Regiochemistry of the Reaction of Chromium–Carbene Complexes with Acetylenes

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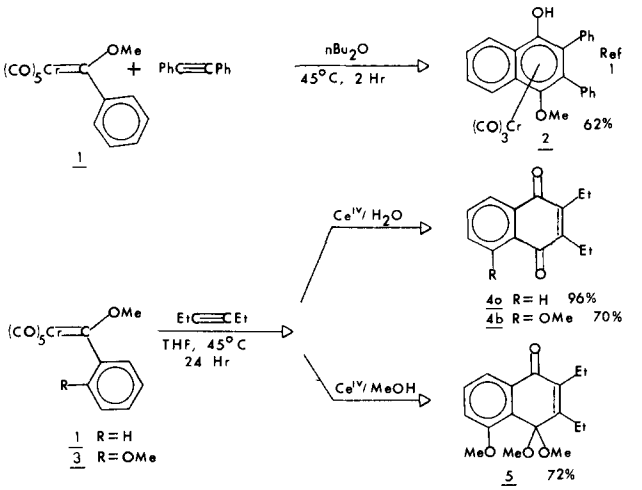
The decidedly interesting observation of the reaction of the chromium–carbene complex **1** with diphenylacetylene appeared in the literature in 1975.[1] This cyclization reaction occurs with incorporation of the acetylene and a carbon monoxide ligand to give the (naphthol)chromium tricarbonyl complex **2**. We anticipate that this reaction will be synthetically valuable and are currently utilizing it in the synthesis of anthracyclines. We report here our results concerning the regiochemistry of this reaction and its extension to several carbene complexes bearing certain aryl substituents.[2]

The key substituent for anthracycline synthesis is an ortho-methoxyl group. We have carried out the reaction[3] of the ortho-methoxyl carbene complex **3**[4] with 3-hexyne and after an oxidative workup[6] [to avoid handling an air-sensitive (naphthol)chromium tricarbonyl complex] obtained the desired naphthoquinone **4b** in 70% yield.[8] An oxidative workup in the presence of methanol yields the naphthoquinone monoacetal **5**[9] in 72% yield; a result which greatly adds to the synthetic flexibility of these reactions.

The question of regioselectivity with unsymmetrical acetylenes is of fundamental concern for synthetic utility. The reaction has been reported to display absolute regioselectivity with a variety of unsymmetrical acetylenes including 2-pentyne.[10,11] Dötz reported in 1976 that the phenylcarbene complex **1** reacts with 2-pentyne to give only the 3-methyl-2-ethyl-1-naphthol complex **6**.[10] No other isomer could be observed, and the structural assignment of **6** was supported by an X-ray diffraction determination. In our hands, however, this reaction upon oxidative workup in methanol[12] gives both of the possible isomeric monoacetals **7** and **8** in a 2.0:1.0 ratio.[13,14] Since all regiochemical assignments in reactions with other unsymmetrical acetylenes have been related to the reactions of **1** with 2-pentyne,[11] we felt compelled to un-

Scheme I



Scheme II

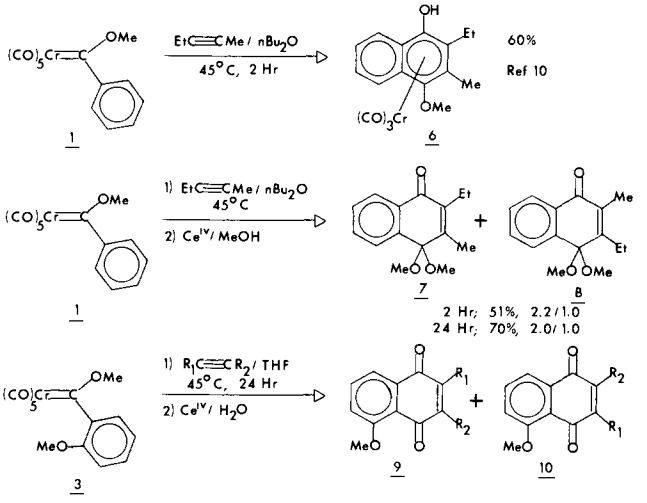


Table I. Regioselectivity of Complex **3**[a]

