

Regioselective Diels-Alder Reactions of 3-Vinylindoles with Quinones

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Abstract. The Diels-Alder reactions of *in situ* generated vinylindoles and several non-symmetrical quinones, such as 2,5,8(1*H*)-quinolinetriones and 6-bromoquinolinequinones, were found to be regioselective.

Keywords. Diels-Alder reactions, vinylindoles, quinones, quinolinones.

INTRODUCTION

Although 2-vinylindoles and 3-vinylindoles have been widely employed as dienes in Diels-Alder reactions [1], the regioselectivity of the cycloadditions of 3-vinylindoles to unsymmetrical dienophiles has received little attention [2]. For this reason, and due to our interest in the chemistry of heterocyclic quinones [3], we describe here our studies on the regiochemistry of the reactions between 1-(3-indolyl)cyclohexene **1** and several non-symmetrical quinones, including four 2,5,8(1*H*)-quinolinetriones **3** and a 6-bromoquinolinequinone derivative. These Diels-Alder reactions are of interest because they provide easy access to a number of polyheterocyclic quinone systems, heterocyclic quinones [4] being a very important class of compounds from a biological point of view, particularly as antitumour agents [5].

RESULTS AND DISCUSSION

The reaction of diene **1** with several quinones gave the results shown in Scheme 1. The unstable **1** was generated *in situ* from indole and cyclohexanone using the protocol developed by Noland [6], and treated initially with naphthoquinone to establish the most suitable reaction conditions. Thus, a brief reflux of a solution of indole, cyclohexanone and naphthoquinone in ethanol containing a trace of hydrochloric acid afforded a complex mixture of products, which gave 38 % yield of compound **2** after oxidation with DDQ in benzene [7].

Because of the interesting antitumor properties found in hetero Diels-Alder adducts of 2,5,8(1*H*)-quinolinetriones, we chose these compounds as model asymmetric quinones on which to study the regioselectivity of the Diels-Alder reactions of **1**. When several 3-substituted derivatives of this system (quinones **3a-c**[8]) were treated with **1** and the crude reaction products were aromatized under thermal conditions, compounds **4** were isolated in moderate yields, together with the hydroquinones derived from reduction of **3**. In the case of the reactions starting from 4-substituted 2,5,8(1*H*)-

quinolinetriones **3d** [9] and **3e** [10], quinones **6a** and **6b** precipitated from the reaction mixtures in moderate yields and evaporation of the reaction media afforded mixtures of hydroquinones **5** and, again, those derived from reduction of the starting quinones **3**. Although compounds **5** could not be purified from these mixtures, their air oxidation in the presence of base afforded additional amounts of quinones **6** [11]. An attempt to increase the yields of compounds **5a** and **6a** by addition of excess of the starting quinone **3** to compensate for the fraction that is reduced to hydroquinone during the reaction led to the isolation of compound **7**, from addition of a molecule of indole to quinone **3d** [12], together with the other previously mentioned reaction products.

The study of the reaction of **1** with an halogenated quinone was also considered of interest because elimination of a molecule of HX from the primary Diels-Alder adduct should lead directly to a compound with an oxidation state similar to that of **5** without consumption of the starting quinone, thus avoiding hydroquinone side products related to **3**. Thus, treatment of **1** with 6-bromo-3-methylquinolinequinone [13] under our standard conditions, followed by oxidation of the crude reaction product without isolation of the hydroquinone intermediate gave the expected fully aromatic quinone **8** as the sole hexacyclic product in 53% yield. As in the previous example, use of two equivalents of quinone in this reaction led to the Michael adduct **9** as the major product.

