

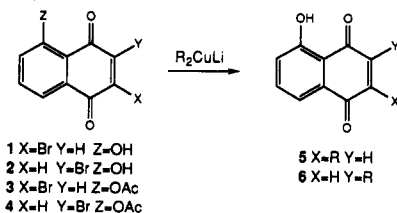
Ester Cleavage Reactions of Bromojuglone Acetates with Dialkylcuprates: Evidence for Hemi Ortho Ester Formation Promoted by Electron Transfer Reactions

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In a recent paper,¹ we reported that lithium dialkylcuprates ($R_2CuLi \cdot LiI$) undergo regiospecific addition reactions with 2- and 3-bromojuglones 1 and 2. In each case, the sole addition product was that resulting from net displacement of the bromine by the alkyl group to form 2- and 3-alkyljuglones 5 and 6, respectively. However, addition of lithium dialkylcuprates to bromojuglone acetates 3 and 4 resulted in simple ester cleavage reactions resulting in formation of 1 and 2 with no addition products formed. This observation is inconsistent with the known reactivity of cuprates toward esters.² Here we describe evidence that this ester cleavage reaction between Gilman reagents and bromojuglone acetates proceeds through the conjugate base of a hemi ortho ester intermediate derived from the hydroquinone dianion.

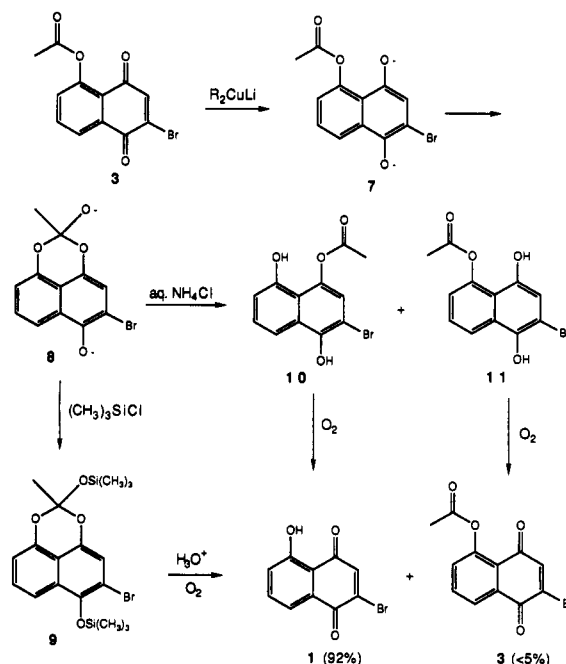


Results and Discussion

Addition of excess lithium dialkylcuprates to 2-bromo-5-acetoxy-1,4-naphthoquinone (3) followed by acidification with aqueous ammonium chloride and atmospheric oxidation resulted in the formation of 2-bromo-5-hydroxy-1,4-naphthoquinone (1) (92%) as the major product. Gas chromatography also revealed trace amounts of 3 present in the crude product (<5%). Solution IR and UV of the reaction solution immediately following addition of cuprate to quinone revealed that 3 had undergone a two-electron reduction to the corresponding hydroquinone dianion 7 (Scheme I). These observations are consistent with the measured redox potential¹ of 3 and the House criteria³ correlating reduction potential and reactivity toward cuprates. Also observed in the IR of the reaction solution was the absence of the ester carbonyl. In view of the absence of carbonyls in the IR, we postulated the formation of the conjugate base of the hemi ortho ester 8 which is the result of nucleophilic attack of the peri oxyanion on the carbonyl carbon of the ester.

