



Short synthesis of methylenecyclopentenones by intermolecular Pauson–Khand reaction of allyl thiourea

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ABSTRACT

N,N,N'-Trimethylallylthiourea promotes the intermolecular Pauson–Khand reaction with alkynes in the presence of $\text{Co}_2(\text{CO})_8$ and moderate pressure of CO followed by thiourea elimination allowing the formation of methylenecyclopentenone derivatives.

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Substituted cyclopentenones are an important class of physiologically and biologically active compounds¹ and versatile intermediates for the synthesis of a range of target molecules.² On the other hand, the 4-methylenecyclopentenone unit, apart from being present in natural compounds such as prostaglandins and antibiotics Methylenomycin A and B,³ provides opportunity for further functionalization by epoxidation⁴ and nucleophilic additions.⁵ This unit has been synthesized mainly by flash vacuum pyrolysis of spirocyclopentenones⁶ and sulfoxides⁷ and by ruthenium- and rhodium-mediated cyclization.⁸ The Pauson–Khand reaction (PKR) is a very appealing methodology for the construction of substituted cyclopentenones in a convergent manner.⁹ However, while considerable progress has been achieved recently for the stoichiometric and catalytic PKR with enynes as substrates¹⁰ and also stoichiometric intermolecular versions,^{10,11} the successful examples of catalytic intermolecular PKR have been limited to the utilization of strained (reactive) alkenes such as norbornene, norbornadiene, and allene¹² or to the use of high pressure and supercritical ethylene intermolecular Pauson–Khand reaction.¹³ So far, to the best of our knowledge, only a few exceptions have been reported. These are directed PKR when dimethyl(2-pyridyl)silyl- and dimethyl(2-pyrimidyl)silyl-groups are successfully applied as new remov-

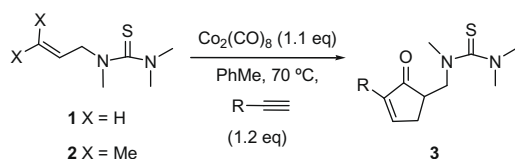
able directing groups in catalytic intermolecular PKR that greatly enhanced the coordinating aptitude of the alkene counterpart to the catalyst;¹⁴ novel zirconia-silica mesoporous powders catalyzed intermolecular PKR where cyclohexene was used as alkene, although quite high pressure of CO should be applied (30 bar)¹⁵ and; Rh(I)-catalyzed reductive cyclocarbonylation of internal alkynes to generate highly substituted cyclopentenones.¹⁶ The intramolecular PKR is an efficient methodology for the synthesis of bicyclic 5-alkylidenecyclopentenones from allenes while the intermolecular version provides mainly the 4-alkylidenecyclopentenones.¹⁷

A directing group provides a powerful strategy for enhancing the efficiency in PKR. In 1988, Krafft et al. elegantly disclosed that a coordinating heteroatom such as sulfur or nitrogen tethered to an alkene counterpart enormously enhanced the regioselectivity and efficiency of the $\text{Co}_2(\text{CO})_8$ -mediated stoichiometric intermolecular PKR.¹⁸ Later Yoshida and co-workers applied successfully the directing group strategy in Ru-catalyzed intramolecular PKR.¹⁴ Recently, discoveries of significantly elevated catalysis of PKR with $\text{Co}_2(\text{CO})_8$ in excess of tetramethylthiourea¹⁹ strongly suggested that it may be possible to perform intermolecular Co-catalyzed PKR directed by thiourea group with allylthioureas. We describe herein a study on the intramolecular Pauson–Khand reaction (PKR) promoted by the *N,N,N'*-trimethylthiourea attached to the olefinic unit that allows the straightforward synthesis of α -methylcyclopentenone motif.

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Table 1
Stoichiometric intermolecular Pauson–Khand reaction of allylthiourea **1**^a and alkynes



Entry	R–C≡C–H (equiv)	t (h)	3 ^b (%)
1	C ₆ H ₁₃ –C≡CH (a) (1.2)	8	48
2	C ₄ H ₉ –C≡CH (b) (1.2)	8	3 ^c
3	C ₅ H ₁₁ –C≡CH (c) (1.2)	2.5	30
4	C ₈ H ₁₇ –C≡CH (d) (1.2)	6	28

^a No reaction was observed for substrate **2**.

^b Compounds isolated by preparative TLC and purity confirmed by NMR, IR, and mass spectroscopy.

