

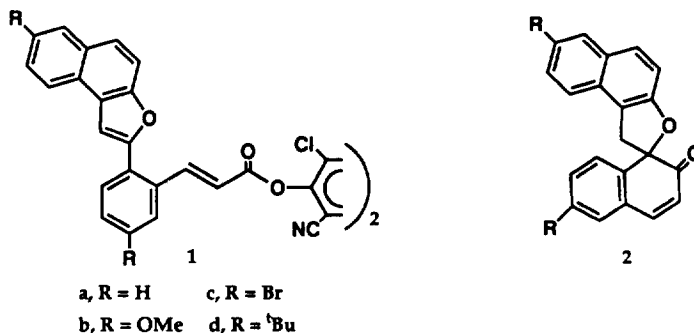
Novel Reduction (Zn-AcOH) of DDHQ Esters¹ - A New Route to Tropone Synthesis

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Abstract : Zn/acetic acid reaction of DDHQ esters **1 a-d** gave the saturated acids **3 a-d** and the hydrocarbons **7 a-d**. The intermediacy of the aldehydes **10** and **11** in the formation of the products has been established. Oxidation of hydrocarbons **7a** and **7b** gave the corresponding tropones (**5a** and **5b**).

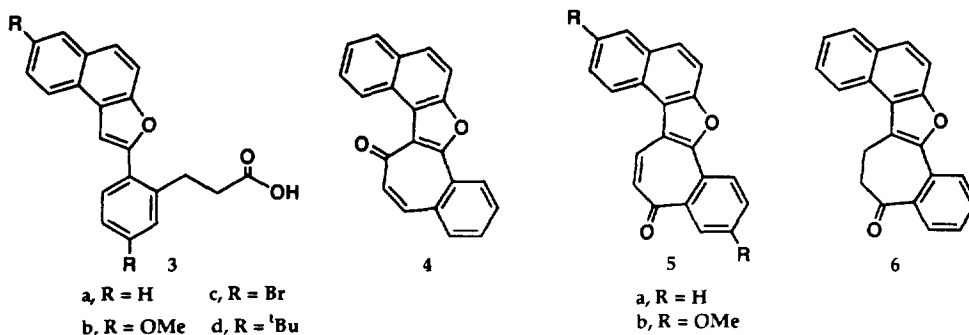
Our studies on oxidation of naphthols and other substrates with high potential quinones, especially 2,3-dichloro-5,6-dicyanoquinone (DDQ), have led to the isolation of novel compounds². We have reported for the first time the formation of 2,3-dichloro-5,6-dicyanohydroquinone (DDHQ) diesters of 2-substituted cinnamic acid **1** in the oxidation of spiroketones **2** with DDQ³. These diesters undergo facile reduction with sodium borohydride to alcohols and this is an efficient method for selective reduction of one of the two acid



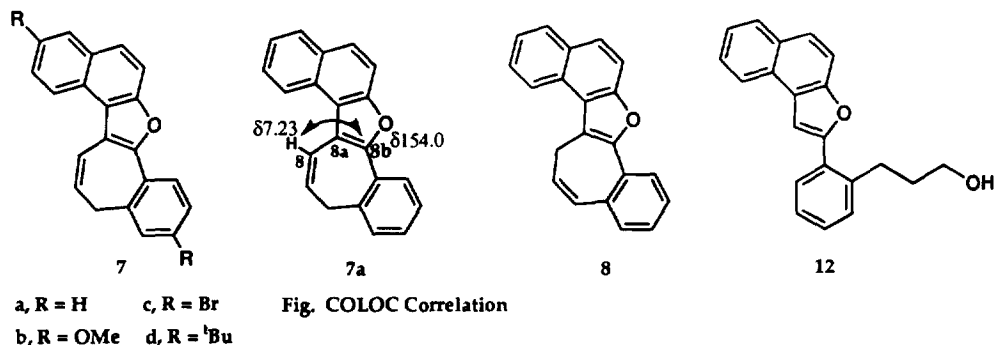
groups in a bifunctional compound¹. In order to explore further the chemistry of these unique DDHQ diesters, reduction under Zn/AcOH condition was studied and the results obtained are discussed in this communication.

