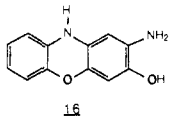


16

prepared by ferricyanide oxidation of 5-methyl-2-aminophenol (**8**).[10] The diastereomeric methyl groups of the Mosher amide of **9** were clearly distinguishable by NMR.[11] Analysis of the enzymatic product demonstrated that the configuration at C4a was racemic.[12] These observations suggest that an intermediate dissociates from the enzyme prior to the second conjugate addition and that subsequent steps do not occur with enzymatic catalysis.

The catalytic requirements for phenoxazinone formation can be greatly simplified if we propose that the aminophenol functionality is regenerated after each conjugate addition by a rapid tautomerization. In this way, what initially appears to be a complex reaction can be reduced to a sequence of three consecutive two-electron aminophenol oxidations. This sequence represents an enzyme-catalyzed oxidative cascade with the rate of oxidation increasing as the aminophenol becomes progressively more electron rich, thus allowing for nonenzymatic steps toward the end of the sequence. The mechanistic details of how the active site copper catalyzes the transfer of electrons from the aminophenol to oxygen are currently under investigation.

Acknowledgment. We thank George H. Jones (University of Michigan) for providing us with the overproducing strain and for helpful advice on how to grow it. We gratefully acknowledge financial support of this research in part by Cornell Biotechnology, the Dreyfus Foundation, Merck, Sharp and Dohme, and the National Institute of Health (CA45251-01).

Supplementary Material Available: Listing of spectral data for **6**, **7**, **9**, and **16** (1 page). Ordering information is given on any current masthead page.

(11) This was prepared by treating **9** with the Mosher acid and DCC in dichloromethane: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (s, 1.5 H), 1.28 (s, 1.5 H), 2.33 (s, 3 H), 3.1 (d, J = 11 Hz, 1 H), 3.18 (d, J = 11 Hz, 1 H), 3.49 (s, 3 H), 6.71 (s, 1 H), 6.83 (d, J = 8 Hz, 1 H), 7.3 (d, J = 9 Hz, 1 H), 7.43 (ArH, 3 H), 7.53 (ArH, 2 H), 8.21 (s, 1 H), 9.4 (d, J = 9 Hz, 1 H); MS, 458 (96), 459 (45%), 269 (41), 189 (100).

(12) When **9** was treated with deuteriated assay buffer at 37 °C for 2 h no deuterium incorporation was detected, thus precluding the possibility of facile racemization of **9** during its isolation.

Cyclopentenones from the Reaction of Alkynes with Cyclopropylcarbene–Chromium Complexes

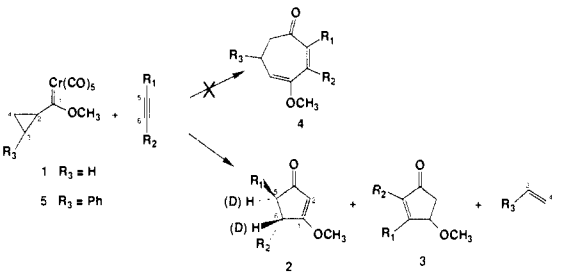
James W. Herndon,* Seniz U. Tumer, and Wayne F. K. Schnatter

Department of Chemistry and Biochemistry
University of Maryland
College Park, Maryland 20742

Received January 25, 1988

As part of a program directed at developing approaches to the synthesis of odd-membered ring size systems employing cycloaddition reactions,[1] we have investigated the reaction of the cyclopropylcarbene–chromium complex **1**[2] with alkynes[3] (Scheme I). Recently, it has been shown that the reaction between alkynes and α,β-unsaturated carbene–chromium complexes produces aromatic rings.[3a] We anticipated that the analogous reaction, which employs cyclopropyl-substituted carbene–chromium complexes and alkynes, would produce cycloheptadienone derivatives such as compound **4**. However, the reaction of cyclopropylcarbene complex **1** and alkynes did not produce cycloheptadienone **4**, rather it gave exclusively the cyclopentenone derivatives **2** and **3**, plus an alkene fragment. This reaction was found to be general for a variety of alkynes. We herein report our preliminary studies of this remarkable five-membered ring-forming reaction.

Scheme I[a]



[a] Table entry letters define R_1 and R_2.

