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QUINONE DIAZIDE CYCLIZATIONS - A DIRECT ROUTE TO DIHYDROBENZOFURANS

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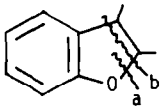
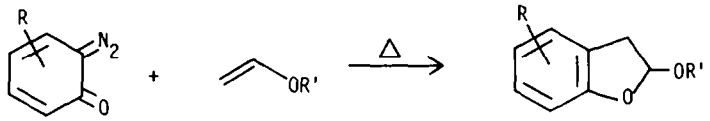
Abstract The reaction of ortho-quinone diazides with electron-rich alkenes produces 2,3-dihydrobenzofurans. The ortho-quinone diazides are formed from the ortho-nitrophenols by reduction and diazotization. The reaction of an ortho-quinone diazide with 2,3-dihydrofuran produces a furo-[2,3-b]benzofuran ring system.

The 2,3-dihydrobenzofuran unit is contained in biologically significant natural products such as morphine, the aflatoxins and the versicolorins.[1] Most synthetic approaches have employed an intramolecular cyclization of an ortho-substituted phenol (path a).[2] In contrast there are few examples of the dissection represented by path b. The most general one involves



the reaction of vinyl ethers with activated quinones.[3] We have examined the reactions of ortho-quinone diazides with electron rich alkenes and wish to report a direct and regiospecific route to the 2,3-dihydrobenzofuran unit by way of path b. The basic reaction is depicted below.

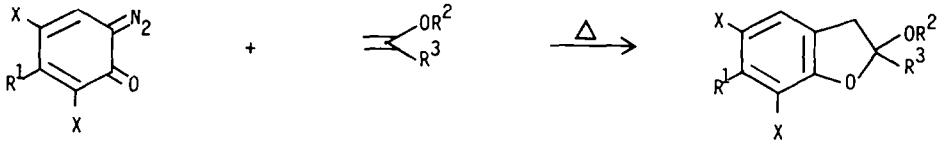


1

Although several ortho-quinone diazides have been prepared,[4,5] a literature search revealed only five references on the reaction of ortho-quinone diazides with alkenes or alkynes.[6] The most definitive work was done by Huisgen and coworkers[6a] who treated the 3,4,5,6-tetrachloroquinone diazide with styrene, phenylacetylene, and dimethylfumarate to produce adducts in 24%, 39% and 60% yields, respectively.

The ortho-quinone diazide **1** was prepared from 2,4-dichloro-6-nitrophenol by catalytic hydrogenation followed by diazotization. The resulting diazonium phenol spontaneously lost HCl to provide **1**. This quinone diazide exhibited a characteristic intense infrared absorption at 2100-2700 cm^{-1}. Quinone diazide **4** was synthesized from 2,4,6-tribromoaniline. N-acetylation followed by benzoxazole formation and acidic hydrolysis produced the ortho-aminophenol which was diazotized to afford **4**. The results of our study are depicted in Table I.

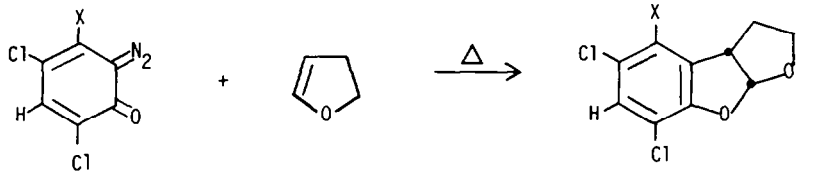
Table I - Quinone Diazide Cyclizations



ENTRY	X	R^1	R^2	R^3	% Yield
1	H	H	Et	H	--
2	Cl	H	Et	H	55
3	Cl	H	$COCH_3$	H	47
4	Cl	H	$COCH_3$	CH_3	50
5	Cl	OCH_3	Et	H	46
6	Cl	H	CH_3	$CH{=}CH_2$	--
7	Cl	H	$COCH_3$	Ph	52

The quinone diazides used in this study did not react with unactivated alkenes or alkynes. The adducts from entries 3, 4 and 7 could be converted to the corresponding benzofurans (pTSA, PhH) in excellent yield. The unsubstituted quinone diazide failed to afford the desired 2,3-dihydrobenzofuran. Apparently the chlorine substituents suppress the competing intramolecular Wolff rearrangement so that intermolecular addition can occur.

The reaction of quinone diazides with 2,3-dihydrofuran provided a rapid entry to the aflatoxin and versicolorin ring system. The structure of **2** is supported by a doublet

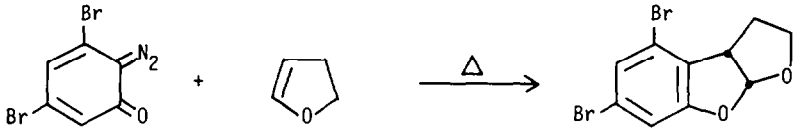


2, X = H 55%

3, X = OCH_3 45%

(J=6 Hz) at 6.40 δ. In aflatoxin B_2 the acetal methine proton is at 6.42 δ.

