

Unprecedented Reactivity Pattern of Chromium Fischer Carbene Complexes. Direct Application to One-Pot Synthesis of 4-Aryl-3,4-dihydrocoumarins on a Multigram Scale

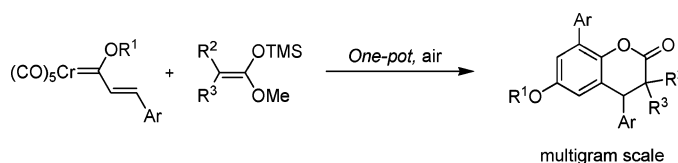
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ABSTRACT



Reaction of alkenyl carbene chromium(0) complexes and ketene acetals triggers the formation of 4-aryl-3,4-dihydrocoumarins. The reaction can be carried out as a simple one-pot protocol in air atmosphere. The huge interest of dihydrocoumarins has prompted us to optimize a multigram-scale process.

Traditional Chinese and Japanese medicines have used tannin-containing plant extracts for the treatment of infections and diseases for centuries.¹ Tannins and other natural products, such as flavonoids, present the skeleton of 4-aryldihydrocoumarins in their structure.² The important biological activities that dihydrocoumarin derivatives present (inhibition of aldose reductase^{2b} and protein kinases,^{2c} antihyperthermic activity,³ and selective inhibition of HIV replication⁴) make them attractive candidates for new lead compounds in biological testing. The preparation of dihydro-

coumarins (DHCs) has been accomplished in different ways,⁵ but the most common approaches are based on hydroarylation processes.⁶

On the other hand, the versatility and efficiency of Fischer carbene complexes (FCCs)⁷ has been widely demonstrated

(1) (a) Yoshida, T.; Ohbayashi, G.; Ishihara, K.; Ohwashi, W.; Haba, K.; Okano, Y.; Shingu, T.; Okuda, T. *Chem. Pharm. Bull.* **1991**, *39*, 2233. (b) Okuda, T.; Hatano, T.; Yakazi, K. *Chem. Pharm. Bull.* **1983**, *31*, 333. (c) Saijio, R.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1989**, *37*, 2063. For more information about natural coumarins, see: Murray, R. D. H.; Medez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; Wiley: New York, 1982.

(2) (a) Iinuma, M.; Tanaka, T.; Asai, F. *Phytochemistry* **1994**, *36*, 941. (b) Iinuma, M.; Tanaka, T.; Mizuno, M.; Katsuzaki, T.; Ogawa, H. *Chem. Pharm. Bull.* **1989**, *37*, 1813. (c) Hsu, F.-L.; Nonaka, G.-I.; Nishioka, I. *Chem. Pharm. Bull.* **1985**, *33*, 3142. (d) Nonaka, G.-I.; Kawahara, O.; Nishioka, I. *Chem. Pharm. Bull.* **1982**, *30*, 4277.

(3) Takechi, M.; Tanaka, Y.; Takehara, M.; Nonaka, G.-I.; Nishioka, I. *Phytochemistry* **1985**, *24*, 2245.

(4) Tillekeratne, L. M. V.; Sherette, A.; Grossman, P.; Hupe, L.; Hupe, D.; Hudson, R. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2763.

(5) (a) Donnelly, D. M. X.; Boland, G. In *The Flavonoids. Advances in Research since 1986*; Hardborne, J. B., Ed.; Chapman & Hall: London, 1993. (b) Wagner, H.; Seligmann, O.; Chari, M. V.; Wollenweber, E.; Dietz, V. H.; Donnelly, D. M. X.; Meegan, M. J.; O'Donnell, B. *Tetrahedron Lett.* **1979**, *20*, 4269. (c) Iinuma, M.; Matsura, S.; Asai, F. *Heterocycles* **1983**, *20*, 1923. (d) Krishnamoorthy, T. V.; Rajagopalan, K.; Balasubramanian, K. K. *Tetrahedron Lett.* **1994**, *26*, 1747. (e) Stephan, E.; Rocher, R.; Aubouet, J.; Pourcelot, G.; Cresson, P. *Tetrahedron: Asymmetry* **1994**, *5*, 41. (f) Asai, F.; Iinuma, M.; Tanka, T.; Mizuno, M. *Chem. Pharm. Bull.* **1990**, *38*, 1079. (g) Wilkinson, J. A.; Rossington, S. B.; Leonard, J.; Hussain, N. *Tetrahedron Lett.* **2004**, *45*, 5481.

