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Tetramethyl Thiourea/$Co_2(CO)_8$-Catalyzed Pauson−Khand Reaction under Balloon Pressure of CO

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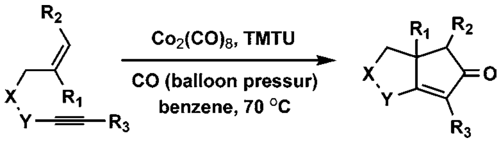
ABSTRACT



A Pauson–Khand type of conversion of enynes to bicyclic cyclopentenones employing the commercially available $Co_2(CO)_8$ and tetramethylthiourea (TMTU) as catalysts is described. This method allows a variety of enynes with diverse functional groups to be cyclized into cyclopentenones of interest.

In the field of organic chemistry, the search for new and more efficient methods of carbon skeleton formation for application to generate frameworks of complex molecules continues to be a fertile area of research. Over the past decades, the Pauson−Khand reaction[1] (PKR), a cobalt-mediated reaction performed by joining an alkyne, an olefin, and carbon monoxide to form a cyclopentenone framework, has received great attention due to its potential application in complex molecule synthesis.[2] Since its initial report there have been a variety of additives discovered that accelerate the PKR, resulting in a significant increase in reaction efficiency,[3] and catalytic PKR with the use of Co,[4] Ti,[5] Ni,[6] Ru,[7] Rh,[8] and Ir[9] complexes have been reported in the past decade. Recently, significant progress using sulfur-based ligands in the catalytic PKR has emerged.[10]

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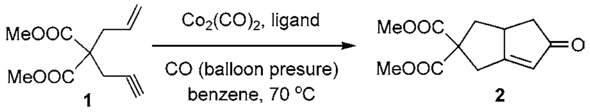
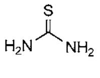
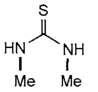
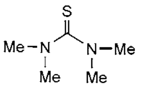
Table 1. Evaluation of Co−Thiourea-Catalyzed PKR

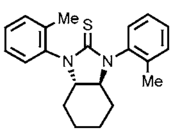


entry	ligand	$Co_2(CO)_8$	$Co_2(CO)_8$/ligand	time (h)	yield (%)[a]
1		3 mol%		24	43
2	TU	5 mol%	1/6	6	22
3	DMTU	5 mol%	1/2	6	81
4	TMTU	5 mol%	1/2	4	90
5	TETRATU	5 mol%	1/2	24	42[b]
6	TMTU	5 mol%	1/4	2	92
7	TMTU	5 mol%	1/6	2	96


TU (**I**)


DMTU(**II**)


TMTU (**III**)

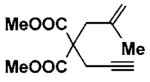
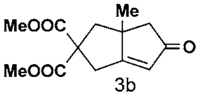
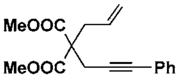
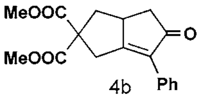
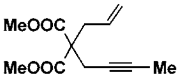
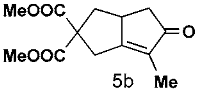
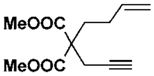
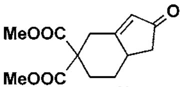
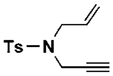
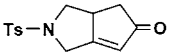
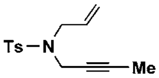
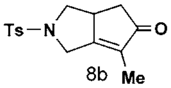
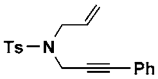
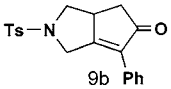
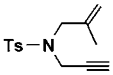
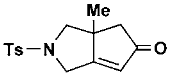
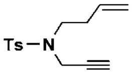
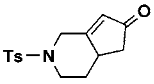
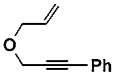
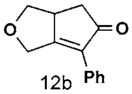
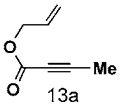
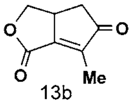
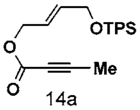
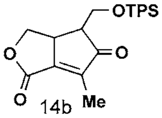
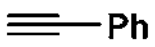
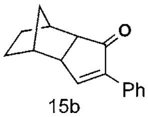

TETRATU (**IV**)

[a] Isolated yield. [b] 91% yield based on recovery starting material.

We recently engaged in the development of thiourea as an effective ligand in the metal-catalyzed reactions and demonstrated its usefulness in the palladium-catalyzed carbonylative annulation,[11] bismethoxycarbonylation of olefins,[12] and Suzuki-type carbonylative reaction.[13] The observed beneficial effect of thiourea as a ligand to incorporate CO into scaffolds of interest prompted us to attempt the catalytic version of PKR. We report herein that the cobalt−TMTU complex can effectively catalyze the intra- and intermolecular PKR, providing various bicyclic enones in high yields.

In the preliminary experiments, we examined the cobalt-catalyzed intramolecular PKR using a catalytic amount of octacarbonyldicobalt ($Co_2(CO)_8$) in the presence of four types of thioureas (Table 1). Enyne **1** was then cyclized to cyclopentenone **2** under the reported conditions.[10h] To our delight, thiuoreas (**I**−**IV**) demonstrated a favorable effect on this cyclization process (entries 2−5) as compared with the ligand-free counterpart (entry 1). Among these four ligands, TMTU (**III**) proved to be the best (entry 4).

