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Microwave-Accelerated Multi-Component Cascade Reactions Involving Fischer Alkoxy Alkynyl Carbene Complexes

*Alexandra Pérez-Anes, Patricia García-García, Manuel A. Fernández-Rodríguez, and Enrique Aguilar**

Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al CSIC, Universidad de Oviedo, Julián Clavería 8, 33006, Oviedo (Spain)

E-mail: EAH@uniovi.es

Abstract

The sequential [2+2]/[2+1] and [2+2+1]/[2+1] multicomponent reactions that occur thermally when treating alkoxy alkynyl Fischer carbene complexes with 2,3-dihydrofuran or norbornene may be accelerated by MW irradiation. They lead to the same adducts in similar yields and diastereoselectivities and, therefore, MW irradiation does not cause a different chemical behaviour but just an accelerating effect.

Introduction

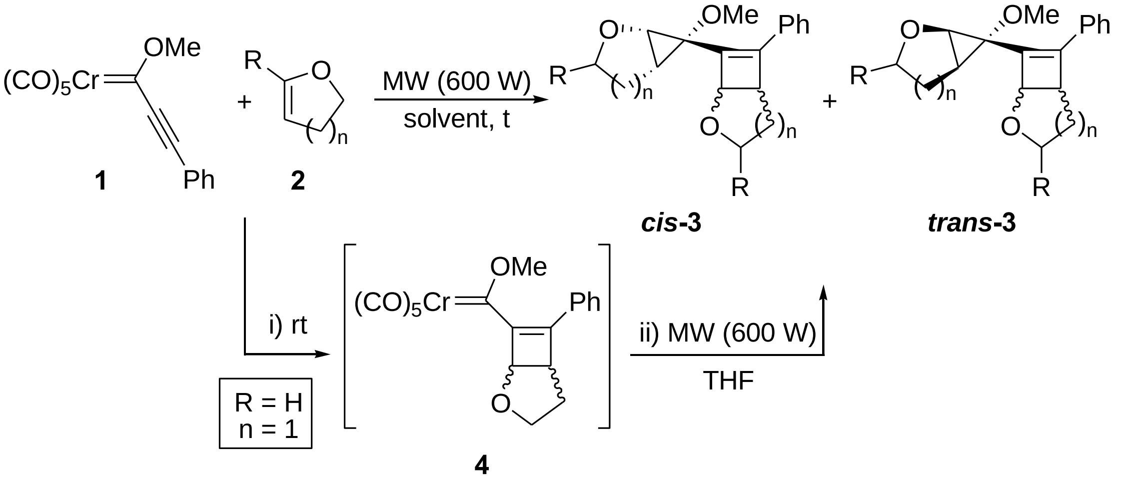
Multi-component reactions (MCRs) have recently emerged as complementary and powerful alternatives to more traditional strategies for the synthesis of complex chemical structures, with relevant applications in both combinatorial chemistry and diversity-oriented synthesis, mainly by means of their operational simplicity and high atom economy.[1] Particularly, group VI metal heteroatom stabilized Fischer carbene complexes (FCCs)[2] have been conferred with a prominent role in this arena, due both to their versatility as well as to their ability to partake in MCRs.[3] On the other hand, since the first application of microwave (MW) irradiation to Organic Synthesis, such technique has shown overwhelming ability to facilitate organic reactions mainly by accelerating them, enhancing their chemical yields, increasing the purity of the product and, occasionally, leading to change the diastereoselection of the process.[4] Moreover, it currently constitutes a cornerstone of the so-called green chemistry due to the excellent results achieved in solvent-free reactions or when solid-supported reagents are used.[5] Recently, we have reported that the cyclopropanation of several types of alkenes by different kinds of FCCs may be accelerated by MW irradiation[6,7] provided that the analogous thermal reaction occurs. While exploring the reactivity of alkoxy alkynyl FCCs towards different types of activated olefins we have found that, when heated conveniently, they react: (1) with an electron-rich alkene such as 2,3-dihydrofuran by a sequential [2+2]/[2+1] MCR and the formation of three σ C–C bonds;[8] (2) with strained bicyclic olefins by a [2+2+1]/[2+1] MCR, which involves the incorporation in the final adducts of four components and the formation of five new σ C–C bonds.[9] In both reactions, two new rings are created and, more importantly, the last step of the processes involves the cyclopropanation of an alkene unit. Taking into account our previous results under MW irradiation,[6] we decided to test if such technique would either modify the course of the processes (leading, for instance to the direct cyclopropanation of the olefin) or either accelerate it.

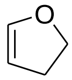
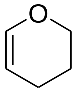
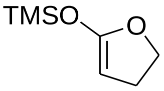
Results and discussion

First, we studied the influence of the microwave irradiation in the [2+2]/[2+1] MCR. The microwave power on the domestic MW-oven was calibrated using previously reported procedures[10] and a set of reactions was performed with chromium carbene complex **1** and 2,3-dihydrofuran **2a** using sealed tubes,[11] to find that the best reaction conditions were 600W power, and a 0.05 M carbene concentration.

Under the optimized conditions, MW irradiation of the reaction mixture led to the formation of the [2+2]/[2+1] adduct ***cis*-3a** (R = H, n = 1) with similar diastereoselectivity and slightly higher yield to those obtained in the thermal reaction,[8] but in just two minutes.[12] THF was the solvent that provided such result (entry 1), while other solvents tested such as toluene or 1,4-dioxane were less efficient (entries 2, 3). The reaction did not take place with other olefins such as 2,3-dihydropyran **2b** (entry 4), or 2,3-dihydro-5-trimethylsilyloxyfuran **2c** (entry 5), which did not partake in the thermal reaction either.[8] The MW promoted [2+1] reaction also occurred with cyclobutenyl carbene complex **4** with slightly higher yield than the thermal reaction (entry 6).

