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Pauson–Khand Reaction Induced by Molecular Sieves[†]

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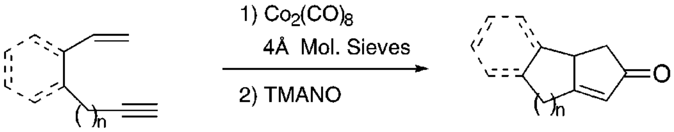
ABSTRACT



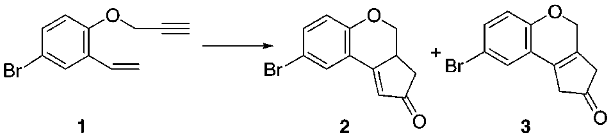
The Pauson–Khand reaction still has a relatively low scope with respect to the used carbon skeleton, while yields are low in many other cases. We have observed that the addition of molecular sieves improves yields remarkably. Experimental protocol is extremely easy, and it has been applied to several substrates including the less favorable ones.

The cocyclization reaction of alkynes, alkenes, and carbon monoxide, the Pauson–Khand reaction, is one of the most powerful ways to construct cyclopentenones[1] and is being widely used in natural product synthesis.[2] Considerable efforts have been made in the past decade to improve the reaction conditions. Although the cobalt–hexacarbonyl–alkyne complex is readily obtained, the substitution of one carbonyl ligand by the olefin in this complex is very difficult, and several promoters such as *N*-oxides[3] or DMSO[4] have been developed to labilize the carbonyls. "Hard" ligands such as amines or water can also facilitate the ligand substitution.[5] The reaction can also be induced by by anchoring of the substrate on silica gel (DSAC procedure).[6] In this case, the reaction may be promoted by stabilization of a pretransition state conformation of the enyne complex.

Nevertheless, many enynes still fail to give the cyclization product or they do so in low yields. Among them are systems derived from hept-1-en-6-yne lacking gem-disubstitution, some oct-1-en-7-yne systems,[7] and most substrates with substituents in the alkene moiety.[8]

We have recently introduced aromatic enynes such as **1** as new substrates for the intramolecular Pauson–Khand reaction.[9] These substrates yield tricycloenones with moderate yields using TMANO as promoter. Isomerization of the emerging double bond is observed in most cases, compound **2** being the only product (Scheme 1).

Scheme 1



1 2 3

In our attempt to improve yields we have found that molecular sieves (zeolites) can promote the Pauson–Khand

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[†] Dedicated to the memory of Dr. Joaquín de Pascual-Teresa.

(1) Recent reviews on the Pauson–Khand reaction: (a) Geis, O.; Schmalz, H.-G. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 911–914. (b) Ingate, S. T.; Marco-Contelles, J. *Org. Proc. Prep. Int.* **1998**, 123–142. (c) Shore, N. E. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon Press: 1995; Vol. 12, pp 703–739.

(2) For some recent examples of natural product syntheses, see: (a) Kowalczyk, B. A.; Shmith, T. C.; Dauben, W. G. *J. Org. Chem.* **1998**, *63*, 1379–1389. (b) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1998**, *63*, 3346–3351. (c) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353–4363.

(3) (a) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S. E.; Sunghee, H. *Synlett* **1991**, 204–206. (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. *Tetrahedron Lett.* **1990**, *31*, 5289–5292.

(4) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220–223.

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reaction. Molecular sieves have been used to promote several organic transformations such as epoxidation of allylic alcohols (Sharpless epoxidation),[10] asymmetric Heck reactions,[11] and Diels−Alder reactions.[12] Some zeolites have been used for DSAC intermolecular Pauson−Khand cyclizations of methylene cyclopropane with alkynes observing, in general, positive effects.[13]

In the Pauson−Khand process, molecular sieves may act to adsorb the enyne and stabilize a pretransition state or they may promote ligand exchange. Thus, compound **1** was submitted to the set of reaction conditions summarized in Table 1. Entries 1−3 showed that toluene was the best of the solvents examined. Other solvents usually used for Pauson−Khand reactions such as MeCN led only to the loss of the propargyl moiety. Comparing entries 8 and 12, we could see that molecular sieves alone are responsible for an increase in the reaction conversion, but best results are obtained by combining the *N*-oxide and the zeolite (entry 10). The isomerization of the double bond may be related to the presence of water in the medium. Thus, the use of powdered activated commercial sieves allows the isolation of compound **3**, a probable intermediate in the isomerization process. Indeed, compound **3** yields the isomerized product **2** after 18 h of stirring at room temperature with traces of acid. The best yield of compound **3** is achieved by carrying out the reaction under completely anhydrous conditions (entry 14).