Table 2. Co−Thiourea-Catalyzed PKR[a]

entry	enyne	cyclopentenone	time/h	yield (%)[b]
1	 3a	 3b	1.5	95[c]
2	 4a	 4b	3.5	91[d]
3	 5a	 5b	1.5	95[e]
4	 6a	 6b	24	64[d] (96)
5	 7a	 7b	2.5	95[e]
6	 8a	 8b	2.5	90[e]
7	 9a	 9b	2.0	86[d]
8	 10a	 10b	8.0	90[c]
9	 11a	 11b	4.0	84[e]
10	 12a	 12b	6.0	92[e]
11	 13a	 13b	24	58[e] (90)
12	 14a	 14b	8.0	75[e]
13	 5eq  1eq	 15b	2.0	93[d]

[a] Reaction conditions: enyne (0.5 mmol) in benzene (10 mL) at 70 °C under CO (balloon pressure). [b] Yield of isolated product, and the yields in parentheses are those obtained based on recovery of starting materials. [c] $Co_2(CO)_8$ (3 mmol %), TMTU (18 mmol %). [d] $Co_2(CO)_8$ (5 mmol %), TMTU (30 mmol %). [e] $Co_2(CO)_8$ (10 mmol %), TMTU (60 mmol %).

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These results encouraged us to select TMTU as a ligand for further investigation of its scope in the co-catalyzed PKR. We studied the effect of various reaction parameters (catalyst loading, solvent, temperature, etc.) on the outcome of the Co−TMTU-catalyzed reaction. It was found that among the ratio of $Co_2(CO)_8$/TMTU [1/2, 1/4, and 1/6 (entries 4, 6, and 7 in Table 1)], 1/6 proved to be the most efficient. Among the solvents used (THF, benzene, CH_2Cl_2, DMF, CH_3CN), benzene was the best choice. Reaction temperature is also important, and a better result was achieved when the reaction was carried out at 70 °C. Overall, a 96% yield of compound **2** was obtained when the reaction was conducted in the presence of a catalytic amount of $Co_2(CO)_8$ (3 or 5 mmol %) at 70 °C for 2 h under a balloon pressure of CO in benzene.[14] Interestingly, the optimized conditions were almost identical with the conditions described by Hashimoto and Saigo.[10h]

To assess the generality of the optimal conditions described above, cyclization of other enynes has also been examined, and the results are listed in Table 2.

To our satisfaction, most of the reactions were completed within less than 6 h to give the corresponding products in high yield. In addition, the following observations were made: (1) Allylpropargyl malonate, allylpropargylamine, and allylpropargyl ether are good substrates for the PKR (entries 1−10). (2) Enynes possessing alkyl and phenyl substituents on the alkyne were transformed into the corresponding bicyclic enones in high yields (entries 2, 3, 6, 7, and 10). (3) Unlike previous examples,[9,15] 1,1-disubstituted olefins were also good substrates for the PKR to give the corresponding products in high yields, which share the same features of phosphane sulfide/$Co_2(CO)_8$-catalyzed PKR.[10h] (4) Electron-deficient enynes gave low yields of cyclization products under the standard conditions. However, prolongation of the reaction time could improve the yields (entries 11 and 12). (5) As demonstrated by Hashimoto and Saigo in their study,[10h] an intermolecular version of PKR was also achieved with TMTU/$Co_2(CO)_8$ under catalytic conditions to produce the corresponding product in 93% yield (entry 13).

In summary, we have demonstrated for the first time that Co−TMTU complex is an effective catalyst in the PKR, and diversified bicyclic enones were synthesized in high yields. Further study regarding the mechanism of thiourea/co-catalyzed PKR by computational calculations and application of this catalytic system with some other difficult substrates (such as electron deficient alkenes in intramolecular processes or unstrained olefins in the intermolecular PKR) with our synthesized thioureas is currently underway in our laboratory, and the results will be reported in due course.

Acknowledgment. We gratefully acknowledge financial support of this work by the National Science Foundation of China (Grant Nos. 20225318 and 20325208) and VivoQuest, Inc., through the sponsored research program.

Supporting Information Available: Experimental procedures and ^1H NMR and ^{13}C NMR spectra for the known product compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] **Typical Experimental Procedure.** A solution of enyne **1** (105 mg, 0.5 mmol), $Co_2(CO)_8$ (8.5 mg, 0.025 mmol), and TMTU (198 mg, 0.15 mmol) in dry benzene (10 mL) was vigorously stirred at 70 °C under CO (supplied from a balloon) until the substrate was consumed. The reaction mixture was stirred at same temperature for 1 h. The resulting solution was passed through a small pad of silica gel using a mixed eluent of hexane and ethyl acetate (4/1, v/v). Purification of the crude products by flash chromatography on silica gel afforded pure bicyclic enone **2** (114 mg; 96%).

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