Chemical evidence for 8 was obtained by treatment of the reaction mixture with excess chlorotrimethylsilane, resulting in the formation of a reddish-brown solid which was determined to be 9. The structure of 9 was assigned on the basis of NMR spectra which showed the presence of four aromatic protons (1H : δ 7.09, 7.25, 7.48, and 7.62), two trimethylsilyl esters (1H : δ 0.24 and 0.28; ^{13}C : δ 1.1

Scheme I



and 1.7), a methyl group (1H : δ 1.39; ^{13}C : δ 29.1), and the absence of all carbonyl groups as indicated by ^{13}C NMR and IR. Elemental analysis of 9 proved impossible due to instability at room temperature. Upon standing several days at room temperature exposed to the atmosphere, 9 decomposed, resulting in the formation of 1 and 3. Likewise, treatment of 9 with dilute aqueous acid under an oxygen atmosphere resulted in the formation of 1 and 3. Melting point and spectral data of 1 and 3 were identical to values previously reported.^{4,5}

Consequently, the formation of 1 under our reaction conditions presumably results from breakdown of the conjugate base of the hemi ortho ester 8. Products formed by way of this tetrahedral intermediate are 10 and 11. As suggested by Schoreder⁶ and others,⁷ the predominant hydrolysis product of the conjugate base of hemi ortho esters at low acid concentrations is the result of expulsion of the anion of lowest pK_a . Using this criterion, expulsion of O-5 would be favored over O-4, which would lead to the formation of the transacylated product 10 in preference to 11. Similar transacylation reactions have been reported for naphthazarins⁸ and anthraquinones.^{9,10} The observed products 1 and 3 are the result of atmospheric oxidation of 10 and 11, respectively.

The formation of 8 from 7 can be attributed to elimination of unfavorable electronic interactions of the 1,4-dioxyanion 7. UV experiments using hydroquinone dissolved in THF as a model system supports this assumption. Hydroquinone displays two absorption bands between 215 and 450 nm corresponding to the B-band (benzenoid band) at 295 nm and the E-band (ethylenic band) at 224 nm. Conversion of hydroquinone to the

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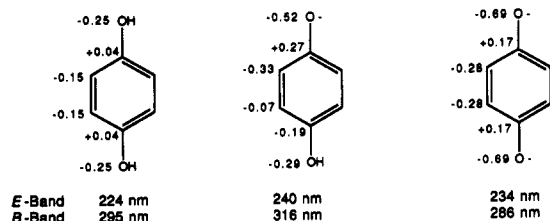


Figure 1. AM1 calculated net atomic charges for all non-hydrogen atoms and UV absorption data for hydroquinone, hydroquinone anion, and hydroquinone dianion.

corresponding anion by addition of 1 equiv of *tert*-butyllithium results in a bathochromic shift of both the *B*-band (316 nm) and the *E*-band (240 nm). This is attributed to interactions between nonbonding electrons of the anion and the benzenoid π -system.¹¹ However, addition of a 2-fold excess of *tert*-butyllithium, which forms the dianion of hydroquinone, results in hypsochromic shifts of the *B* band (286 nm) and a bathochromic shift of the *E*-band (234 nm) relative to the hydroquinone model. This observation can be interpreted as lack of interactions between nonbonding electrons of the vinylogous 1,4-dioxyanion and the benzenoid π -system. This unfavorable electronic interaction can be circumvented by an intramolecular nucleophilic attack of O-4 on the ester carbonyl resulting in the formation of 8.

Semiempirical molecular orbital calculations of the hydroquinone model using the AM1¹² Hamiltonian also support these observations. Calculations of net atomic charge for all non-hydrogen atoms are summarized in Figure 1. For the hydroquinone anion, charge delocalization is observed at the ortho and para positions relative to the oxyanion. However in the hydroquinone dianion system, charge delocalization is restricted to only the respective ortho positions with a positive charge residing on the ipso positions. This is consistent with the hypsochromic shift of the *B*-band for the hydroquinone dianion.

