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NAPHTHOQUINONES FROM ALKYNES AND CHROMIUM-CARBENE COMPLEXES- CONTROL OF REGIOSELECTIVITY THROUGH INTRAMOLECULAR REACTION

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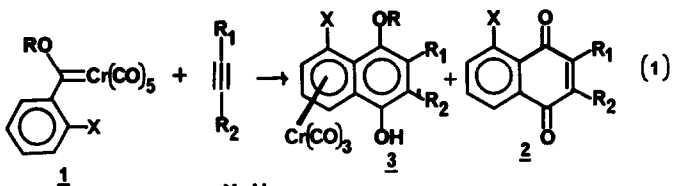
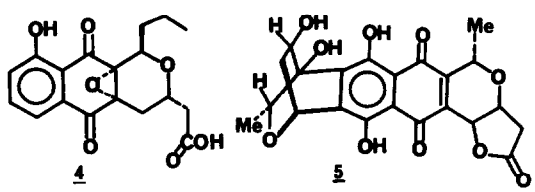
Abstract A series of carbene-chromium complexes bearing a phenyl substituent and an alkoxy-alkyne substituent have been prepared by acetoxy replacement. Intramolecular cycloaddition with carbon monoxide insertion occurs to provide naphthohydroquinones in good yield.

The reaction (1) between carbene-chromium complexes (1) and alkynes is a direct method for preparation of substituted naphthoquinones (2) via η^6-(naphthol)$Cr(CO)_3$ complexes (3),[1] but is severely limited by lack of regioselectivity when R_1 and R_2 have similar steric parameters [1b,2]



1 3 2

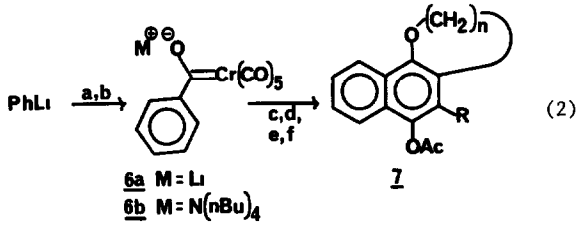
series a X=H
b X=OMe



4 5

The mechanism of the reaction is not established[1c] and no applications in complex synthesis have been reported. Selective synthesis of derivatives such as 3b, where R_1 and R_2 are different alkyl groups, is not possible.[4] An interest in applying this reaction in a general synthesis of the quinone antibiotics frenolicin (4)[2] and granaticin (5)[3] prompted us to consider new approaches to regiochemical control. One effective approach to regiochemical control in cycloaddition reactions is to restrict the transition state geometry by connecting the two reactants, in this paper we wish to report our preliminary efforts to explore the intramolecular carbene-alkyne cycloaddition reaction as a means of selective naphthoquinone synthesis An important simplification in this strategy is the anhydride-like reactivity of acetoxy-carbene complexes which allows replacement of the acetoxy unit by other alkoxy, amino, and thioalkoxy nucleophiles (an analog of acyl transfer).[5]

The successful sequence involved two stages and one isolated intermediate, 6b (equation 2) Reaction of phenyllithium with chromium hexacarbonyl produces the lithium salt 6a which is con-



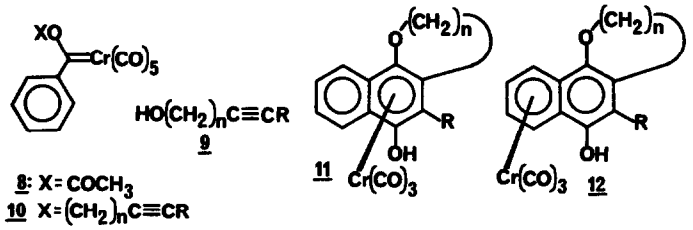
(2)

6a M = Li
6b M = N(nBu)4

7

Reagents: (a) $Cr(CO)_6$, (b) $(nBu)_4N^{\oplus}Br^{\ominus}$, (c) AcCl, (d) $HO(CH_2)_nC{\equiv}CR$, (e) 35°, (f) Ph_3P, Ac_2O

verted to the water-insoluble tetra-(n-butyl)ammonium salt[7] as a means of purification The salt 6b can be prepared in large quantity and stored at 25° indefinitely It is activated for exchange[8] by acetylation at -20° in dichloromethane to produce the delicate, deep red acetate, 8 Without purification, 8 is allowed to react with an alkynol (9) at 25°. The product is a red oil which is characterized as complex 10 by ^1H NMR and IR spectroscopy,[9] but not isolated. It is unstable above 25°, and after 20-30 hr at 35°, complete conversion to a new complex (11) is observed. This product was particularly sensitive to donor solvents such as acetone, in which the $Cr(CO)_3$ unit moves to the less substituted ring (12) and then is detached completely. For ease of isolation, the $Cr(CO)_3$ unit was rapidly detached from 11 with triphenylphosphine in the presence of triethylamine and acetic anhydride to give the acetyl derivatives, 7.