(6) (a) Aresta, M.; Armor, J. N.; Barteau, M. A.; Bechman, E. J.; Bell, A. T.; Bercaw, J. E.; Creutz, C.; Dinjus, E.; Dixon, D. A.; Domen, K.; Dubois, D. L.; Eckert, J.; Fujita, E.; Gibson, D. H.; Goddard, W. A.; Manzaer, L. E.; Marks, T. J.; Morokuma, K.; Nicholas, K. M.; Periana, R.; Que, L.; Rostrup-Nielsen, J.; Sachtler, W. M. H.; Schmidt, L. D.; Sen, A.; Somorjai, G. A.; Stair, P. C.; Stults, B. R.; Tumas, W. *Chem. Rev.* **2001**, *101*, 953. (b) Li, K.; Foresee, L. N.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 2881. (c) Aoki, S.; Amamoto, C.; Oyamada, J.; Kitamura, T. *Tetrahedron* **2005**, *61*, 9291.

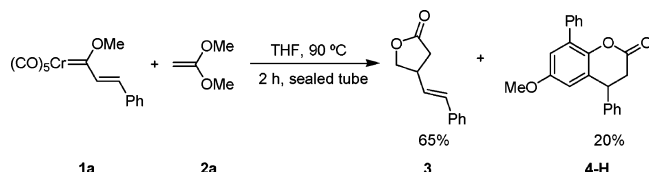
during the past 2 decades. Significant examples of their rich and varied chemistry are their participation in the key step of the synthesis of several natural products,⁸ their ability to form differently sized complex carbo-⁹ and heterocycles¹⁰ from nonelaborated starting materials, and their participation in multicomponent and cascade reactions.¹¹

The reaction of ketene acetals with alkynyl Fischer carbene complexes is a well-known process and generally leads to [2 + 2] cycloadducts.¹² Moreover, as reported by Wulff,¹³ aryl- and alkyl-substituted FCCs react with ketene acetals to furnish butyrolactones.

However, the reaction of ketene acetals with alkenyl FCCs has not been previously studied. Taking into account the behavior of alkenyl FCCs as “chemical multitalents”,¹⁴ we decided to investigate this reaction, in the expectation that it might follow a novel reaction pathway.

First, we tested the reaction of chromium carbene complex **1a** with the nonsubstituted ketene acetal **2a** (Scheme 1). The

Scheme 1. First Attempt: Reaction of Alkenylcarbene Complex **1a** with a Nonsubstituted Ketene Acetal



reaction afforded a mixture of lactone **3**, the analogue of that obtained in the reactions with aryl and alkyl lactones, in 65% yield, and a minor compound, which was identified by NMR experiments as DHC **4-H**, in 20% yield.

In agreement with the mechanistic proposal reported by Wulff for the reaction of aryl- and alkyl-substituted FCCs,¹³ the formation of **3** might be initiated by a 1,2-attack of **2a** to the carbene complex. It has been previously observed that the 1,2-addition of nucleophiles to alkenyl Fischer carbene

complexes is greatly diminished by steric hindrance. Therefore, to inhibit this reaction pathway we decided to use substituted ketene acetals. After screening several reaction conditions, we found that the reaction of FCC **1** with 3 equiv of the corresponding ketene acetal in THF at 90 °C furnished the 4-aryl-3,4-dihydrocoumarins **4** in good yields (Table 1).

