Co₂(CO)₈ Catalyzed Pauson–Khand Reaction under Microwave Irradiation¹

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Abstract: Microwave irradiation is used to accelerate Pauson–Khand reactions. The conditions for the Pauson–Khand reaction, catalytic in Co₂(CO)₈ under microwave irradiation, were optimized. It is possible to obtain various types of [2+2+1] cycloaddition products in 5 minutes without additional carbon monoxide.

Key words: microwave, Pauson–Khand reaction, catalysis, cobalt, cycloaddition

The [2+2+1] cycloaddition of an alkene, an alkyne and carbon monoxide is commonly known as the Pauson–Khand reaction.² This highly convergent process is the transformation of choice for the preparation of cyclopentenones³ and has been utilized in the synthesis of complex natural products and analogues.⁴ During the last decade improvements regarding reaction conditions have been achieved. It is possible to run the reaction catalytically and under significantly milder conditions compared to the classical ones, which required high temperatures and pressures of carbon monoxide.⁵ The use of microwave heating in organic synthesis has gained increasing importance since the pioneering work of Gedye and coworkers.⁶ The advantage of microwave compared to conventional heating is the amplified acceleration of the overall reaction. Direct, fast and homogenous heating of reactants and solvents as well as an increase of the boiling point in closed vessels account for this observation.⁷ These conditions are close to those of the classical Pauson–Khand reaction and we have therefore decided to investigate the influence of microwave irradiation on Pauson–Khand reactions. It has been described that primary amines accelerate the Pauson–Khand reaction significantly when Co₂(CO)₈-alkyne complexes are used.⁸ In those cases stoichiometric amounts of cobalt reagent are required. In contrast, the use of catalytic quantities of cobalt catalyst required reaction times of several hours.^{5k,l}

Under microwave irradiation the polarity is the crucial property of the solvent, which serves for the energy transfer to the substrate. Solvents of low polarity have been described as transparent for microwaves and the energy is transferred directly to the reactants, whereas in polar solvents the energy transfer usually occurs from the solvent to the reactants.

Table 1 Pauson–Khand Reaction in Different Solvents⁹

Entry	Solvent	Dielectric constant	Yield [%] ^a
1	DMSO	46.7	5
2	Acetonitrile	37.5	16
3	Dichloromethane	9.0	21
4	THF	7.6	38
5	1,2-Dimethoxythane	7.2	41
6	Diglyet ^b	5.7	44
7	Toluene	2.4	44
8	Toluene	2.4	43 ^c
9	Dioxane	2.2	41
10	Heptane	1.9	20

^a Isolated yields.

^b Diethylene glycol diethyl ether.

^c No CO saturation.

Due to the distinct influence of solvent properties an optimization of this reaction parameter was conducted first.

As a starting point 10 mol% of Co₂(CO)₈ and a fivefold excess of norbornene to phenylacetylene were used for the cycloaddition in the presence of cyclohexylamine, which has been used previously as an additive in order to allow a catalytic reaction.^{5k} The reactions were performed in sealed vessels and the applied solvents were saturated with carbon monoxide by passing a stream of carbon monoxide through the solution for two minutes.¹⁰ Table 1 shows an increase in yield as the polarity of the solvent decreases. Very polar solvents gave only poor yields (Table 1, entries 1–3). Solvents with dielectric constants from 7.6 to 2.2 gave yields in a range from 38% to 44% (Table 1, entries 4–9). The observation that the non-polar solvents, which have been described as transparent for microwaves, gave comparably good yields clearly indicates that the reagents themselves absorb microwaves to a significant degree and that mediation through the solvent is not necessary. Heptane however proved to be a poor solvent under the applied conditions (Table 1, entry 10). In

this context the observation of a thin film of elementary cobalt covering the glass vessel in all cases is interesting.¹¹ When heptane was used the cobalt precipitation reached its maximum and showed a typical metallic luster. This shows that the cobalt reagent is significantly affected by microwave irradiation. We also made the observation that additional carbon monoxide is not necessary (Table 1, entry 8). As described by Krafft and co-workers all the carbon monoxide taken up in the reaction is obviously taken from the cobalt catalyst.^{5k} This means that the maximum theoretical yield in Table 1 is 80%. Consequently, all following reactions were performed without additional carbon monoxide. The observation of a metal film clearly shows that the catalyst decomposes as a result of the microwave irradiation power needed for heating the reaction medium to 200 °C. We therefore examined lower temperatures next. Table 2 shows the results at different reaction temperatures.