naphthoquinones	R_1	R_2	yield (9 + 10),[b] %	9/10[c]
9a, 10a	Et	Me	81	1.5[d]
9b, 10b	*n*-Pr	Me	64	2.9[e]
9c, 10c	*i*-Pr	Me	61	4.8[e]
9d, 10d	Ph	Me	78	*f*
9e, 10e	*n*-Pr	H	74	≥111[f,g]
9f, 10f	$(CH_2)_3CO_2$-*t*-Bu	H	66	*f*
9g, 10g	$(CH_2)_3CONH$-*t*-Bu	H	70	*f*

[a] With procedure described in footnote 3. [b] Yields of isolated mixtures. [c] Major isomers assumed to be 9 on the basis of structural assignments made for 7 and 8 and for 9e and 10e. [d] Only 9a was isolated in pure form; ratio by ^{1}H NMR spectroscopy. [e] Ratio of isolated products. [f] Only one isomer was found. [g] Product identified as 9e by comparison with an authentic sample. For a determination of a minimum value for this ratio see ref 17.

(1) Dötz, K. H., *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644–645.

(2) A preliminary account of this work was presented at the 1st IUPAC Symposium on Organometallic Chemistry Directed toward Organic Synthesis, Fort Collins, CO, Aug 1981.

(3) The typical procedure involves heating a 0.3 M solution of the carbene complex in tetrahydrofuran under an argon atmosphere with 1.5 equiv of the acetylene at 45 °C for 24 h. The oxidation is affected by pouring the reaction mixture into a 0.5 M cerric ammonium nitrate solution (7.5 equiv) in 0.1 M aqueous nitric acid and stirring at 25 °C in air for 30 min to give naphthoquinones or into a 0.2 M cerric ammonium nitrate solution (7.5 equiv) in methanol slurried over 2 equiv of powdered potassium carbonate to give naphthoquinone monoacetals.

(4) The complex **3** is an air and thermally stable, red crystalline, known compound[5] which can be prepared in one step from chromium hexacarbonyl and *o*-bromoanisole in 80% isolated yield. Preparation of **3** can be carried out in large scale as one crystallization from the crude reaction mixture in hexane is sufficient to obtain pure material.

(5) Fischer, E. O.; Kreiter, C. G.; Kollmeier, H. J.; Muller, J.; Fischer, R. D. *J. Organomet. Chem.* **1971**, *28*, 237–258.

(6) Other oxidants (as 80% aqueous tetrahydrofuran solutions, 7.5 equiv, 25 °C, 1 h) were tried with similar yields of **4b**; iodine (65%), ferric chloride (69%), ferric chloride–DMF complex[7] (64%).

(7) Tobinaga, S., Kotani, E., *J. Am. Chem. Soc.* **1972**, *94*, 309–310.

(8) We are currently attempting to improve this yield by replacing the methoxyl group on the carbene carbon of complex **3** with more electron-withdrawing substituents. That this may be possible is suggested by the fact that the unsubstituted complex **1** gives a 96% yield of **4a**. Unless otherwise stated, all yields refer to isolated products.

(9) Unless otherwise stated, all of the isomeric products (Table I and II) were isolated and fully characterized. Satisfactory spectral data and elemental analysis or high-resolution mass spectra were obtained for all new compounds.

(10) Dötz, K. H.; Dietz, R.; von Imhof, A.; Lorenz, H.; Huttner, G. *Chem. Ber.* **1976**, *109*, 2033–2038.

(11) Dötz, K. Dietz, R. *Chem. Ber.* **1977**, *110*, 1555–1563.

(12) Oxidation in the presence of water after 24 h gave an 88% yield of 3-ethyl-2-methyl-1,4-naphthoquinone.

