Syntheses of Naphthoquinone Compounds Using Chromium Carbonyl Carbene Complexes[1)]

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The chromium carbonyl carbene complexes bearing an acetoxyl group and a phenyl substituent were found to react smoothly with acetylene compounds to produce naphthoquinone derivatives in good yields after oxidation. This cycloaddition reaction proceeded regioselectively and several naphthoquinones were prepared selectively from the complex and unsymmetrical acetylenes.

Naphthoquinones and anthraquinones are important compounds well-known for their characteristic bioactivities. In our laboratory, Suemitsu et al. isolated quinone compounds such as altersolanol,[2,3)] alterporriol,[4—6)] and so on, and investigated their bioactivity. For example, altersolanol B, one of the metabolic pigments produced by *Alternaria porri*, *Alternaria solani*, and *Dactylaria lutea*, has been found to have growth inhibitory activity in lettuce and stone leeks seedlings.[7)] In the course of our study on the bioactivity of these quinone compounds and their derivatives, it has become necessary to synthesize them in large amounts (Chart 1).

Consequently, we began a synthetic study of them. As a key reaction for the synthesis of naphthoquinone skeletons, we used the cycloaddition reaction of Fischer-type carbene complex **1** with acetylene compounds,[8)] (Scheme 1). From naphthol **2**, naphthoquinone **3** was obtained by oxidation. In this paper, we wish to report a preliminary study of a modified quinone synthesis using chromium acetoxycarbene complexes and the regioselectivity of the reaction.

Results and Discussion

The chromium acetoxycarbene complexes **6** were prepared according to the method in the literature (Scheme 2).[9)] For the cycloaddition reaction, usually the methoxycarbene complexes such as **1**, prepared by methylation of the salt **5a** (Scheme 2) using an alkylation reagent such as methyl fluorosulfate,[10)] have been used.[11)] But, the reagent is intractable due to its fuming and is very expensive. Acetyl chloride, used for the preparation of **6**, is easier to handle, and the corresponding complexes **6** were found to be useful for the next naphthoquinone synthesis. Therefore, we used **6** hereafter instead of **1**.

As an acetylene, 1-hexyne was examined first. Reaction of 1-hexyne and complex **6a** in tetrahydrofuran (THF) gave hydroquinone derivative **8a**, which was successively oxidized with diammonium cerium(IV) nitrate. After the usual work-up of the yellow reaction mixture, crude naphthoquinone compound **9a** was obtained in a 71% yield and was purified by column chromatography (Scheme 3).

The results of this and other cycloaddition reactions are listed in Table 1. The corresponding naphthoquinones were obtained in good yields, but the yields decreased with increasing number of carbon atoms in the

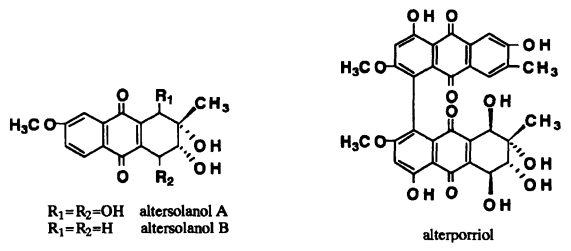
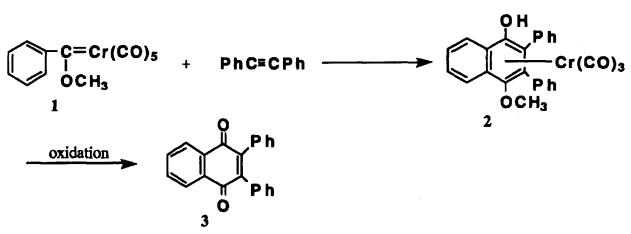
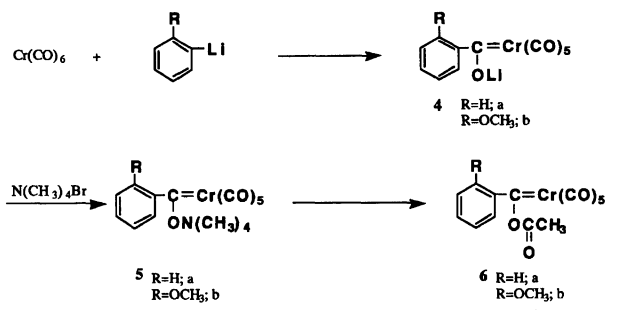