Table 1. Synthesis of 4-Aryl-3,4-dihydrocoumarins

entry	R ¹	R ²	R ³	Ar ^c	4 (%) ^a
a	Me	Me	Me	Ph	71
b	Me	Me	Me	2-Fu	68
c	Me	Me	Me	2-Tf	64 ^b
d	Me	—(CH ₂) ₅ —	Me	Ph	56
e	(CH ₂) ₂ I	Me	Me	2-Tf	53

^a Isolated yield based on the starting carbene complex considering two carbene units in the final product. ^b Structure confirmed by X-ray analysis (see Supporting Information). ^c 2-Fu = fur-2-yl, 2-Tf = thiophen-2-yl.

Moreover, by using an appropriate ketene acetal we were able to obtain the spirodihydrocoumarin **4d** (Table 1, entry d).

During the course of the investigation we observed that the presence of humidity in the reaction media triggered the formation of esters **5** instead of the desired DHCs **4** (Table 2). Several reaction conditions were tested to find a simple and convenient protocol. The performance of the reaction in air and with wet THF provided esters **5** as unique reaction

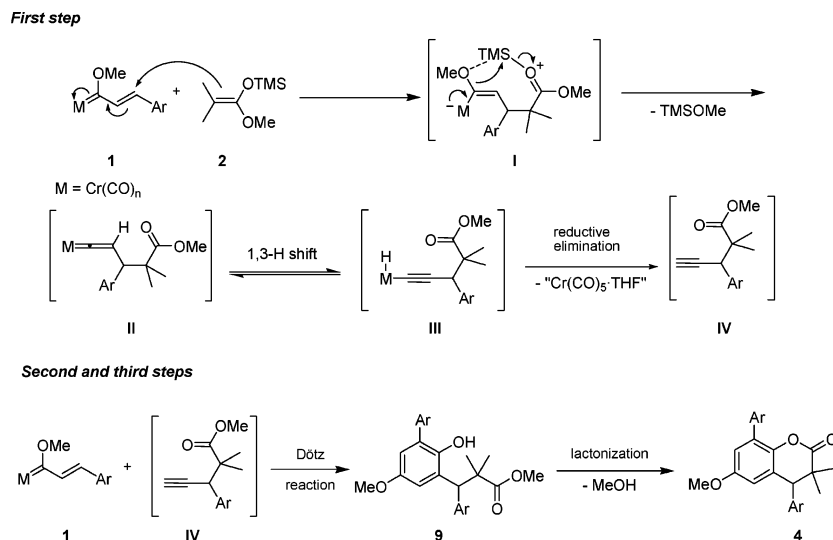
Table 2. Synthesis of 4-Aryl-3,4-dihydrocoumarins in Air

entry	R ¹	R ²	R ³	Ar ^b	5 (%) ^a	4 (%) ^a (via b)	4 (%) ^a (via a)
a	Me	Me	Me	Ph	69	55	70
b	Me	Me	Me	2-Fu	63	48	65
c	Me	Me	Me	2-Tf	63	50	62
d	Me	—(CH ₂) ₅ —	Me	Ph	57	41	41
e	(CH ₂) ₂ I	Me	Me	2-Tf	54	42	50

^a Isolated yield based on the starting carbene complex considering two carbene units in the final product. ^b 2-Fu = fur-2-yl, 2-Tf = thiophen-2-yl.

