Medium-Ring Compounds

Tandem [W(CO)$_5$]-Catalyzed Cycloisomerization–Cyclopropanation Reactions Directed toward the Synthesis of Eight-Membered Carbocycles**

José Barluenga, Alejandro Diéguez, Félix Rodríguez, and Francisco J. Fañanás*

Dedicated to Professor José Elguero
on the occasion of his 70th birthday

The development of new metal-catalyzed reactions for the formation of carbon–carbon bonds is a major research area in organic chemistry.[1] Of particular significance are those tandem processes which allow the formation of several new bonds in a single step from readily available starting materials, thus increasing efficiency and minimizing the amount of waste generated.[2] The potential of Group 6 Fischer carbene complexes to undergo unusual reactions has been widely demonstrated since their discovery almost 40 years ago.[3] However, one of the most important drawbacks of these complexes is that a stoichiometric amount has to be used. Only very few examples of catalytic processes in which a Group 6 Fischer carbene complex is implied have been reported.[4,5] Moreover, for several years we have pursued a program related to the development of new methodologies for the synthesis of medium-sized rings promoted by Fischer carbene complexes.[6] Thus, recently we reported a new one-pot process for the synthesis of eight-membered carbocycles by the use of ketone enolates and alkenyl carbene complexes.[7] To avoid the use of stoichiometric amounts of metallic species and to extend the scope of this method, we initiated an investigation directed toward the design of a catalytic version of this process. These studies culminated with the discovery of a tandem [W(CO)$_5$]-catalyzed cycloisomerization–cyclopropanation reaction, which has been used as the key step for the synthesis of eight-membered carbocycles.

In our previous studies in this field we demonstrated that eight-membered rings **1** were readily available from tricyclic compounds **2** generated from cyclic Fischer carbene complexes **3** (Scheme 1).[7] We envisaged that these complexes **3** could be obtained through a cycloisomerization reaction of 4-alkyn-1-ol derivatives **4** promoted by pentacarbonyltungsten

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[*] Prof. Dr. J. Barluenga, A. Diéguez, Dr. F. Rodríguez, Dr. F. J. Fañanás
Instituto Universitario de Química Organometálica "Enrique Moles"
Unidad Asociada al C.S.I.C.
Universidad de Oviedo
Julián Clavería, 8, 33006 Oviedo (Spain)
Fax: (+34) 98-5103-450
E-mail: barluenga@uniovi.es

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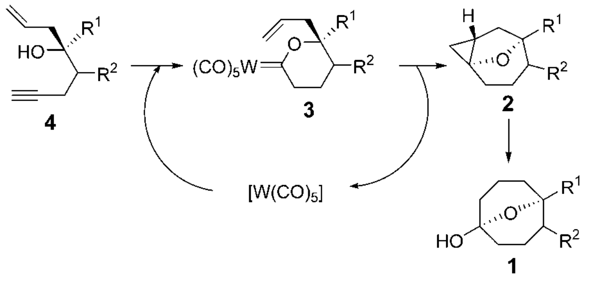
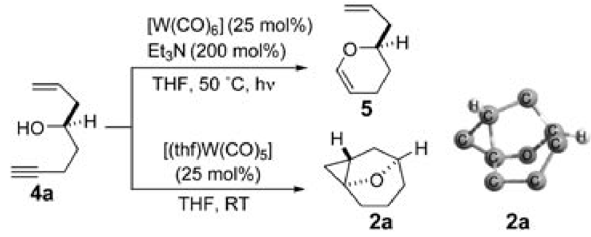


Scheme 1. Proposed catalytic cycle for the synthesis of tricyclic compounds **2**, and further transformation into eight-membered carbocycles **1**.

complexes.[8] The subsequent cyclopropanation reaction of complexes **3** should generate the tricyclic compounds **2**, with regeneration of the pentacarbonyltungsten species. Thus, a catalytic process as shown in Scheme 1 could be feasible.