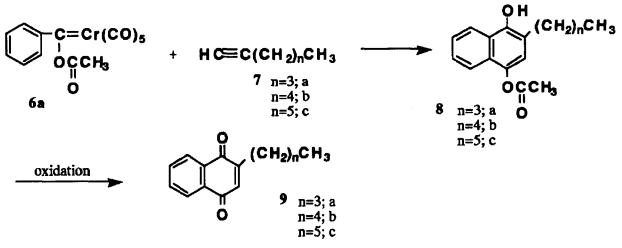
Chart 1.



Scheme 1.



Scheme 2.



Scheme 3.

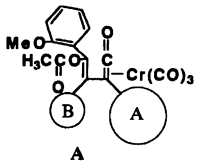
Table 1. The Syntheses of Naphthoquinones Using Chromium Carbonyl Carbene Complex **6a**

1-Alkyne	Product	Yield (%)
1-Hexyne	**9a**: n=3	71
1-Heptyne	**9b**: n=4	58
1-Octyne	**9c**: n=5	47

acetylenes. This suggests that the reaction is influenced by the bulkiness of the acetylene compounds used.

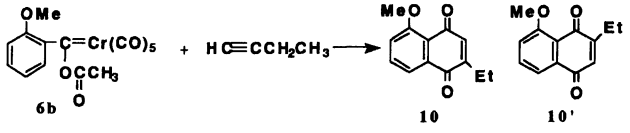
These reactions proceeded regioselectively similar to the reaction already reported by Wulff et al.[12] Chromium ketene complex **A** (Chart 2) via metallacyclobutene is regarded as a key intermediate in this cycloaddition reaction.[13,14] The regioselectivity of the cycloaddition reaction is mainly controlled by steric factors. The carbene carbon reacts with the carbon atom of carbon–carbon triple bond which is connected to less-bulky group B. For example, when chromium carbene complex **6b** was treated with 1-butyne, only **10** was obtained in a 35% yield, and no isomer was found (Scheme 4). Compound **10** was identified by comparison of its ^{1}H and ^{13}C NMR spectra with those of authentic 2-ethyl-5-methoxyl-1,4-naphthoquinone prepared by the method in the literature.[15] Other results are shown in Table 2.

Thus, we found complexes **6a** and **6b** were useful cycloaddition reaction reagents to acetylene compounds to afford naphthoquinone compounds and that this cycloaddition reaction proceeds with high regioselectivity. Further, the synthesis of an anthraquinone skeletone using benzyne instead of alkyne is proceeding. Our method will be useful for synthesizing various bioactive naphthoquinone and anthraquinone derivatives.



A

Chart 2.



Scheme 4.

Table 2. The Syntheses of Naphthoquonones Using Chromium Carbonl Carbene Complex **6b**

1-Alkyne	Product	Yield (%)
1-Butyne	**10a**: n=1	35
1-Hexyne	**10b**: n=3	80
1-Heptyne	**10c**: n=4	51
1-Octyne	**10d**: n=5	33

Experimental

Spectra. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a JEOL GX-400 FT-NMR spectrometer operating at 400 MHz. Peak positions are reported in parts per million relative to tetramethylsilane internal standard. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a JEOL GX-400 FT-NMR spectrometer operating at 100 MHz. Peak positions are reported in parts per million relative to tetramethylsilane. Spectra which were recorded with off-resonance decoupling have peaks reported as singlets (s), doublets (d), triplets (t), quartets (q), or multiplets (m). Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer as KBr pellets, nujol (for solids) or liquid films (for liquids). Mass spectra were recorded on a Hitachi M-80B instrument. All melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected.