Table I. Reaction of Complex **1** with Alkynes in Refluxing Aqueous Dioxane[a,b]

entry[c]	R_1	R_2	yield 2 (%)	trans/cis 2	yield 3 (%)
A	Ph	Ph	79	24:1	4
B	Ph	H	62		0
C	Ph	CH_3	73	9:1	12
D	n-C_3H_7	n-C_3H_7	55	7:1	0
E	n-C_3H_7	H	68		0
F	$-(CH_2)_4OH$	H	54		0
G	$-(CH_2)_4OSi(t\text{-Bu})Me_2$	H	58		0
H	*cis*-CH=CHOCH$_3$	H	42[d]		0
I	-COOEt	H	0		0

[a] In all cases, the alkyne (0.1 M in dioxane) was added to a refluxing solution of complex **1** in aqueous dioxane via syringe pump over a period of 4–6 h. [b] All compounds were fully characterized (see Supplementary Material). [c] Entry letters define R_1 and R_2 for compounds **2** and **3**. [d] The product was obtained as a 3:2 trans/cis mixture about the enol ether double bond.

When complex **1** was allowed to react with diphenylacetylene (1.0 M solution of both components in THF) at 65 °C under nitrogen, an intractable reaction mixture was obtained. Presumably, this was due to polymerization of the alkyne.[4,5] When diphenylacetylene was slowly added to a solution of complex **1** in THF, a new compound, **2A** (R_1, R_2 = Ph),[6] was obtained in 34% yield. A minor product, **3A**, was obtained in 6% yield. Compound **2A** was formed exclusively (41%) when the reaction was performed in refluxing dioxane. The most reasonable correlation between compound **2A** and the reactants is outlined in Scheme I. The carbonyl carbon arises from a CO ligand of the carbene complex, and carbons 1 and 2 of cyclopentenone **2A** come from carbons 1 and 2 of the carbene complex. Carbons 5 and 6 correspond to the alkyne carbons of diphenylacetylene. This

(1) Herndon, J. W. *J. Am. Chem. Soc.* **1987**, *109*, 3165–3166.

(2) Connor, J. A.; Jones, E. M. *J. Chem. Soc., Dalton Trans.* **1973**, 2119–2124.

(3) (a) For a review of metal–carbene complexes, see: Doetz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587–608. (b) Cyclopropylcarbinyl–transition-metal complexes undergo facile ring-opening reactions: Poli, R.; Wilkinson, G.; Montevalli, M.; Hursthouse, M. B. *J. Chem. Soc., Dalton Trans.* **1985**, 931–939. (c) Brown, J. M.; Connelley, J. A.; Mertis, K. *J. Chem. Soc., Perkin Trans. 2* **1974**, 905–907. (d) Bruce, M. I.; Iqbal, M. Z.; Stone, F. G. A. *J. Organomet. Chem.* **1969**, *20*, 161–168.

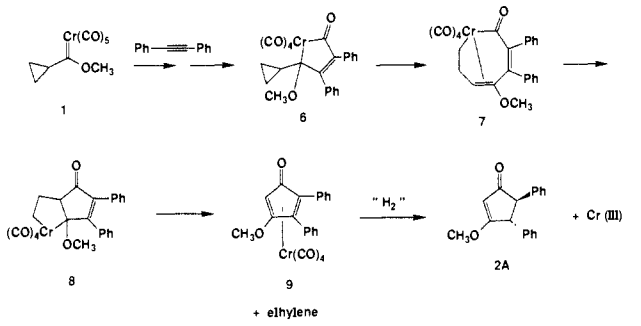
(4) Katz, T. J.; Lee, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 422–424.

(5) The polymerization can be suppressed if the concentration of alkyne is kept low. Wulff, W. D.; Kaesler, R. W.; Peterson, G. A.; Tang, P.-C. *J. Am. Chem. Soc.* **1985**, *107*, 1060–1062.

