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Facile Conversion of *o*-Quinones into 1,3-Dioxoles

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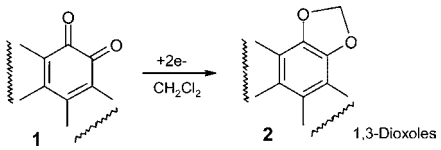
ABSTRACT



***o*-Quinones are transformed into the corresponding 1,3-dioxoles in a single-step process by cathodic reduction in dichloromethane.**

The benzodioxole ring system is common to a significant number of bioactive natural products, including safrole and piperonal, as well as in many different alkaloids.[1]

Furthermore, the 1,3-dioxoles possess several pharmaceutical properties. For example, they exhibit significant in vitro leishmanicidal activity,[2] inhibition of the vaccina enzyme,[3] and potent dual inhibitions of ACE/NEP.[4] 1,3-Dioxoles have also been utilized as selective antagonist ligands of A(2B) adenosine[5] and orally active ETA receptors antagonist,[6] as well as highly potent KCNQ2 openers.[7] Finally, 1,3-dioxoles have applications in the polymer, food, and perfume industries, and agrochemical, pesticidal, or medical uses have been described.[8]

The first preparation of an unsubstituted 1,3-dioxole was performed in 1961.[9] These heterocycles are typically obtained using other heterocycles as starting material,[10] by reaction of phosgene with an enodiol[11] or by cycloaddition of diazodicarbonilic derivatives with aldehydes[12] or ketones.[13] Other more complex 1,3-dioxoles have been synthesized too.[14]

In the present communication *o*-quinones **1a**−**e** are converted into the corresponding 1,3-dioxoles **2a**−**e** in a single step process by cathodic reduction in dichloromethane[15] (Scheme 1). Together with **2a**−**e**, dicarboxilic acid **3a**−**e** was obtained as secondary product.

The starting quinones **1a**−**f** present two one-electron reversible peaks in cyclic voltammetry. These peaks corresponded to the formation of an anion radical and a dianion. When preparative scale electrolysis reactions (see Figure 1)

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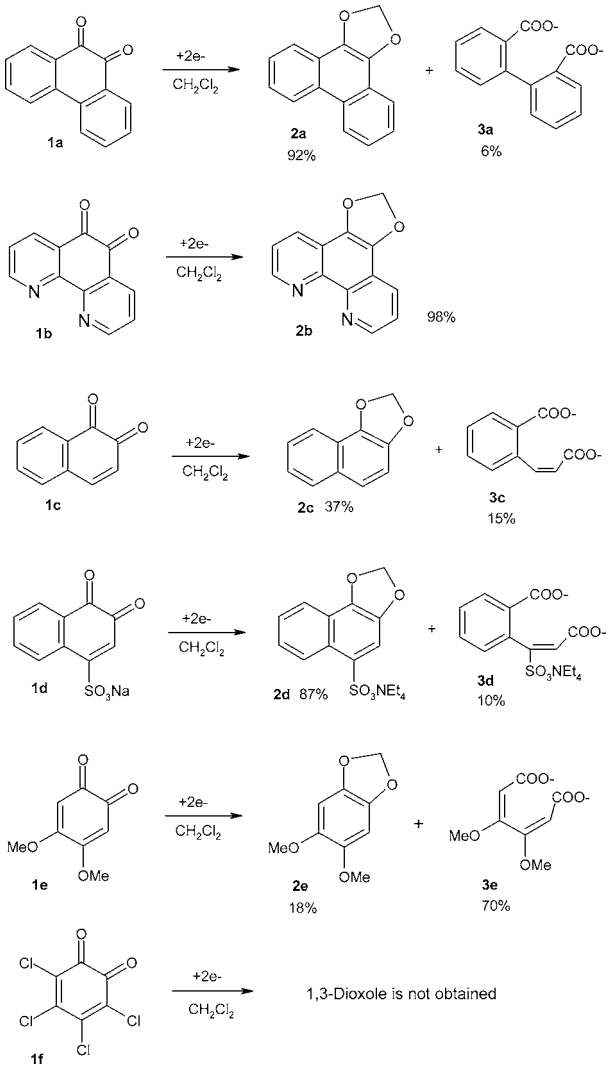
Scheme 1



were carried out at the potential of the first peak, the less negative potential peak, intensely colored solutions were obtained, but after the reaction was further processed, starting **1** was obtained. These intensely colored solutions corresponded to the formation of the anion radical, which under an open-air atmosphere transfers the electron to O_2 thereby regenerating **1**. However preparative electrolysis reactions performed at the constant potential of the second peak, the more negative peak, afforded dioxoles **2**.