Chromatography. Column chromatography was performed with E. Merck silica gel 60 (230—400 mesh). Analytical thin-layer chromatography (TLC) was done with E. Merck Reagents silica gel 60 F-254 with a 0.25 mm thickness. Developed plates were visualized under UV light and by charring with a color-producing reagent (ethanol (425 ml), acetic acid (5 ml), concd-H_2SO_4 (25 ml), H_2O (25 ml), and *p*-anisaldehyde (25 ml)).

Reagents and Solvents. Tetrahydorofuran (THF) was dried and distilled under an argon atmosphere from potassium benzophenone immediately before use. Diethyl ether (ether) was distilled from calcium chloride. Dichloromethane was distilled from calcium chloride. Lithium (pole), bromobenzene, *o*-bromoanisole, hexacarbonylchromium, tetramethylammonium bromide, acetyl chloride, 1-butyne, 1-hexyne, 1-octyne, and diammonium cerium(IV) nitrate were commercial products and were used without further purification. Phenyllithium and *o*-methoxyphenyllithium were prepared from lithium and bromobenzene or *o*-bromoanisole by the usual procedure, and were titrated with 2-butanol using 1,10-phenanthoroline as an indicator.

Tetramethylammonium Salt (5a). Phenyllithium (10 mmol) was added dropwise to a suspension of hexacarbonylchromium (1.10 g, 5 mmol) in ether (100 ml) at −78 °C under an argon atmosphere. After stirring for 1.5 h, the suspension was allowed to warm to room temperature, and stirred for another 2 h. The reaction mixture was concentrated and water (100 ml) was added to the residue. After filtration, a solution of tetramethylammonium bromide (0.77 g, 5 mmol) in water (10 ml) was added to the filtrate with vigorous stirring. After stirring for 5 min, the reaction mixture was extracted with dichloromethane. The organic layer washed with saturated NaCl. After removal of the solvent, the residue was dissolved in a small amount of dichloromethane, and then a large excess of ether was added to the solution. Orange crystals (**5a**) (0.89 g, 48%) precipitated were collected by filtration.

Tetramethylammonium Salt (5b). The above procedure was used to produce 1.54 g (76%) of salt (**5b**), as green crystals, from 10 mmol of *o*-methoxyphenyllithium and 1.10 g (5 mmol) of hexacarbonylchromium.

[Acetoxy(phenyl)methylene]pentacarbonylchromium (6a). To a solution of **5a** (0.93 g, 2.5 mmol) in dichloromethane (15 ml) was added dropwise acetyl chloride

(0.36 ml, 5 mmol) at −20 °C under argon atmosphere, and the solution was stirred for 2 h, followed by addition of water (30 ml). The reaction mixture was extracted with dichloromethane. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and concentrated. The residue was subjected to silica-gel column chromatography (hexane : dichloromethane : ether = 12 : 1 : 1) and chromatographed in two parts. The first band, orange in color, was found to be the desired carbene complex (**8a**) obtained as orange crystals (0.31 g, 37%). Mp 46 °C; ^{1}H NMR ($CDCl_3$) δ=4.70 (3H, s, CH_3) and 7.00—8.18 (5H, m, Ar). ^{13}C NMR ($CDCl_3$) δ=67.01 (CH_3), 123.00, 128.17, 130.33 (Ar), 153.72 (1-C), 216.16 (CO cis), 224.13 (CO trans), and 351.10 (Cr–C). IR (KBr) 1990, 1940, 1440, 1260, 1230, and 990 cm^{-1}. Found: C, 49.95; H, 2.70%. Calcd for $C_{14}H_8O_7Cr$: C, 49.40; H, 2.37%.

