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Synthesis of Alkylidenecyclopentenones via the Coupling of Propargyl Alcohol Derivatives with Cyclopropylcarbene–Chromium Complexes

James W. Herndon* and Jin Zhu

Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, New Mexico 88003, and Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742-2021

jherndon@nmsu.edu

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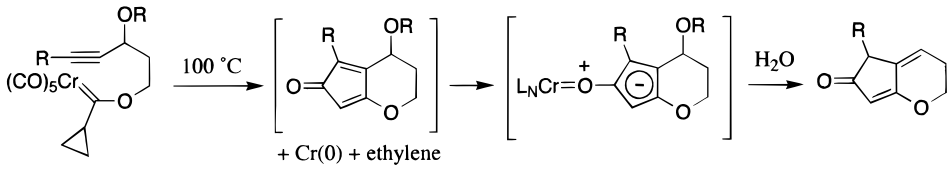
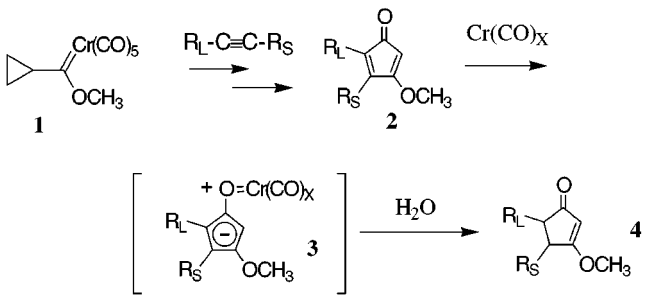
ABSTRACT



The coupling of propargylic alcohols and their derivatives with cyclopropylcarbene–chromium complexes has been investigated. The coupling reaction leads to alkylidenecyclopentenones or alkoxyalkylcyclopentenones, depending on the leaving group ability of the propargyl substituent. A mechanism involving formation of a cyclopentadienone, followed by reduction and β-elimination, was proposed.

In a series of papers, the synthesis of cyclopentenones (cyclopentannulation) via the coupling of alkynes and cyclopropylcarbene−chromium complex **1** has been demonstrated (Scheme 1).[1] In this reaction, a cyclopentadienone

Scheme 1



(**2**), formed through a complex series of steps,[2] is reduced to the cyclopentenone derivative (**4**)[3] under the reaction conditions. In some cases, the cyclopentadienone intermediate can be isolated in good yield.[4] A mechanism involving a net reduction of the cyclopentadienone to the cyclopentadienone dianion equivalent, followed by the addition of two protons, was proposed. This Letter emphasizes the synthesis of 4-alkylidenecyclopentenones using cyclopropylcarbene−chromium complexes and propargyl-functionalized alkynes (Scheme 2). When this reaction reaches the cyclopentadienide stage (e.g. **5**), a β-elimination process can occur,[5]

(1) For the latest reference, see: Yan, J.; Zhu, J.; Matasi, J. J.; Herndon, J. W. *J. Org. Chem.* **1999**, *64*, 1291−1301.

(2) For a detailed mechanistic discussion, see: Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394−8404.

(3) For a mechanistically unrelated route to similar cyclopentenones using alkynes and simple carbene complexes, see: (a) Challener, C. A.; Wulff, W. D.; Anderson, B. A.; Chamberlin, S. A.; Faron, K. L.; Kim, O. K.; Murray, C. K.; Xu, Y.-C.; Yang, D. C.; Darling, S. D. *J. Am. Chem. Soc.* **1993**, *115*, 1359−1376. (b) Harvey, D. F.; Grenzer, E. M.; Gantzel, P. K. *J. Am. Chem. Soc.* **1994**, *116*, 6719−6732.

(4) Herndon, J. W.; Patel, P. P. *Tetrahedron Lett.* **1997**, *38*, 59−62.

(5) This process is analogous to the final step in the synthesis of fulvenes from cyclopentadienides and carbonyl compounds. Bergman, E. D. *Chem. Rev.* **1968**, *68*, 41−84.

