ORGANIC LETTERS

1999
Vol. 1, No. 12
1981−1984

Tandem Aminocarbonylation/ Pauson-Khand Reaction of Haloacetylenes

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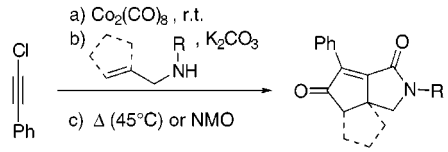
Received October 13, 1999

ABSTRACT



The dicobalt hexacarbonyl complex of 1-chloro-2-phenylacetylene decomposes in solution at room temperature affording similar amounts of two new complexes, to which the structures of a dichloro tetracobalt decacarbonyl complex of 1,4-diphenyl-1,3-butadiyne and of a 1-chloro-2-phenylacetylene acylcobalt complex have been tentatively assigned. The acyl complex can be efficiently trapped by amines, and the resulting aminocarbonylation products submitted to Pauson–Khand reaction to yield cyclopentenones with the regiocontrolled formation of five new bonds in a single synthetic operation.

Organometallic processes nowadays enjoy a prominent position in synthetic organic chemistry. In particular, the possibility of achieving intricate structures by forming several bonds in a single synthetic step has made this chemistry especially attractive. In this context, the chemistry of hexacarbonyldicobalt complexes of acetylenes has elicited considerable attention. Besides their use in the stabilization of propargyl cations (Nicholas reaction),[1] they can be convergently assembled with alkenes to give cyclopentenones, in the process commonly known as the Pauson−Khand reaction (PKR).[2] Over the past few years, much of our research effort has been focused on the development of efficient asymmetric versions of this useful reaction based on the use of chiral auxiliaries covalently bonded to the starting materials. Among chiral acetylenic substrates, the use of alkoxyacetylenes,[3] alkylthioacetylenes,[4] alkynyl sulfoxides,[5] and 2-alkynoate derivatives[6] has been successfully exploited for this purpose. As a continuation of these efforts, and bearing in mind the development of a catalytic enantioselective version of the Pauson−Khand cycloaddition, the unprecedented use of the labile haloacetylenes as substrates for this process was planned, but the course of these studies has evolved into the discovery of a new reaction. Herein we report on how the dicobalt hexacarbonyl complexes of haloacetylenes thermally evolve into new, presumably acylcobalt complexes which can be trapped by amines to form hexacarbonyldicobalt complexes of propynoyl amides, and how this aminocarbonylation process can be coupled in a tandem manner with both inter- and intramolecular Pauson−Khand reactions, with the formation of five bonds in a single synthetic operation. Moreover, the aminocarbonylation process can be combined with previously developed methodol-

(1) For leading references, see: (a) Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Elsevier: Oxford, 1995; Vol. 12, pp 685−702. (b) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207−214.

(2) For recent reviews, see: (a) Chung, Y. K. *Coord. Chem. Rev.* **1999**, *188*, 297−341. (b) Schore, N. E. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S. Ed.; Elsevier: Oxford, 1995; Vol. 12, pp 703−739.

(3) Verdaguer, X.; Vázquez, J.; Fuster, G.; Bernardes-Génisson, V.; Greene, A. E.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 7037−7052 and references therein.

(4) Montenegro, E.; Poch, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1998**, *39*, 335−338 and references therein.

(5) Montenegro, E.; Moyano, A.; Pericàs, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **1999**, *10*, 457−471.

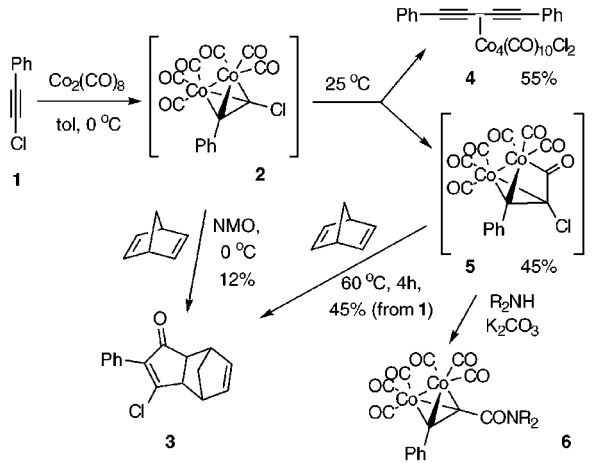
(6) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Am. Chem. Soc.* **1997**, *119*, 10225−10226 and references therein.

