Quinone Alkylation Using Organocadmium Reagents: A General Synthesis of Quinols

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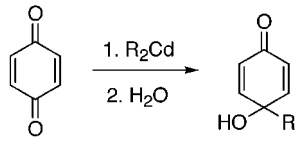
Reactions of *p*-benzoquinone with organocadmium reagents yield quinols, the result of quinone carbonyl monoalkylation. The reactions proceed in good yield and are devoid of bisaddition and hydroquinone byproducts. Quinone alkylations using this method show general applicability to *p*-benzoquinone as well as extended quinone systems using primary alkyl, secondary alkyl, and aryl reagents.

Quinols have been the subject of investigations, both synthetic and mechanistic, for many years. Their importance as synthetic precursors,[1−3] pharmaceuticals,[4] metabolic and biosynthetic intermediates,[5] and chemical photoresists[6] have contributed to much of the experimental interest. The oxidation of 4-alkylphenols has been used in the synthesis of quinols. This transformation can be accomplished by a variety of reagents including peracetic acid,[7] thallium(III) salts,[8] and hypervalent iodine.[9] Most of these procedures suffer from limitations, such as poor yield and various side reactions. Direct alkylation of quinones using alkyllithium and Grignard reagents has been used in quinol synthesis.[10] However, these reactions are complicated by hydroquinone formation via electron-transfer processes[11] and bisaddition byproducts.[12] Approaches which employ "masked quinones" (quinone monoketals[12] and silylcyanohydrins[13]) have alleviated the aforementioned problems of direct quinone alkylation, yet are multistep procedures giving modest overall yields from commercially available materials.

It was recognized that organocadmium reagents have shown greater chemoselectivity[14] and regioselectivity[15] than their Grignard or alkyllithium counterparts with respect to nucleophilic addition. These observations prompted our study of organocadmium reagents as possible selective alkylating agents of quinones. In this paper, we wish to report a general one-step procedure for the synthesis of quinol derivatives using organocadmium reagents.

Scheme 1



1 **2**

R_2Cd	Product (% yield)
R = methyl	**2a** (71%)
R = ethyl	**2b** (87%)
R = propyl	**2c** (62%)
R = butyl	**2d** (89%)
R = isopropyl	**2e** (46%)
R = *sec*-butyl	**2f** (58%)
R = phenyl	**2g** (75%)

Results and Discussion

Organocadmium reagents were prepared from their respective Grignard or alkyllithium reagents by transmetalation reactions with cadmium chloride in THF, using a modified procedure described earlier.[16] Solutions were stirred under nitrogen reflux until a negative Gilman test using Michelor's ketone was obtained.[17] The reaction of benzoquinone with the organocadmium solutions was carried out at temperatures below −10 °C using a 2-fold molar excess of the organocadmium reagents. After a period of stirring, the reaction mixtures were poured into water and extracted with dichloromethane. Purification of the crude product using base-washed silica gel chromatography[18] afforded the quinols as shown in Scheme 1. Organocadmium alkylation of benzoquinone **1** is of general applicability with quinol yields ranging from 46 to 89%. Reactions of **1** with primary dialkylcadmium reagents (methyl, ethyl, propyl, and butyl) resulted in 71% **2a**, 87% **2b**, 62% **2c**, and 89% **2d**, respectively. Secondary dialkylcadmium reagents (isopropyl and *sec*-butyl) gave 46% **2e** and 58% **2f,** while diarylcadmium (R = phenyl) gave 75% **2g**. Benzoquinone-derived quinols **2a**−**g** showed the characteristic

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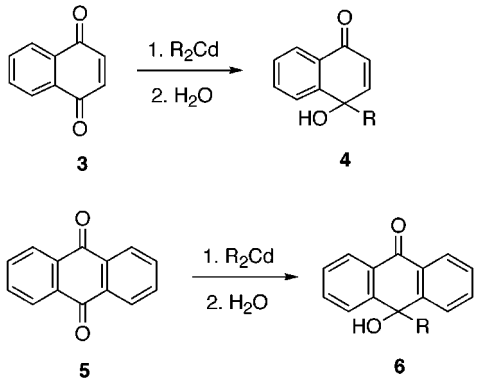
Scheme 2



Quinone	R_2Cd	Product (% yield)
3	R = methyl	**4a** (89%)
3	R = ethyl	**4b** (81%)
3	R = butyl	**4c** (96%)
5	R = methyl	**6a** (32%)
5	R = butyl	**6b** (46%)

^{1}H and ^{13}C NMR spectra previously reported.[11,18] All reactions shown in Scheme 1 where devoid of bisaddition and hydroquinone byproducts as determined by GC−MS and ^{1}H NMR. These results are in stark contrast to organolithium and Grignard additions to benzoquinone, where secondary alkyl and aryl additions result primarly in quinone reduction.[11]

To establish the amount of organocadmium reagent required for complete quinone alkylation, the reaction of benzoquinone with dibutylcadmium was repeated varying the ratio of quinone to organocadmium from 1:1 to 2:1. A 1:1 stoichiometry resulted in 64% isolated yield of **2d,** while a 2:1 quinone:organocadmium ratio resulted in 63% isolated yield. These results indicate that a 2:1 quinone:organocadmium ratio is sufficient for complete alkylation, thus demonstrating that both alkyl groups of the organocadmium reagent are active with respect to quinone alkylation.

