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Studies of the Solid-Phase Pauson-Khand Reaction: Selective in-situ Enone Reduction to 3-Azabicyclo[3.3.0]octanones

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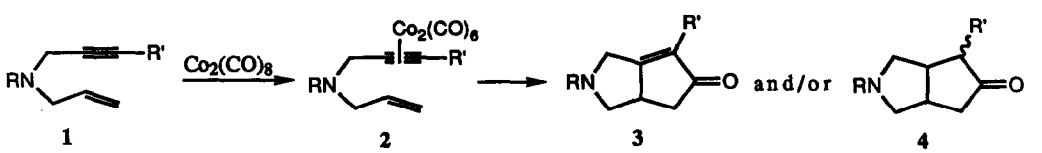
Abstract: The Smit-Caple DSAC Pauson-Khand cyclization of a series of N-protected allyl propargyl amines in the absence of oxygen gave rise to formation of the saturated azabicyclo[3.3.0]octanones in excellent yields. Standard cyclization in air gave mixtures of saturated and unsaturated ketones.

As part of our ongoing efforts in the preparation of serotonergic agents[1] we required an efficient synthesis of 3-azabicyclo[3.3.0]octan-7-ones to complement our previously-described tandem radical annulation/ ionic cyclization methodology.[2] The Pauson-Khand cyclopentenone annulation[3] is a very useful synthetic tool for the preparation of cyclopentane-containing natural and un-natural products,[4] and Pauson has recently described[5] a detailed study of the Pauson-Khand cyclization of a series of N-protected allylpropargyl amine complexes, including **2a** and **2e** (**Scheme I**), to give either 3-azabicyclo[3.3.0]oct-5-en-7-ones **3** or the *in-situ* reduced 3-azabicyclo[3.3.0]octan-7-ones **4**. Sarratosa[6] had previously reported the isolation of saturated cyclopentanones from Pauson-Khand cyclizations run at high temperatures, but the typical product from a Pauson-Khand reaction is the unsaturated ketone, and Pauson's report is the first detailing the isolation of saturated cyclopentanones as major products. Pauson explored[5] a variety of conditions for promoting cyclization of the hexacarbonyldicobalt derivatives **2** and found that the best case for the formation of the saturated 3-azabicyclo[3.3.0]octan-7-one product was 67% for the formation of acetamide **4a** from **2a** (**Scheme 1**) under Smit-Caple[7] dry-state adsorption conditions (DSAC) in air. Jeong and Yoo[8] have reported the efficient preparation of unsaturated 3-azabicyclo[3.3.0]oct-5-en-7-ones via an effective combination of the Nicholas reaction followed by a Pauson-Khand cyclization initiated by N-oxides,[9] but only observed the competitive formation of small amounts of saturated ketone in one isolated case.

Scheme I



1 2 3 4

Compounds 1-4	R	R'
a	Ac	H
b	BOC	H
c	Cbz	H
d	Tosyl	H
e	Benzoyl	H
f	BOC	CH3
g	BOC	TMS
h	H	H

We initially intended to utilize Pauson's chemistry[5] in the formation of a series of N-protected 3-azabicyclo[3.3.0]octan-7-ones which we required for our program. We found the conversion of **2a** to **4a** to be perfectly in accord with Pauson's report in one run, but this reaction was quite unpredictable, as has been observed by others.[8] Typically in our hands the cyclization of complex **2a** in air gave mixtures of **4a** and the unsaturated enone **3a** in ratios ranging from 95:5 to 60:40 along with other impurities.

Although DSAC Pauson-Khand reactions are generally performed in the presence of oxygen[7] and Pauson utilized these conditions in his studies,[5] we decided to examine the effects of performing the cyclization under an inert atmosphere. Indeed, we were prompted to examine this modification by the results of Smit and Caple,[7] who studied the cyclization of allylpropargyl ether complexes under DSAC conditions. They found that the expected bicyclic enone products were obtained when cyclizations were performed in the presence of oxygen, but that hydrogenolysis of the ether moiety occurred when the cyclizations were performed under an inert atmosphere.

Our initial experiments examining the cyclization of allylpropargylamine-hexacarbonyldicobalt complexes **2** revealed that cyclization in the absence of oxygen gave rise to highly selective formation of the saturated 3-azabicyclo[3.3.0]octan-7-ones **4**, as desired. We therefore set out to establish the generality of this useful observation for a series of N-protected allylpropargyl amine complexes **2a-g** by comparing the DSAC Pauson-Khand cyclization of their hexacarbonyldicobalt complexes under nitrogen or air.

