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Modification and limitations of the Livinghouse catalytic Pauson–Khand reaction

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Abstract

The difficult and impractical purification of $Co_2(CO)_8$ is not necessary in the catalytic thermal Pauson–Khand reaction previously described by Livinghouse. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Pauson–Khand reaction; catalytic; cycloaddition; enyne.

Since its inception in 1973 the utility of the Pauson–Khand reaction in synthetic organic chemistry including natural product synthesis has burgeoned.[1] It has been widely used to prepare cyclopentenone ring systems via a formal [2+2+1] cycloaddition of an alkene, an alkyne and carbon monoxide. However, this transformation has, until recently, necessitated a stoichiometric amount of dicobalt octacarbonyl such that considerable efforts have been directed towards developing the catalytic version. Consequently, successful use of catalytic quantities of $Co_2(CO)_8$ in conjunction with either $P(OPh)_3$,[2] ultraviolet light[3] or high pressures of carbon monoxide have been reported.[4] Under seven atmospheres of CO, Sugihara showed that catalytic quantities of $Co_2(CO)_8$ can be used with small amounts of 1,2-dimethoxyethane or water as additives to effect the cyclizations.[5] A noteworthy report by Livinghouse demonstrated that intramolecular Pauson–Khand cyclizations can also be achieved thermally (60–65°C) by employing catalytic amounts (5–10 mol%) of high purity $Co_2(CO)_8$ in 1,2-dimethoxyethane under a blanket of carbon monoxide.[6] Livinghouse also reported that the very high state of purity of the $Co_2(CO)_8$ necessary for efficient catalysis can be obviated by use of an alternative shelf-stable hexacarbonyldicobalt–alkyne complex serving as a convenient surrogate for the labile $Co_2(CO)_8$.[7]

We have investigated the catalytic Pauson–Khand reaction under Livinghouse conditions and have made two important observations. First, in our hands, we found that ultra high purity dicobalt octacarbonyl was not necessary. But rather, when carefully base washed glassware was used, the catalytic reaction proceeded to completion in most cases using 10% of unpurified $Co_2(CO)_8$ in 1,2-dimethoxyethane under a blanket of carbon monoxide (Table 1). Three different bottles of $Co_2(CO)_8$ were used without purification and essentially identical results were obtained (entry 1 in Table 1, 10% $Co_2(CO)_8$, 20%

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$CyNH_2$, 84±5% yield). These bottles of $Co_2(CO)_8$ were stored in a laboratory freezer and had been warmed to room temperature and exposed to air for material transfer. Thus, good commercial samples of $Co_2(CO)_8$ that have been properly stored (not necessarily in a dry box) should be sufficiently reactive for the catalytic process. Second, an apparent limitation of the reaction conditions for catalytic Pauson–Khand cycloaddition under 1 atm of carbon monoxide is that enynes bearing internal alkynes and lacking significant Thorpe–Ingold assistance (entries 16, 17 and 18–20) or are sterically encumbered (entries 13 and 14) do not undergo efficient cyclization using 10% catalyst loadings and higher quantities of catalyst are required (30–60%). It might be speculated that, under one atmosphere of carbon monoxide, the competition between carbon monoxide and the alkene for the newly generated vacant site on the cobalt complex favors CO if steric interactions on the alkene or alkyne inhibit binding or the rate of alkene binding is slow due to significant conformational mobility of the alkene tether. The catalyst subsequently decomposes over prolonged reaction times.

The reactions were each carried out in the presence and absence of cyclohexylamine. Sugihara has shown that additives such as cyclohexylamine promote the Pauson–Khand cycloaddition.[5] In the examples listed in Table 1, the use of cyclohexylamine provided an enhancement in the yield in most cases. The reason for this effect is not necessarily clear at this point and does not appear to be predictable although in most cases addition of $CyNH_2$ was advantageous. While the amine may serve in several capacities during the reaction cycle, a significant role may be as a catalyst carrier thereby increasing the longevity of the intermediate complexes. As can be seen from the results, a delicate balance of $CyNH_2$ and $Co_2(CO)_8$ is essential to the efficiency of this method. Evaluation of the catalytic reaction in different solvents showed that lower yields of cyclized products were obtained in THF or toluene when compared to 1,2-DME.

