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Effect of Solvent Polarity Extremes on the Coupling Of Cyclopropylcarbene-Chromium Complexes and Alkynes: Synthesis of β-Alkoxycyclopentadienones, 2-Cyclopentene-1,3-diones, and cis 4,5-Disubstituted Cyclopentenones

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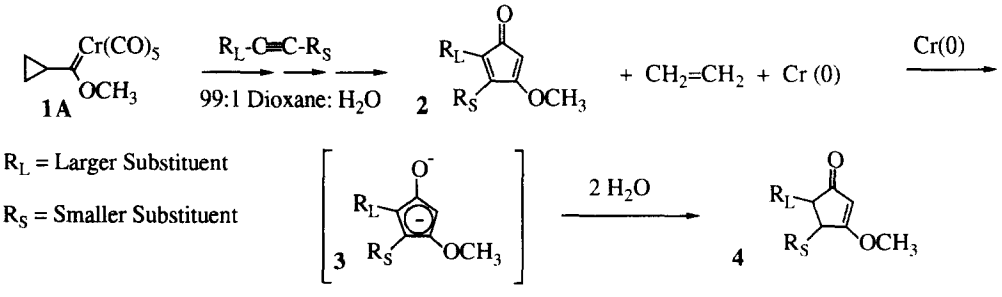
Abstract: The reaction between acetylenes and cyclopropylcarbene-chromium complexes in hexane affords exclusively cyclopentadienone derivatives in good yield, which are readily hydrolyzed to cyclopentenediones. The analogous reaction in 50:50 water dioxane affords cis disubstituted cyclopentenones. Copyright © 1996 Elsevier Science Ltd

In previous studies the synthesis of β-alkoxycyclopentenones (**4**) from the coupling of cyclopropylcarbene-chromium complexes (**1A**) and alkynes (cyclopentannulation) was demonstrated (Scheme 1).[1] The reaction was proposed to proceed via formation of a cyclopentadienone intermediate (**2**) which was reduced to the corresponding trans isomer of cyclopentenone (after cis-trans isomerization) upon exposure to chromium (0) byproducts and water. The proposed mechanism for the cyclopentadienone reduction involves a net two-electron transfer-double protonation process.[1b] Through careful control of the reaction reaction temperature and elimination of water, cyclopentadienone derivative **2A** (R_L, R_S = Ph) was successfully isolated in low yield from the reaction of diphenylacetylene and carbene complex **1**.[2] Cyclopentadienones have proven to be very difficult to synthesize due to their instability,[3] however studies of the metal complexes suggest that the cyclopentadienone ring system can be a versatile precursor to a diverse array of five-membered ring derivatives.[4] In this manuscript we report that extreme variations in the solvent polarity can have a profound effect on the cyclopentannulation reaction, leading to either cyclopentadienones in pure hexane or predominantly the cis isomer of cyclopentenone **4** in 50:50 water:dioxane.

SCHEME 1.

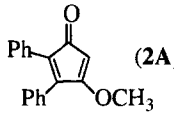
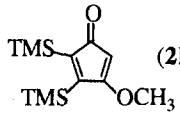
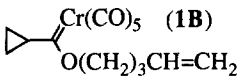
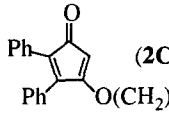
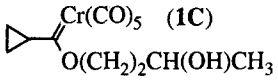
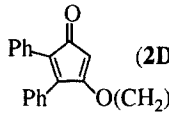
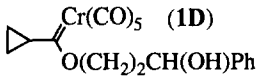
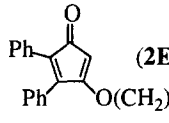
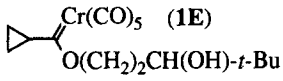
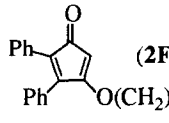


When the solvent for the cyclopentannulation reaction is changed from dioxane or THF to hexane, cyclopentadienone derivatives are the exclusive products of the reaction. The coupling of diphenylacetylene and carbene complex **1A** at 69 °C in hexane affords cyclopentadienone **2A** in 72% yield (Table). None of the reduced compound **4A** (R_L, R_S = Ph) was observed under these conditions. Cyclopentadienone **2A** is an red-orange solid; in the solid

state, this compound is stable in the refrigerator for several days but is 50% dimerized after six months in the refrigerator at -23 °C. The role of hexane in preventing the reduction process has been attributed to suppression of the electron transfer process (conversion of **2** to dianion **3**, Scheme 1) since the electron transfer step is predicted to be less favorable in the less polar solvent.