Table 1 summarizes the preparation of the hexacarbonyldicobalt complexes for use as cyclization substrates. Allylpropargylamine **1h**[10] was protected to give terminal acetylene derivatives **1a-e**. Substituted acetylenes **1f** and **1g** were prepared by alkylation or silylation, respectively, of the lithium acetylide derived from BOC-enyne **1b**. Reaction of allylpropargylamines **1a-g** with dicobalt octacarbonyl gave the dark red hexacarbonyldicobalt complexes **2a-g** in 71-91% yield. These cobalt complexes were purified by column chromatography on silica gel immediately prior to the cyclization experiments.

Table 1

Starting Enyne	R	R'	Conditions for formation of 1	Enyne 1 (% Yield)[a]	Complex 2 (% Yield)[b]
1h	Ac	H	$CH_3COCl/Et_3N/Et_2O$	**1a** (65%)	**2a** (76%)
1h	BOC	H	$(Bu^tOCO)_2O$/THF	**1b** (95%)	**2b** (77%)
1h	Cbz	H	BnOCOCl/py	**1c** (67%)	**2c** (75%)
1h	Tosyl	H	TsCl/py	**1d** (88%)	**2d** (86%)
1h	Benzoyl	H	BzCl/py	**1e** (94%)	**2e** (71%)
1b	BOC	CH_3	n-BuLi/THF/CH_3I	**1f** (77%)	**2f** (79%)
1b	BOC	TMS	n-BuLi/THF/TMSCl	**1g** (92%)	**2g** (91%)

[a]% yields of **1a-g** represent distilled products except for **1d** (mp 62-63°C), which was crystallized from n-pentane. [b]Complexes **2a-9g** were formed by treatment of **1a-8g** with 1 equivalent of $Co_2(CO)_8$ in diethyl ether at room temperature under argon for 14-18 hours. Yields represent chromatographed, analytically pure products.

For the DSAC Pauson-Khand cyclization studies, complexes **2a-g** were each freshly prepared from 2.00 mmol of respective allylpropargylamine **1a-g** and dissolved in diethyl ether. Silica gel (Merck silica gel 60, 10 g/mmol of complex) was added and the ether was removed *in vacuo*. For reactions under nitrogen the rotary evaporator was purged thoroughly with nitrogen prior to immersion of the rotating flask in a preheated 70°C water bath. The nitrogen flow was continued throughout the 2.5 h reaction time. For reactions in air, the rotary evaporator was opened to the atmosphere before immersing the rotating flask in the 70°C bath. After heating for 2.5 h the silica gel was sprinkled onto a bed of 3 g of fresh silica gel in diethyl ether/hexane. Elution with diethyl ether/hexane mixtures served to remove any cobalt-containing residues, and subsequent elution with neat ethyl acetate eluted the cyclized products. Ethyl acetate was sufficient for the elution of all products except in the case of **2a** which required elution with 10/90 methanol/ethyl acetate to elute the cyclized materials.

Table 2 summarizes the results of the DSAC Pauson-Khand cyclizations of hexacarbonyldicobalt complexes **2a-g** either under nitrogen or in air, as indicated. For all complexed terminal acetylene substrates **2a-e**, the yields of cyclized material were significantly higher for reactions under nitrogen versus the corresponding reactions in air, giving rise to highly selective formation of the saturated ketones **4a-e**. Reaction in air of the same substrates **2a-e** gave in all cases a much higher percentage of enone products **3a-e**. Cyclization or the N-BOC-2-butynylallylamine complex **2f** gave predominantly the unsaturated material **3f** in either nitrogen or air, although the more efficient cyclization for this substrate was the reaction in air giving predominantly the unsaturated product. The formation of significant quantities of saturated material **4f** in the reaction under nitrogen is noteworthy, since Pauson did not observe the formation of any saturated ketones from internal acetylenes in his studies. The trimethylsilylacetylene derivative **2g** was extremely sluggish in the DSAC cyclization reaction under the conditions employed, as was observed by Pauson under comparable reaction conditions.[5] For reaction of **2g** under nitrogen or in air, most of the starting complex **2g** was recovered unchanged. Desilylated saturated ketone **4b** was produced along with the trimethylsilyl substituted enone **3g** in the reaction under nitrogen, whereas

Table 2

Cyclization Substrate	R	R'	Under Nitrogen Products (%Yield, ratio)	In Air Products (%Yield, ratio)
2a	Ac	H	**4a/3a** (94, 100:0)	**4a/3a** (86, 94:6)
2b	BOC	H	**4b/3b** (85, 100:0)	**4b/3b** (79, 84:16)
2c	Cbz	H	**4c/3c** (91, 100:0)	**4c/3c** (56, 75:25)
2d	Tos	H	**4d/3d** (77, 96:4)	**4d/3d** (<61[a], 53:47)
2e	Bz	H	**4e/3e** (87, 100:0)	**4e/3e** (<53[a], 0:100)
2f	BOC	CH_3	**4f/3f** (73, 36[b]:64)	**4f/3f** (80, 11[b]:89)
2g	BOC	TMS	**4b/3g** (29[c], 55:45)	**4b,g/3b,g** (11[d], 0:100[e])

