Regioselective Organocadmium Alkylations of Substituted Quinones

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A series of substituted quinones was alkylated with diethylcadmium. Regiochemistry of addition shifted from quinol formation to conjugate addition as a function of the steric and electronic effects of the substituents.

Naturally occurring quinones and hydroquinones possess a variety of biological properties including antitumoral,[1] HIV transcriptase inhibition,[2] and immunomodulation.[3] Quinone derivatives participate in numerous biological functions including cellular respiration in the mitochondria of living cells, electron transport in plant photosynthesis, and blood coagulation.[4]

Quinone substitution, especially alkylation, is essential to elicit biological activity. Alkylation of the quinone nucleus by organometallic reagents represents a direct route toward the synthesis of various quinone-related compounds. Reactions involving quinones with alkyllithium and Grignards,[5] organostannanes,[6] and organocuprates[7] have been reported. Recently, we reported the use of organocadmium reagents with quinones constituting an efficient synthesis of quinols, products resulting from monoalkylation of quinone carbonyls.[8] Our subsequent work has focused on the regioselectivity and chemoselectivity of quinone alkylations. The results of these studies are reported herein.

Discussion

Previous work in our laboratories has shown that organocadmium−quinone alkylations provide a direct route to quinols in good yield.[8] These observations prompted our studies of the regioselective and chemoselective nature of organocadmium−quinone alkylations and their use in the synthesis of quinone related natural products.[9]

Initial investigations focused on the reactivity of diethylcadmium with isomers of dimethylbenzoquinone. As

Scheme 1

Substrate	Product
1a $R_2=R_5=Me$ $R_3=R_6=H$	**2a** $R_2=R_5=Me$ $R_3=R_6=H$ (83%)
1b $R_2=R_3=Me$ $R_5=R_6=H$	**2b** $R_2=R_3=Me$ $R_5=R_6=H$ (78%)
3 $R_2=R_6=Me$	**4** $R_2=R_6=Me$ (82%)
1c $R_2=R_3=R_5=Me$ $R_6=H$	**5a** $R_2=R_3=R_5=Me$ (80%)
1d $R_2=R_3=OMe$ $R_5=Me$ $R_6=H$	**5b** $R_2=R_3=OMe$ $R_5=Me$ (86%)

shown in Scheme 1, reaction of diethylcadmium with 2,5-dimethylbenzoquinone **1a** gave quinol **2a** in 83% yield. Similar results were obtained from 2,3-dimethylbenzoquinone **1b**, resulting in **2b** in 78% yield. In both cases, 1,2-addition products were obtained. These observations are consistent with our previously reported quinone−organocadmium alkylations.

Previous reports have indicated that both steric and electronic factors play a role in the regioselectivity of quinone alkylation.[10] To determine the factors responsible for the selectivity of organocadmium-quinone reactions,

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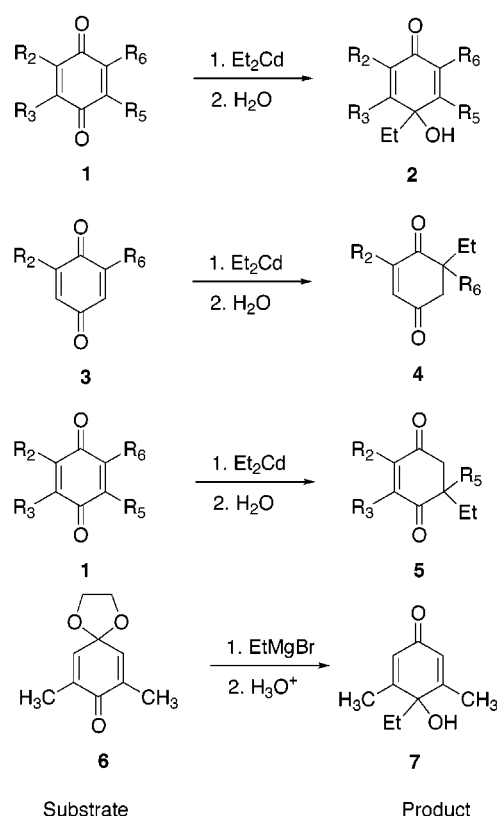
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we investigated a series of unsymmetrically substituted p-quinones where steric and electronic differences between the quinone carbonyls exist. Diethylcadmium alkylation of 2,6-dimethylbenzoquinone **3** resulted in 5-ethyl-3,5-dimethyl-2-cyclohexene-1,4-dione **4** in 82% yield. Similar results were obtained with the trisubstituted benzoquinones 2,3,5-trimethybenzoquinone **1c** and 2,3-dimethoxy-5-methybenzoquinone **1d** resulting in the conjugate addition products 5-ethyl-2,3,5-trimethyl-2-cyclohexene-1,4-dione **5a** (80%) and 5-ethyl-5-methyl-2,3-dimethoxy-2-cyclohexene-1,4-dione **5b** (86%), respectively.

