A New Method to Prepare Alkyl-1,4-naphthoquinone. Synthesis of Lapachol and Phyticol

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Supporting information

Experimental protocols

General procedures

Melting points were observed on a Fischer Jones and are uncorrected. Analytical grade solvents were used. Reagents were purchased from Aldrich or Acros Chemical Co. Column chromatography was performed on silica gel 60 (Merck 70-230 mesh). Yields refer to purified compounds obtained by chromatography techniques and confirmed by spectroscopies data. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and either an ethanolic solution of sulfate. Infrared spectra were recorded on a Perkin-Elmer FT-IR Spectrum One spectrophotometer, calibrated relative to the 1601.8 cm⁻¹
absorbance of polystyrene. NMR spectra were recorded on a Varian Unity Plus VX (300 MHz) equipment in CDCl$_3$ solutions and tetramethylsilane was used as the internal standard ($\delta = 0$ ppm). Elemental analysis was used to ascertain purity $\geq$95% for all compounds were determined in a Perkin Elmer model CHN 2400. The reactor used to perform the reactions in closed vessel was a Bergoff model BR-300. All calculations were done with the G03W software,$^1$ using the B3LYP density functional$^2$ and the 6-311++G(d,p) basis set.

**General procedure for the reduction of aldehydes in the presence of formic acid/H$_2$O.**

In a high-pressure reactor of 600 mL (Berghof, Model: BR-300), lawsone (1 equivalent), 150-250 mL of an ethanol/water mixture 1:1 (v/v), the corresponding aldehyde (1 equivalent) and formic acid (3 equivalents) were mixed. The reaction mixture was heated at 200°C, and this temperature was maintained for a period of 2-3 hours and under a pressure from 3-3000 psi. After the total consumption of the starting material (verified by TLC), the reaction mixture was removed from the reactor and cooled to room temperature, after which time the products mixture was put in a solvent rotary evaporator. The residue obtained was added to water, and this mixture was then extracted with ethyl acetate. The organic phases were combined and dried with anhydrous sodium sulfate, and the solvent

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was removed at reduced pressure. The crude product was purified by column chromatography using a gradient silica gel and a hexane/ethyl acetate mixture as the eluent. The products were obtained in yields ranging from 45-90%.

**Computations.** The geometries of the o-QM, formic acid and the water molecule were fully optimized. Transition state structures were located by the usual procedure. For transition structures and minima, the second-order force constant matrices were calculated to confirm their nature (transition structures with one negative eigenvalue; minima with all eigenvalues positive). Activation enthalpies were calculated taking the difference between the energy of the transition structure and that of the quinone methide and formic acid, or quinone methide, formic acid and water, respectively, at infinite separation. The activation energies were then corrected for the vibrational zero-point energy and the thermal correction to 298 K, resulting in the activation enthalpy at 298 K. All calculations were done with G03W software using the B3LYP density functional and the 6-311++G(d,p) basis set.

**Analytical Data for compounds**

2-hydroxy-3-methylnaphthalene-1,4-dione (6a). 89%. m.p = 172-173°C. (m.p. lit = 168-170°C) IR ν max (cm⁻¹, film): 3420, 2980, 2941, 1713, 1643, 1366, 1173, 944, 752 ; ¹H NMR (300 MHz, CDCl₃) δ (J in Hz): 2.11 (s, 3H); 7.32 (s, 1H); 7.65-7.77 (m, 2H); 8.06-8.14 (m, 2H) ppm; ¹³C NMR (75 MHz. CDCl₃) δ: 8.2, 120.1, 125.6, 126.2, 129.7, 131.1, 132.4, 134.3, 152.3, 180.5, 182.3 ppm. Anal. Calcd for C₁₁H₈O₃: C, 70.21; H, 4.29. Found: C, 70.50; H, 4.23.

