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Synthesis of Isochromene Esters Utilizing 1,6-Addition of Nucleophiles to Benzopyranylidenetungsten(0) Complexes

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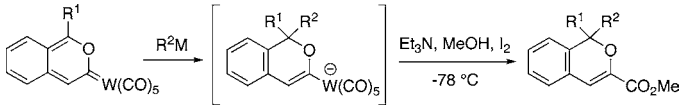
ABSTRACT

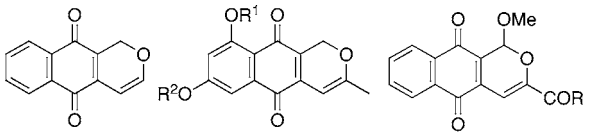


A concise method for the preparation of isochromene carboxylates has been developed by the regioselective 1,6-addition of various nucleophiles such as Grignard reagents, alkoxide, and cyanide onto benzopyranylidenetungsten(0) complexes, followed by iodine oxidation of the addition intermediates.

Isochromene derivatives such as naphtho[2,3-*c*]pyran-5,10-diones **1**−**3** are an important class of compounds due to their broad range of biological activity.[1−3] In particular, synthetic C(3)-carbonylated pyranonaphthoquinones **3** such as BCH-2051 **3b** were found to be very effective antitumor chemotherapeutics (Scheme 1).[4] In fact, several methods have recently been developed for preparation of the 1,3-disubstituted cyclic alkenyl moiety of such compounds.[5]

We recently reported the novel synthesis of pentacarbonylbenzopyranylidenetungsten(0) complexes **6** via the dienone electrocyclization of vinylidene intermediates **5** generated by treatment of *o*-ethynylphenyl ketones **4** with $W(CO)_5$(thf) (Scheme 2).[2] Furthermore, these complexes **6** were found to undergo inverse-electron-demand Diels−Alder reaction with electron-rich alkenes to give the corresponding naphthalene derivatives in good yields.[6a] As it had become clear that benzopyranylidenetungsten(0) complexes **6** possessed high electrophilicity, we decided to examine the reaction of these complexes with various nucleophilic organometallic reagents. In this paper is described a concise method for the preparation of isochromene ester derivatives utilizing a facile 1,6-addition reaction of various nucleophiles

Scheme 1



1 (pentalongin)

2a R^1 = Me R^2 = Me
2b R^1 = H R^2 = Me
2c R^1 = H R^2 = H

3a R = OMe
3b R = $NH(CH_2)_3N(CH_3)_2$ (BCH-2051)

(1) Solis, P. N.; Lang'at, C.; Gupta, M. P.; Kirby, G. C.; Warhurst, D. C.; Phillipson, J. D. *Planta Med.* **1995**, *61*, 62.

(2) (a) Hayashi, T.; Smith, F. T.; Lee, K. H. *J. Med. Chem.* **1987**, *30*, 2005. (b) Lee, H.; Hong, S.-S.; Kim, Y.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 933.

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(4) Wang, W.; Li, T.; Milburn, R.; Yates, J.; Hinnant, E.; Luzzio, M. J.; Noble, S. A.; Attardo, G. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1579.

(5) (a) Ito, T.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1993**, *34*, 6583. (b) Giles, R. G. F.; Green, I. R.; Taylor, C. P. *Tetrahedron Lett.* **1999**, *40*, 4871. (c) Mutter, R.; Campbell, I. B.; Martin de la Nava, E. M.; Merritt, A. T.; Wills, M. *J. Org. Chem.* **2001**, *66*, 3284. (d) Van, T. N.; Kesteleyn, B.; De Kimpe, N. *Tetrahedron* **2001**, *57*, 4213. (e) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251. (f) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028. (g) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139. (h) Yue, D.; Della Cà, N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581.

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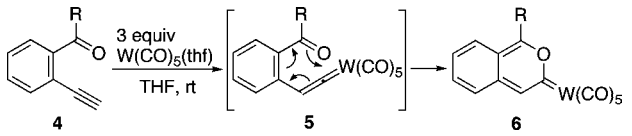
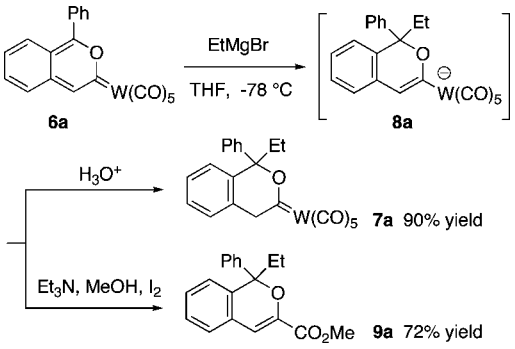
with benzopyranylidene complexes **6** followed by iodine oxidation of the produced alkenyltungsten species.[7]