RESULTS AND DISCUSSION

In a typical experiment, DDHQ ester **1** in glacial acetic acid was heated under reflux with Zn dust for 3h. The hot solution was filtered and the Zn washed with little methanol. After removing the solvent *in vacuo*, the residue was purified by column chromatography to give two compounds. The polar compound [40 %, IR:1700 cm^{-1} ; ^1H NMR: δ 2.76 (t, $J=7.6$ Hz, 2H), 3.34 (t, $J=7.5$ Hz, 2H), 7.35-7.82 (m, 9H), 7.95 (d, $J=8$ Hz, 1H), 8.18 (d, $J=8.2$ Hz, 1H)] was identified as the dihydro acid **3a**³.



The less polar compound (15 %) exhibited a molecular ion at m/e 282 analyzing for $\text{C}_{21}\text{H}_{14}\text{O}$. Significant signals in its ^{13}C NMR spectrum were at δ 152.5(s) & 154.0(s) [oxygen carrying olefinic carbons], 112.9(d) (olefinic) and 34.0(t)(CH₂). The ^1H NMR spectrum exhibiting characteristic signals at δ 3.25 (d, $J = 6.9\text{Hz}$, 2H) and 5.99 (dt, $J=10$ and 6.9 Hz, 1H) suggested the presence of -CH=CH-CH₂- unit in the molecule which was proved by oxidation with CrO_3 in AcOH to give an α,β -unsaturated carbonyl compound [M^+ m/e 296; IR 1628 cm^{-1} ; ^1H NMR: δ 7.1 (d, $J=12.4$ Hz, 1H); ^{13}C NMR: δ 186.0]. An intense ion at m/e 268 corresponding to the loss of a carbonyl in its mass spectrum, was very significant. Formation of stable ions by loss of carbon monoxide is a characteristic feature in the mass spectra of tropones and benzotropones^{4,5} and accordingly, the oxidation product should thus be a tropone. The known tropone **4** exhibits a characteristic signal at δ 9.2 for the H-9 proton³ and its absence in this compound prompted us to assign the isomeric tropone structure **5a** for this molecule. Hydrogenation of **5a** gave the dihydro compound **6** [IR 1660 cm^{-1} ; ^1H NMR: δ 3.26 (t, $J=$ Hz, 2H), 3.59 (t, $J=$ Hz, 2H)]. Based on these transformations and spectral analyses, structure **7a** was tentatively assigned to the parent compound. A study of the long range

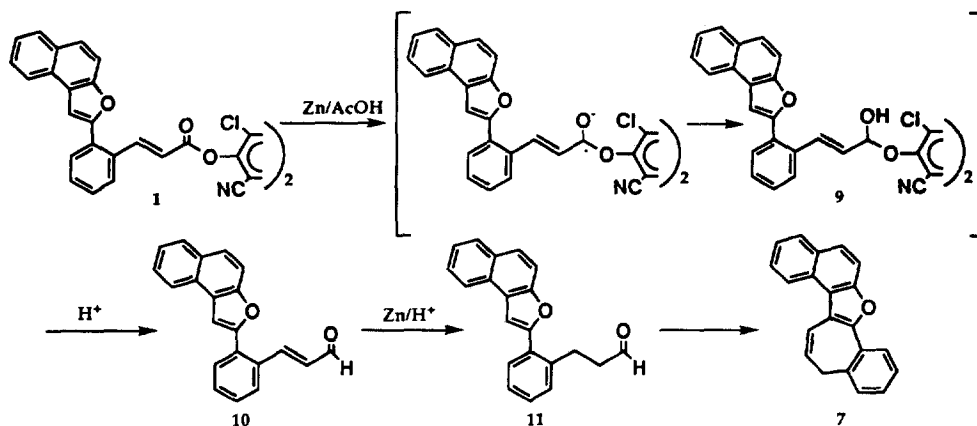


heteronuclear shift correlation (COLOC⁶) spectrum of **7a**, undertaken at the suggestion of the referee⁷, further substantiated our conclusions. The spectrum showed (Fig. 1) the three-bond coupling between C-8b and H-8. Such a correlation would not be expected from an isomeric structure **8**.

