DOI: 10.1002/chem.200500537

$[W(CO)_5]$-Catalyzed *endo*- or *exo*-Cycloisomerization Reactions of 1,1-Disubstituted 4-Pentyn-1-ols: Experimental and Theoretical Studies

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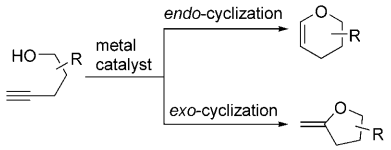
Abstract: The $[W(CO)_5]$-catalyzed cycloisomerization reaction of 1,1-disubstituted 4-pentyn-1-ol derivatives has been studied from both, an experimental and theoretical point of view. Three different catalytic systems have been evaluated {preformed $[(thf)W(CO)_5]$, $[W(CO)_6]$/excess Et_3N, and $[W(CO)_6]$/2 mol% Et_3N]. We have found that the reaction proceeds to give the formal *endo*- or *exo*-cycloisomerization products depending on the amount of Et_3N used and on the substitution along the alkyl chain of the starting alkynol. The theoretical study allowed us to find the mechanisms of the reactions which explain the formation of the formal *endo*- or *exo*-cycloisomerization products.

Keywords: alkynols · density functional calculations · reaction mechanisms · synthetic methods · tungsten

Introduction

Metal-catalyzed cycloisomerization reactions of ω-alkynols (4-pentyn-1-ol derivatives) provide rapid and efficient access to a variety of cyclic compounds for a great range of synthetic applications.[1] In general, these reactions may proceed through two different reaction pathways formally leading to *endo*- or *exo*-cycloisomerization products (Scheme 1). The formation of the *endo*-product proceeds through the formation of a vinylidene intermediate which further evolves to the formation of the final products.[1b,2] This catalytic *endo*-process has been achieved by the use of ruthenium,[3] rhodium,[4] and tungsten complexes.[5] Formation of the *exo*-product implies a simple 5-*exo* addition of the oxygen to the alkyne. Several metal complexes (mercury,[6] silver,[7] palladium,[8] and alkyllithium compounds[9]) have been reported to catalyze this transformation. Also, it has been observed that those ruthenium and tungsten complexes which catalyzed the *endo*-cycloisomerization reaction may, under some reaction conditions, or depending on the structure of the starting material, direct the reaction to the formation of the *exo*-product.[3,5a,c,i]



Scheme 1. *endo*- or *exo*-cyclization products from the cycloisomerization reaction of ω-alkynols.

Recently, as part of a program directed to the synthesis of eight-membered carbocycles from Fischer carbene complexes,[10] we became interested in the $[W(CO)_5]$-catalyzed cycloisomerization reaction of 4-pentyn-1-ols.[11] In order to get some insight into the mechanism of this reaction, we have also carried out a theoretical study about the $[W(CO)_5]$-promoted cycloisomerization reactions of 4-pentyn-1-ol.[12] Thus, we have found new mechanisms for both the *endo*- and *exo*-pathways and we have shown that although the *endo*-route is more favorable, the difference between the rate-determining barriers for both mechanisms is only 1.1 kcal mol^{-1}. In a wider investigation on this cata-

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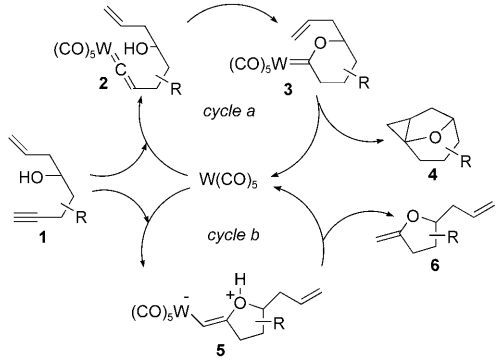
lytic reaction we have found new interesting results related to the high dependence of the reaction on the catalytic system used and the structure of the starting 4-pentyn-1-ol derivative. These findings together with new theoretical studies about the mechanisms of the reactions are reported in deep within this paper.

Results and Discussion

Conceptual background and preliminary studies: Our approach to a catalytic synthesis of eight-membered carbocycles was guided by the perception that tricyclic compounds **4**, which are known to be precursors of eight-membered carbocycles,[10] could be easily available from alkynols **1**.[11] Thus, we argued that these alkynol derivatives **1**, which contain an allyl moiety in their structure, could react with pentacarbonyltungsten complex species, through a cycloisomerization reaction, to give the vinylidene intermediate **2**, which further could evolve to the cyclic carbene complex **3**. A subsequent intramolecular cyclopropanation reaction of complexes **3** should give the tricyclic compounds **4**. This cyclopropanation reaction should regenerate the pentacarbonyltungsten species and so, a catalytic process could be feasible (Scheme 2, cycle a). However, we were aware about the possibility of a competitive 5-*exo-dig* mechanism (Scheme 2, cycle b). As shown, this mechanism implies that after an initial coordination of the pentacarbonyltungsten to the alkyne, the hydroxy group adds to the internal position of the triple bond to give a zwitterionic intermediate **5** which, after migration of the hydrogen atom and elimination of the metal fragment, produces the final furan derivative **6** regenerating the pentacarbonyltungsten species.