Another example which affords a substitution pattern closer to that of the aflatoxins is described below. The dibromoquinone diazide was treated with 2,3-dihydrofuran to afford



4 **5**

adduct **5** in 56% yield. Replacement of the bromine atoms with hydroxyl groups would provide a key intermediate for aflatoxin synthesis.[1]

Quinone diazide chemistry offers an attractive and direct entry to either the 2,3-dihydrobenzofuran or the benzofuran ring system. The reaction with 2,-3-dihydrofuran provides a rapid synthesis of the furo-[2,3-b]benzofuran ring system.

Experimental

2-Amino-4,6-dichlorophenolhydrochloride. Commercially available 2,4-dichloro-6-nitrophenol (Aldrich Chem. Co.) (52 g, 0.250 moles) was carefully hydrogenated with 10% platinum on carbon (2 g) in ethanol at ambient temperature. A hydrogen pressure of 90 psi was applied with a Parr apparatus and the reaction followed by TLC. Periodic cooling of the pressure bottle was necessary in order to prevent overheating due to the exothermic reaction. When complete, the mixture was filtered through Celite to give a dark solution which was not isolated. Acidification with excess ethanolic HCl (2N) gave the crude aniliniumhydrochloride. The solution was evaporated in-vacuo to give a brown solid, which was recrystallized from methanol-ether, yielding 32 g (0.18 moles, 72%) of a white solid: 60 MHz NMR ($D_2O/(CD_3)_2CO$) δ 7.40 (d, J = 2 Hz, 1 H), 7.49 (d, J = 2 Hz, 1 H); 90 MHz C-13 NMR ($D_2O/(CD_3)_2CO$) δ 122.87, 123.90, 125.26, 125.91, 129.16, 146.22.

4,6-Dichloro-1,2-benzoquinonediazide (1). A cooled (0°C), methanolic solution of the hydrochloride (10.0 g, 46.6 mmoles in 150 ml) was treated with neat isoamylnitrite (25 ml) which was added over 30 min., with the reaction protected from light. The mixture very quickly became turbid and gave a fluffy, bright orange precipitate. The solution was warmed to ambient temperature, filtered, and the solid washed with ether-hexane (1:1). The collected mass was dissolved in methylene chloride and washed four times with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated, without heating above room temperature to give **1**. The fluffy, yellow-orange solid (decomposes above 115°C) is light-sensitive, but can be stored indefinitely if cooled to 10°C in the dark. IR (film $CDCl_3$) 2150, 1620, 1610 cm^{-1} (lit. (6c) 2128, 1603 cm^{-1}); 60 MHz NMR ($CDCl_3$) δ 7.12 (br d, 1 H), 7.50 (br d, 1 H); 90 MHz C-13 NMR ($(CD_3)_2CO$) δ 100.80, 116.21, 122.84, 131.75, 139.88. 172.53.

3,5-dibromo-ortho quinone diazide (4). A solution of 2,4,6-tribromoacet-anilide (5.75 g, 15.5 mmol) in 80 ml of THF and 25 ml of HMPA was heated to reflux. Pentane washed sodium hydride was then added until gas evolution ceased. The solution was stirred for two h. Cuprous bromide (2.30 g, 16.0 mmol) was added and the resulting suspension was heated at reflux overnight. The cooled suspension was poured into water and extracted with ether. The organic layer was dried and concentrated in-vacuo. After chromatography on silica gel, a 41% yield of benzoxazole was obtained. The aminophenol hydrochloride was then prepared by refluxing the benzoxazole in ethanol containing concentrated HCl (2 ml for each gram of benzoxazole) for 10 h. The hydrochloride was obtained in 65% yield. The hydrochloride (1.22 g, 4.02 mmol) in 30 ml of methanol at 0°C was treated with isoamyl nitrite (3 ml) over 40 min. After 3 h at 0°C, the reaction was concentrated in-vacuo (cold water bath). The residue was recrystallized from an ether-hexane mixture to afford 0.97 g of pure quinone diazide 4. IR ($CDCl_3$) 2130, 1482, 902, 722 cm^{-1}. NMR ($CDCl_3$) δ 6.60 (d, J = 2 Hz, 1 H), 6.88 (d, J = 2 Hz, 1 H). 90 MHz C-13 NMR ($CDCl_3$) δ 90.20, 113.87, 121.87, 126.22, 135.46, 175.45.

Quinone Diazide Cyclizations - General Procedure

The base washed quinone diazide (1M) was suspended in a solution of the alkene. After the suspension was degassed, the sealed tube was heated at 135°C for 80 min. The crude product was chromatographed on silica gel to afford pure products.