In order to see the generality, this reaction was studied with substrates like **1b-d**, when the corresponding dihydroacids **3b-d** and the hydrocarbons **7b-d** were obtained. Oxidation of **7b** gave the expected tropone **5b**.

MECHANISM

In the proposed mechanism (Scheme I) for the formation of the hydrocarbon **7**, the first step is the formation⁸ of a radical (ketyl) anion. Under the reaction conditions, this gets protonated to the hemiacetal **9** which can undergo hydrolysis⁹ to give the unsaturated aldehyde **10**. The saturated aldehyde **11**, formed by reduction¹⁰ of the unsaturated aldehyde **10**, can undergo facile acid catalyzed intramolecular acylation followed by dehydration to the hydrocarbon **7**.



Scheme I

The unsaturated aldehyde **10** could be synthesized by allylic oxidation with MnO_2 of the unsaturated alcohol obtained by sodium borohydride reduction of the DDHQ diester. Refluxing the unsaturated aldehyde **10** with Zn/AcOH afforded the hydrocarbon **7**. The saturated aldehyde **11**, obtained by reduction of **10**, on reaction with PTS in benzene gave, as expected, the hydrocarbon **7** in 60% yield. On the other hand, the unsaturated aldehyde **10** remained unchanged under these reaction conditions. These experiments undoubtedly established the intermediacy of aldehydes in the formation of the products.

The present investigation has thus led to a new method of synthesis of tropones **5** starting from the DDHQ ester *via* saturated alcohol³ **12** with an overall yield of 30%. This is achieved by the reduction³ (NaBH₄/palladium charcoal) of DDHQ ester to the saturated alcohol, which on oxidation (CrO₃) yields the aldehyde **11**. The hydrocarbon **7** obtained by the PTS reaction of the aldehyde **11** on further oxidation gives the troponone.

ACKNOWLEDGMENT

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EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer model 781 spectrophotometer. PMR spectra were recorded on a Bruker AMX-400 or a WH-270 FT NMR spectrometer with an operating frequency of 400 and 270 MHz respectively. MS (70 ev) were recorded on a JEOL MS-DX 303 spectrometer fitted with a built-in inlet system. All the solvent extracts were dried over anhydrous Na₂SO₄.

General procedure for the reduction of DDHQ esters (**1 a-d**) with Zn/AcOH

The DDHQ ester (**1 a-d**, 1mmol), AcOH (100 mL) was refluxed with Zn dust (3 gm) for 5 hr, The hot solution filtered and the Zn washed with a little methanol. The solvent was removed under reduced pressure and the residue was taken in ethyl acetate. The ethyl acetate layer was washed thoroughly with water and dried over anhydrous Na₂SO₄. The residue obtained after removal of ethyl acetate was chromatographed over silica gel. Elution with benzene-hexane (1:1) gave (**7 a-d**). Further elution with CHCl₃-hexane (4:1) gave the reduced acid (**3 a-d**).

Reduction of 1a: Gave (i) **7a**, 120 mg. m.p 132 °C, IR (nujol): ν_{\max} 1620 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.25(d, *J*=6.9 Hz, 2H), 5.99(dt, *J*=9.0 and 6.0 Hz, 1H), 7.23(d, *J*=10 Hz, 1H), 7.34(d, *J*=6.5 Hz, 1H), 7.35-7.58(m, 4H), 7.76 (dd, *J*=11.7 Hz and 8.9 Hz, 1H), 8.45(d, *J* = 8.2Hz, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 154.0, 152.4, 136.6, 131.3, 130.1, 129.6, 129.2, 128.6, 127.6, 126.8, 126.2, 1224.6, 124.6, 124.3, 123.9, 122.0, 119.2, 112.8, 34.5; HRMS Found C,89.1; H,4.82. C₂₁H₁₄O requires C,89.3; H,4.96. and **3a** (360 mg, m.p. 132 °C³).

