A Versatile One-Pot Synthesis of Fused Polycyclic Imidazole-naphthoquinone Derivatives through Imidazole-4,5-quinodimethane Generation Followed by Diels–Alder Cycloaddition

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Abstract: An efficient procedure for the trapping of an imidazole-4,5-quinodimethane intermediate **3** with quinones in boiling toluene and in the presence of 18-crown-6 is described. In all cases the fully aromatized imidazole-naphthoquinone derivatives were isolated as the main reaction products in satisfactory yields. However, in the case of benzo- and naphthoquinone, aromatized products were also isolated, in which the bromine in the 2-imidazole position was replaced by hydrogen, whereas in the case of the asymmetrical 2phenylbenzoquinone and 5,8-quinoline dione inseparable regioisomeric mixtures were formed.

Key words: crown ether, Diels-Alder reactions, imidazole *o*-quinodimethanes, fused imidazolenaphthoquinones, one-pot reaction

The heterocyclic analogues of *o*-quinodimethanes (*o*-QDMs) are of considerable interest both from a theoretical point of view and for their potential in organic synthesis as useful dienes.¹ Their utilization for the annulations of aromatic systems has now acquired practical importance and has been exploited in efficient synthesis of a wide range of polycyclic natural products.²

On the other hand, quinones occupy an important place among the different classes of antitumor agents. The biological processes involved with the antitumor activity of quinones are DNA intercalation, bioreductive alkylation of biomolecules, and generation of oxy radicals through redox cycling.³⁻⁷ Heterocycle-fused quinones, containing nitrogen, are known to possess antibacterial,⁸ antifungal,⁹ and cytotoxic activities.¹⁰ The clinical significance of this class of compounds has stimulated the synthesis of new lead compounds retaining the 'core' quinone chromophore.¹¹ In addition, it is well known that imidazole-based heterocyclic molecules play important role in various biochemical processes.¹² The imidazolyl moiety is being used as a building block in developing new drugs,^{12b,13} but also has wide-ranging applications in organometallic catalysis,¹⁴ asymmetric catalysis,¹⁶ and coordination chemistry.¹⁵ There are several reports of the synthesis and functionalization of the imidazole moiety.¹⁷

As a part of our research program on heterocyclic *o*-QDMs, we studied recently the synthesis and Diels–Alder reactions of an imidazole *o*-QDM.¹⁸ In continuation of

this study we envisaged that Diels–Alder trapping of an imidazole *o*-QDM with quinones could offer a successful pathway. Moreover, very few reactions between *o*-QDMs¹⁹ (especially heterocyclic *o*-QDMs²⁰) and quinones as dienophiles, leading to quinone derivatives fused to a biologically active heterocyclic ring, have been studied.

Our synthetic approach is depicted in Scheme 1. The tetrabromoimidazole derivative 2, prepared in 60% yield by bromination of 1, was used as an o-QDM precursor.¹⁸ Due to the instability of 2 to column chromatography, it was not purified but was treated directly with sodium iodide in boiling toluene for 3-4 hours in the presence of 18-crown-6 to afford the imidazole o-QDM 3, which was reacted in situ with quinones. From the reaction with the symmetrical benzoquinone the initially formed Diels-Alder cycloadduct was not isolated but, under the reaction conditions, underwent subsequent oxidation to give the aromatized product 4 in 38% yield.²¹ A small amount (6% yield) of a second, aromatized product 5, in which the bromine in the 2-imidazole position was replaced by hydrogen was also isolated (Scheme 1). An analogous result was obtained from the reaction of **3** with naphthoquinone, where the fully aromatized tetracyclic product 6 was isolated in only 10% yield. However, a second fully aromatized tetracyclic product 7 was isolated in 41% yield²² along with a third product, namely the non-aromatized Diels-Alder derivative 8 in 5% yield. In the last two products, 7 and 8, again the imidazole 2-position bromine atom was replaced by hydrogen. Next, the asymmetrical quinones, 2-phenylbenzoquinone and 5,8-quinoline dione were used. In both cases inseparable mixtures of the regioisomeric aromatized compounds 10a,b (3:1) and 11a,b (4:1) were isolated in 43% and 32% overall yield, respectively. Along similar lines, 3 reacted with triptycenoquinone to give only the aromatized polycyclic cycloadduct 9 in 35% yield.

The structural assignments of all isolated products were established by analysis of their NMR spectra (¹H, ¹³C, DEPT, COSY H–H, NOESY H–H, HETCOR C–H, and COLOC C–H). The COLOC correlations measured for compound **7** are depicted in Figure 1.