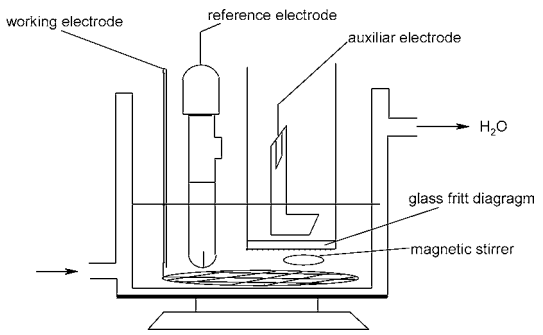


Figure 1. Concentric divided cell for preparative scale electrolysis.

Table 1. Peak Potentials[a] (E) of **1a**−**f** in Dichloromethane/Et_4NCl as Solvent Supporting Electrolyte

1	substrate	E_{pc_1}	E_{pc_2}	E_{pa_1}	E_{pa_2}
a	9,10-phenanthrenequinone	−0.53	−1.03	−0.46	−0.84
b	1,10-phenanthroline-5,6-dione	−0.44	−1.10	−0.23	−0.90
c	1,2-naphthoquinone	−0.42	−0.87	−0.35	−0.77
d	1,2-naphthoquinone-4-sulfonic acid sodium salt	−0.46	−0.98	−0.38	−0.86
e	4,5-dimethoxy-*o*-quinone	−0.60	−0.87	−0.52	−0.78
f	tetrachloro-*o*-quinone	+0.2	−0.47	+0.26	−0.39

[a] In V, vs Ag/Ag^+. Scan rate, 50 mV/s; cathose, Pt; Anode, C.

This reaction is expected to be a nucleophilic substitution, as shown by the fact that tetrachloro-*o*-quinone dianion, a soft nucleophile due to the electron-withdrawing effect of the halogen atoms on the ring, does not experimentally afford 1,3-dioxol. However, the dianion of the 4,5-dimethoxy-*o*-quinone, a better nucleophile toward CH_2Cl_2 due to the presence of two electron-donating groups on the ring, gives only 18% yield of dioxol **2e**. On the other hand, the dianion of the quinone **1d**, despite an electron-withdrawing group at the 4-position, affords 87% dioxol. Therefore, the yields of **2** do not depend on the higher or lower nucleophility of the corresponding dianions.

It is well-known[16] that the formal potential $E^{\circ\prime}$ is taken as the average of the cathodic and the anodic peak potentials (E_{pc} and E_{pa}). In our case there is a correspondence between these $E^{\circ\prime}$ values and the formation of dioxols. As is observed in Table 1, with the more negative $E^{\circ\prime}$ values of the redox pair dianion/radical-anion of the quinone substrates **1a**, **1b**, and **1d** (−0.93, −1.0, and −0.92 V, respectively) the higher yields of **2** are afforded. Substrates **1c** and **1e** (−0.82 V) give moderate-low yields of **2c,e**. However **1f** (−0.43 V) does not provide 1,3-dioxol.