In summary, we have demonstrated a straightforward modification of Livinghouse's conditions for the catalytic Pauson–Khand cycloaddition which makes the catalytic reaction a more practical process by obviating the need to purify the $Co_2(CO)_8$ which is moderately air sensitive, in particular when highly pure and hexane-free (dicobalt octacarbonyl was purchased from Strem Chemicals, Inc. stabilized with 1–5% hexane). The experimental protocol described above is not one that will necessarily be successful with every substrate outside the limitations described herein. Since we still do not have a full understanding of the mechanism of either the Pauson–Khand reaction or the catalytic process, it is difficult to predict in advance when this catalytic protocol will be the most effective procedure for a given substrate.[9] Further work in the area of Pauson–Khand cycloadditions is currently in progress.

Representative experimental procedure: A *base-washed* flask equipped with a three-way stopper and a balloon of CO containing a mixture of diethyl (2-hexynyl) allylmalonate (entry 2 in Table 1) (121 mg, 0.43 mmol) and $Co_2(CO)_8$ (15 mg, 0.04 mmol, 10 mol%) was pumped briefly and purged three times with CO. 1,2-DME (1.6 mL) was added and the resulting solution was stirred at ambient temperature for 30 min. Cyclohexylamine (10 µL, 0.09 mmol, 20 mol%) in 1,2-DME (0.6 mL) was then added and the reaction was heated at 70°C for 11.5 h. Upon completion of the reaction the mixture was cooled to room temperature, diluted with 3 mL of 10% EtOAc in hexanes and plugged through a pad of silica gel. Subsequent removal of the solvent and purification by flash chromatography (SiO_2, 10% EtOAc in hexanes) afforded 120 mg of the corresponding bicyclic enone (90% yield) as a colorless oil. For the reaction without the amine, the mixture was also stirred for 30 min at rt prior to heating at 70°C and was worked up in the same manner upon completion. It was further observed that *inadvertent introduction of air into the system from frequent checking of the reaction by TLC resulted in incomplete consumption of the starting material.* The 1,2-DME was purified by refluxing over potassium in a continuous still and

Table 1
Thermally promoted $Co_2(CO)_8$-catalyzed Pauson–Khand reaction[a]