Series a n=2,R=H
b n=2,R=CH_3
c n=3,R=H
d n=3,R=CH_3
e n=4,R=H
f n=4,R=CH_3

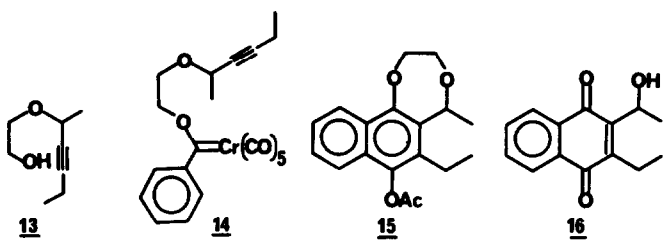
Table Intramolecular Alkyne-Carbene Reaction

Alkyne	Reaction conditions[a]	Naphthol Acetate,7	Isolated Yield[b]
9a	26 hr/25°	7a	16%
9b	20 hr/35°	7b	81%
9c	44 hr/25°	7c	18%
9d	44 hr/35°	7d	62%
9e	20 hr/35°	7e	38%
9f	46 hr/35°	7f	62%

(a) In ether solution with complexes 10 used without purification
(b) The yield is calculated overall from 6b as starting material and is based on chromatographically pure material.

The Table presents the results of reaction of 6b with six alkynols (9a-f) which were chosen to define ring size preferences and the influence of substituents on the alkyne From the reaction conditions required for complete conversion, it is clear that these intramolecular examples proceed considerably faster than related intermolecular cases (60°/10-20 hr).[1,2] All three ring sizes (5, 6, and 7) can form efficiently, but terminal alkynes are distinctly less effective than the disubstituted alkynes

A specific example shows how the method is applied to simple regiochemical control The alkyne 13 is prepared by alkylation of hex-3-yne-2-ol with ethyl bromoacetate and reduction of the ester with lithium aluminum hydride The following sequence is carried out under argon Complex 6b (1.1 mmol) is dissolved in dichloromethane (20 ml) and the yellow solution is cooled to -20° Acetyl chloride (0 87 ml, 1 2 mmol) is added as a solution in dichloromethane over 5 min The resulting deep red solution is warmed to -10° and stirred for 40 min. The alkyne 13 (1 1 mmol) is added and the solution is stirred at 25° for 1 hr After the solvent is removed at aspirator vacuum, the residue is triturated with pentane and filtered. From the filtrate, the pentane is removed to leave a deep red oil (14, 86% yield) It is dissolved in ether and heated at 35° for 20 hr The solvent is removed to leave an orange-yellow powder, which is dissolved in acetone (10 ml) and treated by sequential addition of triphenylphosphine (2.9 mmol), acetic anhydride (1 5 ml), and triethylamine (0 5 ml). After the solution has been stirred for 17 5 hr, the solvent



13 14 15 16

is removed and the residue is purified by mplc (silica gel,hexane followed by 10 1 hexane ether) to yield 15 as a colorless solid in 65% yield Cleavage of the acetate, oxidation with DDQ, and detachment[10] of the hydroxyethyl unit produces the disubstituted quinone, 16 Since nitrogen and sulfur nucleophiles are known[6] to exchange onto carbene-chromium complexes, this one-step construction of two rings may be an important addition to heterocyclic methodology