(15) Compounds **1a**−**d,f** are commercially available and have been used without purification. **1e** was prepared by anodic oxidation of cathecol as described in: Nematollahi, D.; Golabi, S. M. *J. Electroanal. Chem.* **1996**, *405*, 133. The electrochemical reductions were performed under potentiostatic conditions in a concentric cell with two compartments separated by a low porosity (D_4) glass frit diaphragm and equipped with a magnetic stirrer. A platinum net (12 cm^2) was used as the cathode, a platinum plate (2.25 cm^2) as the anode, and a saturated calomel electrode as the reference. The SSE (solvent supporting electrolyte) was nominally anhydrous dichloromethane containing 0.05 M tetraethylammonium chloride. A solution of the electroactive quinone (5.0 mmol in 30 mL of SSE) was electrolyzed under argon atmosphere at a constant potential corresponding to the second reduction peak. When the current fell almost to zero, the reduction was finished and crude was treated under open-air atmosphere. The solvent in the cathodic solution was removed under reduced pressure. The residue was extracted with ether/water, and the organic phase was dried over Na_2SO_4 and concentrated by evaporation. The resulting solid was chromatographed on silica gel (18 × 3 cm) column, using CH_2Cl_2 or CH_2Cl_2/Hex (8:2) as eluent, to get the dioxoles **2a**−**e**. The aqueous phase was acidified using HCl(5%), further extracted with ether, dried over Na_2SO_4, and concentrated by evaporation; the resulting solid was characterized as the corresponding dicarboxylic acid.

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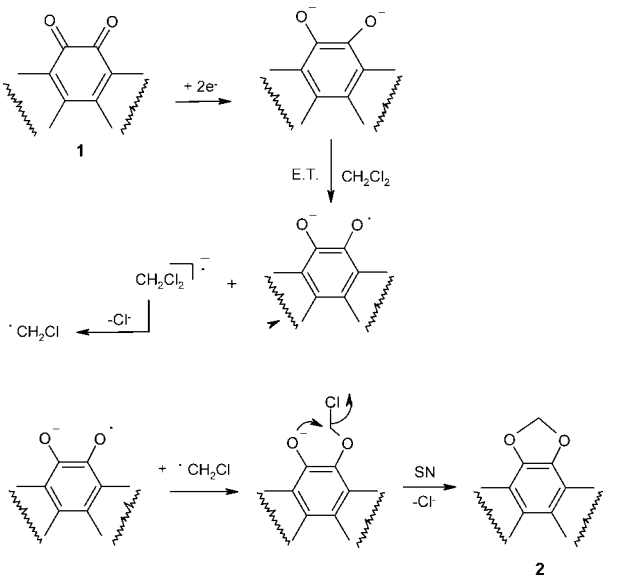
Scheme 2



We can conclude that the more negative the $E^{o\prime}$ values, the higher are the yields of **2** obtained, and the reaction is not a nucleophilic substitution but a homogeneous electron transfer of the dianion to dichloromethane.

The electrogenerated dianion reacts with dichloromethane in a redox process to afford the chloromethane radical $^{\bullet}CH_2Cl$, which then couples with the anion radical of quinone to generate a C−O bond. Subsequently, an internal nucleophilic substitution leads to **2** in good yield (Scheme 2).

Furthermore, the experimental consumed charge was always a little higher than expected (2 F/mol). This is in agreement with our postulated mechanism in which the last radical coupling is only effective when both species are in near proximity. Therefore additional charge would ensure complete consumption of the starting quinone.

The formation of dicarboxylic acids **3** is due to the electron-transfer reaction of the remaining dianion to O_2, during the workup under open-air atmosphere.

In the reduction of 1,2-naphthoquinone (**1c**), together with **2c** and dicarboxylic acid **3c**, secondary products were formed. To avoid the formation of these products, the 4-position of **1c** was substituted with a sulfonic acid sodium salt, and it was electrolyzed. In this case the 1,3-dioxol (**2d**) was successfully obtained in 87% yield.

The physical and spectroscopical descriptions of the new compounds **2a**−**e** are provided in footnote 17.