[Acetoxy(*o*-methylphenyl)methylene]pentacarbonylchromium (6b). The above procedure was used to produce 0.32 g (35%) of the complex (**6b**), as orange crystals, from 1.0 g (2.5 mmol) of salt **5b** and 0.36 ml (5 mmol) of acetyl chloride. Mp 80—83 °C; ^{1}H NMR ($CDCl_3$) δ=3.82 (3H, s, OCH_3), 4.15 (3H, s, CH_3), and 6.77—7.40 (4H, m, Ar). ^{13}C NMR ($CDCl_3$) δ=55.37, 65.28 (CH_3 or OCH_3), 110.97, 120.75, 121.31, 129.67 (Ar), 148.61 (1-C), 216.03 (CO cis), 225.16 (CO trans), and 354.70 (Cr–C). IR (Nujol) 1960, 1250, 1150, 1020, and 930 cm^{-1}. Found: C, 48.40; H, 2.71%. Calcd for $C_{14}H_8O_8Cr$: C, 48.64; H, 2.72%.

General Procedure for the Preparation of Naphthoquinone Compounds. To a solution of **6** (1 mmol) in THF (10 ml) was added dropwise alkynes (3 mmol) at room temperature under argon atmosphere. After stirring for 20 h, the solution was allowed to warm to 50 °C over 2 h. 0.5 M diammonium cerium(IV) nitrate (5.49 g, 10 mmol) in 0.1 M nitric acid was added to the solution for oxidation and the mixture was stirred for 1 h at 50 °C (1 M=1 mol dm^{-3}). The reaction mixture was then extracted with ether, and the organic layer was washed with saturated NaCl, dried over $MgSO_4$, and concentrated. The resulting yellow oil was purified by silica-gel column chromathgraphy (hexane : dichloromethane : ether = 5 : 1 : 1). Naphthoquinone compounds were obtained.

2-Butyl-1,4-naphthoquinone (9a). The above procedure was used to produce 0.15 g (71%) of naphthoquinone **9a**, as a yellow oil, from 0.34 ml (3 mmol) of 1-hexyne and 0.34 g (1 mmol) of complex **6a**. ^{1}H NMR ($CDCl_3$) δ=0.95 (3H, t, J=7.32 Hz, CH_3), 1.38—1.60 (4H, m, $\underline{CH_2}\underline{CH_2}CH_3$), 2.58 (2H, td, J=7.33 and 1.22 Hz, $\underline{CH_2}CH_2CH_2CH_3$), 6.80 (1H, t, J=1.22 Hz, 3-H), 7.71—7.78 (2H, m, 5,8-H), and 8.01—8.13 (2H, m, 6,7-H). IR (Liquid film) 2950, 1660, 1600, 1300, and 940 cm^{-1}. Found: m/z 214.0992. Calcd for $C_{14}H_{14}O_2$: M, 214.0992.

2-Pentyl-1,4-naphthoquinone (9b). The above procedure was used to produce 0.13 g (58%) of naphthoquinone **9b**, as a yellow oil, from 0.39 ml (3 mmol) of 1-heptyne and 0.34 g (1 mmol) of complex **6a**. ^{1}H NMR ($CDCl_3$) δ=0.91 (3H, t, J=7.33 Hz, CH_3), 1.25—1.61 (6H, m, $\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_3$), 2.57 (2H, td, J=7.94 and 1.22 Hz, $\underline{CH_2}CH_2CH_2CH_2CH_3$), 6.80 (1H, t, J=1.22 Hz, 3-H), 7.72—7.76 (2H, m, 5,8-H), and 8.05—8.11 (2H, m, 6,7-H). IR (Liquid film) 2950, 1660, 1480, 1300, 900, and 780 cm^{-1}. Found: m/z 228.1143. Calcd for $C_{15}H_{16}O_2$: M, 228.1149.