10.1021/ol991145h CCC: $18.00
Published on Web 11/17/1999

ogy for stereocontrol in intermolecular Pauson−Khand reaction for the completely diastereoselective synthesis of cyclopentenone derivatives.

At the outset of this research, we studied the Pauson−Khand reaction of 1-chloro-2-phenylacetylene **1** with norbornadiene (Scheme 1). The formation of the dicobalt

Scheme 1. Thermal Behavior of the Dicobalt Hexacarbonyl Complex of 1-chloro-2-phenylacetylene (**2**)



hexacarbonyl complex **2** took place uneventfully at 0 °C, and treatment of this complex with norbornadiene (NBD) and *N*-methylmorpholine *N*-oxide (NMO)[7] at that temperature afforded the expected β-chlorocyclopentenone **3** in 12% yield. This is, in fact, the first example of the PKR of an haloacetylene.[8] However, when the thermally promoted reaction was attempted, an abnormal behavior of complex **2** was observed. When the reaction mixture was warmed to room temperature, complex **2** quickly disappeared and similar amounts of two new complexes, **4** (apolar) and **5** (highly polar), were formed. We subsequently found that the decomposition of **2** takes place readily in toluene without the need for any added reagent and that, for synthetic purposes, this mixture of complexes can be directly prepared at room temperature.

A tentative structural assignment of **4** and **5** is based on the following experimental observations.

Complex **4** was readily isolated by column chromatography (SiO_2, hexanes), and FAB(+) analysis suggested the presence of a PhC≡CC≡CPh·$Co_4(CO)_{10}$ moiety (*m*/*e* = 718). The proposed structure of the organic ligand was confirmed by oxidative decomplexation with NMO,[9] which yielded 1,4-diphenyl-1,3-butadiyne in 42% yield. That **4** is not the tetracobalt dodecacarbonyl complex of 1,4-diphenyl-1,3-butadiyne[10] was readily established by comparison of spectroscopic data with an authentic sample. Finally, the presence of two chorine atoms in its structure was confirmed by elemental analysis. If the composition shown in Scheme 1 is assumed, the amount of **4** formed in the reaction accounts for a 55% of the initial **1** in a highly reproducible manner. Complex **4** shows good stability under a CO atmosphere and does not revert to **2** nor interconvert with **5** on heating.[11]

Complex **5**, in turn, is a polar, very labile compound which could not be isolated. From a structural point of view, **5** appears to be an acylcobalt complex (ν = 1763 cm^{-1}),[12] and in fact, it can very efficiently be trapped by nitrogen nucleophiles to afford the amide complexes **6** (see below).[13] We have established by independent synthesis and reactivity analysis that **5** is not the dicobalt hexacarbonyl complex of phenylpropynoyl chloride.[14] Somewhat surprisingly, **5** reacts with NBD at 60 °C to afford cyclopentenone **3**[15] in 45% yield (from **1**). It is interesting to note that this process and the one leading to **6** involve carbonylation at the two different carbons of the triple bond in **1**. Although the yield for the formation of **5** cannot be directly measured, an estimated value of 45% ensures the balance of matter from **1** (combined yield of **4** and **5** is 100%) and fully accounts for the isolated yields of **3** and **6** (see below).

Our tentative structural proposal for **5**, being compatible with the experimental observations reported here, also appears to be viable from an energetic point of view as indicated by single-point DFT calculations[16] on PM3(tm)[17]-optimized geometries of a model system (Figure 1).

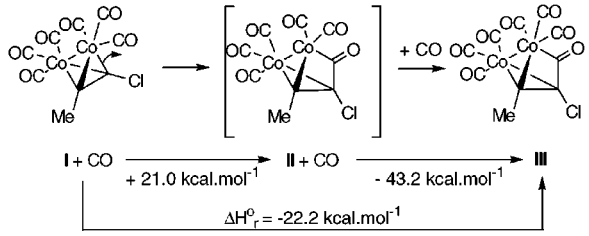


Figure 1. Model DFT studies on the formation of **5**.

The reaction of **5** with amines leading to **6** is of considerable interest. Whereas examples of reductive methoxycarbonylation[3] and aminocarbonylation[18] with concomitant deprotection of alkyne cobalt complexes under forcing conditions are known, the present sequence is the first

(7) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292.

(8) The regiochemical assignment of **3** is based both on the universally observed regiochemical preferences of phenyl substituted acetylenes in PKR and on ^{13}C chemical shift correlations.

(9) Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1993**, *115*, 7199−7207.