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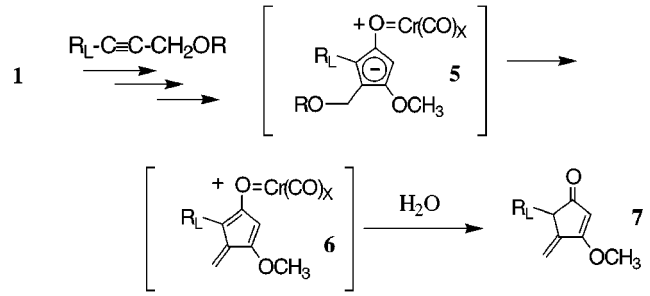
Scheme 2



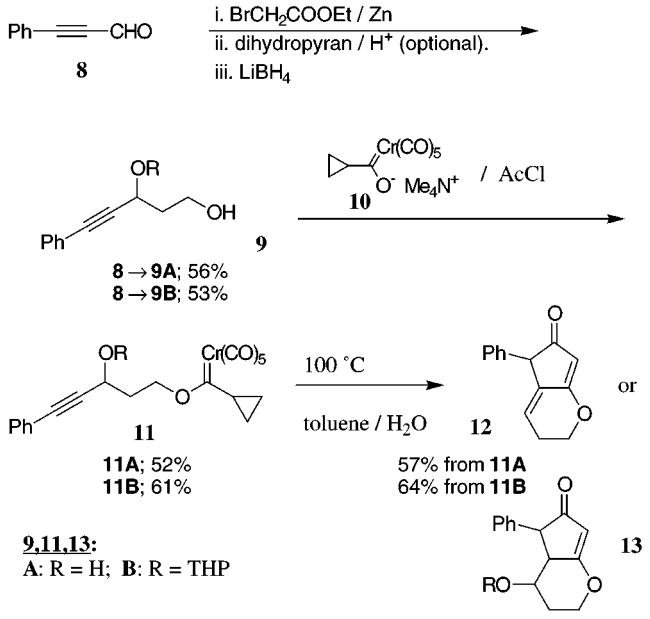
resulting in a fulvene−enolate intermediate (**6**) which would then afford alkylidenecyclopentenone **7** after protonation.

The alkylidenecyclopentenone ring system frequently occurs in a variety of medicinally important compounds, including methylenomycin antibiotics, prostaglandin analogues, kaurene diterpenes, and punaglandin derivatives.[6] One-step cycloaddition reactions have rarely been used to construct this ring system,[7] and the reaction process in Scheme 1 offers such a process using two readily available and very simple components, propargyl alcohol derivatives and cyclopropylcarbene−chromium complexes.

The synthesis of 4-alkylidenecyclopentenones can be achieved in either of two ways: (1) intramolecular alkyne−carbene complex coupling where the propargyl oxygen is within the tether or (2) intermolecular coupling involving an internal alkyne where the propargyl oxygen is part of the smaller alkyne substituent (as depicted in Scheme 2).

The intramolecular approach was evaluated first. Three-carbon-tethered alkyne−carbene complexes (**11A**,**B**) were prepared using the general synthetic protocol in Scheme 3.

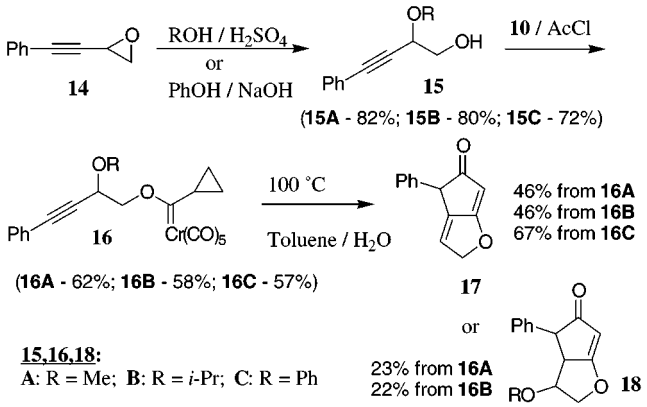
Scheme 3



Thermolysis of either of the moderately stable alkyne−carbene complexes resulted in alkylidenecyclopentenone **12** in good yield (57% from **11A**, 64% from **11B**).[8] In both cases, the alkylidenecyclopentenone was the exclusive product, regardless of the substituent on oxygen.