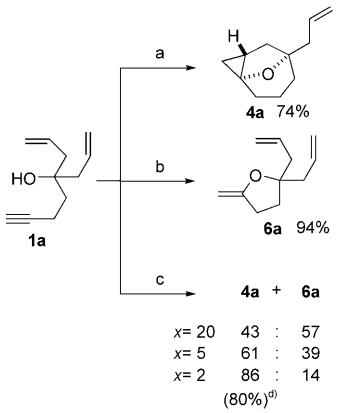
Scheme 2. Proposed catalytic cycles for the cycloisomerization reaction of ω-alkynols.

Abstract in Spanish: *La reacción de cicloisomerización de derivados 1,1-disustituidos del 4-pentin-1-ol catalizada por [W(CO)$_5$] ha sido estudiada tanto desde el punto de vista experimental como desde el teórico. Se han evaluado tres sistemas catalíticos {[(thf)W(CO)$_5$] preformado, [W(CO)$_6$]/exceso de Et$_3$N, y [W(CO)$_6$]/2 mol% Et$_3$N}. Se ha observado que la reacción da lugar al producto formal de cicloisomerizacion* endo *o al* exo *dependiendo de la cantidad de amina usada y de la sustitución en la cadena carbonada del alquinol inicial. El estudio teórico que hemos realizado nos ha permitido encontrar los mecanismos que explican la formación de los productos formales de cicloisomerización* endo *o* exo.

In our preliminary experiments we used the model compound **1a** and we evaluated different reaction conditions (Scheme 3). Thus, we observed that the treatment of this compound **1a** with 25 mol% preformed [(thf)W(CO)$_5$] in THF at room temperature for 24 h led to the formation of the tricyclic compound **4a** in 74% yield. Although this result was a significant achievement, a minor drawback of the method is the fact that the catalyst [(thf)W(CO)$_5$] should be generated in a separated vessel, irradiating a THF solution of [W(CO)$_6$], and then added to the solution of the alkynol **1a**. Experimentally easier are those conditions developed by McDonald and co-workers which suppose the in situ generation of the catalytic [W(CO)$_5$] species by continuous irradiation of a THF solution of the alkynol in the presence of a catalytic amount of [W(CO)$_6$] (5 mol%) and an excess (200 mol%) of an amine (Et$_3$N or DABCO).[5i] Surprisingly, when we carried out the reaction of **1a** under these catalytic conditions, we did not observe the formation of the expected tricyclic compound **4a**; instead, we observed the exclusive formation of the furan derivative **6a** (94% yield). At this point it seemed clear that the presence of an amine in the reaction media was playing an important role directing the reaction to the formation of the tricyclic compound **4a** or the furan derivative **6a**.[13] In fact, we observed different **4a**/**6a** ratios depending on the amount of triethylamine used. Thus, as shown in Scheme 3, treatment of alkynol **1a** with 5 mol% [W(CO)$_6$] and 20 mol% triethylamine under constant irradiation at 350 nm led to the formation of a 43:57 mixture of **4a** and **6a** as determined by ^{1}H NMR analysis of the crude of the reaction. When the amount of triethylamine was reduced to 5 mol%, the ratio **4a**/**6a** increased to 61:39. Finally, by the use of only 2 mol% triethylamine, the ratio was increased to 86:14, allowing the isolation of tricyclic compound **4a** in a pleasant 80% yield. Lower amounts of triethylamine led to the formation of appreciable quantities of decomposition products.

These preliminary studies let us to identify three different catalytic systems: i) first, the catalyst [(thf)W(CO)$_5$] which leads to the formation of tricyclic compound **4a** (method A); ii) the second catalytic system consists in the use of 5 mol% [W(CO)$_6$] and 2 mol% Et$_3$N under constant irradiation (method B). Also, under these conditions the reaction mainly leads to the formation of tricyclic compound **4a**; iii) finally, by the use of 5 mol% [W(CO)$_6$] and an excess of amine (200 mol%), the reaction leads to the exclusive formation of furan derivative **6a** (method C).