(10) (a) Hübel, W.; Merényi, R. *Chem. Ber.* **1963**, *96*, 930−943. (b) Dickson, R. S.; Tailby, G. R. *Aust. J. Chem.* **1969**, *22*, 1143−1148.

(11) Attempts to grow a single crystal from solutions of **4** have failed. Work aimed to the preparation of a crystalline analogue is actively pursued.

(12) For IR spectra of acylmetal complexes, see, for instance: van Asselt, R.; Gielens, E. C. G.; Rülke, R. E.; Vrieze, K.; Elsevier: C. J. *J. Am. Chem. Soc.* **1994**, *116*, 977−985.

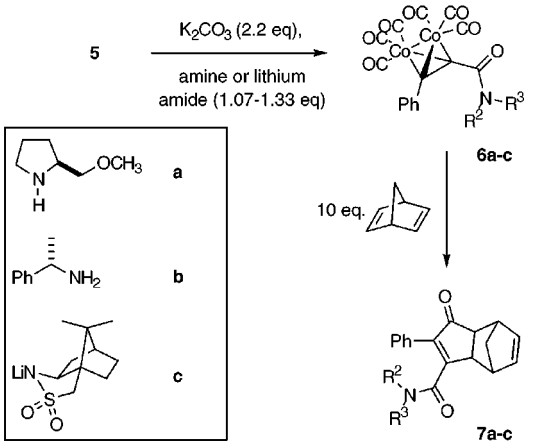
(13) All new compounds were fully characterized by ^1H and ^{13}C NMR, IR, MS, and HRMS.

(14) An authentic sample of this complex, prepared from phenylpropynoyl chloride and octacarbonyl dicobalt exhibited a distinct IR spectrum and did not react with NBD to afford **3**.

(15) In could be established that **4**, isolated by column chromatography, does not react with NBD at that temperature to yield any cyclopentenone adduct.

example of aminocarbonylation of an alkyne dicobalt hexacarbonyl complex.[19] Some examples of the aminocarbonylation reaction have been summarized in Table 1. The reaction

Table 1. Tandem Aminocarbonylation/Pauson−Khand Reactions



entry	yield of **6**[a] [%]	PKR conditions	yield of **7**[b] [%]	d.r.
a	100	5h, 60 °C	95	4:1
b	100	NMO, 20 min, 0 °C	92	1:1
c	67	15h, 45 °C	99	>99:1

[a] From **5**. [b] From isolated **6a**−**c**.

takes place in very high yield with both primary and secondary amines (entries a and b). With less nucleophilic nitrogen species, like Oppolzer's 10,2-camphorsultam, the aminocarbonylation does not take place. However, it can be induced by the use of the corresponding lithium amide (entry c).

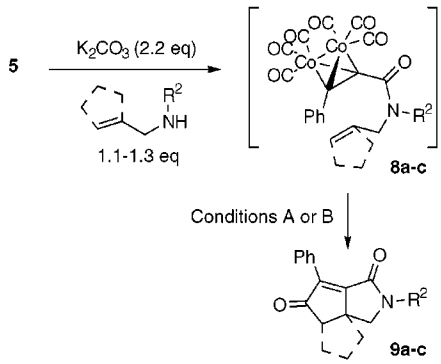
Experiments aimed at determining the effect of substituents of the starting alkyne on the aminocarbonylation process have been performed. With respect to the halogen atom, the use of bromoalkynes instead of chloroalkynes leads to highly decreased yields of amide complexes (28 vs 100% for **6a**). As for the other substituent of the triple bond, electron-donating groups (RS−, R_3Si−) stabilize the initial complex **2**, preventing the formation of the putative acylcobalt intermediate **5**. Probably in connection with this, the aminocarbonylation of 1-alkoxy-2-chloroacetylenes occurs in slightly diminished yields. On the other hand, 1-chloro-2-alkylacetylenes are also convenient substrates for the reaction.

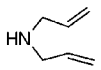
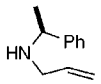
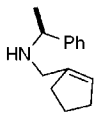
From an experimental point of view, the reaction is performed by treating a mixture of complexes **4** and **5**, generated from **1**, with a slight excess (relative to **5**) of amine or lithium amide (1.07−1.33 equiv) and K_2CO_3 (2.2 equiv) in toluene, the process being complete after 5 min at room temperature. Simple column chromatography allows recovery of the unreacted complex **4** and the isolation of the new complex **6**.[20] The use of soluble bases instead of K_2CO_3 (Hunig's base, 48% **6a**) or more polar solvents (Et_2O, 80%; CH_2Cl_2, 44%; CH_3CN, 0% **6a**) has a deleterious effect on the reaction. Somewhat surprisingly, the presence/absence of a CO atmosphere has no effect on the course and yield of the reaction.