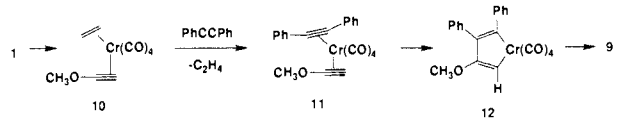
(6) Spectral data for **2A**: ^{1}H NMR ($CDCl_3$) δ 7.2 (m, 6 H), 7.0 (m, 4 H), 5.58 (d, 1 H, J = 1.1 Hz), 3.98 (dd, 1 H, J = 3.3, 1.1 Hz), 3.83 (s, 3 H), 3.59 (d, 1 H, J = 3.3 Hz); ^{13}C NMR ($CDCl_3$) δ 203.7 (s), 190.0 (s), 139.3 (s), 138.8 (s), 128.9, 128.7, 127.6, 127.4, 127.2, 127.0 (overlapping in SFORD spectrum), 104.5 (d), 62.4 (d), 59.0 (q), 56.4 (d); IR ($CDCl_3$) 3040 (m), 2945 (m), 1694 (s), 1598 (s), 1500 (m), 1457 (m), 1443 (m), 1358 (s), 1347 (s), 1170 (s) cm^{-1}; MS, (El), 264 (parent), 233, 205, 187, 159, 128, 115, 102, 91, 69; high resolution MS; calcd for $C_{18}H_{16}O_2$ 264.1150, observed 264.1150. Spectral data for **3A**: ^{1}H NMR ($CDCl_3$) δ 7.15–7.36 (m, 10 H), 5.04 (dd, 1 H, J = 5.9, 2.0 Hz), 3.39 (s, 3 H), 2.96 (dd, 1 H, J = 18.3, 5.9 Hz), 2.66 (dd, 1 H, J = 18.3, 2.0 Hz); IR ($CDCl_3$) 3060 (m), 2930 (m), 1705 (s), 1600 (m), 1440 (m), 1350 (m), 1260 (m), 1210 (s), 1180 (s) cm^{-1}. Compound **3A** rearranges to **2A** upon treatment with sodium methoxide/methanol.

0002-7863/88/1510-3334$01.50/0 © 1988 American Chemical Society

Scheme II



Scheme III



implies that carbons 3 and 4 of the carbene complex are lost as a two-carbon fragment. When complex **5** was reacted with diphenylacetylene under identical conditions, compound **2A** (44%) was obtained along with styrene (41%). To balance the equation for formation of **2A** from **1** or **5**, an external source of hydrogen must be involved. When the reaction was performed in the presence of external hydrogen sources such as water, methanol, triethylsilane,[7] or 1,3-cyclohexadiene, the yield of formation of **2A** increased dramatically. The best yields of **2A** (78%) were obtained with 1% aqueous dioxane. Apparently, water and low-oxidation state chromium interact to form metal hydrides, which furnishes the source of hydrogen.[8] When deuterium oxide was substituted for water in the reaction, compound **2A** was obtained with deuterium atoms at carbons 5 and 6. During the course of the reaction, a dark green color appeared. This color is suggestive of chromium(III) species.

As can be seen in Table I, the reaction is general for a wide variety of alkynes. With monosubstituted alkynes (entries B, E–H), the sole regioisomer obtained was that in which the substituent on the alkyne was α to the carbonyl group in the product.[10] With 1-phenylpropyne (entry C), an unsymmetrically disubstituted alkyne, the major product obtained was the one in which the larger substituent was α to the carbonyl group. The reaction is tolerant of alcohol functionality (entry F), and similar yields were obtained if the alcohol functionality was protected (entry G). The reaction did not proceed with the electron-deficient alkyne ethyl propiolate.

In most cases, the major alkene isomer obtained from the reaction mixture was the thermodynamically more stable vinylogous ester **2**.[6] At shorter reaction times and lower reaction temperatures, other alkene isomers, such as **3**, were obtained from the reaction. This suggested that compound **3** rearranged to compound **2** under the reaction conditions. This alkene isomerization is most likely induced by chromium[11] and not by simple enolization–protonation because no base was present in the reaction mixture. If the reaction was performed in the presence of methanol-d_1, no deuterium incorporation was observed in the product. The trans isomer was the major product in all cases.