Two probable mechanisms exist for the observed regioselectivity, direct 1,4-addition or 1,2-addition followed by rearrangement. Direct conjugate addition could result from a competition between steric and electronic factors. Electron-donating effects of substituents decrease the electrophilicity of conjugated carbonyls. Electronically, this decrease in electrophilicity favors addition to the carbonyls near substituents, C-1 of **3** and C-4 of **1c** and **1d**, respectively. Steric effects, interactions between the quinone carbonyls near substituents and the bulk of the approaching organocadium reagent, disfavor carbonyl addition at these positions. These steric interactions, in combination with electronic effects, constitute a plausible explanation for the observed conjugate addition products in lieu of 1,2-addition for quinones **3**, **1c**, and **1d**. However, since these same electronic effects favor 1,2-addition to carbonyls near substituents, 1,2-addition followed by Lewis acid catalyzed rearrangement could result in formation of the 1,4-adducts. Consequently, the product distribution would depend on the rate of diene-phenol rearrangement. If rearrangement of the quinol intermediate is fast, 1,4-adducts are obtained. Conversely, if rearrangement is slow, quinols are the observed products as in the case of **2a** and **2b**.

To determine if rearrangement of quinol intermediates is responsible for the observed 1,4-adducts, we synthesized the quinol intermediate potentially resulting from the alkylation of quinone **3** using a previously reported method.[11] As shown in Scheme 1, addition of ethylmagnesium bromide to quinone ketal **6** followed by ketal hydrolysis and column chromatography yielded quinol **7** in 66% yield. No evidence of rearrangement was observed under ketal hydrolysis or chromatography conditions. To determine if the potential Lewis acids MgBr$_2$ and CdCl$_2$ found in the reaction conditions of organocadmium alkylations could catalyze rearrangement, quinol **7** was refluxed with a 2 M excess of the metal salts for 2 h. No evidence of rearrangement was observed in either case. Based on these observations, we can conclude that the rearrangement of quinol **7** is not fast under our reaction conditions and the observed conjugate addition product obtained from the organocadmium alkylation of **3** predominately results from direct 1,4-addition.

Alkylated naphthoquinone derivatives constitute the largest group of quinone-related natural products.[12] To expand the synthetic potential of the reaction, we investigated the organocadmium alkylations of a series of substituted 1,4-naphthoquinones as shown in Scheme 2.

Scheme 2
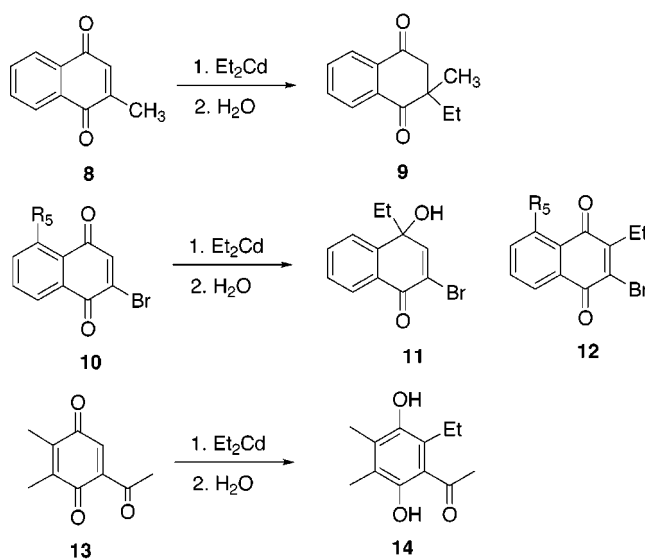
Substrate		Product	
10a	R$_5$=H	**12a**	R$_5$=H (86%)
10b	R$_5$=OH	**12b**	R$_5$=OH (61%)
10c	R$_5$=OAc	**12b**	R$_5$=OH (74%)

Analogous to the trisubstituted quinones **1c** and **1d**, diethylcadmium alkylation of 2-methyl-1,4-naphthoquinone **8** resulted in dione **9** in 81% yield. Based on this information, we envisioned the use of bromine as a control element for directing regiochemistry and serving as a potential leaving group resulting in alkylated naphthoquinones. However, diethylcadmium alkylation of 2-bromo-1,4-naphthoquinone **10a** resulted in a mixture of quinol **11** (60%) and 2-bromo-3-ethyl-1,4-naphthoquinone **12a** (32%) on the basis of ^{1}H NMR and GCMS. Attempts to purify **11** by column chromatography resulted in increased yields of **12a**. Formation of **12a** from **11** is the result of a silica gel-catalyzed dienone−phenol-type rearrangement[13] resulting in the corresponding hydroquinone. Atmospheric oxidation of the hydroquinone derivative results in **12a**.[4] It is noteworthy to mention that stirring the crude product mixture in a slurry of acetone and silica gel resulted in a 86% yield of **12a**, supporting the proposed mechanistic argument.