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References and Notes

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9 Spectral data for the products in the Table For 7a ^{1}H NMR($CDCl_3$) δ 2 43 (s, 3H, $-COCH_3$), 3.37 (t, 2H, J = 7 Hz, $ArCH_2$-), 4.76 (t, 2H, J = 7Hz, $-OCH_2O$-), 7 12 (s, 1H), 7.46 (m, 2H), 7 75 (m, 1H), 7.88 (m, 1H). C-13 NMR($CDCl_3$) δ 20.9, 3017, 71 9, 115 4, 119 1, 120 7, 121 4, 121 8, 125.8, 126.1, 126.4, 138 0, 153 4, 170.0. IR(CCl_4) 3065 (w), 1760 (s, C = O), 1365 (s), 1205 (s), 1060 (s), 905 (m) MS 228 Anal C,H Colorless oil. For 7b ^{1}H NMR-($CDCl_3$) δ 2.10 (s, 3H, $ArCH_3$), 2 34 (s, 3H, $-COCH_3$), 3.08 (t, 2H, J = 8Hz, $ArCH_2$-), 4 50 (t, 2H, J = 0Hz, $-OCH_2$-), 7 01-7189 (m, 4H) C-13 NMR($CDCl_3$) δ 13 6, 20.3, 29.7, 71 6, 119 0, 120 0, 120 9, 121.5, 123.9, 124 6, 126.0, 126.6, 137.5, 152.6, 169 4. IR(CCl_4) 3070 (w), 1760 (s, C = 0), 1400 (s), 1210 (s), 1175 (s). MS 242 Anal C,H. mp 117 5-118 5° For 7c ^{1}H NMR($CDCl_3$) δ 2.08 (m, 2H, $CH_2CH_2CH_2$), 2 38 (s, 3H, $COCH_3$), 2.81 (t, 2H, J = 7Hz, $ArCH_2$), 4 22 (m 2H, $-OCH_2$-), 6.78 (s, 1H), 7 01-7 69 (m, 3H), 8 02 (m, 1H). C-13 NMR ($CDCl_3$) δ 20.9 22 3, 24.9, 66 7, 115 1, 119 6, 120.8, 121 8, 125 6, 126 1, 139.2, 143 0, 169 9. IR(CCl_4) 3081 (w), 1765 (s, C = 0), 1365 (s), 1200 (s), 1065 (s), 910 (s) MS 242 Anal· C,H Colorless oil For 7d ^{1}H NMR($CDCl_3$) δ 2 02 (m, 2H, $-CH_2CH_2CH_2$-), 2 10 (s, 3H, $ArCH_3$), 2.40 (s, 3H, $-COCH_3$), 2 64 (t, 2H, J = 6Hz, $ArCH_2$), 4.18 (dd, 2H, $-OCH_2$-), 7.17-7 65 (m, 3H), 8 02 (m, 1H). C-13 NMR($CDCl_3$) δ14 1, 22.0, 23 8, 29 3, 72 2, 105.3, 114 2, 118.9, 120 2, 122.8, 123 1, 124.4, 135 3, 145.9, 166 6 IR(CCl_4) 3070 (w), 1760 (s, C = 0), 1360 (s), 1210 (s), 1180 (s) mp 117 5-119 5° High resolution MS mole wt 256 1076. Calcd 256 1099 For 7e ^{1}H NMR($CDCl_3$) δ 1 90 (m, 4H, $-CH_2CH_2$-), 2 35 (s, 3H, $COCH_3$), 2 86 (m, 2H, $ArCH_2$), 4 06 (m, 2H, $-OCH_2$-), 6.90 (s, 1H), 7 26-7 75 (m, 3H), 8.10 (m, 1H). C-13 NMR($CDCl_3$) δ 20.9, 25.6, 32 3, 34.3, 73 3, 120.8, 122 5, 125 9, 126 1, 128 6, 129 7, 141.4, 153 3, 170 0 IR(CCl_4) 3065 (w), 1770 (s, C = 0), 1370 (s), 1200 (s), 1055 (s), 915 (s). MS 256 Anal C,H. mp 89 0-90.5°. For 7f ^{1}H NMR($CDCl_3$) δ 1.83 (m, 4H, $-CH_2CH_2$), 2 20 (s, 3H, $ArCH_3$), 2 39 (s, 3H, $COCH_3$), 2 91 (m, 2H, $ArCH_2$-), 4.04 (dd, 2H, $-OCH_2$-), 7 19-7 66 (m, 3H), 7 99 (m, 1H) C-13 NMR($CDCl_3$) δ 13 6, 20 5, 24 5, 28.2, 32 0, 73 0, 120 6, 122 1, 125 3, 126 1, 126 8, 130 5, 140 2, 153 7, 169 2, IR(CCl_4) 3075 (w), 1765 (s, C = 0), 1360 (s), 1200 (s), 1175 (s), 1060 (s) MS 270 Anal C,H mp 109 5-110 5° The carbene-alkyne complexes 10 are obtained as thermally sensitive red oils or powders The samples used for cyclization appeared to be >95% pure by ^{1}H NMR. For example, complex 10a showed ^{1}H NMR(acetone-d_6) δ 2.45 (t, 1H, J = 3H), 2.91 (d of t, 2H, J = 3, 7Hz), 4 83 (t, 2H, J = 7Hz), 7 1-7 5 (br s, 5H) IR(CCl_4) Characteristic CO stretch at 2650 (m sharp), 1985 (sh, sharp), 1900 (two peaks, broad, strong) cm^{-1} For 14 mp 129 5-130 5° Satisfactory spectral data and analysis

10 The 2-hydroxyethyl substituent is removed simply by formation of the tosylate, conversion to the iodide with NaI, and reductive cleavage with zinc metal The quinone unit is also reduced, but can be re-oxidized efficiently (DDQ)

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