The cyclopentadienone synthesis was tested in other systems (Table). Remarkably, even more highly functionalized cyclopentadienone derivatives could be prepared using this method. The reaction of alkenyloxycarbene complex **1B** and diphenylacetylene (Entry C) afforded the corresponding cyclopentadienone (**2C**) in similar yields to the reaction in Entry A. It was anticipated that cyclopentadienone **2C** would undergo a spontaneous intramolecular Diels-Alder reaction, however compound **2C** could be isolated without difficulty. Even after heating to 80 °C for 24 h, cyclopentadienone **2C** does not undergo the intramolecular Diels-Alder reaction. Similarly, the intermolecular Diels-Alder reaction of cyclopentadienone **2C** and dimethyl acetylenedicarboxylate failed.

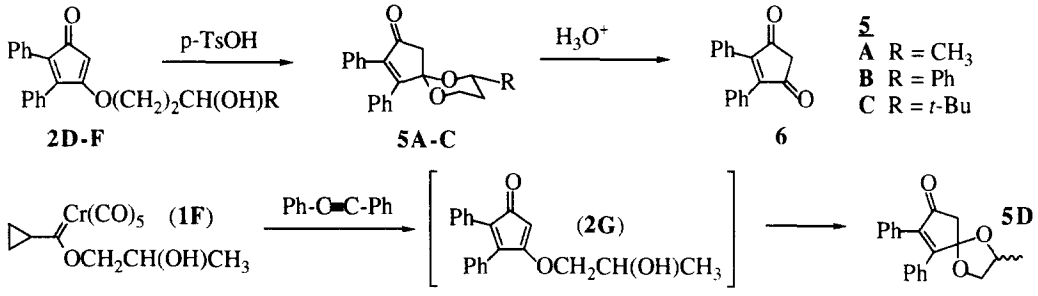
TABLE. Synthesis of Cyclopentadienones from the Coupling of Cyclopropylcarbene Complexes and Alkynes

ENTRY	CARBENE COMPLEX[a]	ALKYNE	CYCLOPENTADIENONE	YIELD[b]
(A)	**1A**	Diphenylacetylene	 (**2A**)	70%
(B)	**1A**	Bis(trimethylsilyl)acetylene	 (**2B**)	35%
(C)	 (**1B**)	Diphenylacetylene	 (**2C**)	69%
(D)[c]	 (**1C**)	Diphenylacetylene	 (**2D**)	59%
(E)[d]	 (**1D**)	Diphenylacetylene	 (**2E**)	45%
(F)[d]	 (**1E**)	Diphenylacetylene	 (**2F**)	45%

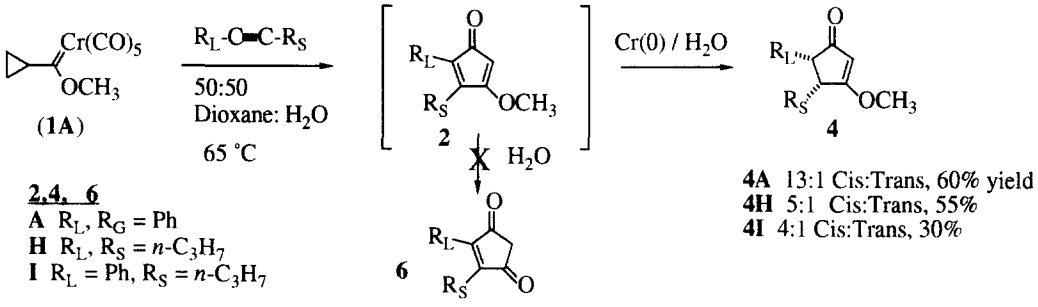
[a]Carbene complexes **1B-D** were prepared from the corresponding alcohol or diol using a known procedure.[5] In the synthesis of complexes **1C-1E**, complete selectivity for the primary alcohol was noted. [b]Unless otherwise noted, all cyclopentadienones were purified by flash column chromatography on silica gel and were pure by high-field proton and carbon-13 NMR analysis. [c]For a detailed procedure, see reference 6. [d]The cyclopentadienone was not stable to silica gel chromatography due to conversion to cyclopentenedione monketal **5**.