[a]The products from the cyclizations of complexes **2d** and **2e** in air were contaminated by a third component. [b]**4f** as a 2:1 mixture of C-6 epimers. [c]Recovered 60% of starting material complex **2g**. [d]Recovered 73% of starting material complex **2g**. [e]The cyclization of **2g** in air gave desilylated enone **3b** in 7% isolated yield and TMS enone **3g** in 4% isolated yield. No trace of reduced products **4b** or **4g** could be detected.

reaction in air produced none of the reduction products **4b** or **4g** and only small amounts of the enone **3g** (4%) along with the desilylated enone **3b** (7%).

Our studies of the DSAC Pauson-Khand reaction of a series of N-protected allylpropargylamine hexacarbonyldicobalt complexes reveal that saturated 3-azabicyclo[3.3.0]octan-7-ones are are formed selectively and reproducibly from complexes of terminal acetylenes when the cyclization is performed under nitrogen. Excellent yields of saturated ketones are obtained on a variety of scales[11] with usually no detectable amount of unsaturated enone, in stark contrast to the corresponding cyclization in air.

REFERENCES AND NOTES

1. Flynn, D. L.; Becker, D. P.; Spangler, D. P.; Nosal, R.; Gullikson, G. W.; Moummi, C.; Yang, D.-C. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1613.
2. a) Flynn, D. L.; Zabrowski, D. L. *J. Org. Chem.* **1990**, *55*, 3673. b) Flynn, D. L.; Zabrowski, D. L.; Nosal, R. *Tetrahedron Lett.* **1992**, *33*, 7281. c) Flynn, D. L.; Becker, D. P.; Nosal, R.; Zabrowski, D. L., *Tetrahedron Lett*, **1992**, *33*, 7283.
3. a) Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc. Perkin Trans. 1* **1973**, 977. b) Pauson, P. L.; Khand, I. U. *Ann. N. Y. Acad. Sci.* **1977**, *295*, 2. c) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. d) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. e) For a review of the Pauson-Khand reaction see Schore, N. E. *Org. Reactions* **1991**, *40*, 1.
4. a) Billington, B. C.; Pauson, P. L. *Organometallics* **1982**, *1*, 1560. b) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477. c) Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. d) Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483. e) Schore, N. E.; Knudsen, M. *J. J. Org. Chem.* **1987**, *52*, 569. f) Magnus, P.; Becker, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 7495. g) Goush, W. R.; Park, J. C. *Tetrahedron Lett.* **1991**, *32*, 6285. h) Krafft, M. E.; Juliano C. A. *J. Org. Chem.* **1992**, *57*, 5106.
5. Brown, S. W.; Pauson, P. L. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1205.
6. a) Almansa, C.; Carceller, E.; Garcia, M. L.; Serratosa, F. *Syn. Comm.* **1988**, *18*, 1079. b) Montana, A.- M.; Moyana, A.; Pericas, M. A.; Serratosa, F. *Tetrahedron* **1985**, *41*, 5995.
7. a) Simonyan, S. O.; Smit, W. A.; Gybin, A. S.; Schashkov, A. S.; Mikaelian, G. S.; Tarasov, V. A.; Ibragimov, I. I.; Caple, R.; Froen, D. E. *Tetrahedron Lett.* **1986**, *27*, 1245. b) Smit, W. A.; Simonyan, S. O.; Tarasov, V. A.; Mikaelian, G. S.; Gybin, A. S.; Ibragimov, I. I.; Caple, R.; Froen, D. E.; Kreager, A. *Synthesis*, **1989**, 475.
8. Jeong, N.; Yoo, S.; Lee, S. J.; Lee, S. H.; Chung, Y. K. *Tetrahedron Lett.* **1991**, *32*, 2137.
9. a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *37*, 5289. b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. *Synlett.* **1991**, 204.
10. Vilenshchik, Ya. M.; Grunina, V. P.; Perova, N. M.; Zayakina, L. P. *Khim. Prom.-st., Ser.: Reakt. Osobo Chist. Veshchestva* **1979**, *46*, 1 (*Chem. Abstr.*, *93*, 94744).
11. The cyclization of **2b** to **4b** has been performed reproducibly on a variety of scales ranging from 1 mmol to 1 mol.

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