With complexes **6a**−**c** in hand, their Pauson−Khand reactivity was explored (Table 1). By working with the isolated complexes, the reaction with NBD took place in almost quantitative yield and, in the case of **6c**, with complete diastereocontrol.[6] Quite interestingly, the carbonylation and Pauson−Khand reaction could be performed in a tandem manner as a one-pot procedure without decrease in yield or diastereoselectivity. In this way, five new bonds can be created in a single process from complex **5** with excellent yield and, in some cases, complete stereocontrol.

In view of these results, we reasoned that the use of allylamines in the aminocarbonylation process, in combination with a subsequent intramolecular Pauson−Khand reaction, could allow the easy assembly of nitrogen containing polycyclic systems. Results in this direction are summarized in Table 2.

Table 2. Assembly of Azadi- and Azatriquinanes by Tandem Aminocarbonylation/Pauson−Khand Reaction



entry	allylamine	**8**[a] [%]	PKR conditions[b]	**9**[c] [%]	d.r.
a		-	A	- (48)	-
b		89	A	63 (55)	1.2:1
c		84	B	64	1.4:1

[a] From **5**. [b] A: 4 h, 45 °C. B: NMO, 20 min, 0 °C. [c] Yields are based on isolated **8**. Values in parentheses are yields for one-pot reaction.

As can be seen, the interesting 3-azabicyclo[3.3.0]oct-1(8)-ene-2,7-dione system[21] is readily constructed through the tandem process. Also in this case, the aminocarbonylation and Pauson−Khand reactions can be performed in a one-pot manner without decrease in the efficiency of the process. The use of a chiral allylamine (entries b and c) allows for a certain degree of stereochemical control; however, given the

distance between the auxiliaries and the newly created stereogenic center, more discriminating agents would be required for achieving practical diastereoselectivities. As a further demonstration of the synthetic potential of this methodology, the straightforward and high-yield construction of the angular triquinane system through the simple use of a cyclic allylamine is illustrated in entry c.

In summary, the aminocarbonylation plus Pauson−Khand reaction of chloroacetylenes, which involves the regiocontrolled formation of five new bonds in a single synthetic operation, allows the immediate assembly of a variety of polycyclic structures from readily available precursors. The process may be amenable to complete stereocontrol by the use of Oppolzer's 10,2-camphorsultam, opening a new route to enantiopure cyclopentenone systems and, due to the diverse availability of synthetic precursors (chloroacetylenes and amines) and easy operation, it holds promise as an efficient method for the preparation of libraries of cylopentenone products through parallel synthesis in solution. Extension and application of this methodology, as well as structural and mechanistic studies on the intermediate complexes **4** and **5** are underway in our laboratories.

Acknowledgment. We thank DGICYT (PB95-0265) and CIRIT (1998SGR-00005) for financial support. J.B. thanks CIRIT for a fellowship. We also thank Mr. Jordi Vàzquez for technical assistance in performing the DFT calculations

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(16) The calculations were performed with the ADF 2.0.1 code, with the II(DZ) small core basis set, using the VWN local exchange correlation potential with Perdew-Wang 91 exchange and correlation corrections: (a) Baerends, E. J.; Ellis, D. E.; Ros, P. E. *Chem. Phys.* **1973**, *2*, 41−51. (b) Versluis, L.; Ziegler, T. *J. Chem. Phys.* **1988**, *88*, 322−328. (c) Fan, L.; Ziegler, T. *J. Chem. Phys.* **1991**, *95*, 7401−7408. (d) teVelde, G.; Baerends, E. J. *J. Comput. Phys.* **1992**, *99*, 84−98.

(17) SPARTAN, version 4.1.1, Wavefunction, Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92612.

(18) Sugihara, T.; Okada, Y.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 768−770.

(19) For the aminocarbonylation of $CpW(CO)_3$ prop-2-ynyl complexes, see: Shiu, L. H.; Wang, S.-L.; Wu, M.-J.; Liu, R.-S. *Chem. Commun.* **1997**, 2055−2056.

(20) When these conditions are applied to complex **4** alone, no aminocarbonylation is observed at all.

(21) The 3-azabicyclo[3.3.0]octan-7-one system has been used as a precursor to α-kainic acid (Yoo, S.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968−6972) and to serotonergic agents (Becker, D. P.; Flynn, D. L. *Tetrahedron* **1993**, *49*, 5047−5054).