{max} (cm^{-1}) 3375, 1698, 1681, 1591, 1330, 1285, 1172, 934, 707; δ (^1H, 200 MHz) ($CDCl_3$-TFA) 8.76 (1H, s, NH), 8.40-8.36 (4H, m), 8.02-7.96 (4H, m), 7.18 (2H, d, J = 8.80 Hz), 6.63 (1H, s), 4.05 (3H, s); δ (^{13}C) 194.89 (ArC=O), 186.56 (C=O), 186.17 (C=O), 165.59 (q), 140.78 (q), 138.47 (q), 137.03, 136.32, 136.25, 133.92 (q), 133.85 (q), 133.74, 133.28 (q), 130.42, 128.95, 128.65, 128.33 (q), 126.91, 117.68, 55.88; m/z (%) 381 (M^+, 51), 368 (10), 247 (7), 207 (4), 152 (13), 135 (100), 107 (8), 77 (13).

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