Scope of the reaction: In order to check the generality of the catalytic reactions above referred we performed a set of experiments starting from different 1,1-disubstituted alky-

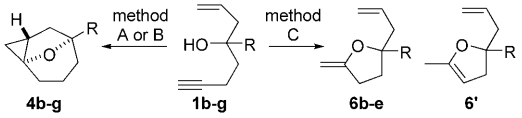


Scheme 3. Different reaction conditions for the cycloisomerization reaction of the alkynol derivative **1a**. a) 25 mol% [(thf)W(CO)$_5$], THF, RT; b) 5 mol% [W(CO)$_6$], 200 mol% Et$_3$N, THF, 50°C, *hv*; c) 5 mol% [W(CO)$_6$], *x* mol% Et$_3$N, THF, 50°C, *hv*. d) Isolated yield of **4a** when $x = 2$.

nols **1b–g** containing an allyl moiety (Table 1). In general, by the use of 25 mol% preformed [(thf)W(CO)$_5$] (method A) or 10 mol% [W(CO)$_6$] and 2 mol% Et$_3$N under constant irradiation (method B), we were able to isolate the tricyclic compounds **4b–g** in very high yield (entries 1–12). On the other hand, reaction of the allyl substituted alkynols **1c,e–g** with 10 mol% [W(CO)$_6$] and excess of Et$_3$N under constant irradiation (method C) led to the formation of furan derivatives **6b–e** (entries 13–16).

Influence of the substitution in the aliphatic chain: In an attempt to further extend the catalytic reactions above described to other 1,1-disubstituted 4-pentyn-1-ols, we attempted the reactions with alkynols **1h–r**. Note that these alkynols are also substituted at C$_2$ position (Table 2). In an initial experiment we treated alkynol **1h** with 10 mol% [W(CO)$_6$], excess of Et$_3$N and constant irradiation (method C), and as expected, the reaction led to the furan derivatives **6f**. Surprisingly, when we treated the same alkynol **1h** with 10 mol% preformed [(thf)W(CO)$_5$] under standard conditions (method A) or by the using of 10 mol% [W(CO)$_6$], 2 mol% Et$_3$N, and constant irradiation (method B), the reaction also produced the furan derivative **6f** and the expected tricyclic compound analogous to **4**, was not observed (Table 2, entry 1). The same behavior was observed for other C$_2$-substituted alkynols such as **1i–r** (Table 2). Thus, the corresponding furan derivatives **6** were isolated in very high yield independently on the catalytic system used. In some cases, the final product was isolated as the corresponding isomerized furan derivative **6′**.

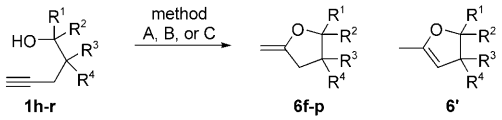
Table 1. Cycloisomerization reactions of the alkynol derivatives **1b–g**.



Entry	Alkynol	R	Method[a]	Product	Yield [%][b]
1	**1b**	Me	A	**4b**	69
2	**1b**	Me	B	**4b**	70
3	**1c**	Bu	A	**4c**	85
4	**1c**	Bu	B	**4c**	87
5	**1d**	*c*-C$_3$H$_5$	A	**4d**	60
6	**1d**	*c*-C$_3$H$_5$	B	**4d**	61
7	**1e**	Ph	A	**4e**	82
8	**1e**	Ph	B	**4e**	83
9	**1f**	4-MeOC$_6$H$_4$	A	**4f**	84
10	**1f**	4-MeOC$_6$H$_4$	B	**4f**	84
11	**1g**	(*E*)-PhCH=CH	A	**4g**	80
12	**1g**	(*E*)-PhCH=CH	B	**4g**	82
13	**1c**	Bu	C	**6b + 6′b**	93
14	**1e**	Ph	C	**6c**	97
15	**1f**	4-MeOC$_6$H$_4$	C	**6d**	94
16	**1g**	(*E*)-PhCH=CH	C	**6e**	96

[a] Method A: 25 mol% preformed [(thf)W(CO)$_5$], THF, RT; method B: 10 mol% [W(CO)$_6$], 2 mol% Et$_3$N, THF, 50°C, *hv* (350 nm); method C: 10 mol% [W(CO)$_6$], 200 mol% Et$_3$N, THF, 50°C, *hv* (350 nm). [b] Isolated yield based on starting alkynol **1**.

Table 2. Cycloisomerization reactions of the C$_2$-substituted alkynol derivatives **1h–r**.

