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Aromatic Enynes as Substrates for the Intramolecular Pauson-Khand Reaction

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Dedicated to Prof. Rafael Pérez A. Ossorio

Abstract: Pauson-Khand reactions are carried out with different substituted aromatic enynes yielding tricyclic cyclopentenones related to natural products. Reaction is promoted by dissolved Me_3NO. Isomerization of the double bond of the cyclopentenone is observed except for compound **2e**, with a non terminal triple bond. © 1999 Elsevier Science Ltd. All rights reserved.

The use of the cocyclization reaction of alkynes, alkenes and carbon monoxide, the Pauson-Khand reaction,[1] is increasing more and more for the synthesis of natural products.[2] The development of this reaction has included many variations in the reaction conditions. Except in favourable cases, low yields are achieved in many intramolecular processes. The use of promoters like *N*-oxides[3] or DMSO,[4] and the dry state absorption conditions (DSAC) on silica gel or other solid supports[5] have improved this problem. Still, the scope of the reaction is relatively low, not with respect to the functional groups compatible but to the carbon skeleton formed. Most studies of the intramolecular Pauson-Khand reaction use systems derived from hept-1-en-6-yne or propargyl allyl ethers or amines. The viability of the reaction is strongly dependent on the substitution pattern and best results are achieved with enynes unsubstituted at both ends, and gem-disubstituted at position 4.[6] Great reduction in yield is observed when introducing substituents in the alkene moiety (except with strained cycles).

Moreover, aromatic rings have not been yet used as part of the skeleton of the enyne in intramolecular Pauson-Khand processes. A great number of natural products, such as metabolites of the shikimate pathway and some systems derived from the acetate pathway, include in their structure policyclic systems with aromatic rings. The Pauson-Khand reaction applied to aromatic enynes derived from salicylaldehyde, would lead, in only three steps, to complex polycycles that can be considered intermediates in the synthesis of many natural products (Figure 1)

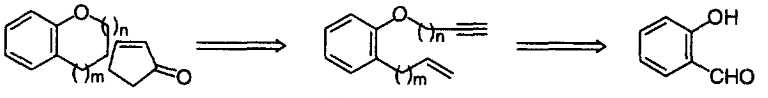

Figure 1

In this paper we report the preliminary results of the Pauson-Khand reaction of enynes derived from salicylaldehyde and other related aldehydes to yield tricyclic cyclopentenones. We have explored the viability of the reaction with substituents introduced in several positions of the aromatic enyne.

Salicylaldehyde was treated with propargyl bromide in the presence of anhydrous potassium carbonate to give quantitatively the corresponding propargylated compound which was reacted with

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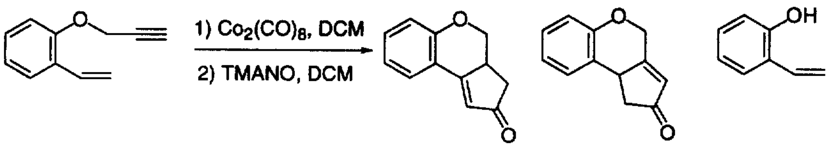
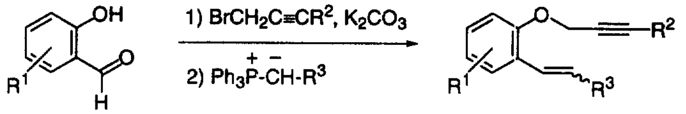
methyltriphenylphosphonium ylide to give enyne **2a** in 46% overall yield. This compound was taken as a model and submitted to the most common conditions used in Pauson-Khand reactions. Early results were disappointing. No reaction was observed in the absence of a promoter or when using DMSO. The reaction on silica gel[7] provided only 6% of the product. The use of cyclohexylamine in 1,2-dichloroethane, as recently reported,[8] was also unsuccessful. We had observed that the starting material was unstable and decomposed after two days at room temperature. When using trimethylamine *N*-oxide as promoter, following standard conditions,[3] a vigorous reaction was observed after addition of the promoter and very low yields were obtained. Thus, we tried slow addition of a DCM solution of the *N*-oxide at 0 °C.[9] We were very pleased to obtain product **3a** in 50% yield. We observed that the double bond of the new cyclopentenone ring had isomerized to conjugate with the aromatic ring, and that no traces of **4a** were present. We also detected a byproduct that proved to be the depropargylated compound **5a** (Scheme 1). This seems to show a relationship between the Pauson-Khand process and a Nicholas type reaction. Related Nicholas-type reactions have been reported in *N*-propargylated-β-lactams.[10]



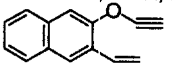
2a **3a** (50%) **4a** **5a**

Scheme 1

A series of aromatic enynes were then prepared by tandem propargylation-olefination of aromatic aldehydes. Yields were good in all cases (Scheme 2). Compounds **2f** and **2g** were obtained as a mixture of Z/E isomers .