Plausible mechanisms for the reaction are outlined in Schemes II and III. In Scheme II, first the alkyne couples with the carbene complex **1** to form the vinylketene complex **6** according to the mechanism of Doetz.[12] Next, the cyclopropane ring of **6** opens[36-d] to give the metallocyclooctadienone complex **7**. Simple reductive elimination in complex **7** would give the originally expected cycloheptadienone **4**. Instead, intramolecular alkene insertion of **7** could occur to give the metallocyclopentane **8**, which can fragment with loss of ethylene[13] to give the cyclopentadienone–chromium complex **9**.[14] Reduction of the cyclopentadienone with water and Cr(0) leads to the observed cyclopentenone derivatives **2** and **3**. Alternatively, compound **9** could also be formed by the mechanism outlined in Scheme III. Initial fragmentation of carbene complex **1** to the mixed alkyne–alkene complex **10**,[15] followed by ligand exchange with diphenylacetylene would lead to the dialkyne complex **11**. Coupling of the alkyne ligands[16] would lead to the chromacyclopentadiene **12**, which would give complex **9** after CO insertion and reductive elimination.

We are actively investigating this novel cycloaddition reaction with regard to its synthetic potential and investigating its scope and possible mechanisms. The availability of the reacting components, alkynes and cyclopropylcarbene–chromium complexes, coupled with the high regioselectivity and functional group tolerability makes this reaction a potentially powerful method for carbocyclic five-membered ring construction.

Acknowledgment. This research was supported by the Petroleum Research Fund, administered by the American Chemical Society, and by Biomedical Research Grant no. RR-07042 to the University of Maryland, from the Division of Research Resources, National Institutes of Health, Public Health Service.

Supplementary Material Available: Experimental procedures and characterization data for the compounds in Table I (5 pages). Ordering information is given on any current masthead page.

(7) Triethylsilane/$Cr(CO)_6$ is an effective reagent for the reduction of ketones and enones. Keinan, E. H.; Perez, D. *J. Org. Chem.* **1987**, *52*, 2576–2580.

(8) Alternatively, chromium(0) may reduce H_2O to H_2, which could also furnish the source of hydrogen[9]. If the cycloaddition reaction was performed in the presence of D_2O and H_2, only deuterium was incorporated into the product. This suggests that hydrogen gas does not provide the source of hydrogen. We thank a reviewer for suggesting this experiment.

(9) (a) Chromium(0) complexes function as hydrogenation catalysts. Cais, M.; Fraenkel, D.; Weidenbaum, K. *Coord. Chem. Rev.* **1975**, *16*, 27–34. (b) While reduction of H_2O to H_2 by Cr(0) complexes is unprecedented, Cr(0) can serve as a catalyst for the reduction of H_2O by carbon monoxide (water gas shift reaction). Weiller, B. H.; Liu, J.-P.; Grant, E. R. *J. Am. Chem. Soc.* **1985**, *107*, 1595–1604. No CO_2 was produced in the cycloaddition reaction.

(10) Assuming the mechanism in Scheme II is operative, similar regioselectivity is observed in the reaction of alkynes with α,β-unsaturated carbene–chromium(0) complexes. Wulff, W. D.; Tang, P.-C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677–7678.

(11) Chromium compounds are known to isomerize alkenes. Barton, D. H. R.; Davies, S. G.; Motherwell, W. B. *Synthesis* **1979**, 265–266.

(12) Fischer, H.; Muhlemeier, J.; Markl, R.; Doetz, K. H. *Chem. Ber.* **1982**, *115*, 1355–1362.

(13) Chappell, S. D.; Cole-Hamilton, D. J. *Polyhedron* **1982**, *1*, 739–777.

(14) Although cyclopentadienones are highly unstable species, transition-metal complexes are stable. Weiss, E.; Merenyi, R.; Huebel, W. *Chem. Ber.* **1962**, *95*, 1170–1178.

(15) The conversion of **1** to **10** is unprecedented for metal–carbene complexes; however, free carbenes are known to do the analogous reaction. Kirmse, W. *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1972; Vol. 1, pp 467–473.

(16) (a) For conversion of alkynes to cyclopentenones using cobalt catalysts, see: Volhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539–556. (b) In one example, the conversion of **11** to **12** has been accomplished by using a chromium complex: Knox, S. A. R.; Stansfield, R. F. D.; Stone, F. G. A.; Winter, M. J.; Woodard, P. *J. Chem. Soc., Dalton Trans.* **1982**, 173–185.