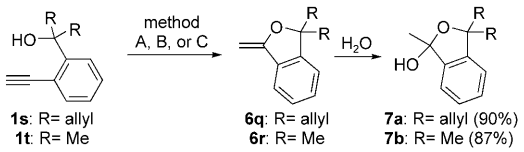


Alkynol	R^1	R^2	R^3	R^4	Product	Yield [%][a]
1h	allyl	allyl	Me	Me	**6f**	97
1i	allyl	allyl	Ph	H	**6g**	94
1j	allyl	allyl	-(CH$_2$)$_5$-		**6′h**	98
1k	Me	Me	Me	Me	**6i**	93
1l	allyl	-(CH$_2$)$_5$-		H	**6′j**	95
1m	allyl	-(CH$_2$)$_4$-		H	**6k**	96
1n	allyl	-(CH$_2$)$_3$-		H	**6′l**	93
1o	vinyl	-(CH$_2$)$_5$-		H	**6′m**	96
1p	vinyl	-(CH$_2$)$_4$-		H	**6n**	96
1q	Me	-(CH$_2$)$_5$-		H	**6′o**	95
1r	Me	-(CH$_2$)$_4$-		H	**6p**	93

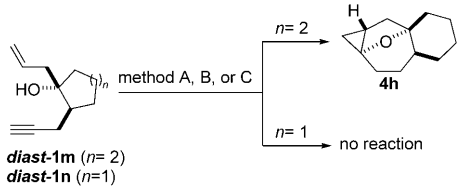
[a] Isolated yield based on starting alkynol **1**. The yield refers to reaction performed following method C. However, similar yields (always >90%) were obtained following methods A or B. Method A: 25 mol% preformed [(thf)W(CO)$_5$], THF, RT; method B: 10 mol% [W(CO)$_6$], 2 mol% Et$_3$N, THF, 50°C, *hv* (350 nm); method C: 10 mol% [W(CO)$_6$], 200 mol% Et$_3$N, THF, 50°C, *hv* (350 nm).

In a similar way, *o*-ethynylbenzyl alcohols **1s**, **t** were transformed into the corresponding isobenzofuran derivatives **6q**, **r** independently on the catalytic conditions used (Scheme 4). These products are easily hydrolyzed and they have been characterized as the corresponding hemiacetal **7a**, **b**.

Some interesting disparities were observed when we performed the catalytic reactions starting from alkynols ***diast*-1m** and ***diast*-1n** (Scheme 5). Thus, the reaction of ***diast*-1m** with both catalytic systems {[(thf)W(CO)$_5$] or [W(CO)$_6$]/Et$_3$N} led to the tricyclic compound **4h**. The furan derivative analogous to **6** which was expected by the use of [W(CO)$_6$]/excess Et$_3$N was not observed. On the other hand, alkynol ***diast*-1n** did not react in any of the catalytic reaction condi-



Scheme 4. Cycloisomerization reactions of the *o*-ethynylbenzyl alcohols **1s**, **t**. Method A: 25 mol% preformed [(thf)$W(CO)_5$], THF, RT; method B: 10 mol% [$W(CO)_6$], 2 mol% Et_3N, THF, 50 °C, *hν*; method C: 10 mol% [$W(CO)_6$], 200 mol% Et_3N, THF, 50 °C, *hν*.



Scheme 5. Cycloisomerization reactions of alkynols ***diast*-1m** and ***diast*-1n**. Method A: 25 mol% preformed [(thf)$W(CO)_5$], THF, RT; method B: 10 mol% [$W(CO)_6$], 2 mol% Et_3N, THF, 50 °C, *hν*; method C: 10 mol% [$W(CO)_6$], 200 mol% Et_3N, THF, 50 °C, *hν*.

tions attempted and starting material was recovered in all attempts.

Mechanisms and theoretical studies: Experimental results previously reported elsewhere[1c,5c] as well as some of the experimental findings presented above show clearly that the *endo*/*exo* ratio for the cycloisomerization of ω-alkynols is very sensitive to the substituents on the carbon backbone. It is also evident from the experimental observations reported above that the amine plays an important role in the mechanism of the process.[13]

Trying to get a deeper understanding of the mechanism of these reactions that helped us rationalize the experimental results we undertook a theoretical investigation of the mechanisms of the [$W(CO)_5$]-promoted *endo*- and *exo*-cycloisomerizations of 1,1-disubstituted 4-pentyn-1-ols in THF using 2-methyl-5-hexyn-2-ol as a model. We studied both a THF-assisted mechanism, analogous to that recently proposed[12] for the cycloisomerization of the C_1-unsubstituted 4-pentyn-1-ol, and a Me_3N-assisted mechanism trying to understand the role played by an amine molecule in this process. We also investigated the influence on the process of a double substitution at C_2 position.

Full geometry optimizations were performed with the B3LYP density functional method, by using the relativistic effective core pseudopotential LANL2DZ for tungsten and the 6-31G* basis set for the remaining atoms. To take into account condensed-phase effects we used a PCM-UAHF model with a relative permittivity of 7.58 to simulate THF as the solvent used in the experimental work (for details see Experimental Section and Supporting Information).