Table 2 Pauson–Khand Reaction under Varying Catalyst Amounts and Reaction Temperatures^a

Entry	Solvent	Temp [°C]	Catalyst [mol%]	Yield [%] ^b
1	Diglyet	150	10	46
2	Diglyet	100	10	47
3	Diglyet	100	20	53
4	Diglyet	100	50	71
5	Dioxane	150	10	43
6	Dioxane	100	10	43
7	Toluene	150	10	47
8	Toluene	100	10	49
9	Toluene	100	20	72
10	Heptane	100	10	43
11	Heptane	100	20	49

^a Catalyst to amine ratio was 1:3 in all cases.

^b Determined by HPLC with 2,4-di-*tert*-butylphenol as an internal standard.

It was found that lowering the reaction temperature led to increased yields in all cases. In the case of non-polar solvents the increase was more significant. Especially, in heptane the yield could be more than doubled when decreasing the temperature from 200 °C to 100 °C (Table 1, entry 11 vs Table 2, entry 10). This result also indicates a decomposition of the cobalt catalyst at higher temperatures when microwave transparent solvents were used.

Lowering the temperature even further resulted in lower yields of the cycloaddition product.

Another parameter of interest is the amount of catalyst needed. Table 2 shows that an increase from 10 mol% to 20 mol% and 50 mol% using diglyet as solvent increases the yield up to 71% (Table 2, entries 2–4). An increase in yield was also observed when heptane was used. In toluene, however, the yield was influenced more drastically by the catalyst amount. Only 20 mol% of $\text{Co}_2(\text{CO})_8$ gave a yield of 72%. Toluene seemed to work best for Pauson–Khand cycloadditions under microwave irradiation.

The cyclohexylamine additive is thought to replace carbon monoxide as a ligand and promotes additional ligand liberation by stabilizing the corresponding coordinatively unsaturated complex. Subsequently, the free site is able to coordinate with the olefin.^{5m} Therefore, changes in the cyclohexylamine concentration also should have an effect. Subsequently, the next parameter to be optimized was the influence of the amount of cyclohexylamine.

Table 3 Pauson–Khand Reaction under Various Cyclohexylamine/ $\text{Co}_2(\text{CO})_8$ Ratios and Reaction Times

Entry	Solvent	Time [s]	Catalyst [mol%]	Amine/catalyst ratio	Yield ^a [%]
1	Toluene	600	20	10	70
2	Toluene	300	20	10	71
3	Toluene	300	20	8	70
4	Toluene	300	20	6	81
5	Toluene	300	20	2	68
6	Toluene	180	20	6	68

^a Determined by HPLC with 2,4-di-*tert*-butylphenol as an internal standard.

Increasing the amine/catalyst ratio from 3:1 to 10:1 with a reaction time of 600 seconds did change the yield only slightly (Table 2, entry 9 vs Table 3, entry 1). The same result is obtained when the reaction time was decreased to 300 seconds. The optimal ratio was determined to be 6:1 where 81% yield was obtained (Table 3, entry 4). Shorter reaction times gave lower yields so 300 seconds was determined to be the optimum (Table 3, entry 4 vs 6).¹²

Using the elaborated optimized conditions we were able to obtain 81% yield of the cycloaddition product of norbornene and phenylacetylene using 20 mol% $\text{Co}_2(\text{CO})_8$ and 1.2 equivalents of cyclohexylamine in 5 minutes by heating the reaction mixture in a sealed vessel to 100 °C by microwave irradiation.¹³

Table 4 Examples for Pauson–Khand Reactions Using the Optimized Conditions¹⁴

Entry	Reactants	Product	Yield [%] ^a
1			72
2 ^b			71
3			48
4			46

^a Isolated yields.^b The acetylene was used in a 5 fold excess.