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2-hydroxy-3-(4-nitrobenzyl)naphthalene-1,4-dione (6b). 90%. m.p = 235-237°C. (m.p. lit = 236-238°C)¹ IR ν max (cm⁻¹, film): 3397, 3277, 1618, 1514, 1336, 1269, 1213, 1132, 616; ¹H NMR (300 MHz, CDCl₃) δ (J in Hz): 3.56 (s, 2H); 7.35 (s, 1H); 7.61 (ddd, 1H, J = 1.5, 7.4 and 8.8); 7.64 (ddd, 1H, J = 1.5, 7.4 and 8.9); 7.76 (dd, 1H, J = 0.6, 7.4 and 8.9); 7.78 (dd, 1H, J = 0.6, 7.4 and 8.9); 8.06-8.10 (m, 2H); 8.38-8.42 (m, 2H) ppm; ¹³C NMR (75 MHz. CDCl₃) δ: 30.1, 114.9, 123.8, 123.9, 126.8, 126.9, 128.6, 130.0, 131.8, 135.0, 135.2, 144.8, 147.0, 153.6, 181.8, 181.7. Anal. Calcd for C₁₇H₁₁NO₅: C, 66.02; H, 3.58. Found: C, 66.05; H, 3.62.

2-benzyl-3-hydroxynaphthalene-1,4-dione (6c). 85%. m.p = 174-175°C. (m.p. lit = 174°C)² IR ν max (cm⁻¹, film): 3068, 3006, 2835, 1688, 1423, 1325, 1292, 933, 706; ¹H NMR (300 MHz, CDCl₃) δ (J in Hz): 3.94 (s, 2H); 7.14-7.28 (m, 2H); 7.37-7.40 (m, 2H); 7.43 (s, 1H); 7.64-7.71 (m, 2H); 8.05-8.13 (m, 2H) ppm; ¹³C NMR (75 MHz. CDCl₃) δ: 29.3, 115.6, 125.7, 126.0, 126.3, 127.9, 128.0, 129.3, 129.6, 130.0, 131.5, 136.2, 136.7, 154.0, 182.0, 182.9. Anal. Calcd for C₁₇H₁₂O₃: C, 77.26; H, 4.58. Found: C, 77.30; H, 4.59.

2-hydroxy-3-(4-methoxybenzyl)naphthalene-1,4-dione (6d). 64%. m.p = 173-175°C. (m.p. lit = 175-176°C)³ IR ν max (cm⁻¹, film): 3321, 3074, 2925, 1671, 1595, 1323, 1281, 1150, 841, 712; ¹H NMR (300 MHz, CDCl₃) δ (J in Hz): 3.75 (s, 3H); 3.88 (s, 2H); 6.79 (d, 2H, J = 8.8); 7.31 (d, 2H, J = 8.8); 7.42 (s, 1H); 7.66 (ddd, 1H, J = 1.16, 7.6 and 8.6); 7.73 (ddd, 1H, J = 1.16, 7.6 and 8.6); 8.05 (ddd, 1H, J = 0.9 and 8.6); 8.10 (dd, 1H, J = 0.9 and 8.6) ppm; ¹³C NMR (75 MHz. CDCl₃) δ: 30.0, 55.8, 114.2, 114.6, 115.8, 125.9, 126.2, 130.0, 130.2, 130.8, 131.8, 133.0, 134.9, 135.3, 154.7, 157.6, 181.3, 183.0 Anal. Calcd for C₁₈H₁₄O₄: C, 73.46; H, 4.79. Found: C, 73.51; H, 4.75.

2-hydroxy-3-isobutynaphthalene-1,4-dione (6e). 78%. m.p = 133-134°C. (m.p. lit = 132-133°C)\(^7\) IR \(v\) max (cm\(^{-1}\), film): 3351, 2962, 2936, 2878, 1650, 11461, 1385, 1095, 1060, 968; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (\(J\) in Hz): 0.94 (s, 3H); 0.96 (s, 3H); 1.99 (q, 1H, \(J = 7.26\)); 2.51 (d, 2H, \(J = 7.26\)); 7.31 (s, 1H); 7.65-7.78 (m, 2H); 8.05-8.13 (m, 2H) ppm; \(^13\)C NMR (75 MHz. CDCl\(_3\)) \(\delta\): 22.5; 27.9; 32.0; 122.3; 126.3; 129.3; 131.9; 134.6; 153.3; 181.2; 184.7 ppm. Anal. Calcd for C\(_{14}\)H\(_{14}\)O\(_3\): C, 73.03; H, 6.13. Found: C, 73.06; H, 6.15.