To determine the general applicability of this reaction, extended quinones were subjected to organocadmium alkylations as shown in Scheme 2. Reactions of 1,4-naphthoquinone **3** with dimethyl-, diethyl-, and dibutylcadmium reagents resulted 89% **4a**, 81% **4b**, and 96% **4c,** respectively. Similar results were observed for the reaction between 9,10-anthraquinone **5** and dimethyl- and dibutylcadmium, resulting in 32% **6a** and 46% **6b,** respectively. Low yield of quinols **6a** and **6b** are due to the poor solubility profile of **5** under our reaction conditions, as indicated by a significant recovery of quinone starting material. In all cases, the alkylation reactions are free from quinone reduction and bisaddition byproducts.

In conclusion, the alkylation of quinones using organocadmium reagents was shown to be an efficient one-step method for the preparation of quinol derivatives. Alkylations occur in good yield and are free from hydroquinone and bisaddition products. Further investigations will be directed toward the application of these findings to the synthesis of natural products and useful synthetic precursors.

Experimental Section

General Methods. ^{1}H (250 MHz) and ^{13}C (62.9 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.[19] 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. Grignard or alkyllithium solution (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.[18] 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 (base washed silica gel, 30% acetone/hexane).[18] Reactions involving benzoquinone gave quinols **2a**−**g,** which gave spectra identical to those previously reported.[11,19] Reactions involving 1,4-naphthoquinone and 9,10-anthraquinone gave compounds having the following properties.

4-Hydroxy-4-methyl-1(4*H*)-naphthalenone (4a). Following the general procedure, 551 mg of naphthoquinone afforded **4a** (540 mg, 89%), a yellow oil. IR (KBr): 3467, 3056, 2984, 1693 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.01 (dd, J = 8.2, 1.4, 1H), 7.74 (dd, J = 7.9, 1.4, 1H), 6.98 (d, J = 10.2, 1H), 6.24 (d, J = 10.2, 1H), 7.59 (dt, J = 8.0, 1.4, 1H), 7.38 (dt, J = 8.1, 1.4, 1H), 2.14 (s, 1H), 1.61 (s, 3H). ^{13}C NMR: δ 184.57, 153.07, 147.27, 133.38, 129.23, 128.12, 126.93, 126.49, 126.35, 68.31, 30.59. Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found C, 75.66; H, 5.86.

4-Hydroxy-4-ethyl-1(4*H*)-naphthalenone (4b). Following the general procedure, 525 mg of naphthoquinone afforded **4b** (506 mg, 81%), a yellow oil. IR (KBr): 3488, 3055, 2973, 1697 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.99 (dd, J = 7.9, 1.5, 1H), 7.68 (dd, J = 7.7, 1.6, 1H), 7.58 (dt, J = 7.2, 1.5 1H), 7.38 (dt, J = 7.3, 1.4, 1H), 7.20 (d, J = 10.3, 1H), 6.45 (d, J = 10.3, 1H), 2.25−2.36 (m, 3H), 0.89 (t, J = 7.5, 3H). ^{13}C NMR: δ 184.90, 152.07, 146.09, 133.31, 128.49, 127.98, 127.84, 126.28, 126.09, 71.81, 36.02, 8.24. Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found C, 76.50; H, 6.62.

4-Hydroxy-4-butyl-1(4*H*)-naphthalenone (4c). Following the general procedure, 861 mg of naphthoquinone afforded **4c** (1.130 g, 96%), a brown oil. IR (KBr): 3459, 3064, 2944, 1688 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.83 (d, J = 7.8, 1H), 7.55 (d, J = 7.8, 1H), 7.44 (dt, J = 7.9, 1.3, 1H), 7.24 (dt, J = 7.8, 1.3, 1H), 6.75 (d, J = 10.3, 1H), 6.14 (d, J = 10.3, 1H), 2.06 (s, 1H), 1.74−1.83 (m, 2H), 0.94−1.13 (m, 4H), 0.61 (t, J = 7.1, 3H). ^{13}C NMR: δ 184.88, 152.64, 146.52, 133.86, 130.08, 127.93, 127.76, 126.28, 126.11, 71.01, 42.72, 25.81, 22.47, 13.67. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found C, 77.86; H, 7.40.

10-Hydroxy-10-methyl-9(10*H*)-anthracenone (6a). Modifying the general procedure by allowing the mixture to react for 72 h, 800 mg of 9,10-anthraquinone afforded **6a** (258 mg, 32%), a yellow oil. IR (KBr): 3426, 3055, 2983, 1663 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.23 (dd, J = 7.3, 1.5, 2H), 7.97 (dd, J = 7.3, 1.3, 2H), 7.68 (dt, J = 7.3, 1.5, 2H), 7.48 (dt, J = 7.3, 1.3, 2H), 1.72 (s, 3H). ^{13}C NMR: δ 183.17, 148.75, 133.82, 129.64, 128.05, 127.11, 125.87, 70.12, 36.99. Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found C, 80.19; H, 5.53.

(19) The presented ratio of quinone to R_2Cd is ∼1:1. No significant change in yield is observed using a 2:1 ratio.

10-Hydroxy-10-butyl-9(10*H*)-anthracenone (6b). Modifying the general procedure by allowing the mixture to react for 72 h, 811 mg of 9,10-anthraquinone afforded **6b** (477 mg, 46%), a yellow oil. IR (KBr): 3427, 3055, 2937, 1665 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.06 (dd, J = 7.8, 1.4, 2H), 7.77 (dd, J = 7.5, 1.0, 2H), 7.53 (dt, J = 7.5, 1.4, 2H), 7.33 (dt, J = 7.6, 1.0, 2H), 4.70 (s, 1H), 1.84−1.91 (m, 2H), 0.74−0.97 (m, 4H), 0.52 (t, J = 7.2, 3H). ^{13}C NMR: δ 183.81, 147.55, 133.56, 127.77, 127.12, 126.58, 125.93, 72.64, 48.19, 22.31, 19.05, 13.64. Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found C, 80.92; H, 6.78.

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