Table. MW-accelerated formation of adducts **3**



Entry	FCC	2	solvent	t (min)	Yield (%)[a]	Yield [Thermal reaction (%)][8]
1	**1**	 **2a**	THF	2	60 (2:3 / 63:32)	52 (2:3 / 65:30)
2	**1**	**2a**	toluene	3	9 (6:4 / 58:32)	24 (9:6 / 53:32)
3	**1**	**2a**	dioxane	17	23[b]	
4	**1**	 **2b**	THF	16	-	-
5	**1**	 **2c**	THF	10	-	-
6	**4**	**2a**	THF	3	55[b]	45 (2:1 / 65:32)

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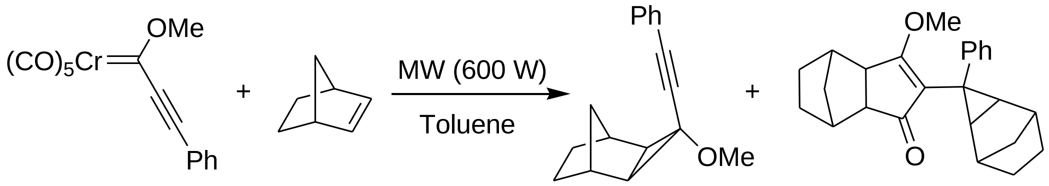
[a] Yields of isolated ***cis*-3** [as a mixture of diastereomers (maj:min)] after flash chromatography, based on starting FCC **1**; in brackets, diastereomeric ratio observed by ^{1}H-NMR (300 MHz) from the crude reaction mixture; diastereomers are listed form low field to high field. [b] dr not determined.

Tungsten FCC analogue of **1** was also tested under the optimized conditions for the MW sequence, but it required longer reaction times (> 6 minutes) and adduct **cis-3a** only could be isolated in 1% yield.

We turned then to examine the MW-promoted reaction of **1** versus a special reactive strained bicyclic olefin. Thus, the reaction of carbene complex **1** with norbornene **5** under thermal conditions (110 ºC, 30 minutes) afforded [2+2+1]/[2+1] bicyclic adduct **7** as mayor product in moderate yield and as a mixture of diastereomers 3:1. Cyclopropane **6** was also isolated in small quantity and with equal diastereoselection.[9a] Similar results in both isolated yields and diastereoselectivities were reached under MW irraditation in just 3 minutes, with the only difference of a slight increase in the relative amount of the cyclopropane derivative **6** (Scheme 1). Moreover, the configuration of the major isomer of adducts **6** and **7**, determined by X-Ray and/or NMR-bidimensional experiments, was the same one observed in the thermal reaction.



1 **5** **6** (d.r. = 3:1) **7** (d.r. = 3:1)

6% 47%

Analogous thermal reaction (ref. 9a) = 12% 43 %

Scheme 1. MW-accelerated [2+2+1]/[2+1] MCR sequence

The feasibility of the MW-accelerated [2+2+1]/[2+1] multicomponent process was also tested with tungsten FCC analogue of **1**. However, only polymerization of the bicyclic olefin and decomposition of the tungsten complex was observed, as we previously reported for the thermal reaction.

In conclusion, alkoxy alkynyl FCCs are suitable substrates to partake in MW-promoted multi-component cascade reactions. The [2+2]/[2+1] sequences were found to give similar yields and diastereoselectivities as the conventional thermally promoted reactions. On the other hand, [2+2+1]/[2+1] processes were also microwave-accelerated affording the same cycloadducts in similar combined yield although in slightly different product ratio.

General experimental procedures

Microwave accelerated [2+2]/[2+1] reaction between 2,3-dihydrofuran 2a and alkynyl FCC 1. Synthesis of adducts *cis*-3: A solution of FCC **1** (0.5 mmol, 168 mg) and 2,3-dihydrofuran **2a** (10 mmol, 20 equiv) in dry THF (10 ml) under an inert atmosphere in a sealed tube is placed in a domestic MW oven at 600 W until the starting carbene complex was completely consumed (2-17 min) as indicated by a color change in the reaction vessel and further confirmed by TLC analysis. The solvents were then removed under vacuum and the residue was re-dissolved in a mixture of hexane/ethyl acetate and exposed to light in an open-air vessel to induce decomplexation of the metal species present. The resulting suspension was filtered through Celite, and the solvents were removed under vacuum. A ^{1}H-NMR was measured from the crude residue to determine the reaction diastereoselectivities, as indicated in the Table. The residue was purified by flash column chromatography, employing mixtures of hexane/EtOAc (20:1 to 5:1) as eluents, to give cyclopropanes ***cis*-3** in the yields reported in the Table.

Microwave accelerated tandem [2+2+1]/[2+1] cycloaddition reaction between norbornene 5 and alkynyl FCC 1. A solution of FCC **1** (0.5 mmol, 168 mg) and norbornene **5** (10 equiv., 5 mmol, 470 mg) in dry toluene (5 mL) under an inert atmosphere in a sealed tube is placed in a domestic MW oven at 600 W until the carbene complex **1** was completely consumed (3 min) as indicated by a colour change in the reaction vessel and further confirmed by TLC analysis. Silica gel (0.5 g) was added and solvents were evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel using hexane/AcOEt (20/1 to 3/1) mixtures as sequential eluents. Cycloadducts **6** and **7** were isolated in the yields reported in Scheme 1.

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