(13) Separation of **7** and **8** was affected by preparative GC on a 5% OV-225 on Chromsorb W-AW column at 200 °C, with retention times of 5.8 and 6.7 min, respectively. The following 500-MHz ^{1}H NMR spectra ($CDCl_3$) were taken. **7**: δ 1.10 (t, 3 H, *J* = 7.7 Hz), 2.05 (s, 3 H), 2.60 (q, 2 H, *J* = 7.7 Hz), 2.89 (s, 6 H), 7.49 (t, 1 H, *J* = 7.5 Hz), 7.64 (t, 1 H, *J*. = 7.2 Hz), 7.72 (d, 1 H, *J* = 7.8 Hz), 8.12 (d, 1 H, *J* = 7.8 Hz). **8**: δ 1.23 (t, 3 H, *J* = 7.6 Hz), 2.11 (s, 2 H), 2.52 (q, 2 H, *J* = 7.6 Hz), 2.88 (s, 6 H), 7.49 (t, 1 H, *J* = 7.6 Hz), 7.64 (t, 1 H, *J* = 7.5 Hz), 7.70 (d, 1 H, *J* = 7.7 Hz), 8.11 (d, 1 H, *J* = 7.7 Hz).

(14) The reaction of **1** with 2-pentyne in tetrahydrofuran gave similar results; 2.0:1.0 ratio of **7**/**8** in 66% yield.

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Scheme III

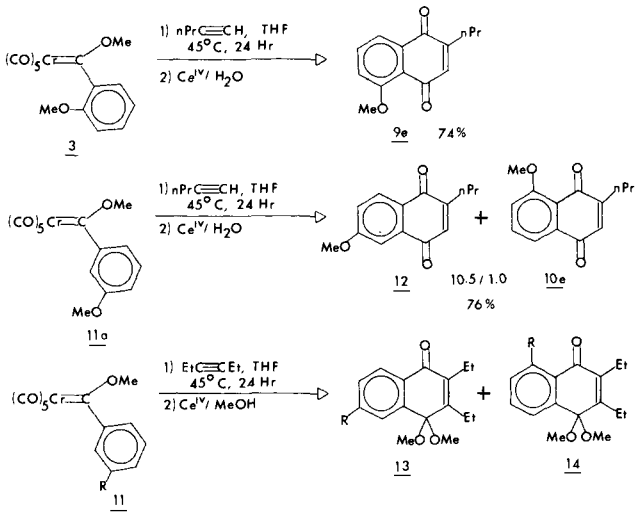


Table II. Regioselectivity of Complex 11[a]

carbene complex	R	yield (13 + 14), %	13/14
11a	OMe	81[b]	2.1[d]
11b	Me	79[c]	1.2[e]
11c	F	70[c]	7.5[e]
11d	CF_3	55[b]	25.5[f]

[a] With procedure described in ref 3. [b] Isolated yield. [c] HPLC yield with internal standard. [d] Ratio of isolated products. [e] Ratio by HPLC with internal standard. [f] Ratio by GC (FID); uncorrected.

ambiguously confirm the structural assignments for the acetals **7** and **8**. We have done this by carrying out an independent synthesis of **8** from 1-hydroxy-2-acetonaphthone in nine steps.[15]

We have investigated in more detail the regiochemistry of the reactions of the ortho-methoxy carbene complex **3** with unsymmetrical acetylenes, and the results are presented in Table I. The reaction of **3** with 2-pentyne also gives both possible isomeric products; in this case the naphthoquinones **9a** and **10a** in a 1.5:1.0 ratio. The regioselectivity increases with increasing steric differences in the acetylene substituents until in the case of terminal acetylenes the reaction is in fact highly regioselective. The reaction of carbene complex **3** with 1-pentyne gives a single isomer that was identified as **9e** by comparison with an authentic sample prepared from 5-methoxy-2-allyl-1-naphthol.[16,17] This corresponds to a selective incorporation of the largest acetylene substituent (*n*-propyl) α to the carbonyl derived from a carbon monoxide ligand.