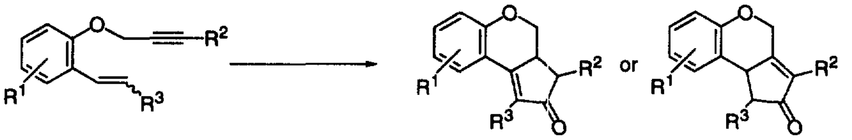
1

2a, R^1= H, R^2=H, R^3= H. 46%
2b, R^1= 4-MeO, R^2=H, R^3= H. 45%
2c, R^1= 5-MeO, R^2=H, R^3= H. 57%
2d,  . 64%
2e, R^1= H, R^2=Me, R^3= H. 60%
2f, R^1= H, R^2=H, R^3= MeO. 44% (Z/E mixture)
2g, R^1= H, R^2=H, R^3= Me. Z/E: 44%/12%

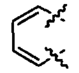
Scheme 2

The Pauson-Khand reaction of compounds **2**, allowed us to obtain the corresponding cyclopentenones **3**, with isomerization of the double bond. Only compound **2e**, led to the Pauson-Khand product **4e** (Table 1).[11] Depropargylation products were detected in some cases and for entries 4 and 6 some hexacarbonyl-alkyne complex was still present after 2 days of reaction. No other significant products were detected. Yields range from moderate to good in all cases except for compound **2g**. Both isomers of this enyne failed to give carbocyclization products. In this case we tried the silica gel procedure and were able to obtain a 10% of the isomerized Pauson-Khand product, **3g**. Due to isomerization of the double bond, both Z and E isomers led to **3g**. Once more, substitution at the alkene seems to reduce the viability of the reaction. Conformational constraints of substrates anchored in silica gel may be responsible for the observed reaction of **2g**, which, in solution is not able to cyclise. On the other hand, compound **2f**, reacts under the general conditions although with moderate yield (20%). The oxygen probably acts in this case as a soft ligand and favors the reaction.[12]

Table 1. Synthesis of tricyclic cyclopentenones 3 and 4.



2 3 4

entry	R^1	R^2	R^3	product	yield (%)[a]	m.p.(°C)
1	H	H	H	**3a**	50%	100-102
2	4-MeO	H	H	**3b**	54%	123-125
3	5-MeO	H	H	**3c**	58%	112-114
4		H	H	**3d**	44%	oil
5	H	Me	H	**4e**	42%	oil
6[b]	H	H	MeO	**3f**	20%	89-91
7[c]	H	H	Me	**3g**	10%	109-111

[a] Of pure material with correct spectroscopic data (^1H, ^{13}C NMR). [b] A mixture of Z/E isomers of **2** were used as starting material. [c] Both Z and E isomers were reacted separately to give **3g**. DSAC method was used.

The isomerization of the double bond that we have observed in most cases deserves some more comment. It may occur in the final stages of the Pauson-Khand reaction or be a separate process in which cobalt salts act as an acid catalyst. Interestingly compound **2e** leads to the usual Pauson-Khand product **4e**, pointing out the possible role of the terminal proton of the alkyne. The stability of this trisubstituted double bond can also explain the absence of isomerization. The commonly accepted mechanism for the Pauson-Khand reaction is based on observations of regio- and stereoselectivities of the many examples described to date. Nevertheless, no intermediates have been isolated except the cobalt hexacarbonyl-alkyne complex, making it difficult to explain this isomerization process. More studies on the scope, limitations and synthetic applications of this reactions are underway currently in our laboratory.

In conclusion, the Pauson-Khand reaction can be applied to aromatic enynes and polycyclic systems are readily obtained in only three steps from commercially available aldehydes with yields going from moderate to good.

Acknowledgments

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