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Thermal Promotion of the Cobalt Catalyzed Intramolecular Pauson-Khand Reaction - An Alternative Experimental Protocol for Cyclopentenone Synthesis

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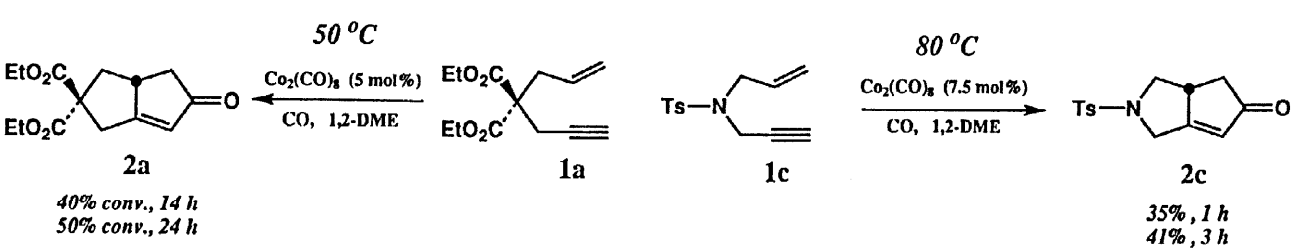
Abstract: Heat alone has been found sufficient to promote intramolecular Pauson-Khand cyclizations catalyzed by high purity $Co_2(CO)_8$. The existence of a very narrow thermal window (e.g., 60 °C - 70 °C) for the attainment of efficient catalysis is a noteworthy characteristic of this process.

The formal [2+2+1] cycloaddition reaction involving an alkene, alkyne and carbon monoxide represents one of the most convergent means for the synthesis of cyclopentenones.[2] The $Co_2(CO)_8$ mediated variation of this process, the Pauson-Khand reaction (PKR), has been known since 1973.[3] Recently carbonylative enyne cyclizations catalyzed by $Co_4(CO)_{12}$,[4] as well as complexes of Ti,[5] Rh,[6] and Ru[7] have been reported. In addition, the beneficial effect of carrying out representative $Co_2(CO)_8$ catalyzed PKR's in supercritical media has been recorded.[8] In 1996, we reported that high intensity visible light promotes the $Co_2(CO)_8$ catalyzed intramolecular PKR.[9] As part of this study, we noted that temperatures of at least 50 °C were necessary to achieve useful reaction rates. This observation suggested that the thermal dependancy of the cobalt catalyzed process remained poorly appreciated.[10] Accordingly, we recently undertook a thorough investigation of this reaction parameter. In this Letter, we describe the results of this study and report the first examples of efficient *thermal* $Co_2(CO)_8$ catalyzed carbonylative enyne cyclizations that proceed in a common laboratory apparatus under one atmosphere of CO pressure.

Cyclization Studies. Upon close examination, it was readily ascertained that a very narrow thermal window exists for the realization of efficient $Co_2(CO)_8$ catalyzed enyne cyclizations. For example, carbonylative cyclization of **1a** (0.1 M in 1,2-DME) in the presence of $Co_2(CO)_8$ (5 mol%) and 1 atm of CO at *50 °C* resulted in only 40 % conversion to **2a** after 14 h. After 24 h, the reaction was only 50 % complete, presumably as a result of slow catalyst degradation. Significantly, temperatures in excess of 70 °C were also found to be deliterous to efficient cyclization. Accordingly, upon heating to *80 °C* in the presence of $Co_2(CO)_8$ (7.5 mol%) and CO (1 atm), a solution of **1c** (0.1 M in 1,2-DME) provided **2c** in 35 % and 41 % isolated yield after 1 h and 3 h respectively.[11]



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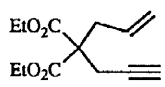
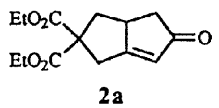
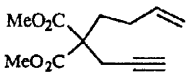
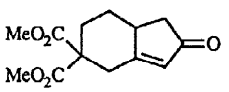
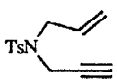
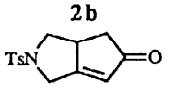
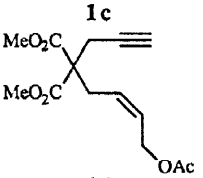
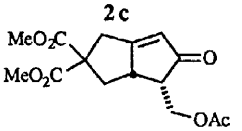
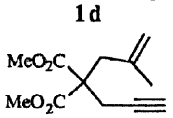
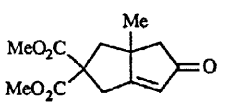
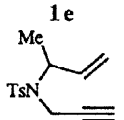
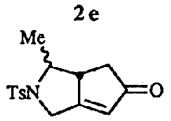
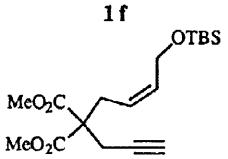
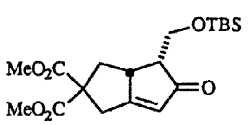
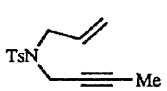
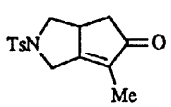
By way of contrast, in a typical cyclization under optimized conditions, a solution of the enyne of interest [i.e., **1a-h** (0.5 mmol)] in degassed 1, 2-DME (5 mL) was simply stirred in the presence of high purity $Co_2(CO)_8$ (0.025 mmol, 5 mol%) at *60 °C* under an atmosphere of CO for the indicated time to provide the corresponding cyclopentenones **2a-h** in good to excellent isolated yield.[12] As we have noted previously,[9] the use of high purity $Co_2(CO)_8$ is essential for successful catalytic PKR cyclizations to be realized.[13] The results obtained for a series of thermal cyclizations conducted according to the above procedure are collected in **Table I.**