In order to further extend the synthetic utility of the cyclopentannulation reaction in Scheme 1, a general method to produce five-membered rings of substitution patterns different from cyclopentenone **4** was sought. Due to the highly electrophilic nature of cyclopentadienones,[3] it was anticipated that hydroxyl-containing derivatives (**2D-F**, Scheme 2) would undergo spontaneous ketalization, affording cyclopentenedione monoketals (*e.g.* **5**); cyclopentenediones (*e.g.* **6**, Scheme 2) have proven to be very useful intermediates for organic synthesis.[7] As noted in the Table (Entries D-F), these cyclopentadienones were stable and did not undergo the spontaneous ketalization reaction. Exposure of cyclopentadienones **2D-2F** to trifluoroacetic acid led to formation of ketal **5** in quantitative yield; which hydrolyzed to cyclopentenedione **6** upon exposure to aqueous acid. Addition of acid to the orange solution of cyclopentadienones **2D-F** causes immediate discoloration. In all of the cases examined, compound **5** was a single diastereomer tentatively identified as one depicted due to its greater thermodynamic stability.[8] As anticipated, cyclization of the alcohols containing the bulky substituents was more facile, and could be induced by silica gel. To speed up the cyclization even further, and perhaps avoid isolation of the cyclopentadienone altogether, carbene complex **1F** was prepared and treated with diphenylacetylene. Cyclopentadienone **2G** was obtained in unusually low yield (24%), however cyclization to ketal **5D** occurred upon exposure to silica gel; a 2:1 mixture of diastereomers was produced in this reaction.

SCHEME 2.



SCHEME 3.



A more obvious approach for enhancing the cyclopentenedione hydrolysis pathway is to increase the concentration of water during the coupling reaction (Scheme 3). Reaction of diphenylacetylene and carbene complex **1A** in 50:50 water dioxane affords only cyclopentenone **4A** as a 13:1 cis:trans mixture. Cyclopentenedione **6** was not observed under these conditions, suggesting that reduction is very rapid in this solvent system. The reaction between other alkynes and carbene complexes also exhibited cis-selectivity. Although previous studies had suggested that the cis isomer was the kinetic product from the cyclopentadienone reduction process, only mediocre selectivity for the cis isomer (best case 60:40 cis:trans for **4A**) was achieved using 1% aqueous solvent systems.[1] Cis selectivity in the

aqueous environment might result from suppression of the cis-trans isomerization, or might even be the result of a "hydrophobic effect" whereby the nonpolar surface area is minimized in the cis isomer relative to the trans isomer.[9]

In summary, the effect of extremes in solvent polarity on the cyclopentannulation reaction has been investigated. In hexane, cyclopentadienones can be produced in good yield, and their formation can be attributed to suppression of the electron transfer reduction process. In 50:50 water:dioxane, cis 1,4-disubstituted-3-alkoxy-2-cyclopentenones are produced, perhaps due to a hydrophobic effect. Development of a method to produce cyclopentenediones directly from the cyclopentannulation reaction continues to be a goal of these studies.

ACKNOWLEDGEMENTS

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5. Herndon, J.W.; Matasi, J.J. *J. Org. Chem.* **1990**, *55*, 786-788.
6. A solution of carbene complex **1D** (0.067 g, 0.20 mmol) and diphenylacetylene (0.071 g, 0.40 mmol) in hexane (20 mL) under nitrogen in a thick-walled closed vessel was heated to 110 °C for a 3h period. After cooling to 25 °C, the solution was gravity-filtered through Celite (*Caution:* a pyrophoric precipitate is generated which ignited if an aspirator was used), and the residue after evaporation was purified by flash chromatography on silica gel pretreated with 1% triethylamine using 3:2 hexane:ethyl acetate as eluent. Cyclopentadienone **1E** was isolated as a red oil. ^{1}H NMR ($CDCl_3$): δ 7.33-7.15 (m, 5 H), 4.85 (s, 1 H), 4.30 (ddd, 1 H, J = 10.3, 7.6, 5.6 Hz), 4.22 (dt, 1 H, J = 10.3, 5.6 Hz), 3.98 (m, 1 H), 1.94 (m, 2 H), 1.22 (d, 3 H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$): δ 198.0, 179.8, 143.8, 130.7, 130.3, 130.1, 130.0, 129.7, 129.5, 128.8, 128.7, 128.5, 128.2, 128.0, 127.9, 127.5, 87.7, 69.6, 65.3, 37.4, 23.8; IR: 1700 cm^{-1}; HRMS: calcd. for $C_{21}H_{20}O_3$ 320.1412, found 320.1397.
7. Cyclopentenediones have been employed extensively for rethrolone and prostaglandin syntheses. a. Jondiko, I.J.O; Pattenden, G. "A New Approach to Rethrolone Synthesis," *J. Chem. Soc., Perkin Trans. 1*, **1983**, 467-469. b. Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717-6725.
8. The isomer depicted is 2.5 kcal/mol more stable than its diasteromer according to molecular mechanics calculations. To simplify the energy minimization process, the phenyl groups of **5A** were replaced by methyl groups.
9. For a recent review, see Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023-2035.

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