Tandem Carbene Insertion-Semipinacol Rearrangement of 1-Alkynylcyclobutenols: A Facile Synthesis of 2-Alkenyl-4-cyclopentene-1,3-diones[1]

Metin Zora and James W. Herndon*

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742-2021

Received October 8, 1993®

Summary: Reaction of chromium carbene complexes and 1-alkynylcyclobutenols leads to 2-alkenyl-4-cyclopentene-1,3-diones. Initial alkyne insertion affords a highly electrophilic carbene complex, which then undergoes an alkyl shift-ring expansion, ultimately producing 2-alkenyl-4-cyclopentene-1,3-diones.

Ring expansion reactions represent a versatile method for construction of cyclic molecules.[2] Many ring expansion reactions employ pinacol-type rearrangements, which require an electrophilic center exocyclic to carbon-1 of a cyclic alcohol. Insertion of an alkyne into a Fischer carbene complex provides a non-heteroatom-stabilized vinylcarbene complex,[3] which is highly electrophilic.[4] The reaction of 1-alkynyl cyclic alcohols (*e.g.*, **1**) and carbene complexes (*e.g.*, **2**) could thus lead to ring expansion and carbon-carbon double bond formation in a single operation (Scheme 1).[5] Herein is reported initial studies of the reaction between carbene complexes and propargylic alcohols derived from alkynyl anions and cyclobutenediones,[6] which affords 4-cyclopentene-1,3-diones (*e.g.*, **6**), a structural feature in a variety of medicinally-important compounds.[7]

As noted in Table 1, the ring expansion is surprisingly general for a variety of examples, regardless of the identity of R_4 (Table 1 entry letters correlate with substituent letters for compounds **3-7**). Reaction of carbene complex **2A** with alkyne **1A** led to cyclopentenedione **6A** in 76% yield, as a 7:1 mixture of *E*/*Z* isomers. Treatment of these compounds with aqueous hydrochloric acid led to a single compound, identified as ketone **7A** (entry A). Carbene complex **3** has been proposed as an intermediate in numerous reactions between alkynes and carbene complexes and typically enters into other reaction pathways. For example, if R_4 is phenyl (**3C**), CO insertion and cyclization to a naphthol[8] (*e.g.*, **9**, Dötz benzannulation reaction) or furan (*e.g.*, **10**)[9] would be expected (Scheme 2). Reaction of phenylcarbene complex **2C** with compound **1A** leads after hydrolysis to triketone **7C** (entry C); none of the expected naphthol **9** was observed. Although vinylcarbene intermediates such as **3** have often been trapped by intramolecular cyclopropanation reactions,[10] only in one example has a vinylcarbene intermediate capable of benzannulation been trapped.[11] Clearly, the ring expansion process is faster than the CO insertion step of the Dötz and/or furan-forming reactions.[12] A similar preference for ring expansion is observed in the reaction of alkenylcarbene complex **2D** with alkyne **1A** (entry D). A complication in this reaction was isomerization of the diene functionality, and isomerized diene **11** was a significant proportion of the cyclopentenedione product. Similarly, the two-alkyne Dötz-type annulation[13] can be interrupted in favor of ring expansion. Reaction of dialkyne **1C** with complex **2A** produces only the expected cyclopentenedione **12**, and none of the expected phenol **13** (entry H). A similar trend is observed in the reaction of cyclopropylcarbene complex **2E** with alkyne **1A** (entry E), where only **6**, **7E**, and none of the cyclopropane ring-opened product **14** were obtained.[14] The reaction of excess carbene complex **2A** and dialkyne **15**, where the regiochemistry of alkyne insertion does not favor two-alkyne

* Abstract published in *Advance ACS Abstracts,* February 1, 1994.

(1) Zora, M.; Herndon, J. W. *Abstracts of Papers*; 204th National Meeting of the American Chemical Society, Washington, DC; American Chemical Society: Washington, DC, 1992; ORGN 138.

(2) (a) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH Verlagsgesellschaft: Weinheim, Germany, 1991. (b) Coveney, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Pattenden, G., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 777-801. (c) Wokluvich, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon: Oxford, 1991; Vol. 1, pp 843-899.

(3) For reviews of the chemistry of transition metal carbene complexes, see: (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587-608. (b) Wulff, W. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1065-1113.

