



Microwave promoted Pauson–Khand reactions

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Abstract—The synthesis of various cyclopentenones via the Pauson–Khand reaction, employing for the first time microwave energy to initiate this cycloaddition process is reported. © 2002 Elsevier Science Ltd. All rights reserved.

The Pauson–Khand reaction (PKR)¹ is the now classic method for the synthesis of cyclopentenones **4** from an alkyne **1** and an alkene **3** under the influence of a transition metal carbonyl, usually dicobaltoctacarbonyl (Fig. 1).² Traditional reaction conditions for the synthesis of cyclopentenones in this manner include thermal promotion (for example, toluene, 110°C) or the use of the *N*-oxides³ at ambient temperature. Pauson–Khand cycloadditions are often hampered by sluggish reaction periods; additionally low yields (dependent on the choice of alkene and alkyne) and troublesome purification protocols are frequently encountered. In recent years various groups have reported the inclusion of additional additives⁴ and modifications of the standard conditions⁵ that appear to accelerate or promote the PKR.

Microwave promoted reactions⁶ are gaining more widespread use in organic chemistry particularly as efficient, practical machines for the generation of microwaves in a laboratory environment become available.⁷ These published examples clearly demonstrate that microwave energy may be harnessed, significantly reducing reaction periods for a diverse selection of chemical processes traditionally performed under conductive heating via an external thermal source. We were intrigued to ascertain whether the use of microwaves could reduce

the prolonged reaction periods of standard PKR processes.⁸ Therefore, we selected a series of Pauson–Khand processes and performed the cyclisations under microwave conditions.

Gratifyingly, initial experiments⁷ confirmed that this was indeed the case (see Table 1). The intermolecular PKR, performed in a sealed vessel, between the preformed trimethylsilylacetylene–dicobalthexacarbonyl complex **2a**⁹ and norbornadiene **3a** (5 equiv.) proceeded efficiently under a variety of experimental conditions. Using toluene as the solvent gave excellent yields of the corresponding cyclopentenone **4a** after only 5 minutes of microwave irradiation (entry 1). However, purification proved difficult, presumably due to norbornadiene derived by-products; additionally small amounts of the corresponding *endo*-diastereoisomer¹⁰ were observed. Use of 1,2-dichloroethane (DCE) required increased reaction periods in order to obtain comparable yields at identical temperatures (entry 2). Product purification proved simpler by comparison and less of the corresponding *endo*-diastereomer was detected. Toluene (exhibiting no dipole moment) is almost transparent to microwave energy, whereas it is absorbed more efficiently by DCE. Consequently, the amount of energy required to reach a given temperature is far greater in toluene than in DCE and is almost quantita-

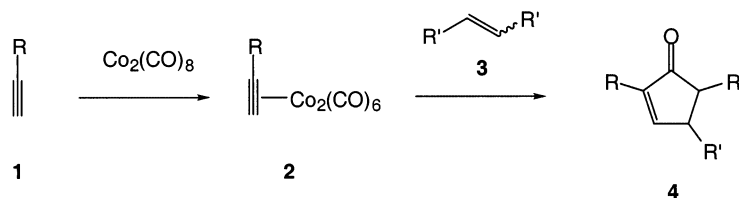


Figure 1. The Pauson–Khand cycloaddition reaction.

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tively absorbed by the reagents. This possibly explains the experimental observation that the reaction process is more rapid in toluene than DCE and somewhat less selective and clean. Increased temperature (entry 3) drastically reduced the reaction period; however, concomitant pressure increases proved problematic.

Significantly this process could be effectively performed using 0.5 equiv. of $\text{Co}_2(\text{CO})_8$ (entry 4). In this experiment the dicobaltoctacarbonyl, trimethylsilylacetylene **1a** ($\text{R} = \text{SiMe}_3$) and norbornadiene **3a** were combined in DCE and heated in the microwave at 120°C for 100 seconds. The pressure of carbon monoxide was vented and the reaction mixture heated for a further 100 seconds at 120°C . Purification by flash column chromatography afforded **4a** in 93% yield. By way of comparison identical thermal (entry 5) and NMO (entry 6) mediated cycloadditions were performed, demonstrating the difference in both time and efficiency under these typical conditions for this particular reaction.