While unexpected, the regiochemistry of **10a** alkylation can be explained by a decrease in electronic stabilization in combination with the steric effects of the bromine substituent. While bromine has been shown to exert a positive resonance effect in some reactions,[14] the effect is smaller than methoxy substituents or the hyperconjugational effects of methyl groups. In addition, the inductive withdrawing effects of the halogen of bromonaphthoquinones have been shown to direct conjugate addition of electron-rich dienes to the nonhalogenated carbon.[15] Thus, the mixed electronic effects of bromine at C-2 result in addition at both C-3 and C-4.

We envisaged the possibility of decreasing the electrophilicity of the carbonyl at C-4 of bromoquinones by substitution at C-5. Resonance stabilization by donating

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groups at C-5 have been shown to decrease the electrophilicity of the carbonyl at C-4.[16] Since 2-bromojuglone (2-bromo-5-hydroxy-1,4-naphthoquinone) derivatives are readily available,[15] our investigations focused on the reactivity of diethylcadmium with 5-substituted bromoquinones. Reaction of diethylcadmium with 2-bromojuglone **10b** resulted in 2-bromo-3-ethyl-5-hydroxy-1,4-naphthoquinone **12b** in 61% yield. Similar results were obtained from 2-bromo-5-acetoxy-1,4-naphthoquinone **10c** resulting in **12b** in 74% yield. The observed products are derived from the corresponding alkylated naphthhydroquinone intermediates which have been shown to be prone to atmospheric oxidation.[4] In both cases, conjugate addition at C-3 constituted the only observed products. To our knowledge, this is the first case of organometallic alkylation of bromoquinones resulting in conjugate addition at the nonhalogenated carbon. The observed ester cleavage with **10c** is the result of hydrolysis catalyzed by hydrogen bonding between the ester carbonyl and the hydroxyl group at C-4 of the hydroquinone.

Acetyl quinone derivatives are versatile synthetic intermediates,[17] biosynthetic precursors,[18] and natural products.[18] In the context of our study, acetyl substituents are strong electron-withdrawing groups and should result in exclusive conjugate addition products. Previously, we reported an efficient synthesis of acetylquinones employing a Fries rearrangement of hydroquinone esters.[19] This prompted our studies of the organocadmium alkylation of an acetylquinone derivative. Diethylcadmium alkylation of 5-acetyl-2,3-dimethylbenzoquinone **13** resulted in 5-acetyl-6-ethyl-2,3-dimethylhydroquinone **14** in 71% yield as the only observed product. Conjugate addition to **13** is the result of the electon-withdrawing effects of the acetyl group at C-5, which increases the electrophilicity of C-6.

In summary, the regiochemistry of organocadmium-quinone alkylations are strongly affected by both steric and electronic effects of the substituents. The application of these reactions, especially the alkylation of bromonaphthoquinone derivatives, has allowed us to develop strategies aimed at numerous natural products which are the subject of further investigations.

Experimental Section

General Methods. [1]H (300 MHz) and ^{13}C (75 MHz) NMR spectra were determined in CDCl$_3$ unless otherwise specified. Chemical shifts are reported in ppm downfield from internal TMS (δ). Tetrahydrofuran was distilled under nitrogen from LiAlH$_4$. All other materials were obtained from commercial suppliers.

General Procedure for Addition of Organocadmium Reagents to Quinones. In a two-neck, 250 mL round-bottom flask equipped with a condenser and a stir bar were placed anhydrous CdCl$_2$ (0.740 g, 4.2 mmol) and THF (60 mL). The cadmium chloride suspension was cooled below −10 °C and purged with nitrogen. Ethylmagnesium bromide (8.0 mmol) was then introduced via syringe, and the resulting solution was allowed to warm to room temperature. Heat was then applied, and the mixture was refluxed for 45 min. A qualitative test for the presence of Grignard reagent was then performed using a previously reported procedure.[20] Upon a negative test result, the solution was then returned to −10 °C. A solution of quinone (4.0 mmol of quinone in 10 mL of THF) was then added to the organocadmium reagent. The resulting solution was stirred for 1 h at −10 °C, after which time the reaction mixture was raised to room temperature. The reaction mixture was then poured into water (200 mL) and extracted with dichloromethane (2 × 40 mL). The organic phase was washed with water (3 × 60 mL) and dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure. The crude products were purified by flash chromatography (silica gel, acetone/hexane).

Supporting Information Available: Compilation of NMR data for all isolated compounds, MS spectra of compounds **11** and **12a**, and a copy of ^{1}H NMR data for the mixture of **11** and **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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