Two-carbon-tethered alkyne−carbene complexes (**16A**−**C**) were prepared according to Scheme 4. The epoxide ring

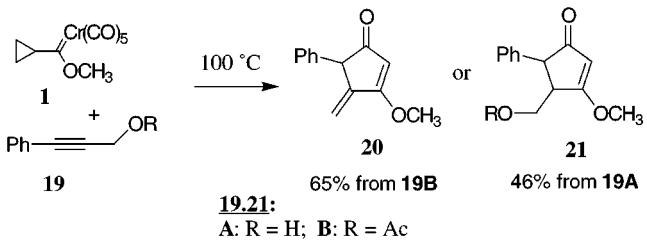
Scheme 4



opening afforded mostly (but not exclusively) the primary alcohol regioisomer of alcohol **15**; however, the primary alcohol derivative was more reactive in the preparation of the carbene complex.[1] Thermolysis of the alkyl ether derivatives **16A**,**B** afforded mixtures (∼2:1) of the alkylidenecyclopentenone **17** and minor amounts of the compound where the oxygen atom was retained (**18**). The phenoxy derivative afforded exclusively the alkylidenecyclopentenone in 67% yield.

The intermolecular coupling of phenylpropargyl alcohol (**19A**) and cyclopropylcarbene complex **1** afforded the hydroxymethylcyclopentenone derivative **21A** in 46% yield (Scheme 5); none of alkylidenecyclopentenone **20** was

Scheme 5



observed in this reaction. When the corresponding propargylic acetate **19B** was used in this coupling, only alkylidenecyclopentenone **20** was obtained in 65% yield.[9]

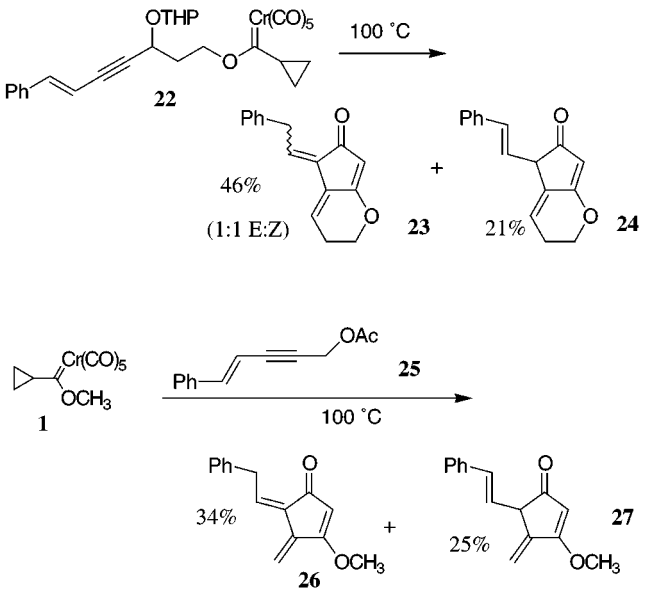
(6) For a more detailed discussion of the synthetic utility of alkylidenecyclopentenones, see: Lola, D.; Belakovs, S.; Gavars, M.; Turovskis, I.; Kemme, A. *Tetrahedron* **1998**, *54*, 1589−1600.

(7) (a) For Pauson−Khand-type approaches, see: Brummond, K. M.; Wan, H.; Kent, J. L. *J. Org. Chem.* **1998**, *63*, 6535−6545 and references therein. (b) Eaton, B. E.; Rollman, B.; Kaduk, J. A. *J. Am. Chem. Soc.* **1992**, *114*, 6245−6246. (c) Ihle, N. C.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 560−563.