Our initial attempts to promote the tandem sequence described above employed the method developed by McDonald et al. for the synthesis of cyclic enol ethers from 4-alkyn-1-ol derivatives.[4c] The established conditions for this cycloisomerization are treatment with triethylamine or 1,4-diazabicyclo[2.2.2]octane (dabco, 200 mol %) in the presence of [W(CO)$_6$] (5–25 mol %) under constant irradiation, with THF as the solvent.

Unfortunately, when we employed this method with the starting alkynol derivative **4a**, the reaction did not lead to the expected tricyclic compound **2a**; instead the cyclic enol ether **5** was obtained exclusively (Scheme 2). This result indicates that the carbene complex **3a** (R^1 = R^2 = H) formed does not undergo cyclopropanation of the double bond of the allylic moiety, but instead reacts with the triethylamine present in the reaction medium to give the enol ether **5**. It was clear at this point that an alternative method to generate the catalytic [W(CO)$_5$] species in the absence of an amine was required. We next turned our attention to the use of preformed [(thf)W(CO)$_5$]. To our delight, when we treated the alkynol derivative **4a** with [(thf)W(CO)$_5$] (25 mol %) in THF at room temperature for 24 h, the tricyclic compound **2a** was obtained in 90 % yield (Scheme 2; for clarity, a 3D representation of compound **2a** has been included).[9]



Scheme 2. Different reaction conditions for the cycloisomerization reaction of the alkynol derivative **4a**.

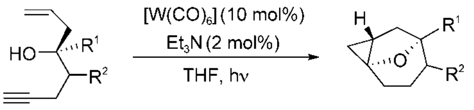
To check the scope of the reaction, a number of allyl-substituted 4-alkynol derivatives **4** were tested. As summarized in Table 1 (method A), the reaction gave the expected tricyclic compounds **2** in very high yield starting from both secondary and tertiary alcohol derivatives **4**. The reaction is completely diastereoselective, and a single diastereoisomer of the product was observed in all cases.[9] It should be noted that the alternative diastereoisomer would be significantly more strained. The enantiopure tricyclic compound **2j** was isolated when the reaction was performed with the alkynol derivative **4j**.

Table 1: Tricyclic compounds **2** from the catalytic cycloisomerization reaction of alkynol derivatives **4**.

4	R^1	R^2	2	Method A[a] Yield [%][c]	Method B[b] Yield [%][c]
4a[d]	H	H	**2a**	90	–
4b[d]	Me	H	**2b**	69	70
4c[d]	Bu	H	**2c**	85	87
4d[d]	allyl	H	**2d**	74	80[e]
4e[d]	*c*-C_3H_5	H	**2e**	60	61
4f[d]	Ph	H	**2f**	82	83
4g[d]	4-MeOC_6H_4	H	**2g**	84	84
4h[d]	(*E*)-PhCH=CH	H	**2h**	80	82
4i[f]	–(CH$_2$)$_4$–		**2i**	88	86
4j[g]	H	OBn	**2j**[h]	91	–

[a] The alkynol **4** was stirred as a solution in THF with preformed [(thf)W(CO)$_5$] (25 mol %) at room temperature for 24 h. [b] A solution of the alkynol **4** in THF was irradiated with [W(CO)$_6$] (10 mol %) and Et$_3$N (2 mol %) for 12 h. [c] Yield of the isolated product based on the starting alkynol **4**. [d] Racemic mixture. [e] In this case the amount of [W(CO)$_6$] can be decreased to 5 mol % without any observed decrease in the yield of the reaction. [f] The racemic 1*S**,2*S** diastereoisomer was used. [g] The 4*S*,5*S* enantiomer was used. [h] The 1*R*,3*S*,5*S*,6*S* enantiomer was obtained; $[\alpha]_D^{20} = -26.7$ ($c = 0.45$, CH_2Cl_2).