To investigate further the scope and limitations of these initial experiments a series of additional microwave promoted Pauson–Khand reactions were performed (see Table 2).¹¹

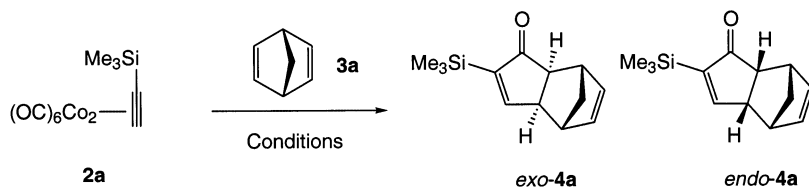
The acetylene–dicobalthexacarbonyl complex **2b** reacted smoothly with norbornadiene **3a** under microwave irradiation, either in toluene (90°C , 5 min) or DCE (90°C , 20 min), generating the corresponding enone **4b** in good yield (entry 1). Interestingly, a significant improvement in diastereoselectivity was observed under the microwave mediated conditions by comparison to the corresponding thermal and NMO promoted processes. Similarly, phenylacetylene complex **2c** gave the adduct **4c** on reaction with norbornadiene **3a** (entry 2). 1,2-Disubstituted cyclopentenones were also efficiently accessed from the corresponding internal alkynes and norbornadiene **3a** (entries 3 and 4). The

regiochemistry of the adduct **4e** was confirmed by HMBC ^1H NMR experiments. The efficiency of the microwave mediated process decreased with less reactive alkenes (entries 5–7) in parallel with standard PK processes.² For example, reaction between the phenylacetylene–dicobalthexacarbonyl complex **2c** and dihydrofuran gave the corresponding cyclopentenone **4f** in 55% yield comparing favourably with the literature yield for the corresponding thermal process (35%).^{4c} Cyclohexene gave the corresponding adduct **4g** in 20% yield, compared to the previously reported 3% yield¹² (entry 6). The *cis*-stereochemistry was suggested from an NOE between the 4- and 5-protons. This trend was also seen with 4,4-dimethoxycarbonylcyclopentene, synthesised via ring closing olefin metathesis (entry 7). In this case cyclopentenone **4h** was isolated in 11% yield.

Intramolecular Pauson–Khand reactions may also be effectively performed under microwave conditions (entries 8 and 9). In the standard examples selected it proved crucial to both perform the reaction at reduced concentration (0.05 mol dm^{-3}) and to reduce the reaction periods in comparison to their intermolecular counterparts. Thus, both the reactions were complete after 100 seconds at 90°C ; indeed prolonged microwave irradiation led to reduced yields. Reactions that proceed efficiently only under ambient temperature, *N*-oxide mediated conditions, for example allenes^{13a} and α,β -unsaturated esters,^{13b} were found not to generate the corresponding cyclopentenones under the conditions described in this communication.

In summary, we have demonstrated that microwave technology may be efficiently applied for the extremely rapid synthesis of various cyclopentenones. A demonstration of the robustness of this method was given when the cycloadditions described in Table 1 were also successfully performed using CEM ‘Discover,’

Table 1.



Entry	Solvent	Temperature ($^\circ\text{C}$)	Time	Yield (%) ^d	<i>exo</i> - 4a : <i>endo</i> - 4a ^e
1 ^a	PhMe	90	5 min	97	95:5
2 ^a	DCE	90	20 min	98	>95:5
3 ^a	DCE	180	100 s	91	95:5
4 ^b	DCE	120	200 s	93	>95:5
5 ^a	PhMe	110	16 h	99	>95:5
6 ^c	DCM	25	16 h	50	90:10

^a Method: **3a** (5 equiv.) was added to a solution (0.25 mol dm^{-3}) of **2a**.

^b Method: **1a** ($\text{R} = \text{SiMe}_3$; 1 equiv.), cobalt octacarbonyl (0.5 equiv.) and **3a** (5 equiv.) were dissolved in DCE (0.25 mol dm^{-3}).

^c Method: NMO (5 equiv.) was added to a solution of **2a** (1 equiv.) and **3a** (5 equiv.) in DCM (0.25 mol dm^{-3}) at room temperature.

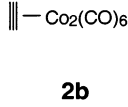
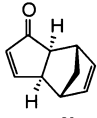
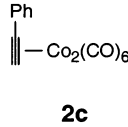
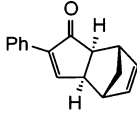
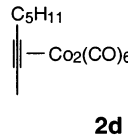
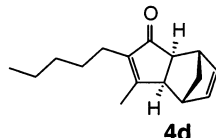
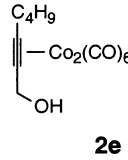
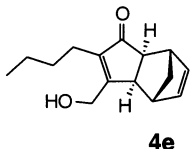
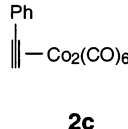
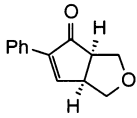
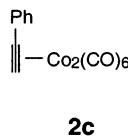
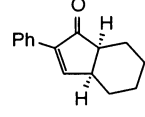
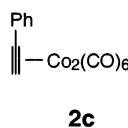
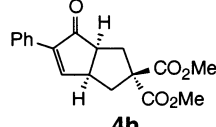
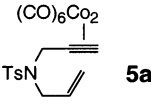
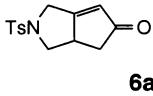
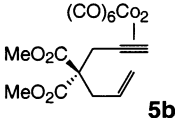
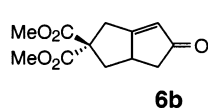
^d Yield after purification by flash column chromatography.