These studies reveal a clear dependence on the leaving group ability for the 4-alkylidenecyclopentenone synthesis. In the formation of the six-membered ring heterocycle, alkylidenecyclopentenone **12** was the exclusive product of the reaction regardless of the propargyl leaving group. Alkylidenecyclopentenone formation was less favorable in the five-membered heterocycle cases, possibly due to the greater ring strain in the smaller ring cycloalkene; however, the alkylidenecyclopentenone was the exclusive product of the reaction when the better leaving group (phenoxy) was present at the propargylic position. Formation of the alkylidenecyclopentenone derivative appears to be considerably less favorable in the acyclic case, possibly due to the formation of a less substituted alkene. In this case, a hydroxy leaving group led to no detectable quantities of the alkylidenecyclopentenone **20**; however, the acetate leaving group was sufficient to drive the reaction completely toward alkylidenecyclopentenone formation.

Alkenylacetylene analogues were also tested as substrates for the alkylidenecyclopentenone synthesis (Scheme 6). In

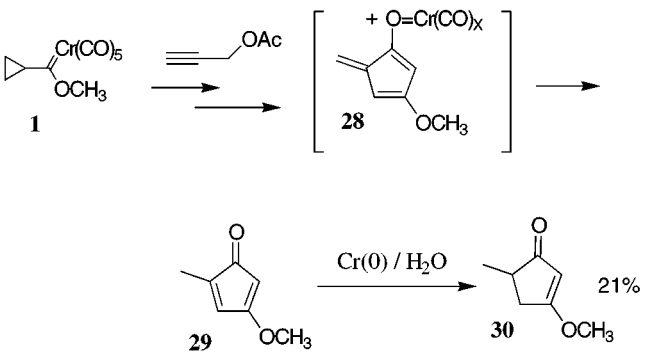
Scheme 6



both the cyclic (**22**) and acyclic (**25**) cases, a mixture of 4,5-dialkylidenecyclopentenone (**23**, **26**) and 5-alkenyl-4-alkylidenecyclopentenone (**24**, **27**) was obtained. Monoalkylidenecyclopentenones **24** and **27** could never be isolated free of the corresponding dialkylidenecyclopentenone, possibly due to isomerization under the purification conditions. The dialkylidenecyclopentenone ring system is very rare, and in the only report of this ring system one of the alkenes is heavily resonance-stabilized.[10]

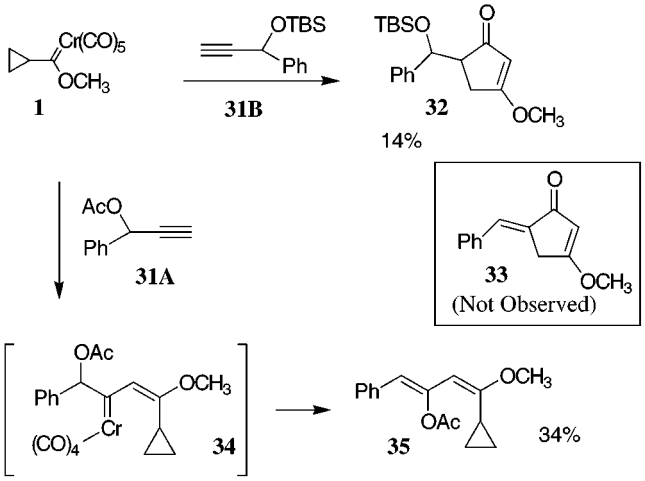
Coupling of propargyl-functionalized terminal alkynes with cyclopropylcarbene complexes could result in the formation of 5-alkylidenecyclopentenones (Scheme 7). Previous studies have shown that cycloaddition processes

Scheme 7



involving the coupling of Fischer carbene complexes and terminal alkynes bearing propargyl ether functionality are often problematic.[2,11] The abnormal reaction pathways observed in these systems have been attributed to coordination of propargylic oxygen; however, the use of bulky oxygen substituents[11a] or reduction of the basicity of the carbonyl oxygen[12] can overcome this effect. All of the terminal alkyne−propargylic alcohol derivatives tested, therefore, feature either *tert*-butyldimethylsilyl or acetate protecting groups. The reaction of carbene complex **1** and propargyl acetate resulted in methylcyclopentenone **30** in 21% yield (Scheme 7). A possible mechanism for the formation of the elimination/reduction product is protonation of intermediate alkoxyfulvene **28** to give methylcyclopentadienone **29**,[6] followed by the previously observed reduction process to give methylcyclopentenone **30** (Scheme 1). Alkylidenecyclopentenone formation also failed with propargyl acetate **31A** (Scheme 8); the only observable product from this