^c Partial evaporation of volatile 1-hexyne (bp 71 °C) may have occurred under the reaction conditions (argon atmosphere).

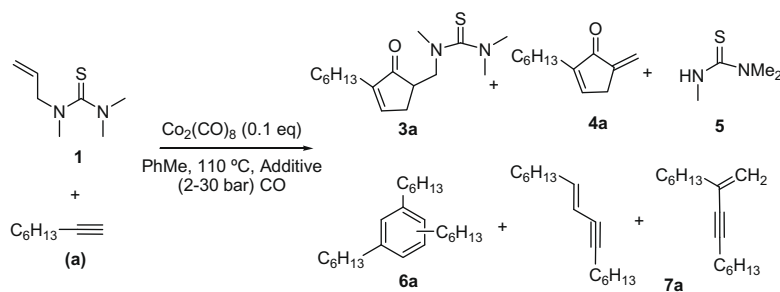
However, our initial attempts to perform the catalytic PKR at 70 °C, using the *N,N,N'*-trimethylallylthiourea **1**, under atmosphere of carbon monoxide were not successful. However, stoichiometric reaction of **1** and various alkynes provided thioureas **3** in moderate to low yields as the only isolated isomer (Table 1). On the other hand, the dimethylallylthiourea **2** did not undergo the PKR under different experimental conditions. Gratifyingly, further reaction studies at elevated temperature provided not only catalytic reaction but also thiourea group elimination (TE) and formation of

methylenecyclopentenone **4a** as the product of tandem PKR+TE process. In respect to CO pressure and reaction time applied, some thiourea **3a**, octyne cyclotrimerization product **6a**, and dimerization products **7a** were also formed (Table 2).

We tried to improve the yield of **4a** in tandem PKR+TE by exploration of a range of some additives. A selection of additives is shown in Table 2²⁰ but most of them failed to make any effect at all. Only the *N,N,N,N'*-tetramethylthiourea (TMTU) slightly improved the yield to 39% (entry 3). We assume that radical mechanism may be involved in the TE step. In order to prove this, (*n*Bu₃Sn)₂ was tested as additive, providing significant decrease in reaction yield and reaction rate (entries 4 and 5). The combined results suggest that mechanism of thiourea elimination could be more complicated than simple acid-base-assisted elimination as there is (a) no conversion for the thiourea **3a** in toluene at 110 °C to **4a** in the absence of additives; (b) partial elimination is observed in the presence of BF₃·Et₂O (1 equiv); and (c) complete conversion to **4a** occurred in the presence of DBU (1 equiv, 16 h) or Co₂(CO)₈ (1 equiv, 6 h).²¹ To exclude the possibility of the carbonyl group exclusive formation from cobalt-bounded CO we performed the reaction identical to entry 3 under argon instead of CO atmosphere (entry 12). In this case **4a** was isolated in only 6% yield and 57% of the starting material was recovered. High discrepancy in PKR product yield between entries 12 and 3 appoints clearly that carbon monoxide atmosphere is fundamental for better performance of reaction and that most of CO units incorporated into product in the presence of CO atmosphere are from carbon monoxide origin.

When octyne was added in high excess (entry 2) the effect on the product was detrimental, but the increase in the recovery of starting material **1** was substantial. When *N,N,N'*-trimethylthiourea

Table 2
Catalytic intermolecular Pauson–Khand reaction of allylthiourea **1** and 1-octyne



Entry	1-Octyne (equiv)	Additive (equiv)	CO (bar)	t (h)	4a ^a (%)	1 ^{a,b} (%)
1	1.2	None	2	6	30 [*]	26
2	5.0	None	2	6	18	82
3	1.2	Me ₂ NCSNMe ₂ (1.0 equiv)	2	15	39	54
4	1.2	(<i>n</i> Bu ₃ Sn) ₂ (1.5 equiv)	2	15	<3 ^c	76
5	1.2	(<i>n</i> Bu ₃ Sn) ₂ (1.5 equiv)	2	72	7	22
6	1.2	4a (0.15 equiv)	2	22	2 ^d	44
7	1.2	5 (0.25 equiv)	2	22	18	40
8	1.2	None	3	6	30	48
9	1.2	None	4	6	21 ^e	36
10	1.2	None	8	17	4 ^f	80
11	1.2	None	30	15	4 ^{f,g}	70
12	1.2	Me ₂ NCSNMe ₂ (1.0 equiv)	None ^h	15	6	57

^a Compounds isolated by preparative TLC and purity confirmed by NMR, IR, and mass spectroscopy.

