Cyclohexadienone Annulation via α,β-Unsaturated Fischer Carbene Complexes[1]

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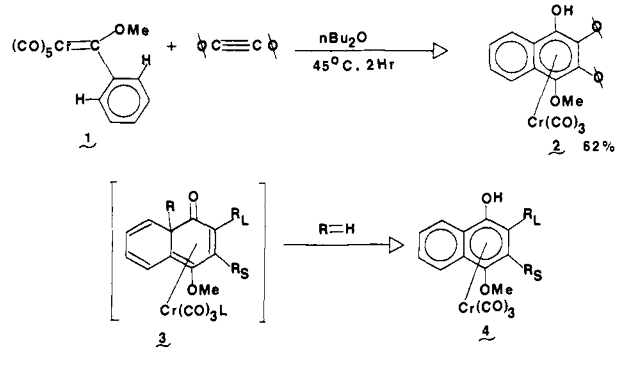
Received October 11, 1983

The benzannulation reaction of chromium carbene complexes was first reported 8 years ago by Dötz for the reaction of the phenyl-substituted complex **1** and diphenylacetylene.[2] Many aspects of this reaction[3] have since been reported including those concerning the regiochemistry,[4] mechanism,[3a,5] and applications to natural product synthesis.[6] The last step of a likely complicated mechanism is presumably the tautomerization of the intermediate complex **3** (R = H) where one of the ortho hydrogens of **1** migrates to the carbon monoxide derived oxygen to become the phenolic hydrogen of **4** (Scheme I). The complex **3** or the corresponding free cyclohexadieneone would be the the expected end product if R were a non-hydrogen substituent with sufficiently low migratory propensity.

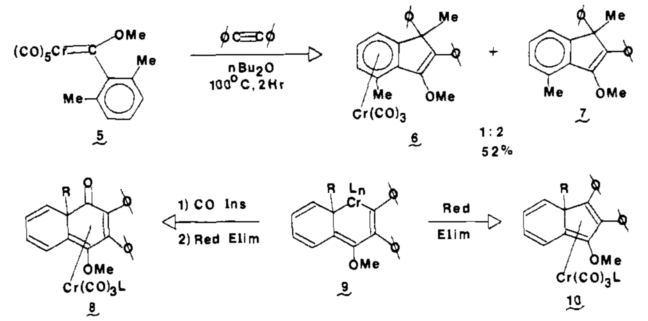
There is only one report in the literature of a reaction where the tautomerization of **3** to **4** is blocked (R = Me) and that is of the 2,6-dimethylphenyl complex **5** and diphenylacetylene for which the only reported products were the complexed and uncomplexed indene **6** and **7**[7] (Scheme II). Thus cyclization has occurred but without the normal carbon monoxide insertion. One possible explanation centers on the intermediate **9**. If a reductive elimination occurs rather than a carbon monoxide insertion, then **10** can be related to the product by a 1,5-sigmatropic methyl shift. Indenes have been observed from this reaction on one other occasion,[8,9] however, in this instance the ortho positions of the aryl ring were not blocked to the normal benzannulation.

A few examples of the benzannulation of alkenyl-substituted chromium carbene complexes have appeared in the literature,[6c,10] however, none have been reported where the final tautomerization to an aromatic ring has been blocked such as it would be for the β,β-disubstituted, α,β-unsaturated complex **11**. On the basis of the above single precedent, it is to be expected that an annulation of the complex **11** would give rise to the five-membered ring annulated product **13**. We were therefore quite surprised to find that the isobutenyl complex reacts with a variety of acetylenes to give good yields of the cyclohexa-2,4-dienone **14** into which one of the carbon monoxide ligands of **11** has been incorporated (Scheme III).[15,16] None of the five-membered ring product **13**

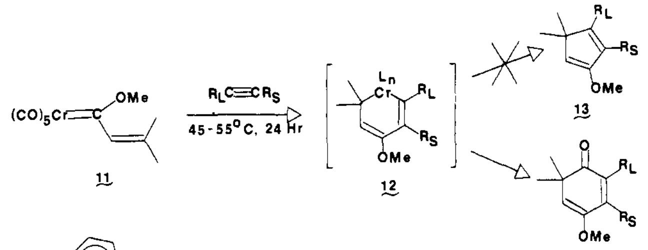
Scheme I

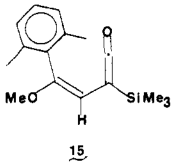


Scheme II



Scheme III





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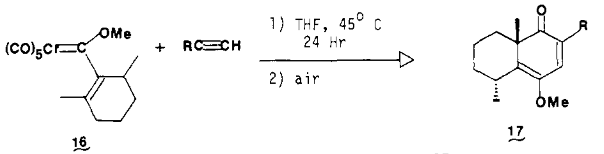
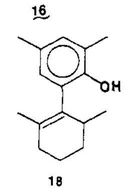
R_L	R_S	% Yield of 14 in THF	% Yield of 14 in CH_3CN
ø	H	55	81
Me_3Si	H	50	73
nBu	H	60	80
Et	Et	39	42
Me	H	59	62
CH_2OAc	H		55