Scheme 8



coupling reaction was diene **35**, which results from a 1,2-acetate shift in intermediate vinylcarbene complex **34**.[11b]

(8) All purified alkylidenecyclopentenone products were characterized by proton and carbon-13 NMR, IR, and either MS or elemental analysis, and unless otherwise noted determined to be homogeneous by either GC, TLC, analysis, or by examination of the NMR spectra.

Coupling of silyl ether analogue **31B** and carbene complex **1** afforded only silyl ether **32** as a 2:1 mixture of diastereomers (unassigned).[13]

The coupling of propargyl alcohol derivatives with cyclopropylcarbene complexes appears to be a general method for the synthesis of 4-alkylidenecyclopentenones; however, the synthesis of 5-alkylidenecyclopentenones by this method is not viable due to competing net hydrogenation of the exocyclic double bond and/or unusual reaction processes resulting from oxygen coordination. The leaving groups required for the elimination step of the 4-alkylidenecyclopentenone synthesis vary depending upon the stability of the alkylidene substituent; however, propargylic acetates appear to uniformly undergo the critical β-elimination event. The synthesis of rare 4,5-dialkylidene-2-cyclopentenones can be effected by coupling of cyclopropylcarbene complexes with enyne−propargyl alcohol derivatives.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and New Mexico State University for financial support of this research.

Supporting Information Available: Complete experimental procedures for the synthesis of carbene complexes **11A** and **11B**, **16C**, and **22** and complete experimental procedures for successful alkylidenecyclopentenone syntheses in Schemes 3−6 and the reactions in Schemes 7 and 8. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Procedure. To a 99/1 mixture of toluene/water (30 mL) at reflux were added a solution of carbene complex **1** (136 mg, 0.49 mmol) and phenylpropargyl acetate (**19B**) (85 mg, 0.49 mmol) in toluene (20 mL) over a 2 h period. After the addition was complete, the solution was refluxed an additional 24 h and then cooled to room temperature. The resulting green suspension was filtered through Celite, and the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 4/1 hexane/ethyl acetate as the eluent. A single fraction (64 mg, 65%) identified as alkylidenecyclopentenone **20** was obtained. ^{1}H NMR ($CDCl_3$): δ 7.28 (m, 5 H), 5.77 (d, 1 H, J = 1.6 Hz), 5.57 (d, 1 H, J = 1.6 Hz), 5.13 (t, 1 H, J = 1.6 Hz), 4.13 (t, 1 H, J = 1.6 Hz), 3.96 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ 200.9, 181.2, 143.3, 137.4, 128.5, 128.2, 127.0, 111.5, 105.4, 58.4, 55.4. IR (neat): 1695, 1574 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_2$: C, 78.02; H, 6.04. Found: C, 77.85; H, 6.02. For the preparation of carbene complex **1**, see ref 2.

(10) Kascheres, A.; Kascheres, C.; Braga, A. C. H. *J. Org. Chem.* **1993**, *58*, 1702−1703.

(11) (a) Semmelhack, M. F.; Jeong, N.; Lee, G. R. *Tetrahedron Lett.* **1990**, *31*, 609−610. (b) For possibly related studies involving molybdenum, see: Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *112*, 8424−8434. (c) In some cases, the propargyl oxygen substituent does not affect the annulation process. Hsung, R. P.; Wulff, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 6449−6450.

(12) Pulley, S. R.; Carey, J. P. *J. Org. Chem.* **1998**, *63*, 5275−5279.

(13) Anhydrous solvent was used to suppress the direct protonation−net reduction of the cyclopentadienide intermediate. A low yield is anticipated under these conditions (see refs 1 and 2).