Scheme 2



We first examined the reaction of phenyl-substituted benzopyranylidene complex **6a** with several organometallic reagents. Although the reaction of the complex **6a** with *n*-BuLi in THF at −78 °C gave a complex mixture of products, the reaction with ethylmagnesium bromide proceeded smoothly in THF at −78 °C to give a cyclic Fischer-type carbene complex **7a** having an ethyl group at the 1-position in 90% yield. Thus, ethylmagnesium bromide added cleanly in a 1,6-manner to give alkenyltungsten species **8a**, which was protonated on quenching at the *β*-position of the tungsten to give the cyclic Fischer-type carbene complex **7a** (Scheme 3).[7] In this reaction, none of the products derived

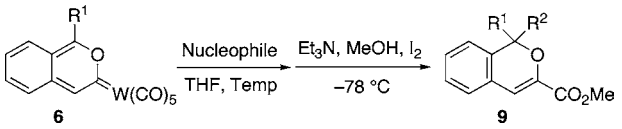
Scheme 3



from 1,2-addition of the nucleophile could be detected. We then expected that synthetically useful isochromene esters such as **9a** would be obtained by the iodine oxidation of the alkenyltungsten intermediate **8a**.[8] Thus, after treatment of complex **6a** with ethylmagnesium bromide in THF at −78 °C, MeOH, Et_3N, and iodine were added successively, and the mixture was further stirred for 30 min at this temperature. Workup of the reaction mixture afforded the desired isochromene ester derivative **9a** having an ethyl group at 1-position in 72% yield.

As the desired isochromene ester **9a** was obtained in good yield, we next examined the generality of this reaction (Table 1). The reaction of vinylmagnesium chloride or phenylethynylmagnesium chloride with the complex **6a** also gave the isochromene ester **9b,c** having an alkenyl or an alkynyl group at the 1-position in good yield. Although addition of phenylmagnesium bromide proceeded sluggishly to give a complex mixture of products, the desired isochromene ester **9d** was obtained in good yield by using diphenylcopper lithium reagent. The reaction of these organometallic reagents to alkyl-substituted benzopyranylidene complex **6b** followed by iodine oxidation proceeded smoothly to give the corresponding isochromene esters **9e**−**h** in good yield.

Table 1. Synthesis of the Isochromene Ester Derivatives **9** from Benzopyranylidenetungsten(0) Complexes **6**



entry	R^1	nucleophile	T (°C)	R^2	yield (%)
1	Ph (**6a**)	EtMgBr	−78	Et	86 (**9a**)
2		vinylMgCl	−78	vinyl	76 (**9b**)
3		PhC≡CMgCl	rt	PhC≡C	84 (**9c**)
4		Ph_2CuLi	−78 to −30	Ph	80 (**9d**)
5	*i*-Pr (**6b**)	EtMgBr	−78	Et	92 (**9e**)
6		vinylMgCl	−78	vinyl	85 (**9f**)
7		PhC≡CMgCl	rt	PhC≡C	84 (**9g**)
8		Ph_2CuLi	−78 to −30	Ph	60 (**9h**)

We next examined the reaction with less reactive carbonucleophiles. When the complex **6a** was treated with sodium dimethyl malonate at −78 °C in THF, the dark blue color of the complex **6a** turned yellow immediately. However, when water was added, the mixture unexpectedly turned back to dark blue to give the starting complex **6a**. As the change of the color suggested that the complex **6a** reacted with sodium dimethyl malonate to form the addition intermediate, the mixture was directly treated with Et_3N, MeOH, and iodine successively, and it was found that the desired isochromene ester derivative **9i** having a $CH(CO_2Me)_2$ group at the 1-position was in fact obtained in good yield (Scheme 4). Thus, it was confirmed that there is an equilibrium between the complex **6a** and the addition intermediate **8b**, the latter of which can be trapped by iodine oxidation to give isochromene ester **9i**.

Sodium cyanide was also found to react with the complexes **6a**,**b** to give the corresponding isochromene ester **9j**,**l** in good yield after iodine oxidation (Table 2).[9] Thus, not

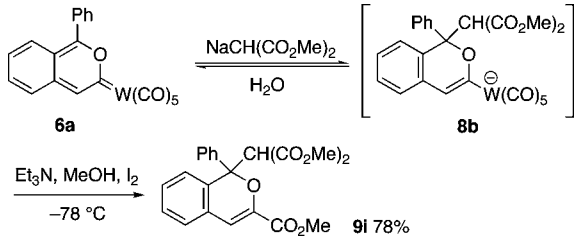
(6) (a) Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226. (b) Kusama, H.; Shiozawa, F.; Shido, M.; Iwasawa, N. *Chem. Lett.* **2002**, 124. (c) Ohe, K.; Miki, K.; Yokoi, T.; Nishino, F.; Uemura, S. *Organometallics* **2000**, *19*, 5525. (d) Miki, K.; Yokoi, T.; Nishino, F.; Ohe, K.; Uemura, S. *J. Organomet. Chem.* **2002**, *645*, 228. (e) Wang, S. L. B.; Wulff, W. D. *J. Am. Chem. Soc.*, **1990**, *112*, 4550. (f) Aumann, R. *Eur. J. Org. Chem.* **2000**, 17 and references therein.

