STERIC CONTROL IN THE PAUSON CYCLOADDITION: FURTHER SUPPORT FOR THE PROPOSED MECHANISM

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Summary: Dicobalthexacarbonyl complexes of internal alkynes react with olefins to give cyclopentenones with a high degree of regiocontrol. Analogous reactions of terminal alkynes give rise to regioisomeric mixtures of cyclopentenones.

The cobalt catalyzed olefin acetylene cycloaddition (eq 1) was first described by Pauson in 1973.¹ Since the initial report, the reaction has been utilized as a key step in several natural product syntheses,² and has been the subject of other studies.³ One major problem associated with the intermolecular cyclo-



addition is the formation of regioisomeric cyclopentenones when unsymmetrically substituted olefins are used, although unsymmetrically substituted acetylenes prefer an orientation which places the larger substituent in the α -position of the cyclopentenone (eq 2). We have recently⁴ shown that ligands could be used, for the first time, to control the regiospecificity of cyclopentenone formation (eq 3). We now report that disubstituted acetylenes provide steric control over the cycloaddition. These results support the proposed mechanism.⁵



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Several examples have been published which show that steric interactions can bias the regiochemical outcome of the intermolecular cycloaddition. Schore has shown that substituents in the allylic position exert a modest (eq 4)⁶ to excellent (eq 5)⁷ degree of regiocontrol. In each case, the larger of the two ring fusion substituents becomes β to the new enone carbonyl. Pauson² reported the first



example of a regioselective cycloaddition (eq 6). Our previous results⁴ showed that oxygen did not provide any ligand directed regiocontrol, thus, we reasoned that the additional substituent on the acetylene must be the important factor.

OTHP

$$+ \cdot | - \operatorname{Co}_2(\operatorname{CO})_6$$
 $\xrightarrow{\text{Toluene, 110 °C}}$
 $\xrightarrow{\text{ThPO}}$
 $\xrightarrow{\text{OTHP}}$
 (6)

We investigated the cobalt catalyzed olefin acetylene cycloaddition using a series of internal acetylenes and observed a very high degree of regiocontrol over cyclopentenone formation. These results are summarized in the Table.^{8,9} A comparison of the reaction of 1-octene with phenylacetylenedicobalthexacarbonyl (eq 2, entry 1 in Table) and with (1-phenyl-1-propyne)dicobalthexacarbonyl (entry 2 in Table) shows the dramatic influence the internal acetylene exerts over the regiochemistry of the cycloaddition. The regioselectivity improves from 1:1 to 19:1. Further comparison of entries 3 and 4, 5 and 6, and 8 and 9 clearly demonstrates that steric interactions affect the regiochemical outcome of the cycloaddition.



One important consequence of these results is the support they provide for the proposed mechanism shown in the Scheme.⁵ With terminal acetylenes (R' = H), coordination of the alkene to the cobalt carbonyl, just prior to cycloaddition, is directed toward the terminal end of the alkyne due to steric interactions with the acetylene substituent. It is apparent that there is very little steric interaction between the olefin substituents and the terminus of the acetylene, thus, subsequent carbon-carbon bond formation takes place readily from either olefin rotamer 1 or 2. When two different alkyne substituents are present, olefin coordination to cobalt occurs near the smallest acetylene substituent (R = Ph, R' = Me, entries 2, 6 and 10). Steric interactions between the substituents on the olefin and alkyne now seem to be very important and complex 1 undergoes carbon-carbon bond formation much more readily than 2.

Entry	Alkene	Cobalt Complex	Product(s)	Yield (%)
	C ₆ H ₁₃	R - H - Co₂(CO) ₆ R'	C_6H_{13} H_R C_6H_{13} R' C_6H_{13} R'	
1 2 3 4		R = Ph; R' = H R = Ph; R' = Me R = Bu; R' = H R = Me; R' = Me	1 ; 1 19 : 1 1 : 1 20 : 1	49 18 41 20
	\sim	R │ ─∰∼Co₂(CO)6 R'		
5 6 7		R = Ph; R' = H R = Ph; R' = Me R = Me: R' = Me	2.5 : 1 oniy only	45 22 23
	омом	R -∭-Co₂(CO)6 R'		
8 9 10		R = Bu; R' = H R = Me; R' = Me R = Ph; R' = Me	3 : 2 40 : 1 40 : 1	41 26 41

TABLE

These results further demonstrate that steric interactions^{3,5-7} play an important role in determining the regiochemical outcome of the cobalt catalyzed olefin acetylene cycloaddition. Application of these results to the synthesis of natural products are in progress and will be reported in due course.

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- 8. Typical experimental: entry 2: A solution of 368 mg (3.28 mmol) of 1-octene in 2 mL of toluene was added to a solution of 1.6 g (3.9 mmol) of (1-phenyl-1-propyne)hexacarbonyldicobalt in 18 mL of toluene at ambient temperature. The resulting red solution was warmed for 12 h at 97 98 °C and then additional complex (1.6 g, 3.9 mmol) was added and the resulting solution was stirred for 36 h at 97 98 °C. The cooled reaction mixture was diluted with ethyl acetate (10 mL) followed by the slow addition of 1 2 mL of ethylenediamine (to complex the cobalt residues). Filtration through a plug of silica gel using 25% ethyl acetate in hexanes followed by purification of the resulting red oil using flash chromatography (10% ethyl acetate in hexanes) yielded 140 mg (18%) of 2-phenyl-3-methyl-5-*n*-hexyl-2-cyclopentenone and 7 mg (<1%) of 2-phenyl-3-methyl-4-*n*-hexyl-2-cyclopentenone. Dicobalt octacarbonyl obtained from Strem Chemical company was of higher purity than that which was obtained from other sources and was found to give more satisfactory results.
- 9. All yields refer to isolated material. All new compounds gave satisfactory spectral data; major compounds were analyzed by high resolution mass spectroscopy or elemental analysis.