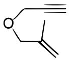
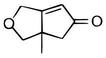
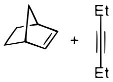
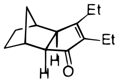
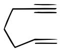
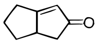
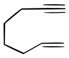
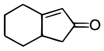
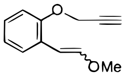
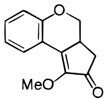
Table 1. Reaction of Compound **1** in Different Conditions

					yield (%)[a]	
no.	solvent	promoter	mol sieves	*T* (°C)	**2**	**3**
1	DCM	TMANO		−10	2	
2	benzene	TMANO		−10	21	
3	toluene	TMANO		−10	40	
4	1,2-DCE	$CyNH_2$ [b]		112	13	
5	toluene	DMSO		112	18	
6	toluene	H_2O		25	0	
7	toluene	H_2O		112	42	
8	toluene			112	13	
9	toluene	TMANO	4 Å,2x[c]	−10	60	
10	toluene	TMANO	4 Å,8x[c]	−10	90	
11	toluene		4 Å,8x[c]	−10	0	
12	toluene		4 Å,8x[c]	112	45	
13	toluene	TMANO	4 Å,8x[d]	−10	25	50
14	toluene	TMANO	4 Å,8x[e]	−10	15	75
15	toluene	TMANO	3 Å,8x[c]	−10	70	
16	toluene	TMANO	5 Å,8x[c]	−10	85	

[a] Of pure material with correct spectroscopic data (^1H, ^{13}C NMR, IR). [b] Cy = cyclohexyl, see ref 5a. [c] Powdered molecular sieves preheated in an oven at 125 °C for 4 h and cooled under argon. Two or eight times the mass of the starting material. [d] Commercial powdered and activated 4 Å molecular sieves (Aldrich, ref 233668). [e] Same as entry 13 but using strictly anhydrous conditions and under argon.

Our best reaction conditions (entry 10)[14] were applied to five substrates, and yields were compared with standard TMANO-promoted reaction conditions, reflux in the presence of molecular sieves, and thermal promotion (Table 2). In all cases, yields improved remarkably when molecular sieves were used.

Table 2. Pauson−Khand Reaction of Different Substrates[a]

No	Starting Material	Product	Yield(%) A	B	C	D
1			85	40	35	5
2	 	 	90	35	70	45
3			60	25	25	10
4			70	40	30	15
5	 	 	45	20	15	<5

[a] Conditions: A, see ref 14. B, standard conditions with TMANO from −10 °C to rt. C, reflux in toluene with eight times the mass of 4 Å molecular sieves. D, reflux in toluene of the alkyne complex.

In conclusion, molecular sieves improve the conversion of the Pauson−Khand reaction. We are currently studying the role of the zeolite in the reaction mechanism.

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(14) **Typical Experimental Procedure**: 1.00 mmol of the enyne **1** was dissolved in dry toluene at room temperature under argon, in a flask containing eight times the mass of the enyne of powdered 4 Å molecular sieves (oven dried for 4 h at 120 °C). To this solution was added 1.10 mmol of $Co_2(CO)_8$, and the resulting mixture was stirred for 2 h until total complexation of the enyne (TLC). The reaction was then cooled to −10 °C with an ice/salt bath, and a suspension of Me_3NO (9.0 mmol) in toluene at 0 °C was added dropwise. After 18 h of stirring and filtration, the solvent was evaporated under vacuum and the crude product purified by flash chromatography (hexanes/EtOAc mixtures).