

The Journal of Organic Chemistry

VOLUME 57, NUMBER 20

SEPTEMBER 25, 1992

© Copyright 1992 by the American Chemical Society

Communications

Pauson-Khand Reaction with Electron-Deficient Alkynes

Marie E. Krafft,* Romulo H. Romero, and Ian L. Scott

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306-3006

Received June 30, 1992

Summary: Cobalt carbonyl complexes of electron-deficient internal alkynes undergo Pauson-Khand cycloaddition efficiently and regioselectively.

Recent advances in Pauson-Khand methodology¹ have dramatically increased the synthetic applicability of the cyclization. Little attention, however, has been focused on Pauson-Khand reactions of electron-deficient alkynes or alkenes. There are no reported examples of successful Pauson-Khand reactions using electron-deficient alkynes,² and, until recently, only dienes³ were obtained in the reaction of electron-deficient alkenes.⁴ Recent accounts of mild, amine oxide promoted reactions,^{5,6} Caple and Smit's success with cycloadditions of electron-deficient alkenes,⁴ and our increased understanding of the Pauson-Khand reaction⁷ led us to reconsider electron-deficient alkynes as substrates. We have found that electron-deficient alkynes undergo cycloaddition to yield cyclopentenones. Results for both intra- and intermolecular cycloadditions are listed in Table I.

The best results for the intramolecular cycloadditions were obtained under *N*-methylmorpholine *N*-oxide (NMO) promoted reaction conditions at ambient temperature.^{5,6} High yields of fused cyclopentenones were obtained upon addition of solid NMO monohydrate⁸ (in portions) to a CH₂Cl₂ solution of the cobalt complexed enyne at 0 °C followed by warming to ambient temperature.⁹ Addition of NMO in one portion or use of anhydrous NMO resulted in lower yields and recovery of varying amounts of decomplexed enyne. A substantial amount of decomplexation also occurred upon reaction with either form of NMO in THF/CH₂Cl₂ solvent mixtures.¹⁰ No dienes were observed as products from any of the cycloaddition reactions.

(8) NMO monohydrate is commercially available or may be prepared from *N*-methylmorpholine: VanRheenen, V.; Cha, D. Y.; Hartley, W. M. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 342. *N*-Methylmorpholine *N*-oxide monohydrate exhibits a sharp melting point at 75 °C. Purification of the *N*-oxide by precipitation from acetone, as described in the *Organic Synthesis* procedure, gives highly crystalline monohydrate.

(9) The enynes were prepared by a dicyclohexylcarbodiimide-mediated coupling of the corresponding carboxylic acids and alcohol or amine (CH₂Cl₂, DCC, rt, cat. 4-pyrrolidinopyridine). Representative experimental procedures. **Synthesis of Co Alkyne Complexes.** A solution of 123 mg of enyne 2 (0.99 mmol) and 377 mg of Co₂(CO)₈ (1.1 mmol) in 5 mL of CH₂Cl₂ was stirred at room temperature until complex formation was complete as judged by TLC (1 h). The excess solvent was removed under reduced pressure, and the Co-alkyne complex was purified by filtration through a short plug of silica gel (77%). **Synthesis of Cyclopentenone 10.** The isolated Co-alkyne complex (315 mg, 0.77 mmol) was dissolved in 38 mL of CH₂Cl₂ and cooled to 0 °C. Solid NMO monohydrate (2 equiv) was added, and the solution was warmed to room temperature by immediate removal of the ice bath. After 30 min, the solution was again cooled to 0 °C, 2 equiv of solid NMO monohydrate was added, and the solution was warmed to room temperature by immediate removal of the ice bath. This procedure was repeated until 10 equiv of NMO monohydrate had been added. After the solution was stirred for 2 h at room temperature, a purple precipitate had formed, and TLC analysis indicated the consumption of all starting material with formation of a more polar, UV active spot. Since the cyclopentenone appeared to be sensitive to flash silica gel chromatography, it was purified by rapid filtration through a plug of silica gel, yield 72%.

(10) Krafft, M. E.; Scott, I. L. Unpublished results.

(1) For reviews on the Pauson-Khand reaction, see: Pauson, P. L.; Khand, I. U. *Ann. N. Y. Acad. Sci.* 1977, 295, 2. Pauson, P. L. *Tetrahedron* 1985, 41, 5855. Pauson, P. L. In *Organometallics in Organic Synthesis*; de Meijere, A., tom Dieck, H., Eds.; Springer-Verlag: Berlin, 1987; p 234. Schore, N. E. *Org. React.* 1991, 40, 1. Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 1037.

(2) Pauson, P. L. *Tetrahedron* 1985, 41, 5855.

(3) Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Chem. Commun.* 1974, 379.

(4) Veretenov, A. L.; Smit, W. A.; Vorontsova, L. G.; Kurella, M. G.; Caple, R.; Gybin, A. S. *Tetrahedron Lett.* 1991, 32, 2109.

(5) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* 1990, 31, 5289.

(6) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, H. L.; Yoo, S.-E. *Synlett* 1991, 204.

(7) Krafft, M. E.; Juliano, C. A.; Scott, I. L.; Wright, C.; McEachin, M. D. *J. Am. Chem. Soc.* 1991, 113, 1693. We have also found that the intramolecular thermal cycloaddition is accelerated by the presence of ligands in the homo- and bishomopropargylic position. Krafft, M. E.; Scott, I. L.; Romero, R. H. *Tetrahedron Lett.* 1992, 33, 3829.