^e Ratio determined by ^1H NMR spectroscopy.

monomode cavity system (both in open and closed reaction vessels¹⁴) and the Milestone multimode cavity apparatus. At this stage it seems to be a matter of conjecture as to whether the rate enhancements described in this study stem directly from an effect of

the microwave energy, or from ‘super-heating’ of the media as recently highlighted.^{6c,15} Future work will include studies aimed towards determining a specific microwave effect in addition to broadening the substrate scope of the process.

Table 2.

Entry	Alkyne-dicobalt Complex	Adduct	Conditions	Yield (%) ^a	<i>exo:endo</i> ^b
1	 2b	 4b	PhMe, 90°C, 20 min	72%	90:10
			DCE, 90°C, 20 min	89%	95:5
			PhMe, 110°C, 16 h	70%	80:20
			DCM, 5 NMO, 25°C, 16 h	73%	70:30
2	 2c	 4c	DCE, 90°C, 20 min	90%	>95:5
3	 2d	 4d	DCE, 90°C, 10 min	77%	>95:5
4	 2e	 4e	DCE, 90°C, 20 min	56%	>95:5
5	 2c	 4f	DCE, 90°C, 20 min	55%	-
6	 2c	 4g	DCE, 150°C, 10 min	20%	-
7	 2c	 4h	DCE, 150°C, 10 min	11%	-
8	 5a	 6a	DCE (0.05 M), 90°C, 100 sec	72%	-
			DCM, 5 NMO, 25°C, 16 h	95%	-
9	 5b	 6b	DCE (0.05 M), 90°C, 100 sec	60%	-

^aYield after purification by flash column chromatography; ^bRatio determined by ¹H-NMR spectroscopy.

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- For a theoretical study concerning the energetics of the various reaction intermediates along the Magnus pathway see: Yamanaka, M.; Nakamura, E. *J. Am. Chem. Soc.* **2001**, *123*, 1703.
- Representative experimental procedure: *exo*-2-trimethylsilyl-3a,4,7,7a-tetrahydro-4,7-methanoindole-1-one **4a**: At room temperature Co₂(CO)₈ (352 mg, 1.03 mmol, 1 equiv.) was added to a solution of trimethylsilylacetylene **1a** (0.15 cm³, 1.06 mmol, 1 equiv.) in DCE (4 cm³). Stirring was continued for 1 h. Norbornadiene **3a** (0.55 cm³, 5.0 mmol, 5 equiv.) was added and the mixture was heated in the microwave⁶ at 90°C for 20 min. Silica (ca. 2 g) was added to the crude reaction mixture and the solvent was removed under reduced pressure. Purification by flash column chromatography (Hex→Hex/EtOAc; 9:1) afforded the *title compound 4a* (218 mg, 94%) as a colourless solid. *R*_f *exo*-**4a**=0.25 [*endo*-**4a**=0.2] (Hex/EtOAc; 9:1); *v*_{max} (CDCl₃/cm⁻¹) 3062, 2972, 1689, 1570, 1247; *δ*_H (400 MHz, CDCl₃) -0.17 (9H, s, CH₃), 1.05 (1H, d, *J*=11.25 Hz, CH₂), 1.22 (1H, d, *J*=11.25 Hz, CH₂), 2.01 (1H, d, *J*=6.25 Hz, CH), 2.52 (1H, s, CH), 2.72–2.74 (1H, m, CH), 2.80 (1H, s, CH), 6.21–6.30 (2H, m, 2×CH), 7.65 (1H, d, *J*=2.5 Hz, CH); *δ*_C (100 MHz, CDCl₃) -2.1, 41.1, 42.8, 43.7, 51.9, 53.2, 137.2, 138.1, 152.0, 172.7, 213.0; *m/z* (CI) 219 (MH⁺, 100%); Found: C, 71.50; H, 8.31%, C₁₃H₁₈OSi requires C, 71.60; H, 8.30%.
- The *exo:endo* ratios were calculated from characteristic signals in the ¹H NMR spectra after the crude reaction mixture was purified by flash column chromatography. No attempt was made to separate the diastereomers, however, the ratios given must be considered approximate.
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