In conclusion, an efficient route for the in situ reaction of the imidazole o-QDM 3 with quinones, yielding fully aromatized polycyclic benzimidazole derivatives as the main products in satisfactory yields in one-pot reactions has been described. Because of the extended coplanarity

SYNLETT 2007, No. 16, pp 2596–2598 Advanced online publication: 12.09.2007 DOI: 10.1055/s-2007-986656; Art ID: D21807ST © Georg Thieme Verlag Stuttgart · New York



Scheme 1 Bromination of compound 1, preparation and Diels-Alder trapping of *o*-QDM 3 in a one-pot reaction in boiling toluene with various quinones



Figure 1 Diagnostic COLOC correlations between protons and carbons (via ${}^{3}J_{C-H}$) in compound **7**

of the fully aromatized polycyclic heterocyclic derivatives, these compounds are promising intercalating agents and their biological activity is under investigation. Furthermore, the presence of bromine atom in position 2 of the imidazole ring allows the opportunity to substitute this by other desirable substituents. Further applications, especially with asymmetrically substituted quinones are being studied.

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- (21) All melting points were determined on a Büchi apparatus and are uncorrected. The ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AM300 spectrometer in CDCl₃ with TMS as internal standard. All coupling constants are given in Hz and chemical shifts are given in ppm. Selected Data for Compound 4: Mp 125–127 °C. IR (mull) $v_{max} = 1666, 1604 \text{ cm}^{-1}$. ¹H NMR²² (300 MHz, CDCl₃): $\delta =$ 3.570 (s, 3 H, NMe), 6.418 (m, J = 9.1, 2.6 Hz, 2 H, C-2', C-6'), 6.982 (d, J = 10.4 Hz, 1 H, C-7 or C-6), 7.014 (d, J = 10.4 Hz, 1 H, C-6 or C-7), 7.365 (m, J = 9.1, 2.6 Hz, 2 H, C-3', C-5'), 7.900 (d, J = 0.5 Hz, 1 H, C-9), 8.43 (d, J = 0.5 Hz, 1 H, C-4). ¹³C NMR (75 MHz, CDCl₃): $\delta = 40.3$ (NMe), 108.6 (C-9), 114.2 (C-4'), 114.4 (C-2', C-6'), 116.2 (C-2), 119.6 (C-4), 128.6 (C-8a), 132.6 (C-3', C-5'), 136.4 (C-4a), 137.1 (C-9a), 138.9 (C-7), 139.4 (C-6), 144.4 (C-1'), 145.6 (C-3a), 184.2 (C-5), 184.5 (C-8). Anal. Calcd (%) for $C_{18}H_{11}Br_2N_3O_2$ (461.11): C, 46.89; H, 2.40; N 9.11. Found: C, 46.79; H, 2.52; N 8.94.
 - Selected Data for Compound 7: Mp 235–237 °C. ¹H NMR²² (300 MHz, CDCl₃): δ = 3.590 (s, 3 H, NMe), 6.504 (m, J = 9.1, 2.6 Hz, 2 H, C-2', C-6'), 7.372 (m, J = 9.1, 2.6 Hz, 2 H, C-3', C-5'), 7.796 (m, J = 7.9, 7.6, 2.2 Hz, 1 H, C-8 or C-7), 7.817 (m, J = 7.9, 7.6, 2.2 Hz, 1 H, C-7 or C-8), 8.18 (d, J = 0.5 Hz, 1 H, C-11), 8.307 (m, J = 7.9, 2.2, 0.5 Hz, 1 H, C-9 or C-6), 8.34 (s, 1 H, C-2), 8.366 (m, J = 7.9, 2.2, 0.5 Hz, 1 H, C-6 or C-9), 8.82 (d, J = 0.5 Hz, 1 H, C-4). ¹³C NMR (75 MHz, CDCl₃): $\delta = 41.9$ (NMe), 109.9 (C-11), 114.6 (C-4'), 115.2 (C-2', C-6'), 121.6 (C-4), 127.4 and 127.5 (C-9 and C-6), 129.9 (C-4a), 130.2 (C-10a), 132.5 and 133.8 (C-5a and C-9a), 132.6 (C-3', C-5'), 134.0 and 134.2 (C-7 and C-8), 135.5 (C-11a), 145.3 (C-3a), 147.1 (C-1'), 147.4 (C-2), 182.7 (C-5), 183.0 (C-10). MS (EI, 70 eV): m/z $(\%) = 431/433 (72) [M^+], 416/417 (10) [M - CH_3]^+, 352 (7),$ 281 (43), 207 (100). Anal. Calcd (%) for $C_{22}H_{14}BrN_3O_2$ (432.27): C, 61.13; H, 3.26; N 9.72. Found: C, 61.25; H, 3.17; N, 9.65.
- (22) The multiplicities and chemical shifts of the aromatic protons have been confirmed after simulation with program SpinWorks, version 2.2.0, available from ftp:// davinci.chem.umanitoba.ca.