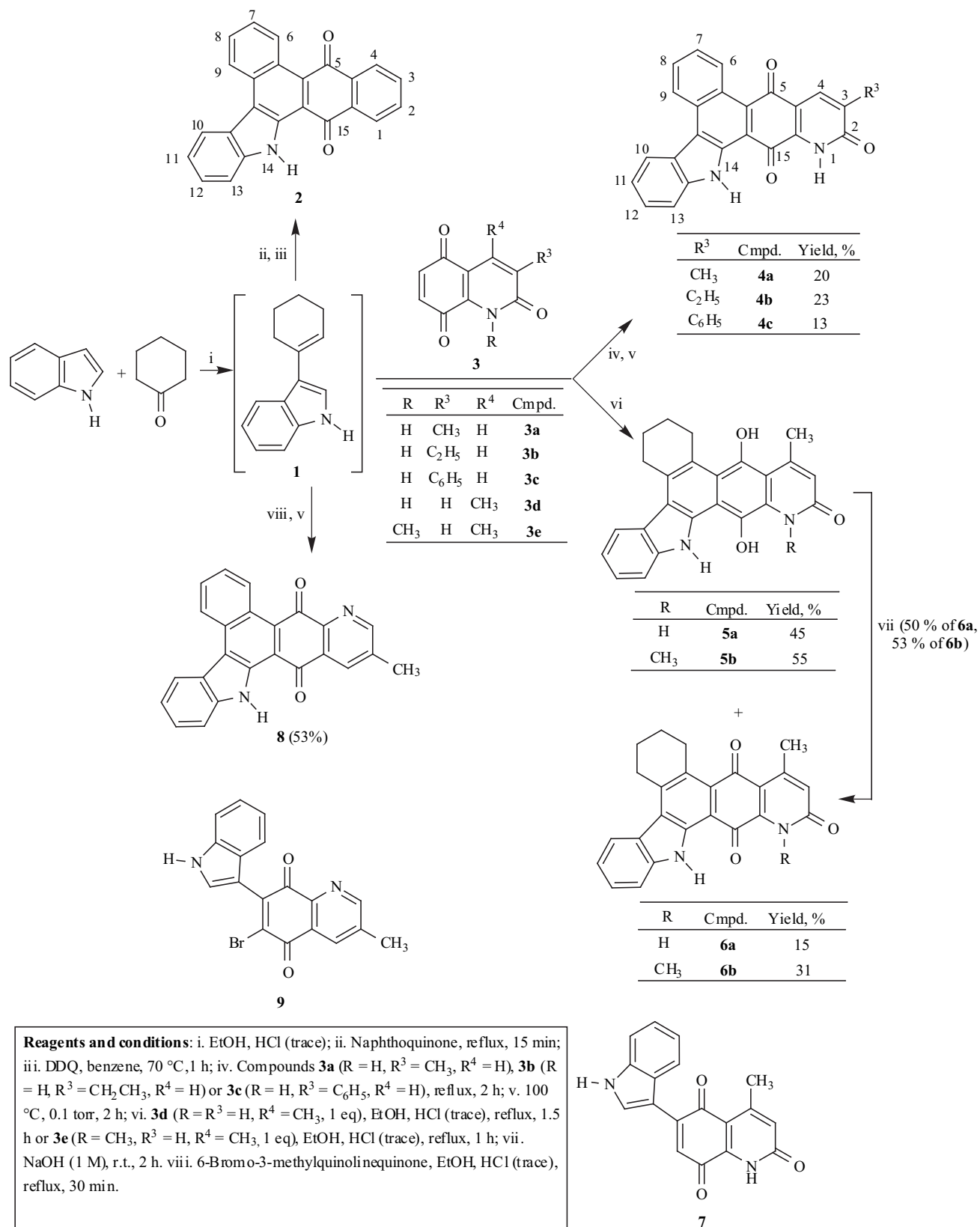
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- [7] **Experimental procedure:** To a solution of cyclohexanone (290 mg, 3 mmol) in ethanol (10 mL) was added indole (349 mg, 3 mmol), naphthoquinone (470 mg, 3 mmol) and 35 % aqueous HCl (0.2 mL). The mixture was refluxed for 15 min, cooled and evaporated *in vacuo*. The residue was dissolved in ethyl ether (10 mL) and was washed with water (3 x 5 mL). The ether layer was evaporated and the residue was dissolved in dry benzene (5 mL), under an argon atmosphere. After addition of dichlorodicyanoquinone (DDQ) (2.83 g, 12.5 mmol), the solution was heated at 70 °C for 1 h. Upon cooling, a precipitate was formed, which was filtered off and washed with CHCl₃ (3 x 5 mL). The combined filtrates were evaporated and chromatographed on silica gel, eluting with 1:1 ethyl ether-petroleum ether, to yield 200 mg (38%) of compound **2**, as a brown solid. Mp 165 °C. ν_{\max} (KBr) 1671, 1630 (CO) cm⁻¹. ¹H-NMR (250 MHz, CDCl₃) δ 8.71 (br. s, 1H, H-1); 8.25 (d, 1H, *J* = 3.0 Hz, H-10); 8.19-8.08 (m, 2H, H-1,4); 8.05-7.95 (m, 1H, H-9); 7.75-7.70 (m, 4H, H-2,3,10,13); 7.50-7.45 (m, 2H, 7,8); 7.30-7.25 (m, 2H, H-11,12). δ_C (63 MHz, CDCl₃) 185.4 and 185.2 (C-5,15); 146.1 (C-13a); 142.2 and 137.1 (C-14a, C-14b, C-5a); 133.6 and 133.2 (C-2, C-3); 132.9 and 132.1 (C-15a, C-4a); 130.8 and 129.6 (C-6, C-9); 126.7 (C-1, C-4); 125.7 and 123.3 (C-7 and C-8); 125.4 (C-9b); 121.8 (C-11); 120.3 (C-10, C-12); 119.6 (C-5b); 117.9 (C-9a); 111.8 (C-13); 109.4 (C-9c). Analysis: Found: C, 82.35; H, 3.54; N, 4.93. C₂₄H₁₃NO₂ requires C, 82.99; H, 3.74; N, 4.03.