^b Recovered **1**; * a mixture of cyclotrimerization product **6a** (12%) and dimerization product **7a** (32%) was also isolated and characterized by NMR—in other cases it was detected frequently on TLC, but not isolated.

^c The sample of compound **4a** was impure with some (*n*-Bu₃Sn)₂.

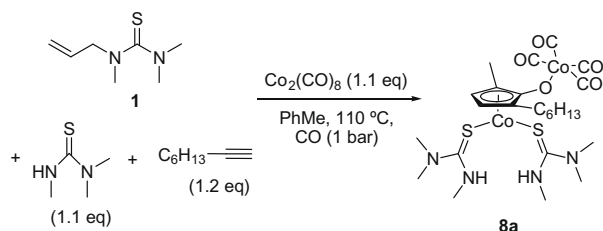
^d The yield determined after subtraction of initial value of added **4a**.

^e Some thiourea product **3a** (6%) was also isolated.

^f Unreacted alkyne–Co₂(CO)₈ complex was isolated.

^g Dirty reaction.

^h The reaction was run under argon.

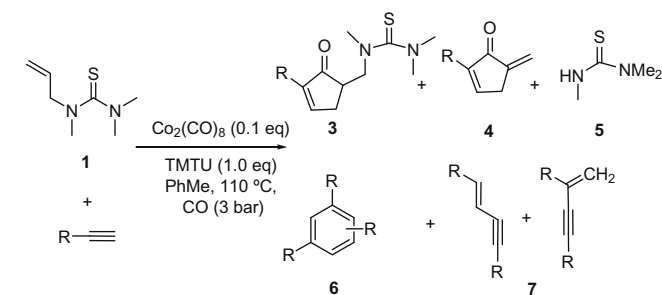


Scheme 1.

rea **5** was used as the additive the yield of product **4a** was diminished (entry 7). However, the most unusual behavior was recorded when product **4a** itself was present as the additive from the beginning of the reaction (entry 6): the reaction practically did not progress at all and the starting material was significantly consumed. At the end we explored the behavior of the system at elevated pressure of CO. Although the product yield remained the same at 3 bar the starting material was preserved from decomposition (entry 8). Higher CO pressure was detrimental (entries 9–11). The elimination process was slowed down and thiourea **3a** was isolated even after a prolonged period of time.

We suspected that perhaps product **4a** reactivity toward cobalt catalyst (entry 6) assisted by thiourea **5** (entry 7) plays a crucial role for the catalyst inactivation making impossible further improvement of the PKR+TE process. And this secondary process seems to be related directly to the formation of undesired cyclotrimerization product **6a** and alkyne dimerization products **7a**. Attempt of stoichiometric reaction with thiourea elimination at 110 °C provided only 7% yield of PKR product **4a** with the formation of the new compound of suggested structure **8a**.²² Compound **8a** was isolated as a brown oil and its synthesis optimized to 22% when the reaction was performed in the presence of additional 1.1 equiv of *N,N,N'*-trimethylthiourea (Scheme 1).

Table 3
Catalytic Intermolecular Pauson–Khand reaction of allylthiourea **1** and alkynes



Entry	R–C≡C–H (equiv)	t (h)	3 (%)	4^a (%)	6 + 7^c (%)	1^d (%)
1	C ₆ H ₁₃ –C≡CH (a) (1.2)	15	0 ^b	39 ^e (85)	12 + 32	54
2	C ₄ H ₉ –C≡CH (b) (2.4)	19	0 ^b	0 ^b (0)	^f	60
3	C ₄ H ₉ –C≡CH (b) (1.2)	24	0 ^b	27 (90)		70
4	C ₈ H ₁₁ –C≡CH (c) (1.2)	24	0 ^b	21 (47)	^f	56
5	C ₈ H ₁₇ –C≡CH (d) (1.2)	22	0 ^b	17 (31)	5 + 7	46
6	Ph–C≡CH (e) (1.2)	24	3 (9)	13 (43)	45 + 0	70
7	Ph–C≡CH (e) (1.2)	48	2 (5)	13 (30)		57

^a Compounds isolated by preparative TLC and its purity confirmed by NMR, IR, and mass spectroscopy; yield in brackets based on recovery of **1**; TON = 3.9 for entry 1.

^b Not detected by TLC.