We will discuss in the text the evolution of the relative Gibbs energy in solution along the above mentioned mechanisms.

THF-Assisted mechanism: To investigate this mechanism we employed, as in our previous theoretical study,[12] a mixed model in which one THF molecule is coordinated to the hydroxyl hydrogen atom while bulk solvent effects are evaluated by the PCM-UAHF method.

The critical structures located along the THF assisted *exo*-cycloisomerization of 2-methyl-5-hexyn-2-ol are similar to those previously obtained for 4-pentyn-1-ol.[12] This is a two-step process in which the rate-determining step is the second one (see Figure 1). Initially the alkyne–[$W(CO)_5$] complex, **M1**, evolves into the cyclic intermediate $\mathbf{M2}_{exo}$ (5.4 kcal mol^{-1}) after surmounting an energy barrier of 13.9 kcal mol^{-1} corresponding to the transition state (TS) $\mathbf{TS12}_{exo}$. $\mathbf{M2}_{exo}$ yields the corresponding enol ether $\mathbf{P}_{exo}$ (−33.4 kcal mol^{-1}) through the TS $\mathbf{TS2P}_{exo}$ (18.7 kcal mol^{-1}) for the migration of the hydrogen atom from the oxygen to the C_α atom.

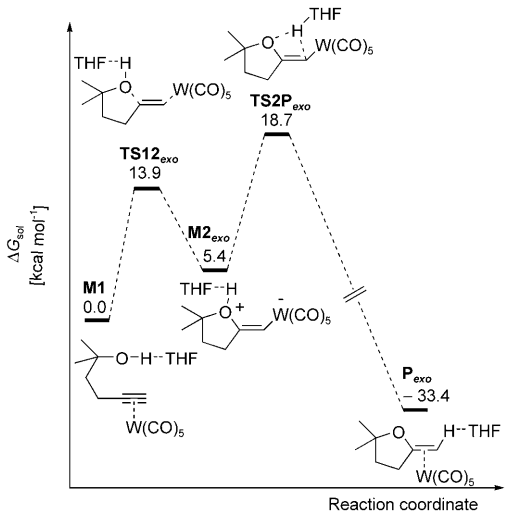


Figure 1. Gibbs energy profile in solution for the THF assisted *exo*-cycloisomerization of 2-methyl-5-hexyn-2-ol. For a more detailed drawing of all structures, see Supporting Information.

The critical structures along the *endo*-cycloisomerization of 2-methyl-5-hexyn-2-ol also resemble those previously reported for 4-pentyn-1-ol.[12] The process follows a three-stage mechanism (see Figure 2) in which the first and the third TSs display similar energy barriers. **M1** transforms into the vinylidene complex $\mathbf{M2}_{endo}$ (2.2 kcal mol^{-1}) after surmounting a barrier of 17.6 kcal mol^{-1} corresponding to $\mathbf{TS12}_{endo}$, and in turn $\mathbf{M2}_{endo}$ evolves into the cyclic structure $\mathbf{M3}_{endo}$ (1.4 kcal mol^{-1}) through the TS $\mathbf{TS23}_{endo}$ (5.4 kcal mol^{-1}). Finally $\mathbf{M3}_{endo}$ yields the carbene complex $\mathbf{P}_{endo}$ (−24.0 kcal mol^{-1}) through the TS $\mathbf{TS3P}_{endo}$ (17.5 kcal mol^{-1}) for the H transfer from the oxygen atom to the C_β atom.

By comparing the above results with those previously reported for 4-pentyn-1-ol[12] we see that the two methyl groups at C_1 position favor both processes kinetically by practically 1 kcal mol^{-1}. Therefore, as in the case of 4-pentyn-1-ol, the present theoretical results for 2-methyl-5-

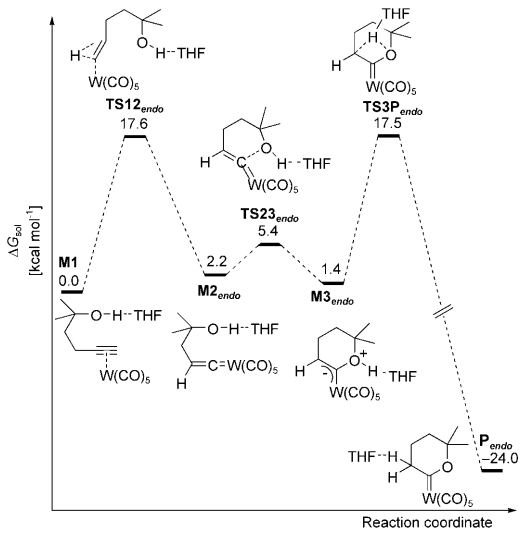


Figure 2. Gibbs energy profile in solution for the THF assisted *endo*-cycloisomerization of 2-methyl-5-hexyn-2-ol. For a more detailed drawing of all structures, see Supporting Information.

hexyn-2-ol render the *endo*-route more favorable than the *exo* one by only 1.2 kcal mol^{-1} and, consequently, the cyclic carbene complex $\mathbf{P}_{endo}$ as the major product in agreement with experiment.