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- [11] **Representative experimental procedure:** To a solution of cyclohexanone (72 mg, 0.74 mmol) in ethanol (10 mL) was added indole (87 mg, 0.74 mmol), quinone **3e**¹⁰ (150 mg, 0.74 mmol) and 35 % aqueous HCl (0.2 mL). The mixture was refluxed for 1 h, cooled, washed with water (3 x 3 mL) and diluted with ethyl ether (5 mL). The red precipitate was filtered and identified as compound **6b** (45 mg, 31 %). The organic phase was evaporated and the residue was chromatographed on silica gel eluting with 1:1 ethyl acetate-ethyl ether, to yield 117 mg of a mixture of the hydroquinone derived from **3e**¹⁰ (13 %) and compound **5b** (45 %, yields estimated by NMR). To this mixture was added 1 M aqueous NaOH (5 mL) and the suspension was stirred at room temperature for 2 h. The solid was decanted from the aqueous phase and dissolved in ethanol (10 mL), which was diluted with ethyl ether. A red precipitate of 50 mg (53 %) of compound **5b** appeared and was filtered. *Data for 6b:* Mp 290 °C. ν_{\max} (KBr) 3432, 3237 (NH), 1655 (CO) cm⁻¹. ¹H-NMR (250 MHz, d₆-DMSO) δ 10.60 (s, 1H, H-14); 8.19 (d, 1H, *J* = 7.0 Hz, H-10); 7.54-7.50 (m, 3H, H-11,12,13); 6.68 (s, 1H, H-3); 4.00 (s, 3H, N-CH₃); 3.46 (t, 2H, *J* = 5.0 Hz, H-6); 3.29 (t, 2H, *J* = 5.5 Hz, H-9); 2.62 (s, 3H, C₄-CH₃); 2.02 (m, 2H, H-7); 1.90 (m, 2H, H-8). Analysis: Found: C, 75.43; H, 4.86; N, 7.35. C₂₅H₂₀N₂O₃ requires C, 75.75; H, 5.05; N, 7.07. *Data for 5b:* ¹H-NMR (250 MHz, d₆-DMSO) δ 10.93 (s, 1H, H-14); 9.25 (br. s, 1H, C₅-OH); 7.82 (d, 1H, *J* = 7.5 Hz, H-10); 7.35 (br. s, 1H, C₁₅-OH); 7.22 (d, 1H, *J* = 7.9 Hz, H-13); 7.16-6.90 (m, 2H, H-11,12); 6.19 (s, 1H, H-3); 3.92 (s, 3H, N-CH₃); 3.81 (t, 1H, *J* = 12.0 Hz, H-6); 2.53 (s, 3H, C₄-CH₃); 2.35-2.28 (m, 1H, H-6); 1.93 (br. s, 2H, H-9); 1.51 (br. s, 2H, H-7); 1.30-1.27 (m, 2H, H-8).
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