Meta substitution of the carbene complex introduces a second regiochemical aspect to this reaction. For the metamethoxyl carbene complex **11a** cyclization can occur at either of the two ortho hydrogens, and thus upon reaction with an unsymmetrical acetylene four isomeric naphthoquinones could be produced. The reaction of **11a** with 1-pentyne, however, gives only the two naphthoquinones **12** and **10e**. Exclusive cyclization to the position ortho to the methoxyl group with concomitant indiscriminate incorporation of 1-pentyne would give the quinones **10e** and **9e**. The fact that **9e** was not formed in this reaction reveals that complex **11a** also reacts regioselectively with 1-pentyne.[18]

The substituent effect on the direction of cyclization was examined in the reactions of several meta-substituted carbene

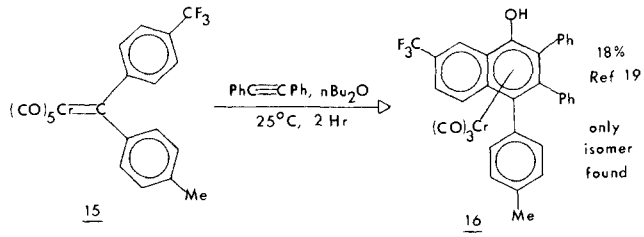
(15) An account of this synthesis will be presented in a full paper on this work.

(16) Eisenhuth, W.; Schmid, H. *Helv. Chim. Acta* **1958**, *41*, 2021-2041.

(17) The crude mixture from this reaction was submitted to an HPLC analysis (Waters RCM radial pak B, ether/methylene chloride/hexane, 1:1:4.7, 6.0 mL/min, retention time of **9e** 5.9 min. By comparison with the retention time of **10e** (3.9 min) it was determined that **10e** was not present in greater than 0.9%.

(18) On this basis the other naphthoquinone produced in this reaction has been assigned the structure **12**.

Scheme IV



complexes with 3-hexyne, and the results are presented in Table II. In all cases cyclization away from the meta substituent predominates to give the acetal **13** as the major product. A steric argument could account for this but not for the fact that the meta-fluoro complex **11c** gives a ratio of *13/14* six times greater than that of the meta-methyl complex **11b**. This indicates that cyclization preferentially occurs at the more electron-rich position. This observation and conclusion is in direct contrast to the report by Dötz that the diarylcarbene complex **15** reacts with diphenylacetylene to give only **16**, the product resulting from cyclization to the more electron-deficient ring.[19]

The differences in selectivity between the reactions of complex **11a** with 1-pentyne and 3-hexyne is intriguing. It is not clear how the substituents on the acetylene can affect the direction of cyclization via either the proposed mechanism for this reaction[20] or any of the reasonable alternatives. Therefore, we are continuing an investigation of this and other aspects of this reaction. We have shown here that the reaction of the ortho-methoxy carbene complex **3** with terminal acetylenes gives 2-substituted-5-methoxy-1,4-naphthoquinones in good yields and with high regioselectivity. We are currently employing this result in anthracycline synthesis.

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(19) Dötz, K. H.; Dietz, R. *Chem. Ber.* **1978**, *111*, 2517-2526.

(20) Dötz, K. H.; Fügen-Köster, B. *Chem. Ber.* **1980**, *113*, 1449-1457.

First Evidence for the Existence of Intramolecular C-H-C Hydrogen Bonds: Carbanions of [1.1]Ferrocenophane, 1-Methyl[1.1]ferrocenophane, and 1,12-Dimethyl[1.1]ferrocenophane

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We wish to report the observation of rapid proton transfer between two carbon atoms, which we believe to constitute the first case of an *intra*molecular C-H-C hydrogen bond. *Inter*molecular hydrogen bonding between strongly acidic sp-hybridized carbons as in acetylenes and strong acceptor sp carbon functionalities in compounds such as isonitriles has been known for a long time,[1,2] but intramolecular hydrogen bonds between carbon atoms only have, at least to our knowledge, never been observed up to now, although their presence has been postulated occasionally.[3]

(1) Ferstandig, L. L. *J. Am. Chem. Soc.* **1962**, *84*, 3553.

(2) Allerhand, A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1963**, *85*, 1715.

(3) For instance, an intramolecular H bond has been assumed to account for the preferred endo conformation of allylpotassium and allylcesium compounds: Schlosser, M.; Hartmann, J. *J. Am. Chem. Soc.* **1978**, *98*, 4674.

0002-7863/81/1503-7678$01.25/0