Reduction of 1b : Gave (i) **7b**, 140 mg. m.p. 141 °C; IR (nujol) : ν_{\max} 1615 cm⁻¹ (weak); ¹H NMR (400 MHz, CDCl₃): δ 3.25(d, *J*=6.0 Hz), 3.90(s, 3H), 3.95(s, 3H), 5.95(td, *J*=10 and 6 Hz, 1H), 6.8-6.95(m, 2H), 7.05(d, *J*=8.0 Hz, 1H), 7.2-7.4(m, 2H), 7.6-7.7(m, 2H), 7.95(d, *J*= 7.0 Hz, 1H), 8.35(d, *J*=8.0 Hz, 1H). MS *m/e* 342 (M⁺, 100). HRMS found 342.1258. C₂₃H₁₈O₃ requires 342.1256 and (ii) **3b**, 400 mg; IR (nujol): ν_{\max} 1700 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 2.8 (t, *J*=7.0 Hz, 2H), 3.3(t, *J*=7.0 Hz, 2H), 3.93(s, 3H), 3.98(s, 3H), 6.8-8.3(m, 9H). Anal found C, 73.12; H, 5.1. C₂₃H₂₀O₃ requires C, 73.4; H, 5.3%.

Reduction of 1c : Gave (i) **7c**, 150 mg, m.p 221 °C; IR (nujol): ν_{\max} 1610 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 3.13(d, *J*=7.0 Hz, 2H), 6.0(dt, *J*=10.0 and 6.0 Hz, 1H) 7.2 (d, *J*=9.0 Hz, 1H), 7.45-7.95(m, 6H), 8.18(d, *J*=2.0 Hz, 1H) 8.35 (d, *J*=9.0 Hz, 1H). Anal Found C, 57.1; H, 2.62. C₂₁H₁₂Br₂O requires C,

57.3; H, 2.7%. and (ii) **3c**, 500 mg; m.p 101 °C(d); IR (nujol): ν_{\max} 1700 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 2.78(t, $J=8.0$ Hz, 2H), 3.35 (t, $J=8.0$ Hz, 2H) 7.3-7.9(m, 8H), 8.0-8.15(m, 1H). Anal. Found C, 52.8; H, 2.81. $\text{C}_{21}\text{H}_{14}\text{Br}_2\text{O}_3$ requires C, 53.16; H, 2.95%.

Reduction of 1d : Gave (i) **7d**, 120 mg, m.p 154 °C; IR (nujol): ν_{\max} 1610 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.35(s, 9H, t-Bu), 1.4(s, 9H, t-Bu), 3.2(d, $J=6.0$ Hz, 2H), 5.9(dt, $J=10.0$ and 6.0 Hz, 1H), 7.1-7.5(m, 3H), 7.55-7.95(m, 5H), 8.35(d, $J=8.0$ Hz, 1H); MS m/e 394(M+, 100); HRMS found 394.2300. $\text{C}_{29}\text{H}_{30}\text{O}$ requires 394.2296 and (ii) **3d**, 400 mg; m.p. 138 °C; IR (nujol): ν_{\max} 1705 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 1.4 (s, 9H, t-Bu), 1.48(s, 9H, t-Bu), 2.78(t, $J=7.0$ Hz, 2H), 3.40(t, $J=7.0$ Hz, 2H), 7.30-7.45(m, 3H), 7.65-7.90(m, 5H), 8.15(d, $J=9.0$ Hz, 1H). Anal found C, 79.9; H, 7.23. $\text{C}_{29}\text{H}_{32}\text{O}_3$ requires C, 81.3; H, 7.4%.