A minor drawback of this method for the catalytic synthesis of tricyclic compounds **2** is the fact that the catalyst has to be generated in a separate vessel by irradiation of a solution of [W(CO)$_6$] in THF and then added to the solution of the corresponding alkynol derivative. However, the conditions described by McDonald et al.[4c] for the in situ generation of [W(CO)$_5$] species were shown not to be applicable to our substrates as a result of the amine-promoted formation of enol ethers analogous to **5** (see Scheme 1). We reasoned that we could find appropriate catalytic conditions if we were able to lower the amount of amine used to such an extent that the amine could only act to stabilize the [W(CO)$_5$] species. With this idea in mind, we carried out a set of experiments with different [W(CO)$_6$]/triethylamine ratios under a variety of reaction conditions. We were delighted to find that constant irradiation at 350 nm of a solution of the corresponding alkynol **4** in THF in the presence of 10 mol % of [W(CO)$_6$] and only 2 mol % of triethylamine gave similar results to those obtained when preformed [(thf)W(CO)$_5$] was used (Scheme 3 and Table 1, method B). As before, the

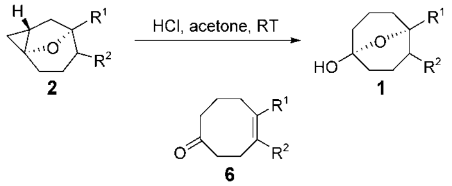


Scheme 3. Cycloisomerization reactions of alkynols **4** with catalytic amounts of [W(CO)$_6$] and Et$_3$N to give compounds **2**.

reaction led to a single diastereoisomer of the products in all cases studied.[9]

To illustrate the synthetic utility of the tungsten-catalyzed process described, we further transformed the tricyclic compounds **2** into eight-membered carbocycles **1** following the protocol developed previously by our research group.[7] Thus, the treatment of compounds **2** with hydrochloric acid in acetone at room temperature yielded the corresponding eight-membered carbocycles **1** (Table 2).[9] Under the same reaction conditions, dehydrated compounds **6** were obtained when the R^1 group of the starting compound **2** was an electron-rich aryl group (i.e. **2g**) or an alkenyl group (i.e. **2h**). Interestingly, compounds with structures analogous to that of **1h** (R^1 = H, R^2 = OBn, 1*R*,4*S*,5*S* enantiomer) have shown remarkable activity as herbicides. The methodology described herein provides straightforward access to such compounds.[10]

Table 2: Eight-membered carbocycles **1** or **6** from tricyclic compounds **2**.



2	R^1	R^2	Product	Yield [%][a]
2a	H	H	**1a**	98
2b	Me	H	**1b**	97
2c	Bu	H	**1c**	97
2d	allyl	H	**1d**	95
2e	c-C_3H_5	H	**1e**	98
2f	Ph	H	**1f**	98
2g	4-$MeOC_6H_4$	H	**6a**	95
2h	(E)-PhCH=CH	H	**6b**	97
2i	$(CH_2)_4$		**1g**	96
2j	H	OBn	**1h**[b]	97

[a] Yield of the isolated product based on the starting cyclic ether **2**. [b] The 1*R*,4*S*,5*S* enantiomer was obtained; $[\alpha]_D^{20} = -13.0$ ($c = 1.15$, CH_2Cl_2).

In summary, we have developed an effective and general method for the synthesis of eight-membered carbocycles based on a new tandem tungsten-catalyzed cycloisomerization–cyclopropanation reaction. This process is one of very few examples of a catalytic reaction in which a heteroatom-stabilized Fischer carbene complex is implied. The method described herein opens the door to the development of new catalytic methods which avoid the use of large quantities of metallic species, thus overcoming one of the main limitations of Fischer carbene complexes. Moreover, as the procedure has been shown to be applicable to the synthesis of functionalized and biologically active compounds from very simple starting materials, it is expected to find wide application in organic synthesis.

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