(4) (a) Casey, C. P.; Boggs, R. A.; Anderson, R. L. *J. Am. Chem. Soc.* **1978**, *95*, 5833-5834. (b) Dötz, K. H.; Popell, M.; Müller, G.; Ackerman, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 911.

(5) (a) A similar reaction pathway occurs with free carbenes. Wilt, J. W.; Kosturik, J. M.; Orlowski, R. C. *J. Org. Chem.* **1965**, *30*, 1052-1057. (b) For a mechanistically-unrelated ring expansion involving carbene complexes, see: Zora, M.; Herndon, J. W. *Organometallics* **1993**, *12*, 248-249.

(6) (a) For palladium-catalyzed ring expansion of these substances, see: Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc.* **1987**, *109*, 7908-7910. (b) In some cases, thermolysis of compounds such as **1** leads to cyclopentenediones. Foland, L. D.; Karlsson, J. O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975-989.

(7) (a) For a listing of references to important synthetic targets and syntheses, see reference 6a. Cyclopentenediones are also valuable precursors to 5-alkylidenefuranones[7b,c] and prostaglandins.[7d] (b) Campbell, A. R.; Maidment, R. S.; Pick, J. H.; Stevenson, D. F. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1567-1576. (c) Pattenden, G. In *Progress In the Chemistry of Natural Products*; Herz, W., Griesbach, H., Kirby, G. W., Eds.; Springer-Verlag: New York, 1978; Vol. 35, pp 133-198. (d) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717-6725.

(8) Bos, M. A.; Wulff, W. D.; Miller, R. A.; Shamberlin, S.; Brandvold, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 9293-9319.

(9) Alkynes having neighboring coordination sites are more prone to furan-forming reaction pathways. (a) Semmelhack, M. F.; Jeong, N.; Lee, G. R. *Tetrahedron Lett.* **1990**, *31*, 609-610. (b) Harvey, D. F.; Lund, K. P.; Neil, D. A. *J. Am. Chem. Soc.* **1992**, *114*, 8424-8434. (c) Although furan formation was not mentioned as a problem, propargyl alcohol itself does participate in the benzannulation reaction. Dötz, K. H.; Sturm, W. *J. Organomet. Chem.* **1985**, *285*, 205-211.

(10) (a) Hoye, T. R.; Rehberg, G. M. *Organometallics* **1989**, *8*, 2070-2071. (b) Parlier, A.; Rudler, H.; Yefsah, R.; Alvarez, C. *J. Organomet. Chem.* **1987**, *328*, C21-C24. (c) See also ref 7b.

(11) Katz, T. J.; Sivavec, T. M. *J. Am. Chem. Soc.* **1985**, *107*, 757-758.

(12) McCallum, J. S.; Kunng, F.-A.; Gilbertson, S. R.; Wulff, W. D. *Organometallics* **1988**, *7*, 2346-2360.

(13) Wulff, W. D.; Kaesler, R. W.; Peterson, G. A.; Tang, P.-C. *J. Am. Chem. Soc.* **1985**, *107*, 1060-1063.

(14) Tumer, S. U.; Herndon, J. W.; McMullen, L. A. *J. Am. Chem. Soc.* **1992**, *114*, 8394-8404.