(7) (a) Caro, B.; Poul, P. L.; Guen, F. R.-L.; Sénéchal-Tocquer, M.-C.; Saillard, J.-Y.; Kahlal, S.; Ouahab, L.; Golhen, S. *Eur. J. Org. Chem.* **2000**, 577. (b) Barluenga, J.; Trabanco, A. A.; Flórez, J.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1996**, *118*, 13099. (c) Aumann, R.; Meyer, A. G.; Fröhlich, R. *J. Am. Chem. Soc.* **1996**, *118*, 10853. (d) Aumann, R.; Roths, K.; Jasper, B.; Fröhlich, R. *Organometallics* **1996**, *15*, 1257. (e) Barluenga, J.; Flórez, J.; Fañanás, F. J. *J. Organomet. Chem.* **2001**, *624*, 5.

(8) (a) Fuchibe, K.; Iwasawa, N. *Tetrahedron* **2000**, *56*, 4907. (b) Iwasawa, N.; Ochiai, T.; Maeyama, K. *Organometallics* **1997**, *16*, 5137. (c) Li, C.-L.; Liu, R.-S. *Chem. Rev.* **2000**, *100*, 3127.

(9) Aqueous workup of the addition intermediate partially gave back the starting material, along with a mixture of unidentified products.

Scheme 4



only highly nucleophilic reagents such as Grignard reagents but also less reactive nucleophiles such as malonate and cyanide could be employed for this isochromene ester synthesis.

Table 2. Reaction of Less Reactive Nucleophiles with Benzopyranylidenetungsten(0) Complexes **6**

entry	R^1	nucleophile	conditions	R^2	yield (%)
1[a]	Ph (**6a**)	$NaCH(CO_2Me)_2$	THF, −78 °C	$CH(CO_2Me)_2$	78 (**9i**)
2[b]		NaCN	DMF, 0 °C	CN	60 (**9j**)
3[a]	*i*-Pr (**6b**)	$NaCH(CO_2Me)_2$	THF, −78 °C	$CH(CO_2Me)_2$	78 (**9k**)
4[b]		NaCN	DMF, 0 °C	CN	60 (**9l**)

[a] Oxidation was conducted at −78 °C. [b] Oxidation was conducted at 0 °C.

Isochromene ester derivatives having a hetero substituent such as a methoxy group at the 1-position possess high antitumor activity as exemplified in **3**. We next examined introduction of a hetero group at this position. After treatment of the complex **6a** with sodium methoxide in MeOH at room temperature, Et_3N and iodine were added successively. Workup of the reaction mixture afforded the desired isochromene ester derivative **9m** having a methoxy group at the 1-position in 74% yield. Furthermore, lithium carbamate (LiN(Cbz)Me) or sodium carbazate ($NaN(Cbz)NMe_2$) reacted in a similar manner to give the isochromene esters **9n**,**o** having a nitrogen substituent in good yield (Table 3). In these cases also, aqueous workup of the addition intermediates gave back the starting pyranylidene complex **6a**.

Finally, the synthesis of isochromene esters having only one substituent at the 1-position was examined. As the parent nonsubstituted benzopyranylidene complex **6c** (R = H) is unstable, the possibility of adding hydride in a 1,6-addition manner to the complex was tried. After examination of several typical hydrides, it was found that treatment of the complexes **6a**,**b** with DIBALH or L-Selectride in THF at

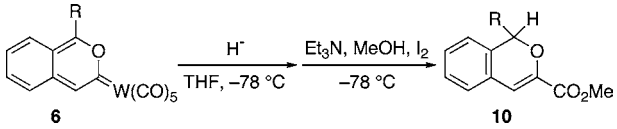
Table 3. Reaction of Heteronucleophiles with Benzopyranylidenetungsten(0) Complexes **6**[a]

entry	R^1	nucleophile	conditions	R^2	yield (%)
1	Ph (**6a**)	NaOMe	MeOH, rt	OMe	74 (**9m**)
2		LiN(Cbz)Me	THF, −78 °C to rt	N(Cbz)Me	82 (**9n**)
3		$NaN(Cbz)NMe_2$	THF, −78 °C	$N(Cbz)NMe_2$	92 (**9o**)
4	*i*-Pr (**6b**)	NaOMe	MeOH, rt	OMe	82 (**9p**)

[a] Oxidation was conducted at −78 °C.

−78 °C followed by iodine oxidation gave the desired isochromene ester derivatives **10a**,**b** in good yield (Table 4).

Table 4. Reaction of Hydride Reductants with Benzopyranylidenetungsten(0) Complexes **6**



entry	R	nucleophile	yield (%)
1	Ph (**6a**)	DIBALH	80 (**10a**)
2		L-Selectride	95 (**10a**)
3	*i*-Pr (**6b**)	L-Selectride	86 (**10b**)

In summary, benzopyranylidenetungsten(0) complexes **6** were found to react with a variety of nucleophilic reagents in a 1,6-addition manner, and iodine oxidation of the addition intermediates gave isochromene ester derivatives **9** and **10** in good yield. Even with less reactive nucleophiles, addition intermediates were found to be trapped efficiently by this iodine oxidation. Thus, this reaction would be a convenient method for the preparation of these synthetically useful compounds.

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Supporting Information Available: Preparative methods and spectral and analytical data of compounds **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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