- (7) Fischer, E. O.; Maasböl, A. *Angew. Chem.* **1964**, 76, 645.
 (8) Recent examples: (a) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. Fernández-Marí, F.; Salinas, A.; Olano, B. *Chem. Eur. J.* **2001**, 7, 3533. (b) Minatti, A.; Döt, K. H. *J. Org. Chem.* **2005**, 70, 3745. (c) Gupta, A.; Sen, S.; Harmata, M. *J. Org. Chem.* **2005**, 70, 7422.
 (9) For some representative examples, see: (a) Barluenga, J.; Diéguez, A.; Rodríguez, F.; Florez, J.; Fañanás, F. *J. Am. Chem. Soc.* **2002**, 124, 9056. (b) Barluenga, J.; López, S.; Trabanco, A. A.; Fernández-Aceves, A.; Florez, J. *J. Am. Chem. Soc.* **2000**, 122, 8145. (c) Barluenga, J.; Aznar, F.; Palomero, M. A. *Angew. Chem., Int. Ed.* **2000**, 39, 4346. (d) Barluenga, J.; Alonso, J.; Rodríguez, F.; Fañanás, F. *J. Angew. Chem., Int. Ed.* **2000**, 39, 2460. (e) Barluenga, J.; Aznar, F.; Valdés, C.; Martín, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, 115, 4403. (f) Barluenga, J.; Aznar, F.; Martín, A.; Vázquez, J. T. *J. Am. Chem. Soc.* **1995**, 117, 9419.
 (10) Barluenga, J.; Santamaría, J.; Tomás, M. *Chem. Rev.* **2004**, 104, 2259.
 (11) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *J. Organomet. Chem.* **2005**, 690, 539.
 (12) (a) Camps, F.; Miravittles, C.; Moretó, J. M.; Molins, E.; Viñas, J. M. Ricart, S. *Chem. Commun.* **1989**, 1560 (b) Camps, F.; Llebraría, A. Moretó, J. M.; Ricart, S.; Viñas, J. M. *Tetrahedron Lett.* **1990**, 31, 2479.
 (13) Wang, S. L. B.; Su, J.; Wulff, W. D. *J. Am. Chem. Soc.* **1992**, 114, 10665.
 (14) (a) De Meijere, A. *Pure Appl. Chem.* **1996**, 68, 61. (b) De Meijere, A.; Schirmer, H.; Duestsch, M. *Angew. Chem., Int. Ed.* **2000**, 39, 3964. (c) Wu, Y.-T.; De Meijere, A. *Top. Organomet. Chem.* **2004**, 13, 21.

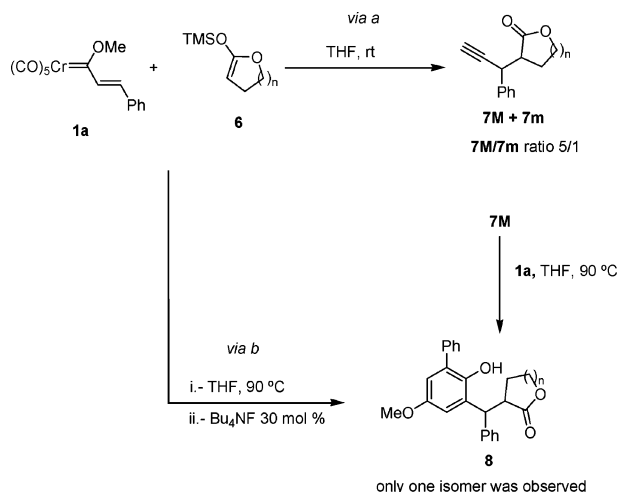
Scheme 2. Mechanistic Proposal



products. Furthermore, subsequent treatment with sub-stoichiometric amounts of Bu_4NF (30 mol %) furnished the DHCs **4** (*via b* in the scheme of Table 2). In this case yields are lower than the ones in Table 1 but an alternative one-pot protocol can be used to increase them (*via a* in the scheme of Table 2).

When this one-pot protocol was applied to ketene acetals derived from five- and six-membered lactones (**6a** and **6b**), a unique isomer of phenols **8** were obtained (Table 3). Several reaction conditions were tested in an attempt to obtain the corresponding DHCs from the phenols **8**, but none of them was successful.