0022-3263/94/1959-0699$04.50/0

Scheme 1

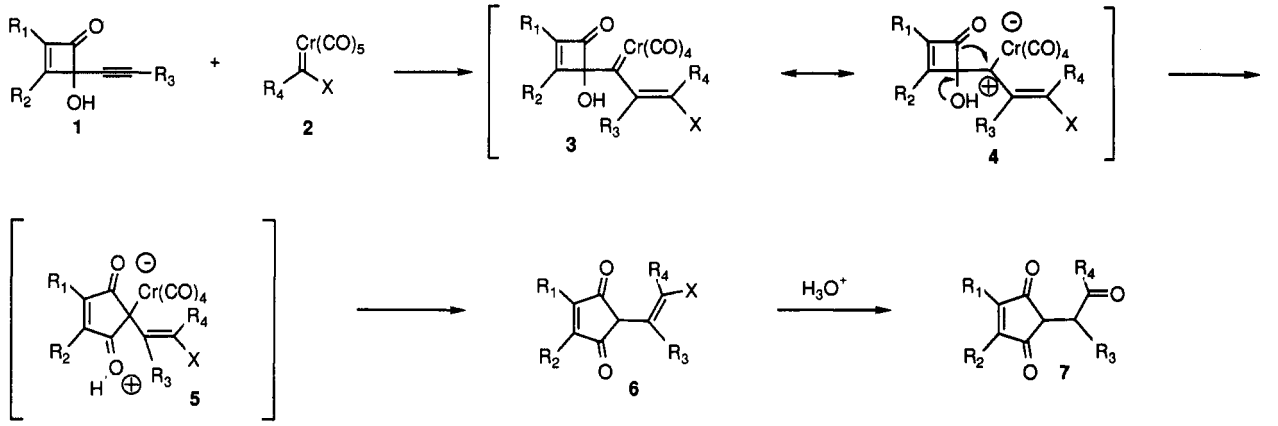
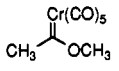
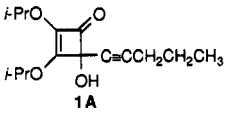
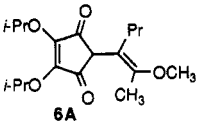
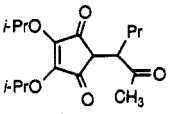
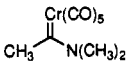
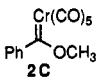
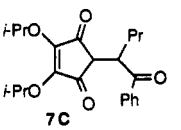
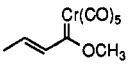
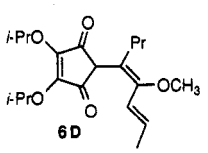
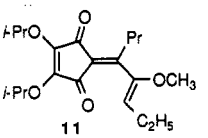
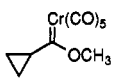
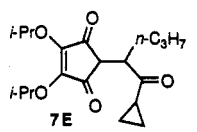
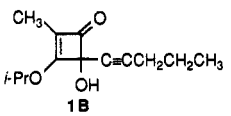
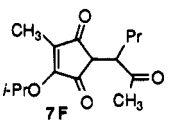
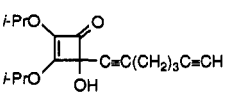
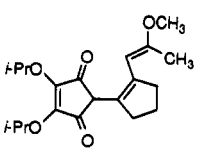
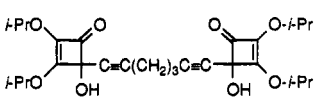
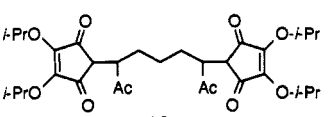
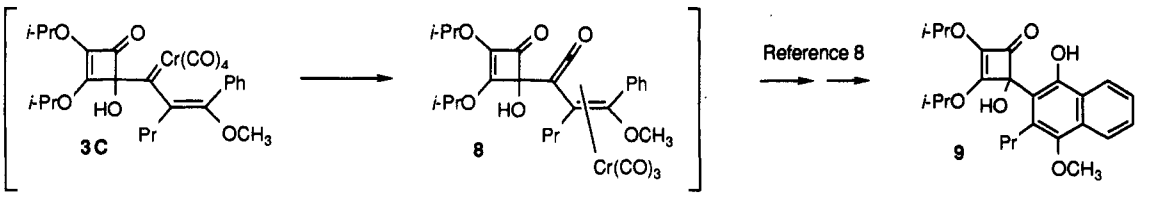


Table 1. Scope and Limitations of the Tandem Alkyne Insertion–Semipinacol Rearrangement[a]

entry	carbene complex	alkyne	ring expansion products (yield, %) (*E*:*Z*)	hydrolysis products (yield, %)
A	 **2A**	 **1A**	 **6A** (72) (7:1)[b]	 **7A** (95)
B	 **2B**	**1A**	*c*	**7A** (20%)
C	 **2C**	**1A**	*c*	 **7C** (72)
D[d]	 **2D**	**1A**	 **6D** (39) (2.8:1)[b] +  **11** (21)[e,f]	
E	 **2E**	**1A**	*c*	 **7E** (66)
G	**2A**	 **1B**		 **7F** (58) (2.2:1)[g]
H	**2A**	 **1C**	 **12** (50) (4:1)[f]	
I	**2A**	 **15**	*c*	 **16** (60) (1:1)[g]