In conclusion, the ester cleavage reaction between bromojuglone acetates and Gilman reagents proceeds through the conjugate base of a hemi ortho ester intermediate derived from the hydroquinone dianion. Breakdown of this tetrahedral intermediate results in a *peri* transacylation reaction which upon atmospheric oxidation results in the formation of the respective bromojuglone as the major product.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 1600 FT-IR spectrometer. Ultraviolet spectra of tetrahydrofuran solutions were recorded on a Varian 2300 UV-vis spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker AC 250 (250 MHz) instrument. Chemical shifts are reported in δ (ppm) downfield from internal tetramethylsilane. Tetrahydrofuran was distilled under nitrogen from CaH₂. Bromojuglone acetates 3 and 4 were synthesized according to the literature.⁵

General Procedure for Addition of Lithium Dialkylcuprates to Quinones. In a 250-mL round-bottom flask were placed CuI (4.0 g, 21 mmol) and THF (90 mL) under nitrogen. The solution was cooled to -78 °C and maintained at that temperature throughout the reaction. Added to the solution was 42 mmol of alkylolithium solution (*tert*-butyl or methyl¹³). The

reaction mixture was allowed to stir for 20 min. To this solution was added 4 mmol of quinone dissolved in THF (50 mL). The reaction mixture was allowed to stir for 4 h followed by addition of saturated NH₄Cl (50 mL) at -78 °C. The resulting solution was stirred for 1 h, allowing the solution to warm to room temperature. The solvent was removed under reduced pressure and the residue diluted with dichloromethane (125 mL). The solution was washed with aqueous NH₄Cl (2 \times 30 mL) and water (2 \times 40 mL) and dried over MgSO₄. The solvent was removed under reduced pressure. Flash chromatography was performed on the crude product.

2-Bromo-5-hydroxy-1,4-naphthoquinone (1). Following the general procedure, quinone 3 afforded 1 (0.93 g, 92%); mp 134–135 °C (lit.⁴ mp 136 °C). The spectra of the obtained product 1 were identical to those previously reported.⁵

3-Bromo-5-hydroxy-1,4-naphthoquinone (2). Following the general procedure, quinone 4 afforded 2 (0.88 g, 87%); mp 169–171 °C (lit.⁴ mp 172 °C). The spectra of the obtained product 2 were identical to those previously reported.⁵

Procedure for Trapping the Hemi Ortho Ester Derived from 3. In a 250-mL round-bottom flask were placed CuI (2.0 g, 10.5 mmol) and THF (40 mL) under nitrogen. The solution was cooled to -78 °C and maintained at that temperature throughout the reaction. Added to the solution was 12.5 mL of 1.7 M *tert*-butyllithium (21 mmol). The reaction mixture was allowed to stir for 20 min. To this solution was added quinone 3 (1.2 g, 4 mmol) dissolved in THF (15 mL). The reaction mixture was allowed to stir for 30 min. Chlorotrimethylsilane (10 mL, 79 mmol) was added to the resulting solution, which was allowed to stir for 2 h. The reaction mixture was allowed to warm to room temperature and the solvent was removed under reduced pressure. The residue was diluted with pentane (250 mL) and filtered to remove the resulting salts. The filter cake was washed with CH₂Cl₂ (25 mL). The combined organic phases were dried over MgSO₄ and the solvent was removed under reduced pressure to afford 9 (650 mg, 38%); mp 29–31 °C dec; IR (CHCl₃ solution) 3020, 2958, 1211, 742 cm⁻¹; ¹H (CDCl₃) δ 0.24 (s, 9 H), 0.28 (s, 9 H), 1.39 (s, 3 H), 7.09 (s, 1 H), 7.25 (dd, *J* = 1.1, 7.7, 1 H), 7.48 (t, *J* = 7.7, 1 H), 7.62 (dd, *J* = 1.1, 7.7, 1 H); ¹³C δ 1.1, 1.7, 29.1, 106.3, 115.4, 116.8, 117.1, 121.9, 122.0, 123.3, 124.4, 125.3, 126.5, 134.6.

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A Simple High-Yield Preparation of Alkynylphosphonium Triflates

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Unsaturated phosphonium salts represent a useful class of reagents in organic synthesis.¹ They serve as valuable dienophiles in Diels–Alder cycloadditions, as precursors to certain ylides, and undergo numerous other desirable transformations.^{1,2}

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