5,7-Dichloro-2-ethoxy-2,3-dihydrobenzofuran: isolated a yellow oil.
IR (film) 2940, 1590, 1465, 1105 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, 3 H), 2.9-3.9 (m, 4 H), 5.49 (dd, J = 2 Hz, 1H), 6.80 (br d, J = 4 Hz, 2 H); 90 MHz C-13 NMR ($CDCl_3$) δ 15.02, 37.39, 64.77, 107.04, 115.62, 123.43, 127.91, 128.56, 152.82, 153.15. Mass spectrum m/e calc for $C_{10}H_{10}Cl_2O_2$ (M^+) 232.00592, found 232.00676.

5,7-Dichloro-2-ethoxy-5-methoxy-2,3-dihydrobenzofuran: isolated as a colorless oil.
IR (film) 2980, 1600, 1470, 1440, 1110, 1060 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.21 (t, J = 5 Hz, 3 H), 3.30 (dd, J = 4 Hz, 2 H), 3.85 (q, J = 5 Hz, 2H), 3.85 (s, 3 H), 5.80 (dd, J = 4 Hz, 1 H), 7.15 (s, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 15.03, 36.16, 60.00, 64.82, 107.18, 110.16, 118.61, 118.72, 129.23, 151.22, 154.20.

5,7-Dichlorofuro[2,3b]-2,3-dihydrobenzofuran (2): isolated as a yellow oil.
IR (film) 2990, 1585, 1455, 1075, 1030 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.8-2.6 (m, 2 H), 3.4-4.3 (m, 3 H), 6.40 (d, J = 6 Hz, 1 H), 7.0-7.3 (m, 2 H); 90 MHz C-13 NMR δ 33.17, 47.21, 67.31, 111.92, 114.78, 123.23, 125.83, 128.43, 130.76, 154.12. Mass spectrum - m/e 230.

5,7-Dichloro-5-methoxyfuro[2,3b]-2,3-dihydrobenzofuran (3)
IR (film) 2995, 2950, 1595, 1470, 1430, 1060; 60 MHz NMR ($CDCl_3$) δ 1.8-2.6 (m, 2 H), 3.6-4.3 (m, 3 H), 3.90 (s, 3 H), 6.28 (d, J = 6 Hz, 1 H), 7.08 (s, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 31.93, 46.34, 60.54, 67.58, 112.33, 121.81, 130.10, 131.56, 135.73, 151.39, 155.07.

4,6-Dibromofuro[2,3b]-2,3-dihydrobenzofuran (5)
IR (film) 2950, 1590, 1430 cm^{-1}. 60 MHz NMR ($CDCl_3$) δ 1.95-2.40 (m, 2 H), 3.30-4.40 (m, 3 H), 6.30 (d, J = 6 Hz, 1 H), 6.83 (d, J = 1 Hz, 1 H), 7.17 (d, J = 1 Hz, 1H). 90 MHz C-13 NMR δ 31.47, 47.80, 67.24, 111.66, 111.92, 119.01, 122.39, 122.61, 127.59, 160.56. Anal. calcd for $C_{10}H_8Br_2O_2$: C, 37.53; H, 2.52. Found: C, 37.70; H, 2.64.

Benzofurans from 2-Acetoxy-2,3-dihydrobenzofurans
The acetoxy-2,3-dihydrobenzofuran, 1 M in a benzene solution containing a crystal of p-toluenesulfonic acid, was heated to reflux overnight. The solution was washed with sodium bicarbonate, dried and concentrated in vacuo. The crude product was chromatographed on silica gel.

5,7-Dichlorobenzofuran: mp 58-59°C (lit. (7) mp 60°C).
IR (film) 2940, 1580, 1445, 1410 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 6.8 (br d, J = 1 Hz, 1 H), 7.30 (br d, J = 1 Hz, 1 H), 7.45 (d, J = 1 Hz, 1 H), 7.70 (d, J = 1 Hz, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 106.96, 117.47, 119.42, 124.46, 128.63, 129.72, 146.89, 149.44.

5,7-Dichloro-2-methylbenzofuran: mp 64-66°C (lit. (8) mp 66°C).
IR (film) 2920, 1575, 1440, 1175 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 2.50 (s, 3 H), 6.35 (br s, 1 H), 7.20 (br d, J = 1 Hz, 1 H), 7.35 (br d, J = 1 Hz, 1 H); 90 MHz C-13 NMR ($CDCl_3$) δ 14.11, 103.14, 116.42, 118.43, 123.23, 128.24, 131.49, 149.18, 158.09.

5,7-Dichloro-2-phenylbenzofuran: mp 121-123°C (lit. (6b) mp 125-126°C).
IR (nujol mull) 1610, 1580, 1440, 1418, 1180, 915, 845, 765, 750, 690, 665 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 6.97, (s, 1 H), 7.27-7.60 (m, 5 H), 7.8-8.0 (m, 2 H); 90 MHz C-13 NMR ($CDCl_3$) δ 101.19, 117.18, 119.07, 124.34, 125.25 (3C), 128.89 (2C), 129.41 (2C), 131.56, 149.31, 158.22.

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