Oxidation of 7a with CrO_3 : Compound **7a** (120 mg) in acetic acid (2 ml) was added to chromic oxide (120 mg) in 4 ml of $\text{AcOH-H}_2\text{O}$ (4:1) mixture and the mixture was stirred overnight at room temperature. It was diluted with brine and extracted with chloroform. The chloroform layer was then washed water and dried. The residue obtained after removal of solvent was chromatographed (silica gel, benzene) to give the tropone **5** (80 mg, 65%), m.p. 248 °C (CHCl_3 -hexane); IR (nujol): ν_{\max} 1628 cm^{-1} ; $^1\text{H NMR}$ (270 MHz, CDCl_3): δ 7.1 (d, $J=12.4$ Hz, 1H), 7.58-7.93 (m, 7H), 8.03(d, $J=8$ Hz, 1H), 8.45(d, $J=7.0$ Hz, 1H), 8.62-8.7(m, 2H). MS m/e 296(M+, 80), 268(M-CO, 100). HRMS found 296.0857. $\text{C}_{21}\text{H}_{12}\text{O}_2$ requires 296.0837.

Similar oxidation of **7b** gave the tropone **5b** (70%), m.p. 262-4 °C (CHCl_3 -hexane); IR (nujol): ν_{\max} 1628 cm^{-1} ; $^1\text{H NMR}$ (270 MHz, CDCl_3): δ 3.96 (s, 3H, OMe), 3.97 (s, 3H, OMe), 7.05 (d, $J=12.4$ Hz, 1H), 7.16 - 7.28 (m, 4), 7.38 (d, $J=12.4$ Hz, 1H), 7.68 (d, $J=8.4$ Hz, 1H), 7.81 (d, $J=8.4$ Hz, 1H), 8.03 (d, $J=8.4$ Hz, 1H), 8.42 (d, $J=8.4$ Hz, 1H). Anal found C, 77.85; H, 4.49. $\text{C}_{23}\text{H}_{16}\text{O}_4$ requires C, 77.51; H, 4.53%.

Hydrogenation of 5a : Compound **5a** (50 mg) in 20 ml dry THF was stirred with 10% Pd-C (5 mg) in hydrogen atmosphere till the H_2 uptake ceased (10 h). The catalyst was filtered off and the solvent removed *in vacuo* to give **6** (45 mg, 95%), m.p. 192 °C; IR (nujol): ν_{\max} 1660 cm^{-1} ; $^1\text{H NMR}$ (270 MHz, CDCl_3): δ 3.26 (t, $J=6.2$ Hz, 2H), 3.59 (t, $J=7.0$ Hz, 2H), 7.34-7.65(m, 5H), 7.75 (d, $J=9.0$ Hz, 1H), 7.85(d, $J=7.0$ Hz, 1H), 7.94 (d, $J=8.0$ Hz, 1H).

Reduction of 10 : A mixture of Zn dust (3 gm), AcOH (100 mL) and the unsaturated aldehyde **10** (298 mg, 1mmol) was refluxed for 6 hr. After the completion of the reaction, AcOH was removed *in vacuo* and the residue taken up in ether. The ether layer was washed with 5% NaHCO_3 solution followed by brine and dried. Removal of solvent and purification of the residue on column (silica gel, hexane) gave the hydrocarbon **7a** (170 mg).

Cyclisation of 11 : To a solution of **11** (300 mg, 1mmol) in dry benzene catalytic amount of PTS was added and stirred for 24 hr. The benzene layer was then washed with 5% NaHCO_3 solution, brine and dried. Removal of solvent followed by column chromatography gave **7a** (155 mg).

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8. The formation of radical anion must be occurring under these conditions due to the presence of a highly electron withdrawing phenyl group which helps in reducing the electron density at the phenolic oxygen, which otherwise would have destabilised the radical anion as in a normal ester.
9. There is literature precedence for the formation of aldehydes in the dissolving metal reductions of esters and lactones. See Fisher, E.; *Ber.*, **1889**, *22*, 2204 and Fischer, E.; *ibid.* **1890**, *23*, 930.
10. The reduction of enones to saturated carbonyl compounds is well known. see Fieser, L. F.; Hertz, J. E.; Huang, W. -Y; *J. Am. Chem. Soc.*, **1951**, *73*, 2397.

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