Effect of two methyl substituents at C_2 position: To study the effect of two methyl substituents at C_2 position on the nature of the product obtained in the THF-assisted cycloisomerization of tertiary 1-alkyn-5-ols we investigated the structure and corresponding energy barrier of the rate-determining TSs for the *endo*- and *exo*-cycloisomerizations of 2,3,3-trimethyl-5-hexyn-2-ol (see Figure S3 of the Supporting Information and Table 3).

Table 3. Relative electronic energies and relative Gibbs energies in THF solution [kcal mol^{-1}] corresponding to the rate-determining TSs for the THF-assisted *endo*- and *exo*-cycloisomerization of 2,3,3-trimethyl-5-hexyn-2-ol.

Structures	ΔE_{elec}	ΔG_{sol}
endo-pathway		
M1′	0.0	0.0
TS12′$_{endo}$	17.1	13.6
TS3P′$_{endo}$	15.7	16.2
exo-pathway		
M1′	0.0	0.0
TS2P′$_{exo}$	14.2	14.0

The presence of two methyl substituents at C_2 position provokes a diminution of the C_1-C_2-C_3 angle with respect to the unsubstituted system all along the reaction coordinate.[14] This distortion due to steric repulsions is larger in the initial complex **M1′** thus explaining the decrease of all the energy barriers theoretically obtained for the rate-determining TSs for both mechanisms (see Table 3). For the *exo*-cycloisomerization the rate-determining TS is **TS2P′**$_{exo}$ (14.0 kcal mol^{-1}) which presents a geometrical structure quite similar to that of **TS2P**$_{exo}$. For the *endo*-cycloisomerization the rate-determining energy barrier (16.2 kcal mol^{-1}) corresponds to **TS3P′**$_{endo}$ for the migration of the H atom from the oxygen atom to the C_β atom. The geometrical structure of this TS shows clearly that the trajectory of the migrating H atom is appreciably modified by one of the methyl substituents at C_2 position (see Supporting Information and compare the geometrical structures of **TS3P**$_{endo}$ and **TS3P′**$_{endo}$) giving rise to an *endo* route less favorable than the *exo* one by 2.2 kcal mol^{-1}. Therefore, these theoretical results rationalize the experimental findings as the products obtained in the cycloisomerization of C_2-substituted alkynols are the *exo* ones (see Table 2).[15]

Me_3N-Assisted mechanism: To take into account the effect of an amine in the [W(CO)$_5$]-catalyzed cycloisomerization of tertiary 4-pentyn-1-ols we included a Me_3N molecule coordinated to the hydroxyl hydrogen atom of 2-methyl-5-hexyn-2-ol instead of a THF molecule.

Along the Me_3N-assisted *exo*-route (see Figure 3) the alkyne–[W(CO)$_5$] complex, **M1″**, evolves through the TS **TS12″**$_{exo}$ (16.0 kcal mol^{-1}) to form the cyclic intermediate

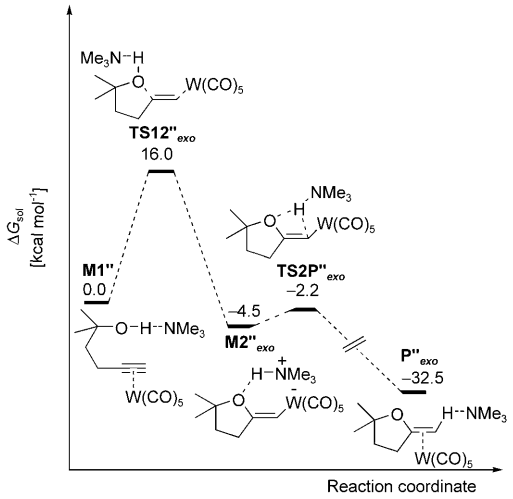


Figure 3. Gibbs energy profile in solution for the Me_3N assisted *exo*-cycloisomerization of 2-methyl-5-hexyn-2-ol. For a more detailed drawing of all structures, see Supporting Information.