2-hydroxy-3-(2-oxopropyl)naphthalene-1,4-dione (6f). 45%. m.p = 175-177°C. (m.p. lit = 177-177.5°C)\(^8\) IR \(v\) max (cm\(^{-1}\), film): 3422, 2927, 1723, 1675, 1207, 719; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (\(J\) in Hz): 1.79 (d, 3H, \(J = 0.9\)); 3.29 (t, 1H, \(J = 0.9\)); 3.31 (t, 1H, \(J = 0.9\)); 7.34 (s, 1H); 7.66 (ddd, 1H, \(J = 1.5, 7.4\) and 9.0); 7.74 (ddd, 1H, \(J = 1.5, 7.4\) and 9.0); 8.06 (ddd, 1H, \(J = 0.6, 7.4\) and 9.0); 8.12 (ddd, 1H, \(J = 0.6, 7.4\) and 9.0) ppm; \(^13\)C NMR (75 MHz. CDCl\(_3\)) \(\delta\): 30.2, 39.6, 119.7, 126.2, 126.9, 127.0, 130.2, 131.0, 135.3, 135.5, 153.5, 180.0, 181.6, 200.3. Anal. Calcd for C\(_{13}\)H\(_{10}\)O\(_4\): C, 67.82; H, 4.38. Found: C, 67.47; H, 4.42.

5-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pentanal (6g). 60%. m.p = 125-128°C. IR \(v\) max (cm\(^{-1}\), film): 3328, 2937, 2872, 1726, 1671, 1371, 1274, 1128, 728; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (\(J\) in Hz): 1.17-1.28 (m, 2H); 1.57-1.76 (m, 3H); 2.25-2.66 (m, 3H); 7.35 (s, 1H); 7.67 (ddd, 1H, \(J = 1.4, 7.4\) and 9.0); 7.74 (ddd, 1H, \(J = 1.4, 7.4\) and 9.0); 8.07 (ddd, 1H, \(J = 0.5, 7.4\) and 9.0); 8.11 (ddd, 1H, \(J = 0.5, 7.4\) and 9.0); 9.52 (s, 1H) ppm; \(^13\)C NMR (75 MHz. CDCl\(_3\)) \(\delta\): 16.2, 22.6, 29.8, 40.3, 125.2, 126.9, 127.0, 130.7, 131.5, 135.0, 135.5, 153.4, 180.4, 183.6, 196.3. Anal. Calcd for C\(_{15}\)H\(_{14}\)O\(_4\): C, 69.76; H, 5.46. Found: C, 69.58; H, 5.42.

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2-hydroxy-3-(3-methylbut-2-enyl)naphthalene-1,4-dione (Lapachol, 1). 78%. m.p = 140-141°C. (m.p. = 139-140°C)\(^9\) \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) (J in Hz): 1.68 (s, 3H); 1.79 (s, 3H); 3.29 (t, 1H, J = 0.9); 3.31 (t, 1H, J = 0.9); 5.17-5.24 (m, 1H,); 7.34 (s, 1H); 7.70 (dddd, 2H, J = 1.2, 7.4, 9.0 and 14.9); 8.08 (dddd, 2H, J = 1.2, 7.4, 9.0 and 14.9) ppm. \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 18.6, 22.7, 26.6, 120.9, 123.5, 126.8, 130.9, 131.2, 133.7, 136.0, 153.4, 181.2, 183.5. Anal. Calcd for C\(_{15}\)H\(_{14}\)O\(_3\): C, 74.36; H, 5.82. Found: C, 74.30; H, 5.80.