2-Hexyl-1,4-naphthoquinone (9c). The above procedure was used to produce 0.11 g (47%) of naphthoquinone **9c**, as yellow crystals, from 0.44 ml (3 mmol) of 1-octyne and 0.34 g (1 mmol) of complex **6a**. Mp 44 °C; ^{1}H NMR ($CDCl_3$) δ=0.89 (3H, t, J=7.33 Hz, CH_3), 1.29—1.62 (8H, m, $\underline{CH_2}\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_3$), 2.57 (2H, td, J=7.93 and 1.22 Hz, $\underline{CH_2}CH_2CH_2CH_2CH_2CH_3$), 6.79 (1H, t, J=1.22 Hz, 3-H), 7.71—7.76 (2H, m, 5,8-H), and 8.04—8.13 (2H, m, 6,7-H). IR (KBr) 2930, 1660, 1600, 1310, 940, and 790 cm^{-1}. Found: C, 78.85; H, 7.49%; M^+, 242. Calcd for $C_{16}H_{18}O_2$: C, 79.30; H, 7.49%; M, 242.

2-Ethyl-5-methoxy-1,4-naphthoquinone (10a). The above procedure was used to produce 0.07 g (35%) of naphthoquinone **10a**, as yellow crystals, from an excess amount of 1-butyne and 0.40 g (1.01 mmol) of complex **6b**. When 1-butyne was added to a solution of complex **6b**, they were cooled to −78 °C. Mp 65—69 °C; ^{1}H NMR ($CDCl_3$) δ=1.19 (3H, t, J=7.33 Hz, CH_3), 2.56 (2H, qd, J=7.33 and 1.22 Hz, CH_2), 4.01 (3H, s, OCH_3), 6.68 (1H, t, J=1.22 Hz, 3-H), 7.29 (1H, dd, J=7.93 and 1.22 Hz, 6-H), 7.66 (1H, t, J=7.93 Hz, 7-H), and 7.76 (1H, dd, J=7.93 and 1.22 Hz, 8-H). ^{13}C NMR ($CDCl_3$) 11.70 (CH_3), 22.06 (CH_2), 56.50 (OCH_3), 117.65 (3-C, 6-C, 7-C, or 8-C), 119.41 (3-C, 6-C, 7-C, or 8-C), 134.67 (3-C, 6-C, 7-C, or 8-C, and 9-C, or 10-C), 136.16 (3-C, 6-C, 7-C, or 8-C, and 9-C, or 10-C), 150.40 (2-C), 159.41 (5-C), 184.81 (1-C or 4-C), and 185.46 (1-C or 4-C). IR (KBr) 2950, 1675, 1600, 1490, 1300, and 1280 cm^{-1}. Found: m/z 216.0768. Calcd for $C_{13}H_{12}O_3$: M, 216.0785.

2-Butyl-5-methoxy-1,4-naphthoquinone (10b). The above procedure was used to produce 0.07 g (80%) of naphthoquinone **10b**, as yellow crystals, from 0.13 ml (1.1 mmol) of 1-hexyne and 0.14g (0.37 mmol) of complex **6b**. Mp 67—69 °C; ^{1}H NMR ($CDCl_3$) 0.95(3H, t, J=7.33 Hz, CH_3), 1.36—1.59 (4H, m, $\underline{CH_2}\underline{CH_2}CH_3$), 2.52 (2H, td, J=7.33 and 1.22 Hz, $\underline{CH_2}CH_2CH_2CH_3$), 4.01 (3H, s, OCH_3), 6.68 (1H, t, J=1.22 Hz, 3-H), 7.28 (1H, dd, J=7.94 and 1.22 Hz, 6-H), 7.66 (1H, t, J=7.94 Hz, 7-H), and 7.76 (1H, dd, J=7.94 and 1.22 Hz, 8-H). ^{13}C NMR ($CDCl_3$) δ=13.95 (CH_3), 22.50, 28.95, 30.00 (CH_2×3), 56.62 (OCH_3), 117.83 (3-C, 6-C, 7-C, or 8-C), 119.51 (3-C, 6-C, 7-C, or 8-C), 134.42 (3-C, 6-C, 7-C, or 8-C, and 9-C, or 10-C), 136.89 (3-C, 6-C, 7-C, or 8-C, and 9-C, or 10-C), 148.95 (2-C), 159.00 (5-C), 184.36 (1-C or 4-C), and 185.22 (1-C or 4-C). IR (KBr) 2950, 1675, 1640, 1600, 1590, 1300, 1280, and 795 cm^{-1}. Found: C, 73.29; H, 6.64%; M^+, 244. Calcd for $C_{15}H_{16}O_3$: C, 73.73; H, 6.61%; M, 244.