Next, the scope and limitations of this reaction was investigated by using different substrates under optimized reaction conditions.

The example in entry 1 of Table 4 shows that the alkynes with an hydrocarbon chain can also be used in microwave accelerated Pauson–Khand reactions. Branching does not significantly influence the reaction (Table 4, entry 2) and 3-methyl-but-1-yne reacted with norbornene in 71% yield along with the cyclotrimerisation side product. When diethyl acetylenedicarboxylate was used a 48% yield was obtained (Table 4, entry 3). As an example for intramolecular cyclizations the enyne of entry 4 (Table 4) was examined and also provided the Pauson–Khand product although in lower yield.

In summary, we have elaborated conditions for performing Pauson–Khand reactions in 5 minutes using only 20 mol% Co₂(CO)₈ under microwave irradiation. It was observed, that no additional carbon monoxide is required which allows an user friendly experimental protocol. The conditions were used for inter- and intramolecular cycloadditions.

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- (9) It should be stated that low boiling solvents usually cannot be heated to 200 °C but in our case the desired temperature could be reached in all cases except dichloromethane, which reached a maximum at 140 °C.
- (10) All experiments were performed using a Smith Synthesizer from Personal Chemistry. For a detailed instrument description, see: Stadler, A.; Kappe, C. O. *Comb. Chem.* **2001**, 3, 624.

- (11) Deposition of a metal film has recently also been observed in a $\text{Pd}(\text{OAc})_2$ catalyzed C–P cross-coupling reaction: Stadler, A.; Kappe, C. O. *Org. Lett.* **2002**, *4*, 3541.
- (12) When conventional heating of the sealed vessel was provided under identical conditions the yield did not exceed 40% even after 4 h.
- (13) **Typical Experimental Procedure:** To a 10 mL glass vial 942 mg (10 mmol, 5 equiv) norbornene **1** and 137 mg (0.4 mmol, 0.2 equiv) $\text{Co}_2(\text{CO})_8$ were added under an inert gas atmosphere in a glove box and sealed with a Teflon septum and an aluminum crimp top. After the addition of 2 mL toluene (freshly distilled from sodium), 220 μL (2 mmol) phenylacetylene **2** and finally 275 μL (2.4 mmol, 1.2 equiv) cyclohexylamine were added through the Teflon septum. The vessel was then heated to 100 °C under microwave irradiation using the Smith Synthesizer (monomode microwave cavity at 2.45 GHz; temperature control by automated adjustment of irradiation power in a range from 0 to 300 W). After 300 s the vial was cooled to r.t. by gas jet cooling. The reaction mixture was then subjected to a typical aqueous workup. The dried organic phase was then liberated from solvent and purified by flash chromatography on silica eluting with EtOAc/petroleum ether to give 363 mg (1.62 mmol, 81%) of *exo*-**3**.
- (14) All spectral data were in full accordance with those reported in literature: (a) Entry 1: Devasagayaraj, A.; Periasamy, M. *Tetrahedron Lett.* **1989**, *30*, 595. (b) Entry 3: Hayakawa, K.; Schmid, H. *Helv. Chim. Acta* **1977**, *60*, 2160. (c) Entry 4: Grossman, R. B.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 5803. (d) Entry 2: ^1H (CDCl_3 , 400 MHz): δ = 7.00 (d, J = 2.4 Hz, 1 H), 2.54 (sept., J = 6.6 Hz, 1 H), 2.48 (m, 1 H), 2.30 (m, 1 H), 2.08 (m, 2 H), 1.58 (m, 1 H), 1.51 (m, 1 H), 1.21 (m, 2 H), 1.01 (d, J = 6.6 Hz, 6 H), 0.86 (m, 2 H). ^{13}C (CDCl_3 , 100 MHz): δ = 210.7, 156.5, 155.4, 54.1, 47.7, 38.9, 37.9, 30.8, 29.0, 28.3, 24.5, 21.5, 21.2.