M2″$_{exo}$ (−4.5 kcal mol^{-1}). It is interesting to note that this cyclization takes place simultaneously with the transfer of the hydroxyl hydrogen atom to the amine in contrast with the THF assisted mechanism. **M2″**$_{exo}$ yields the final *exo*-product **P″**$_{exo}$ through the TS **TS2P″**$_{exo}$ (−2.2 kcal mol^{-1}). Therefore, the rate-determining step is now the first one which corresponds to the intramolecular cyclization of the alkyne moiety.

The *endo*-cycloisomerization (see Figure 4) proceeds through **TS12″**$_{endo}$ (17.3 kcal mol^{-1}) to yield the vinylidene intermediate **M2″**$_{endo}$ (1.8 kcal mol^{-1}), which transforms into the cyclic structure **M3″**$_{endo}$ (−3.8 kcal mol^{-1}) through

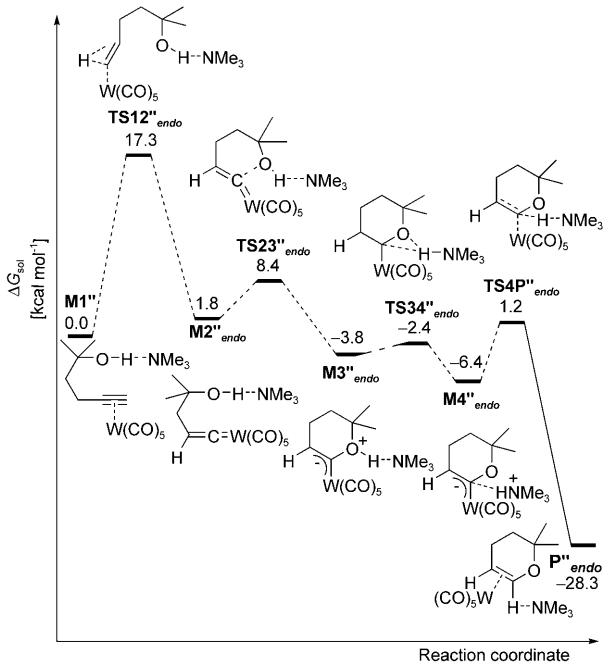


Figure 4. Gibbs energy profile in solution for the Me_3N assisted *endo*-cycloisomerization of 2-methyl-5-hexyn-2-ol. For a more detailed drawing of all structures, see Supporting Information.

TS23$''_{endo}$ (8.4 kcal mol^{-1}). As in the *exo*-mechanism, this cyclization takes place with the concerted transfer of the hydroxyl hydrogen atom to the amine. **M3**$''_{endo}$ evolves to the intermediate **M4**$''_{endo}$ (−6.4 kcal mol^{-1}) through the TS **TS34**$''_{endo}$ (−2.4 kcal mol^{-1}) for the shift of the H-NMe_3 moiety close to the C_α atom. The final enol ether, **P**$''_{endo}$ (−28.3 kcal mol^{-1}), is obtained from **M4**$''_{endo}$ by the transfer of the hydrogen atom of the H-NMe_3 moiety to the C_α atom through the TS **TS4P**$''_{endo}$ (1.2 kcal mol^{-1}). Thus the rate-determining step is the first one corresponding to the alkyne–vinylidene rearrangement.

It is interesting to note that in contrast with the THF assisted mechanisms both in **M2**$''_{exo}$ and **M3**$''_{endo}$ the hydroxyl hydrogen atom is completely transferred to the amine thus facilitating its migration. Therefore, an important effect of the assistance by the amine molecule consists in considerably stabilizing the last part of the energy profiles thus reducing the implied energy barriers so that the rate-determining step for both processes is the first one. Also the presence of the Me_3N molecule modifies the *endo*-mechanism so that the system does not evolves through the carbene complex anymore the final product being the enol ether **P**$''_{endo}$.

According to the present theoretical results the Me_3N-assisted *exo*-mechanism is now favored over the *endo* one by 1.3 kcal mol^{-1} and, consequently, the major product predicted is the enol ether **P**$''_{exo}$ in agreement with experiment.

Conclusion

We have studied in deep the [$W(CO)_5$]-catalyzed cycloisomerization of 1,1-disubstituted 4-pentyn-1-ol derivatives from both the experimental and theoretical point of view. Experimentally, we observed that the reaction is highly dependent on the amount of amine used in the catalytic system. Thus, by the use of an excess of amine, the reaction proceeds through an *exo*-cyclization reaction furnishing furan derivatives. On the other hand, when only 2 mol% amine is used, the reaction proceeds through a formal *endo*-cyclization reaction. Following this later catalytic strategy we were able to easily access to tricyclic derivatives which are precursors of eight-membered carbocycles. Moreover, the substitution along the alkyl chain of the alkynol may also play a fundamental role on the reaction pathway. Specifically, we observed that *exo*-products are exclusively formed when the starting alkynol is substituted at the C_2 position.