Table I

entry	enyne ^a	condns ^b	cyclopentenone	yield (%)
1		A		66
2	1 n=2	B (4d)	9 n=2	14
3	1 n=2	A	10 n=1	72
4	2 n=1	B (16h)	10 n=1	22
5		A		26
6	3 n=2	B (4d)	11	--
	4 n=1		12	
7		A		66
8	5 n=2	A	13 n=2	41
9	6 n=1	B (1d)	14 n=1	15
	6 n=1		14 n=1	
10		A		59
11	7	B (3d)	15	18
12		B, norbornene (2h)		78
13	8	B, 1-heptene (2d)		48

^aReactions carried out with the corresponding dicobalthexa-carbonyl complex. ^bA = NMO, rt, CH₂Cl₂, 4–5 h; B = 71 °C, toluene (time).

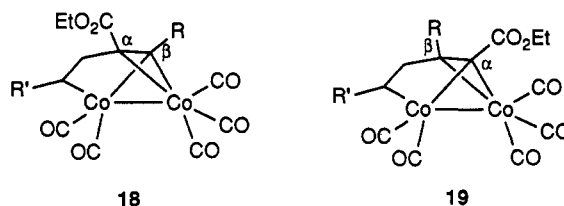
Intramolecular cycloadditions of the alkynoate complexes under thermal conditions, in general, resulted in lower yields of cyclopentenones.

Cobalt complexes of terminally unsubstituted alkynoates gave very low yields of cyclopentenones when treated with NMO in CH₂Cl₂ at ambient temperature (entry 5). No cyclopentenones were obtained upon warming the cobalt complex of the unsubstituted enyne (entry 6) to 71 °C in toluene. Difficulties encountered in complex formation also resulted in low yields of alkyne hexacarbonyl complex.¹¹

Intramolecular Pauson–Khand cycloadditions of cobalt-complexed alkynes conjugated with metal carbenes¹² are known to occur at ambient temperature, in THF, in the absence of NMO. Cobalt-complexed amide 7, which

is analogous to the carbene complexes, was shown to be inert to cycloaddition under identical conditions. However, in the presence of NMO, amide 7 undergoes cycloaddition smoothly to yield the fused cyclopentenone 15.

The intermolecular thermal cycloaddition (entries 12 and 13) of cobalt-complexed alkynoates with alkenes gave good to excellent yields of cyclopentenones in a regioselective manner. Previous reactions of internal alkynes with terminal alkenes seem to suggest that steric interactions, between substituents on the alkene and alkyne, during the metallacycle-forming step are responsible for the selective formation of the 2,3,5-trisubstituted cyclopentenone rather than the 2,3,4-trisubstituted enone.^{1,13} Generally, in the reaction of unsymmetrical alkynes, the larger substituent ends up α to the carbonyl in the product cyclopentenone. Alkyne polarization can be used to rationalize the observed preference for selective formation of the 1,4-dicarbonyl compound instead of the 1,3-dicarbonyl (see Table I). We account for the effect of alkyne polarization in two ways. Cycloaddition can occur by formation of the carbon–carbon bond α to the electron-withdrawing group to give metallacycle 18 (which leads to the observed product) or β to give metallacycle 19. Polarization of the alkyne could



increase the rate at which carbon–carbon bond formation occurs at the α carbon. Alternatively, carbon–carbon bond formation at the α carbon would be expected to decrease the electropositive character of the α carbon whereas formation at the β carbon should lead to an increase in the electropositive nature of the α carbon. Thus, it is anticipated that complex 18 would be formed more readily.¹⁴

The failure of electron-deficient alkynes to undergo cycloaddition, as stated in early accounts, may be due to the fact that intermolecular reactions with only methyl propynoate were reported.² It is this absence of alkyne substitution which is most likely responsible for the initial lack of success. Even intramolecular reactions (entries 5 and 6) with terminally unsubstituted alkynoate complexes failed to give cyclopentenones under thermal conditions and gave only low yields under the milder *N*-oxide promoted conditions.

We have demonstrated that electron-deficient alkynes will undergo Pauson–Khand cycloaddition efficiently. Further work on the Pauson–Khand reaction and its mechanistic consequences is in progress and these results will be reported in due course.

Acknowledgment. We are grateful to the National Science Foundation, the National Institutes of Health, the Sloan Foundation, and the Camille and Henry Dreyfus Foundation for partial support of this work.

Supplementary Material Available: Characterization data for 1–7, 9–11, and 13–17 (5 pages). This material is contained in many 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.

(13) Krafft, M. E. *Tetrahedron Lett.* 1988, 29, 999.

(14) Cyclopentenones formed via the reaction of π -allyl nickel carbonyl complexes with acetylenic ketones and esters exhibit the same regioselectivity. Camps, F.; Llebaria, A.; Moreto, J. M.; Pages, L. *Tetrahedron Lett.* 1992, 33, 109, 113.

(11) Cobalt carbonyl complexes of terminal alkynes have been known to couple under oxidative conditions. Khand, I. U.; Pauson, P. L. *J. Chem. Soc., Chem. Commun.* 1974, 379. Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* 1972, 37, 45.

(12) Camps, F.; Moreto, J. M.; Ricart, S.; Vinas, J. M. *Angew. Chem., Int. Ed. Engl.* 1991, 30, 1470. See also: Liuch, A. M.; Jordi, L.; Sanchez-Baeza, F.; Ricart, S.; Messeguer, A.; Moreto, J. M. *Tetrahedron Lett.* 1992, 33, 3021.