Scheme IV

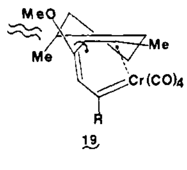


R	% yield of 17	trans/cis
ø	58	95:5[a]
Me_3Si	75	92:8[a]
nBu	78	90:10[a]
Me	44 (+7% of 18)	91:9[b]

[a] ratio by ^1H NMR [b] ratio of isolated enediones 20



18



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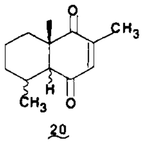

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(3) For reviews that discuss this reaction see: (a) Casey, C. P. In "Reactive Intermediates"; Jones, M., Jr., Moss, R. A., Ed.; Wiley: New York, 1981; Vol. 2 (b) Brown, F. J. *Prog. Inorg. Chem.* **1980**, *27*, 1.

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(8) Dötz, K. H. *J. Organomet. Chem.* **1977**, *140*, 177 (1977).

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(11) The isobutenyl complex **11** is a known compound;[12] however, improved yields from isobutenyl bromide can be obtained by metal–halogen exchange with *tert*-butyl[13] lithium and subsequent reaction with $Cr(CO)_6$ at 25 °C followed by methylation with $MeSO_3F$. Flash chromatography[14] on silica gel with hexane ($R_f = 0.28$) gives a 75% yield of pure **11**.

(12) Casey, C. P.; Brunsvold, W. R. *Inorg. Chem.* **1977**, *16*, 391.

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or any derivatives thereof have been observed for these reactions. This cyclohexadienone annulation is regioselective such that the acetylene substituent becomes adjacent to the carbon monoxide derived carbonyl. The direction of the regioselectivity is the same as has been observed for the benzannulation reaction,[4] and it is confirmed by the magnitude ($J = 3$ Hz) of the coupling constants between the two vinyl hydrogens of **14** ($R_S = H$) and also confirmed by the independent synthesis described below. By way of comparison we have found that the 2,6-dimethylphenyl complex **5** reacts with (trimethylsilyl)acetylene to give the vinyl ketene **15** in 69% yield.[17] Vinyl ketenes have been observed before but only with silyl-substituted acetylenes and the reasons for this are unclear.[18]

The annulation of the carbene complex **16**,[20] which bears an asymmetric carbon, has been examined and occurs with substantial diasterioselectivity in the decalindienone products as indicated in Scheme IV.[16] The annulated products **17** can be obtained in good yields as the trans isomers with a minimum of 90% stereoselectivity in all cases. The trans configuration of **17** (and the regiochemistry as well) was confirmed for the reaction of **16** and propyne. A THF solution of the cycloadduct **17** (R = Me) was hydrolyzed with 10% aqueous HCl to give a 5.5:4.2:1 ratio of three of the four possible diastereomeric enediones **20**, which were separated and characterized. A trans configuration of the methyl groups for the two major diastereomers **20** was consistent with the spectral data and was confirmed by comparison with authentic samples which were prepared by a Lewis acid mediated Diels–Adler reaction of 2,6-dimethylbenzoquinone and *trans*-piperylene[23] followed by hydrogenation and epimerization.[22] The reaction of **16** with propyne also gave a 7% yield of the phenol **18**.[24] We have observed this type of product in other reactions of chromium carbene complexes and acetylenes and will report on their formation separately.

One possible explanation of the observed diastereoselectivity involves an electrocyclic ring closure of the 1-chromatriene functionality in intermediate **19**.[3] If there is an $A^{(1,2)}$ interaction[25] of the methoxyl and the pseudoaxial methyl group, then this would cause the chromium to approach from the face syn to the methyl. The origin of the differences in the reactivity of the complexes **5** and **11** (and **16**) are not clear at this time, nor is the fact that 3-hexyne gives reduced yields compared to terminal acetylenes. We are continuing to investigate these observations and have made similar ones for other reactions of Fischer carbene complexes and acetylenes.[26]

Cyclohexa-2,4-dienones are versatile intermediates that have been employed in number of syntheses.[27] That their synthetic potential has not been fully realized is largely due to the paucity of methods for their preparation.[28,29] The cyclohexadienone annulation of Fischer chromium carbene complexes provides for a direct, regio- and stereoselective approach to this ring system under neutral conditions at near ambient temperatures. It also offers quite attractive approaches to the synthesis of a number of natural products. We will report on further studies and applications of this reaction.