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(17) **Phenanthrene[9,10-*d*]1,3-dioxole (2a)** (817 mg, 92% yield). Mp 120−121 °C. IR (KBr) ν = 3063, 2906, 1658, 1609, 1520, 1450, 1372, 1118, 1073, 751, 720 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.27(s, 2H), 7.57(t, 2H, J = 7 Hz), 7.64(t, 2H, J = 7 Hz), 7.94(d, 2H, J = 7.8 Hz), 8.66(d, 2H, J = 7.8 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 101.77, 120.0, 121.2, 123.3, 124.7, 126.9, 127.3, 137.8. MS *m*/*e* (relative intensity) EI: 223(M^+ + 1, 16), 222(M^+, 100), 194(11), 180(11), 163(45), 152(6), 111-(12), 82(15), 63(8). Anal. Calcd for $C_{15}H_{10}O_2$: C, 81.08; H, 4.50. Found: C, 81.27; H, 4.39. **1,10-Phenanthroline[5,6-*d*]1,3-dioxole (2b)** (1098 mg, 98% yield). Mp 240−242°C. IR (KBr) ν = 3058, 2921, 1661, 1590, 1517, 1459, 1364, 1067, 1027, 794, 734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.32(s, 2H), 7.61(dd, 2H, J_1 = 8.1 Hz, J_2 = 4.4 Hz), 8.25(dd, 2H, J_1 = 8.1 Hz, J_2 = 1.8 Hz), 9.07(dd, 2H, J_1 = 4.4 Hz, J_2 = 1.8 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 103, 118.2, 123.2, 128.3, 137.4, 142.8, 148.5. MS *m*/*e* (relative intensity) EI: 225(M^+ + 1, 15), 224(M^+, 100), 196(6), 166(32), 139(20), 112(14), 88(5). Anal. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.57; N, 12.50. Found: C, 69.39; H, 3.33; N, 12.71. **Naphtho[1,2-*d*]1,3-dioxole (2c)** (320 mg, 37% yield). Mp 84−87°C. IR (KBr) ν = 3058, 2887, 1650, 1604, 1466, 1413, 1281, 1060, 799 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.16(s, 2H), 7.2(d, 1H, J = 8.6 Hz), 7.29−7.36(m, 1H), 7.4−7.48(m, 2H), 7.8(t, 2H, J = 7.4 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 101.8, 110.6, 119.8, 121.9, 124.1, 126.4, 128.6, 130.2, 141.3, 143.4. MS *m*/*e* (relative intensity) EI: 173(M^+ + 1, 12), 172(M^+, 100), 171(M^+ − 1, 72), 130(11), 114(55), 86(21), 74(11), 63(23), 51(12). Anal. Calcd for $C_{11}H_8O_2$: C, 76.74; H, 4.65. Found: C, 76.61; H, 4.82. **4-Sulfonic acid tetraethylammonium salt-naphtho[1,2-*d*]1,3-dioxole (2d)** (1657 mg, 87% yield). Mp 144−146°C. IR (KBr) ν = 3050, 2987, 1644, 1605, 1461, 1326, 1204, 1022, 763, 733, 630 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.82(t, 12H, J = 7 Hz), 2.77(c, 8H, J = 7 Hz), 6.0(s, 2H), 7.15−7.35(m, 2H), 7.62(d, 1H, J = 8 Hz), 7.77(s, 1H), 8.72(d, 1H, J = 7.7 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 7.2, 52.0, 102.0, 110.8, 119.6, 119.8, 124.7, 126.1, 127.8, 137.2, 141.3, 142.3. MS *m*/*e* (relative intensity) ESI(−): 252(M^+ + 1, 8), 251(M^+, 100). ESI(+): 131(M^+ + 1, 11), 130(M^+, 100). Anal. Calcd for $C_{19}H_{27}NO_5S$: C, 59.84; H, 7.09; N, 3.67. Found: C, 60.10; H, 6.92; N, 3.72. **5,6-Dimethoxy-benzo[1,3]dioxole (2e)** (164 mg, 18% yield). Mp 77−79°C. IR (KBr) ν = 3003, 2925, 1509, 1466, 1215, 1184, 1165, 1031, 925, 813 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.82(s, 6H), 5.88(s, 2H), 6.58(s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 57.3, 96.4, 101.2, 125.7, 140.9. MS *m*/*e* (relative intensity) EI: 183(M^+ + 1, 10), 182(M^+, 100), 167(63), 121-(18), 109(76), 81(49), 69(56), 53(77). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 6.59. Found: C, 59.60; H, 6.68.