2-Pentyl-5-methoxy-1,4-naphthoquinone (10c). The above procedure was used to produce 0.1 g (51%) of naphthoquinone **10c**, as yellow crystals, from 0.3 ml (2.8 mmol) of 1-heptyne and 0.28 g (0.77 mmol) of complex **6b**. Mp 68—70 °C; ^{1}H NMR ($CDCl_3$) δ=0.90 (3H, t, J=7.33 Hz, CH_3), 1.25—1.58 (6H, m, $\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_3$), 2.51 (2H, td, J=7.33 and 1.22 Hz, $\underline{CH_2}CH_2CH_2CH_2CH_3$), 4.01 (3H, s, OCH_3), 6.69 (1H, t, J=1.22 Hz, 3-H), 7.29 (1H, dd, J=7.93 and 1.22 Hz, 6-H), and 7.66 (1H, t, J=7.93 Hz, 7-H), 7.76 (1H, dd, J=7.93 and 1.22 Hz, 8-H). ^{13}C NMR ($CDCl_3$) δ=14.00 (CH_3), 22.72, 27.83, 28.98, 31.76 (CH_2×4), 56.62 (OCH_3), 117.78 (3-C, 6-C, 7-C, or 8-C), 119.62 (3-C, 6-C, 7-C, or 8-C), 134.81 (3-C, 6-C, 7-C, or 8-C, and 9-C, or 10-C), 137.00 (3-C, 6-C, 7-C, or 8-C, and 9-C, or 10-C), 149.37 (2-C), 159.76 (5-C), 184.87 (1-C or 4-C), and 185.48 (1-C or 4-C). IR (KBr) 2950, 1680, 1600, 1495, 1280, 970, and 795 cm^{-1}. Found: m/z 258.1254. Calcd for $C_{16}H_{18}O_3$: M,

258.1254.

2-Hexyl-5-methoxy-1,4-naphthoquinone (10d). The above procedure was used to produce 0.03 g (33%) of naphthoquinoe **10d**, as yellow crystals, from 0.04 ml (0.9 mmol) of 1-octyne and 0.12 g (0.3 mmol) of complex **6b**. Mp 70—71 °C; ^{1}H NMR ($CDCl_3$) δ=0.89 (3H, t, J=7.33 Hz, CH_3), 1.28—1.58 (8H, m, $\underline{CH_2}\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_3$), 2.51 (2H, td, J=7.33 and 1.22 Hz, $\underline{CH_2}CH_2CH_2CH_2CH_2CH_3$), 4.01 (3H, s, OCH_3), 6.68 (1H, t, J=1.22 Hz, 3-H), 7.29 (1H, dd, J=7.33 and 1.22 Hz, 6-H), 7.66 (1H, t, J=7.33 Hz, 7-H), and 7.75 (1H, dd, J=7.33 and 1.22 Hz, 8-H). ^{13}C NMR ($CDCl_3$) 14.00 (CH_3), 22.81, 27.98, 29.02, 29.97, 31.57 (CH_2 5), 56.64 (OCH_3), 117.85 (3-C, 6-C, 7-C, or 8-C), 119.72 (3-C, 6-C, 7-C, or 8-C), 134.87 (3-C, 6-C, 7-C, or 8-C, and 9-C or 10-C), 137.02 (3-C, 6-C, 7-C, or 8-C, and 9-C, or 10-C), 149.32 (2-C), 159.76 (5-C), 184.82 (1-C or 4-C), and 185.87 (1-C or 4-C). IR (KBr) 2950, 1680, 1600, 1270, 960, and 780 cm^{-1}. Found: m/z 272.1408. Calcd for $C_{17}H_{20}O_3$: M, 272.1410.

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