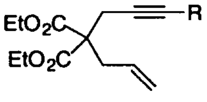
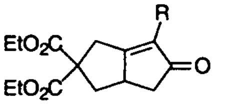
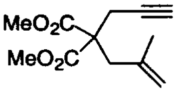
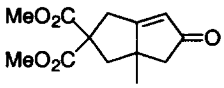
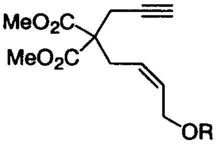
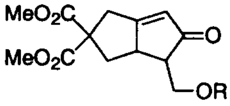
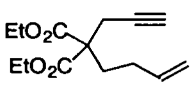
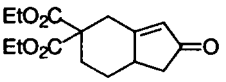
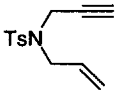
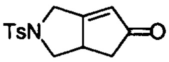
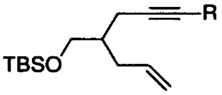
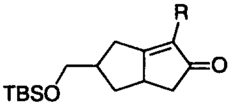
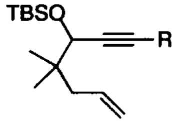
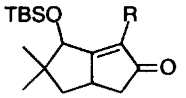
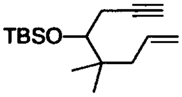
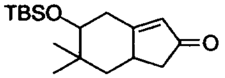
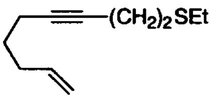
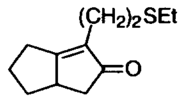
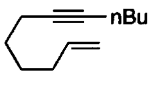
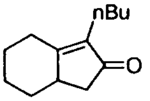
Entry	Enyne	Product[8]	% Yield (time, h) mol% $Co_2(CO)_8$: mol% $CyNH_2$				
			5:20	10:0	10:20	30:0	30:60
1		 R= H	67 (5)[b] **94** (2.5)[c]	80 (15)	84 (2.5)	–	–
2		R= nPr	5 (16) 59 RSM	56 (11.5)	**90** (11.5)	–	–
3			81 (14.5)[b] 44 (14.5)	**96** (15)	68(15)	–	–
4		 R= TBS[d]	**80** (14.5)	74 (15.5)	68 (15.5)	–	–
5		R= Ac[d]	11 (16.5) 66 RSM	**78** (15.5)	76 (15.5)	–	–
6			27 (14.5) 51 RSM	**85** (15.5)	**85** (15.5)	–	–
7			62 (13.5)	63 (10.5)	**89** (14)	–	–
8		 R= H[e]	**89** (16)	40 (16) 12 RSM	85 (16)	–	–
9		R= nPr[e]	8 (15) 86 RSM	_	46 (15) 52 RSM	54 (15.5)	**95** (15.5)
10					86 (14)[f] 12 RSM		
11					50 (15)[g] 22 RSM		

Table 1 (continued)

Entry	Substrate	Product[8]	% Yield (time, h) mol% $Co_2(CO)_8$: mol% $CyNH_2$				
			5:20	10:0	10:20	30:0	30:60
							
12		R= H[e]	24 (16.5)	71 (3.5)	**83** (3.5)	-	-
13		R= Me[h]	–	39 (16)[i]	22 (13)[j] 36 RSM	38 (13)	**61** (16.5)
14		R= TMS	-	NR	NR	NR	NR
15			72 (12)[k]	74 (3.5)[k]	**96** (3.5)[k]	-	-
16			-	55 (6) 7 RSM	16 (6) 66 RSM	**84** (15.5)	80 (15.5)
17					57 (13.5)[l] 36 RSM		
18			-	-	-	31 (17) 21 RSM	19 (17) 42 RSM
19						65(16)[m] 29 RSM	21 (16)[m] 62 RSM
20						64 (16)[n] 15 RSM	40 (16)[n] 28 RSM

a. All reactions were carried out using a substrate concentration of 0.2M in dimethoxyethane (DME) with varying amounts of $Co_2(CO)_8$ and cyclohexylamine ($CyNH_2$) under CO atmosphere at 70 °C. b. 5 mol% $Co_2(CO)_8$. c. 5 mol% $Co_2(CO)_8$ and 10 mol% $CyNH_2$. d. >20:1 ratio of diastereomers. e. 1:1 ratio of diastereomers. f. 10 mol% $Co_2(CO)_8$ and 40 mol% $CyNH_2$. g. 10 mol% $Co_2(CO)_8$ and 50 mol% $CyNH_2$. h. 1:3 ratio of diastereomers. i. 15 mol% $Co_2(CO)_8$ only j. complex formed during a two hour period. k. 1:4 ratio of diastereomers. l. 10 mol% $Co_2(CO)_8$ and 40 mol% $CyNH_2$. m. 60 mol% $Co_2(CO)_8$ and 0 or 120 mol% $CyNH_2$. n. stoichiometric amounts of $Co_2(CO)_8$ and 0 or 2 equivalents of $CyNH_2$.
RSM= Recovered Starting Material, NR=No Reaction.

was distilled immediately prior to use. A fresh bottle of anhydrous DME from Aldrich (sure seal bottle under N_2) also yielded similar results.

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