Table 3. Reaction with Ketene Acetals Derived from Lactones



entry	<i>n</i>	7M (%) ^a	8 (%) ^a (<i>via a</i>)	8 (%) ^a (<i>via b</i>)
a	1	53	31	71
b	2	42	27	65

^a Isolated yield based on the starting carbene complex considering two carbene units in the final product.

Interestingly, when the FCC **1a** was stirred at room temperature in the presence of 3 equiv of ketene acetals **6**, a mixture of alkynes **7M** (major isomer) and **7m** (minor isomer) were obtained in a 5:1 ratio. The major isomer, **7M**, was isolated with moderated yields (*via a*). Moreover, reaction of the alkyne **7M** with an additional load of carbene **1a** provided lactones **8**.

These observations clearly suggested that alkynes **7** might be intermediates in the formation of esters **5** and dihydrocoumarins **4** and allowed us to delineate the mechanistic proposal represented in Scheme 2.

The first step would be a Michael-type addition of the ketene acetal **2** to the FCC **1**, to give the intermediate **I**, which would evolve to form the vinylidenechromium(0) complex **II**. This process could be aided by an interaction between the methoxy and the trimethylsilyl groups and would finally release the methyl trimethylsilyl ether. A 1,3-H shift on vinylidene complex **II** would generate the metal hydride **III**. Subsequent reductive elimination would lead to alkyne **IV**, which is the intermediate **7** that was isolated when ketene acetals derived from lactones were used (Table 3).

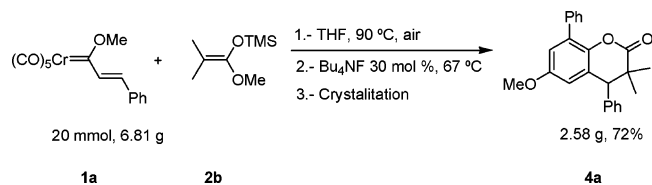
It is worth noting that the formation of vinylidene complexes of group VI metals from alkynes is a well-established process in organometallic chemistry,¹⁵ but the inverse reaction, to the best of our knowledge, has no precedent. Although some examples with other metals are known,¹⁶ this is the first time that formation of alkynes from vinylidenechromium(0) complexes has been observed.

The second and third steps of our mechanistic proposal are well-established reactions. Alkynes **IV** react with another FCC moiety to generate phenols **9** in a classical Dötz

(15) For a review, see: Weyershausen, B.; Dötz, K. H. *Eur. J. Inorg. Chem.* **1999**, 1057.

(16) (a) Akita, M.; Sugimoto, S.; Takabuchi, A.; Tanaka, M.; Morooka, Y. *Organometallics* **1993**, *12*, 2925. (b) Slugovc, C.; Sapunov, V. N.; Wiede, P.; Mereiter, K.; Schmid, R.; Kirchner, K. *J. Chem. Soc., Dalton Trans.* **1999**, 4209.

Scheme 3. Synthesis of Dihydrocoumarins on a Multigram Scale



reaction. Finally, when the lactonization is possible, it occurs to give rise to the corresponding dihydrocoumarins.

Given the simplicity of the experimental protocol for the formation of the dihydrocoumarins, we decided to optimize the process for a multigram scale. Thus, FCC **1a** (20 mmol) was treated with 2.4 equiv of the commercial ketene acetal **2b** in refluxing THF during 5 h. Then Bu_4NF was added and heated for an additional 1 h. After crystallization, 2.58 g (72% yield) of the dihydrocoumarin **4a** was obtained.

In summary, Fischer alkenyl carbenes react in a unknown manner with ketene acetals to generate alkynes (isolated in some cases). From a synthetic point of view, we have optimized a simple and efficient protocol to obtain 4-aryl-3,4-dihydrocoumarins in only one step and from unelaborated materials. A modification of this protocol could be used to obtain the same DHCs in a multigram scale and under an atmosphere of air.

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Supporting Information Available: Experimental procedures and characterization data of products, including a file in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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