Acknowledgment. This work was supported by a grant from Dow Chemical Co. The NMR instruments used were funded in part by the NSF Chemical Instrumentation Program and by NCI via The University of Chicago Cancer Research Center (CA-14599)

Registry No. 5, 72532-29-7; **11**, 60920-65-2; **14** ($R_L = Ph$; $R_S = H$), 88563-56-8; **14** ($R_L = Me_3Si$; $R_S = H$), 88563-57-9; **14** ($R_L = Bu$; $R_S = H$), 88563-58-0; **14** ($R_L = R_S = Et$), 88563-59-1; **14** ($R_L = Me$; $R_S = H$), 88563-60-4; **14** ($R_L = CH_2OAc$; $R_S = H$), 88563-61-5; **15**, 88563-62-6; **16**, 88563-63-7; *trans*-**17** (R = Ph), 88563-64-8; *cis*-**17** (R = Ph), 88563-65-9; *trans*-**17** ($R = Me_3Si$), 88563-66-0; *cis*-**17** ($R = Me_3Si$), 88563-67-1; *trans*-**17** (R = Bu), 88563-68-2; *cis*-**17** (R = Bu), 88563-69-3; *trans*-**17** (R = Me), 88563-70-6; *cis*-**17** (R = Me), 88563-71-7; **18**, 88563-72-8; **20**, 88563-73-9; $PhC{\equiv}CH$, 536-74-3; $Me_3SiC{\equiv}CH$, 1066-54-2; $CH_3(CH_2)_3C{\equiv}CH$, 693-02-7; $CH_3CH_2C{\equiv}CCH_2CH_3$, 928-49-4; $CH_3C{\equiv}CH$, 74-99-7; $AcOCH_2C{\equiv}CH$, 627-09-8.

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(15) Unless otherwise specified, satisfactory spectral data and elemental analysis or high-resolution mass spectra were obtained for all new compounds.

(16) The reactions were carried out under argon at 0.1 M in **11** with 1.5 equiv of acetylene. Workup involved opening to air, removal of reaction solvents, and purification of the cyclohexadienone by flash chromatography.[14] With acetonitrile as reaction solvent acetonitrile pentacarbonyl chromium[19] was also obtained in each case (50–70%). The reactions of **16** have not been examined in acetonitrile. We have not yet looked for any organometallic complexes in the THF reactions before subjecting to air oxidation.

(17) The *E* configuration of the vinylketene **15** was confirmed by a difference NOE experiment giving a 20% enhancement for the vinyl hydrogen upon irradiation at the methoxyl. The vinyl ketene **15** was unchanged after heating as a C_6D_6 solution in a sealed ampule at 200 °C for 24 h as monitored by ^1H NMR (500 MHz), IR, and TLC.

(18) Dötz, K. H.; Fuegen-Koester, B. *Chem. Ber.* **1980**, *113*, 1449.

(19) Ross, B. L.; Grasselli, J. G.; Ritchey, W. M.; Kaesz, H. D. *Inorg. Chem.* **1963**, *2*, 1023.

(20) Complex **16** can be prepared according to the general procedure in ref 11 by using a vinyllithium generated from the trisylhydrazone[21] of 2,6-dimethylcyclohexanone in 39% yield.[22]

(21) Chamberlin, A. R.; Stinke, J. E.; Bond, F. T. *J. Org. Chem.* **1978**, *43*, 147.

(22) The full details on this synthesis will be reported in a full paper on this work.

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(24) The reaction of **16** with 4 equiv of propyne gives a 28% of **17** and a 20% yield of **18**.

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(26) Unpublished results from this laboratory.

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Stereocontrolled Total Synthesis of (+)-Actinobolin by an Intramolecular Diels–Alder Reaction of a Chiral *Z* Diene Derived from L-Threonine

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Received August 30, 1983

Bactobolin, recently isolated from the culture broth of a *Pseudomonas*, has been shown to be a structural analogue of actinobolin isolated from a *Streptomyces* in 1959.[1,2] The unique polyfunctional structure containing five asymmetric carbons located consecutively within such a simple bicyclic system and biological activity of actinobolin (**1**, free amine) and bactobolin (**2**, free amine) distinguish these molecules as unusually interesting targets for synthesis. We report here the first total synthesis of (+)-actinobolin. The key step of the present strategy is the stereocontrolled formation of the bicyclic γ-lactam **8** by the intramolecular Diels–Alder reaction of the *Z* diene **7**.[3] Among recent studies on the intramolecular Diels–Alder reactions, only Fuchs and his co-workers recently showed a remarkable success in the chiral and stereochemical control of a potential intermediate

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