Theoretically, we have found the *endo*- and *exo*-mechanisms of the reactions in the absence and in the presence of amine and also we have studied the effect of the substitution at C_2 position. All the theoretical results are in agreement with the experiments and clearly show that the rate determining barriers found for both the *endo*- and *exo*-mechanisms are energetically close thus explaining that small changes in the reaction conditions or the structure of the starting alkynol may affect the distribution of the products.

Although the compounds obtained following the catalytic reactions here described are of undoubted interest from a synthetic point of view, probably the most interesting aspect of the present study is that it provides an important advance in the understanding of the mechanisms of the [$W(CO)_5$]-catalyzed reactions. This will help to predict, in many cases, the result of a proposed reaction and/or to choose the right conditions to obtain the desired product.

Experimental Section

General methods: ^{1}H NMR spectra were recorded on a Bruker AMX-400 (400 MHz) or Bruker DPX-300 (300 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the residual solvent resonance as the internal standard ($CHCl_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s: singlet, d: doublet, dd: double doublet, td: triplet of doublets, t: triplet, q: quartet, br: broad, m: multiplet), coupling constants (J in Hz), integration and assignment. ^{13}C NMR spectra were recorded on a Bruker AMX-400 (100 MHz) or Bruker DPX-300 (75 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$: δ 76.95). Two-dimensional NMR experiments (COSY, HMQC, HMBC and NOESY) were recorded on a Bruker AMX-400 (400 MHz). High-resolution mass spectrometry was carried out on a Finnigan-Mat 95 spectrometer. All reactions were conducted in flame-dried glassware under an inert atmosphere of argon. Tetrahydrofuran was distilled from sodium/benzophenone and triethylamine was distilled from calcium hydride and stored under nitrogen. Photochemical reactions were performed with a medium-pressure mercury lamp (350 nm, 400 W) using a Pyrex reactor.

General procedure for the domino tungsten-catalyzed cycloisomerization–cyclopropanation of ω-alkynols 1

Method A: The corresponding ω-alkynol **1** (1 mmol) was added to a THF solution of $[W(CO)_5]$·THF complex (10 mL, 0.025 M), previously prepared according to the literature procedure.[1] The solution was concentrated under vacuum to approx. 2 mL volume and carefully degassed following a standard freeze-pump-thaw method (three cycles). The resulting mixture was stirred at room temperature, in the absence of light, during one or two days until complete conversion (monitored by TLC). After removing of the solvent, the crude was purified by flash column chromatography on silica gel or activated aluminum oxide neutral (compound **2h**). Hexane/ethyl acetate or pentane/diethyl ether were used as eluents.

Method B: $[W(CO)_6]$ (36 mg, 0.1 mmol), ω-alkynol (1 mmol), dry triethylamine (2.8 μL, 0.02 mmol), and freshly distilled THF (2 mL), were placed in a sealed tube (Pyrex) under argon. The resulting slurry was carefully degassed following a standard freeze-pump-thaw (three cycles). The mixture was placed under an inert atmosphere of argon and irradiated with a medium-pressure mercury lamp (350 nm, 400 W) during 12 h without refrigeration. Solvent was removed and residue was worked up as described in method A.

General procedure for the tungsten-catalyzed 5-*exo*-cycloisomerization of ω-alkynols 1

Method C: $[W(CO)_6]$ (36 mg, 0.1 mmol), ω-alkynol (1 mmol), dry triethylamine (0.18 mL, 2 mmol), and freshly distilled THF (2 mL), were placed in a sealed tube (Pyrex) under argon. The resulting slurry was carefully degassed following a standard freeze-pump-thaw (three cycles). The mixture was placed under an inert atmosphere of argon and irradiated with a medium-pressure mercury lamp (350 nm, 400 W) during 12 h without refrigeration. Solvents were removed and residue was filtered over a short plug of dry Celite with hexane and the resulting solution was concentrated in vacuo. The crude product was usually chromatographically pure. α-Methylene enol ethers thus obtained were very sensitive to moisture and, in general, purification by flash-chromatography in silica gel or alumina affords the corresponding hemiacetal or hydrolysis derivative.

Acknowledgements

This research was supported by the DGICYT of Spain (BQU-2001-3853 and PB97-1271) and Principado de Asturias (PR-01-GE-9). A.D. acknowledges predoctoral grants from FICYT of Principado de Asturias and Universidad de Oviedo. F.R. is grateful to MEC of Spain ("Ramón y Cajal" contract). Generous financial support from Merck Sharp & Dohme and computer facilities from CIEMAT are acknowledged.

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Received: May 13, 2005
Published online: July 20, 2005