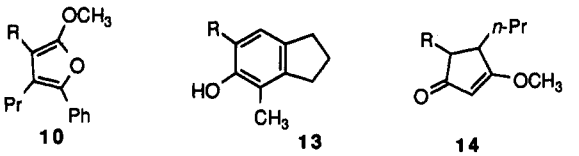
[a] For a procedure, see reference 16. [b] The E:Z configuration was not assigned. [c] The crude enol ether(s) or enamines were hydrolyzed prior to characterization. [d] The hydrolysis reaction was not attempted. [e] A 2.5:1 mixture of two alkene stereoisomers was obtained. [f] The major isomer was assigned as E based on ^{13}C NMR chemical shift comparisons.[18] [g] Ratio of diastereomers. [h] The hydrolysis was not successful.

Scheme 2

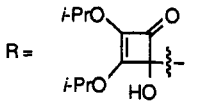


annulation,[15] led to the bis(cyclopentenedione)-substituted diketone **16** (entry I).

In summary, we have developed a new ring-expansion methodology for the synthesis of cyclopentenediones,



Compounds 10,13,14:



which appears to be a rare example of process that occurs in preference to other well-established reaction processes for alkynes and metal–carbene complexes. We are continuing to explore the generality of these reactions with respect to ring size and ring substitution pattern.

Acknowledgment. We thank the Petroleum Research Fund, administered by the American Chemical Society, and the General Research Board of the University of Maryland for support of this research.

Supplementary Material Available: ^{1}H NMR and ^{13}C NMR spectra and characterization data of **1A–C, 15, 6** (minor and major stereoisomers), **7A, 7C, 6D, 11, 7E, 7F, 12** (minor and major stereoisomers), and **16** (34 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) (a) Wulff, W. D.; Tang, P.-C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677–7678. (b) Dötz, K. H.; Muhlemeier, J.; Schubert, U.; Orama, O. *J. Organomet. Chem.* **1983**, *247*, 187–201.

(16) **Procedure for the Ring Expansion Reaction.** A solution of alkyne **1A**[17] (0.266 g, 1.00 mmol) and carbene complex **2A** (0.300 g, 1.20 mmol) in THF (10 mL) was heated at reflux under nitrogen for a 4-h period. The mixture was cooled to room temperature and the solvent was removed on a rotary evaporator. The residue was dissolved in 9:1 hexane/ethyl acetate (50 mL) and the solution filtered through Celite. After removal of the solvent on a rotary evaporator, final purification was achieved by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent. After chromatographic purification, two factors were isolated. The product in the first fraction (0.030 g, 9% yield, R_f = 0.35 in 4:1 hexane/ethyl acetate) was identified as compound **6A** (minor alkene stereoisomer). The product in the second fraction (0.205 g, 63% yield, R_f = 0.30 in 4:1 hexane/ethyl acetate) was identified as compound **6A** (major alkene stereoisomer). **Hydrolysis Procedure.** A mixture of the alkene stereoisomers of **6A** (0.162 g, 0.500 mmol) was dissolved in dichloromethane (25 mL), and concentrated aqueous hydrochloric acid (5 drops, ca. 0.25 mL) was added. The reaction mixture was stirred at room temperature until all starting material had been consumed as diagnosed by TLC analysis. Water (10 mL) was added and the mixture was extracted with dichloromethane. After the combined organic layers were dried, over sodium sulfate, the solvent was removed on a rotary evaporator. Final purification was achieved by flash chromatography on silica gel using 19:1 hexane/ethyl acetate followed by 9:1 hexane/ethyl acetate as eluents. A single fraction (0.147 g, 95% yield, R_f = 0.29 in 4:1 hexane/ethyl acetate) was isolated and identified as triketone **7A**.

(17) For synthesis of these types of compounds, see: (a) Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482–2488. (b) Reed, M. W.; Polart, D. J.; Perri, S. T.; Foland, L. D.; Moore, H. W. *J. Org. Chem.* **1988**, *53*, 2477–2482.

(18) Strobel, P.; Andrieu, C. G.; Paquer, D.; Vazeaux, M.; Pham, C. C. *Nouv. J. Chim.* **1980**, 44, 101–107.