Table I. Thermally Promoted Pauson-Khand Cyclizations Catalyzed by $Co_2(CO)_8$

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1	 **1a**	12 4	 **2a**	83 78[b]
2	 **1b**	12	 **2b**	77[c]
3	 **1c**	12	 **2c**	86[d]
4	 **1d**	12	 **2d**	78[d]
5	 **1e**	12	 **2e**	85
6	 **1f**	12	 **2f**	78[e]
7	 **1g**	12	 **2g**	84[c,f]
8	 **1h**	15	 **2h**	78

a. All reactions were performed with 5 mol% $Co_2(CO)_8$ at 60 °C, unless stated otherwise. b. 65 °C c. 10 mol% $Co_2(CO)_8$. d. 7.5 mol% $Co_2(CO)_8$ e. 1.3/1.0 ratio of diastereomers. f. >20/1 cis/trans by ^1H NMR spectroscopy.

The results presented above suggested that thermal promotion alone can serve as a synthetically viable means for effecting $Co_2(CO)_8$ catalyzed carbonylative enyne cyclizations. In a direct comparison with the photopromoted PKR[9] at two different reaction temperatures, the thermal variation was found to be slightly inferior. Accordingly, cyclization of enyne **1a** using Q-Beam irradiation, $Co_2(CO)_8$ (5 mol%) and 1 atm CO at 55 °C (14 h) and 60 °C (4 h) provided enone **2a** admixed with 8% and 48% of the starting material **1a** respectively. The corresponding dark reactions conducted under conditions that were otherwise identical furnished **2a** containing **1a** (15% and 58% respectively).

In conclusion, heat alone, under the appropriate conditions, is capable of promoting efficient $Co_2(CO)_8$ catalyzed Pauson-Khand cyclizations using standard laboratory apparatus. A novel experimental protocol that obviates the requirement for very high purity $Co_2(CO)_8$ is the topic of the second Letter in this series.

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11. The narrow thermal window may be a result of decreased solubility of CO as the solvent approaches its boiling point. Side reactions of hexacarbonyldicobalt 1,6-enyne complexes in refluxing toluene yield predominantly 1,3-dienes under a nitrogen atmosphere: Krafft, M. E.; Wilson, A. M.; Dasse, O. A.; Bonaga, L. V. R; Cheung, Y. Y.; Fu, Z.; Shao, B.; Scott, I. L. *Tetrahedron Lett.* **1998**, *39*, 5911-5914.
12. Representative procedure: A solution of enyne **1a** (119 mg, 0.5 mmol) and dicobalt octacarbonyl (8.5 mg, 0.025 mmol, 5 mol %) in degassed 1,2-DME (5 mL) was magnetically stirred at room temperature under an atmosphere of CO. After 30 min, the reaction mixture was heated to 60 °C using a constant temperature bath for 12 h. After cooling to room termperature, brine and ethyl acetate were added (1 mL each) and the biphasic mixture was stirred open to air for 30 min. Workup with EtOAc (50 mL), brine (25 mL) and drying (Na_2SO_4) followed by evaporation of solvent and final purification by flash chromatography on silica gel (15-30% EtOAc /hexane gradient for elution) afforded 111 mg (83%) of enone **1b** as a slightly yellow oil. On preparative scale, comparable results can be obtained. Accordingly, a solution of enyne **1a** (2.38 g, 10.0 mmol) and dicobalt octcarbonyl (171 mg, 5 mol %) in degassed 1,2-DME (100 mL) was magnetically stirred at room temperature under an atmosphere of CO for 30 min. The resulting solution was then heated for 12 h at 60 °C. The reaction mixture was concentrated in vacuo, and the resulting oil was purified by chromatography on silica gel (0-30% EtOAc/hexane gradient for elution) to afford 2.10 g (79%) of enone **1b** as a yellow oil.
13. Impure samples of commercial $Co_2(CO)_8$ must be rigorously purified by recrystallization from degassed HPLC grade hexane or room temperature sublimation at 50 mTorr immediately prior to use. For the majority of the cyclizations described herein, a freshly opened sample of $Co_2(CO)_8$ (Strem Chemical Co., Inc.) that was stored in a Vacuum Atmosphere drybox was utilized.