^c Unpolar fraction.

^d Recovered **1**.

^e Reaction reproduced up to six times using 0.3–0.6 mmol of **1**.

^f Observed the presence of product of cyclotrimerization by mass spectroscopy from complicated mixture of inseparable highly unpolar products.

Due to the high interest for the synthesis of molecules containing the α -methylene-cyclopentenone motif, the novelty of our approach prompted us to test the optimized reaction conditions on other alkynes (Table 3).²³ Other terminal alkynes generally behave similar to 1-octyne in PKR+TE tandem reaction versus cyclotrimerization/dimerization (compare Table 3 and Table 2). However, sometimes few peculiarities were seen: reaction with 1-hexyne was extremely sensitive to alkyne quantity (Table 3, entry 2 vs 3), and in the case of phenylacetylene, traces of thiourea **3e** were not transformed into **4e** even after 48 h (entries 6 and 7).

In summary we described herein a novel stoichiometric Pauson–Khand (PKR) and a tandem catalytic intermolecular PKR and concomitant thiourea group elimination (TE) of *N,N,N'*-trimethylallylthiourea **1**. Although the chemical yield of this reaction was very moderate (up to 48% for stoichiometric reaction and 13–39% for catalytic reaction), the resulting methylenecyclopentenones were formed as a sole regioisomer in one-step reaction from two very simple molecules: terminal alkynes and allylthiourea. Additionally, unreacted starting material was also recovered in high yield.

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Supplementary data

Supplementary data (general experimental remarks, experimental procedures for the synthesis of compounds; screening of different additives in the Pauson–Khand reaction and thiourea group elimination (PKR+TE), characterization of new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.025.

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20. A complete list of additives tested is provided in the [Supplementary data](#).
21. We suspect that elimination is not just simple Lewis acid-assisted process. We performed additional elimination experiments followed by simple TLC analysis with compound **3a** dissolved in toluene at 110 °C in the presence of stoichiometric quantity of (1) Lewis acid (BF₃·Et₂O); (2) DBU; (3) Co₂(CO)₈; (4) Fe(CO)₅; (5) no additive. In the sample, Lewis acid process was slower and only partial after 16 h; in the sample containing DBU, there occurs complete elimination only after 16 h, and Co₂(CO)₈ provided elimination in 6 h. Samples containing Fe(CO)₅ and no additive provided no elimination, or any change at all. There was also one curiosity regarding Co₂(CO)₈-assisted process; the elimination reaction took some time to start and then it was finished quite rapidly. Such a pattern made us believe that possible mechanism for elimination could involve abstraction of β-hydrogen atom from coordinated transient η²-ketone **3a** to form cobalt hydride enolate species, just as the group IV metal centers; see for example: Scott, M. J.; Lippard, S. J. *Organometallics* **1998**, *17*, 466–474 and references therein. Cobalt hydride/enolate could afterwards eliminate **4a** and recover the catalyst by free radical pathway. The whole process must be rather sluggish. Free radicals themselves could abstract β-hydrogen atom from thiourea **3a** coordinated to metal and restart fragmentation cycle. As radical concentration increases much faster radical fragmentation pathway could become predominant. The final products of elimination are in any case **4a** and **5**. To test the hypothesis we tried to trap free radicals with vinylcyclopropanedicarboxylate ester but failed to isolate any product.
22. The molecular structure suggested for **8a** was based on ¹H NMR and IR spectroscopy and mass spectrometry. Unfortunately, various attempts to get suitable crystals for X-ray analysis failed.
23. *General procedure for the synthesis of methylenecyclopentenones 4a–e*: To the stirred solution of allylthiourea **1** (50 mg; 0.316 mmol) and *N,N,N',N'*-tetramethylthiourea (42 mg; 0.316 mmol; 1.0 equiv) in dry toluene (5 mL) under argon were added 1-alkyne (0.372 mmol; 1.2 equiv) and Co₂(CO)₈ (10.8 mg; 0.0316 mmol; 0.1 equiv, commercial). After 5 min the solution was transferred to autoclave; the autoclave was purged several times with carbon monoxide and pressure was adjusted to 3 bar. The reaction mixture was kept at 110 °C for the time designated in Table 2. After cooling, the reaction mixture was filtered on Celite, the solvent was evaporated, and the remaining oil was purified by thin layer chromatography (eluent hexane/ethyl acetate = 7:3). The yield of each product is shown in Tables 2 and 3 and SM1.