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One-Pot, Two-Step Synthesis of Substituted Anthraquinones from Chromium(0) Alkynyl Carbenes and Isobenzofurans

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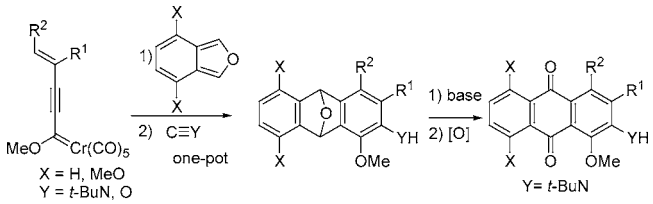
ABSTRACT



The reaction of alkynyl Fischer carbenes and isobenzofurans gives rise to the corresponding [4 + 2] cycloadducts. The newly formed carbene adducts are suitable for benzannulation processes in the presence of *tert*-butylisocyanide or carbon monoxide to yield a variety of new highly substituted polycyclic structures having the anthraquinone framework. The whole two-step process is conducted in a one-pot fashion from easily available 1,4-dihydro-1,4-epoxynaphthalenes.

Alkynyl Fischer carbenes are recognized as highly activated dienophiles in [4 + 2] cycloaddition reactions because of the presence of the strongly electron-withdrawing pentacarbonyl carbene metal fragment.[1] However, their major advantage over the isolobal unsaturated esters relies on the further elaboration of the cycloadduct by taking advantage of the synthetic versatility of the remaining metal carbene (Figure 1). In particular, the pentannulation[2] (via A) and benzannulation[3] (via B) reactions have become very useful for polycyclic syntheses. Recently, the consecutive [4 + 2] cycloaddition/pentannulation sequence of arylalkynyl(methox-

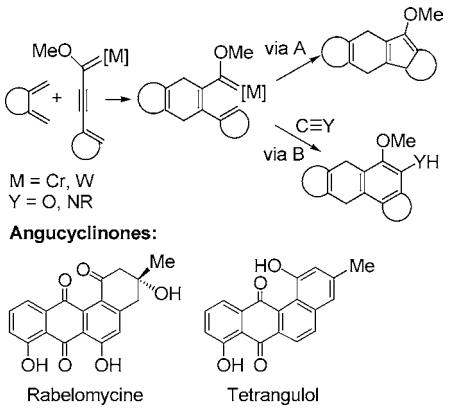


Figure 1. [4 + 2] Cycloaddition of alkynyl Fischer carbenes, followed by pentannulation or benzannulation.

(1) For reviews, see: (a) de Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964−4002. (b) Barluenga, J.; Rodriguez, F.; Fañanás, F. J.; Flórez, J. *Top. Organomet. Chem.* **2004**, *13*, 59−121. (c) Barluenga, J.; Fernández-Rodríguez, M.; Aguilar, E. *J. Organomet. Chem.* **2005**, *690*, 539−587. (d) Herndon, J. W. *Coord. Chem. Rev.* **2007**, *251*, 1158−1258.

(2) For a review of 1-metalla-1,3,5-hexatrienes, see: (a) Aumann, R. *Eur. J. Org. Chem.* **2000**, 17−31. (b) Barluenga, J.; Aznar, F.; Barluenga, S. *Chem. Commun.* **1995**, 1973−1974. (c) Barluenga, J.; Aznar, F.; Barluenga, S.; Fernández, M.; Martín, A.; García-Granda, S.; Piñera-Nicolás, A. *Chem. Eur. J.* **1998**, *4*, 2280−2298.

(3) (a) Merlic, C. A.; Burns, E. E.; Xu, D.; Chen, S. Y. *J. Am. Chem. Soc.* **1992**, *114*, 8722−8724. (b) Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 7418−7420.

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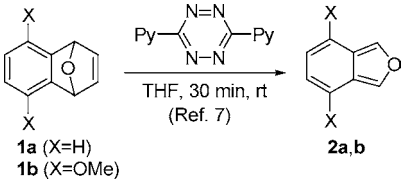
y)carbenes with *o*-quinodimethane species was reported to provide the benzo[*b*]fluorene nucleus (via A).[4]

We were motivated to accomplish a new protocol that would allow to access the C_6-C_6-C_6-C_6 polycyclic structure (via B), which represents the basic skeleton of the angucyclinone antibiotic family (Figure 1).[5] Herein we report that various types of tri- and tetracyclic structures are efficiently assembled by the [4 + 2] cycloaddition of isobenzofuran dienes with aryl- and alkenyl-substituted alkynyl(methoxy)-carbenes of chromium followed by benzannulation in the presence of *tert*-butylisocyanide or carbon monoxide.

We have selected isobenzofurans **2** because (i) they are readily available as well as highly reactive and easy-to-handle dienes, and (ii) they would produce cycloadducts with a synthetically useful ether bridge, e.g., as precursor of the quinone moiety.[6] The isobenzofuran dienes **2a,b** were generated, as already described, by the [4 + 2] cycloaddition/double [4 + 2] retrocycloaddition process between 1,4-dihydro-1,4-epoxynaphthalenes **1a,b** and 3,6-di(pyridin-2′-yl) *s*-tetrazine (Scheme 1).[7]

Scheme 1. Synthesis of Isobenzofurans **2**

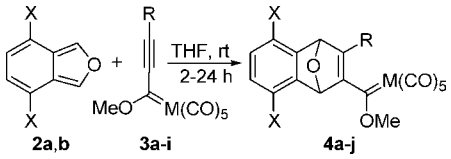


Thus, the model process involves in situ preparation of isobenzofuran **2** in THF at room temperature followed by addition of the metal carbene **3** (1.1 equiv) at the same temperature. The reaction mixture was stirred at room temperature for 2−24 h and then chromatographed on silica gel (hexanes/EtOAc, 5:1) to afford the expected metal carbene cycloadducts **4** in general with high yield (60−85%) (Table 1). Therefore, this [4 + 2] cycloaddition provides an efficient entry into diverse oxabenzonorbornadiene carbenes having an alkenyl or aryl substituent adequately placed to accomplish a further cyclization. Moreover, it should be noted that the alkyl-substituted alkynyl carbene **3h** (R = *t*-Bu) gives rise to the cycloadduct **4i** (60% yield), though it is not relevant within the context of the present study (see below). We observed that the pentacarbonyl[phenylethynyl-(methoxy)carbene] tungsten(0) complex **3i** produces the corresponding cycloadduct **4j** in somewhat lower yield (74%) than the analogous chromium carbene (product **4d**, 85%) (see Supporting Information).

Having the carbene cycloadducts in hand, we considered the possibility to undertake the benzannulation reaction in the presence of isocyanide[3a] or carbon monoxide.[3b] Such a process would give rise in a later step to polycyclic compounds containing a functionalized anthraquinone skeleton (Scheme 2).[8] Thus, metal carbene **4a** was stirred overnight with *tert*-butylisocyanide (2.1 equiv) in THF at room temperature to afford the cycloadduct **5a** in 90% yield after purification of the reaction mixture by column chromatography. The benzannulation reaction is well established to proceed through the isocyanide insertion intermediate **I**, which evolves by electrocyclic ring closure and aromatization.

Significantly, the whole process could be effected in one pot from the epoxynaphthalene **1**, which makes it more attractive in terms of simplicity and efficiency. Such a

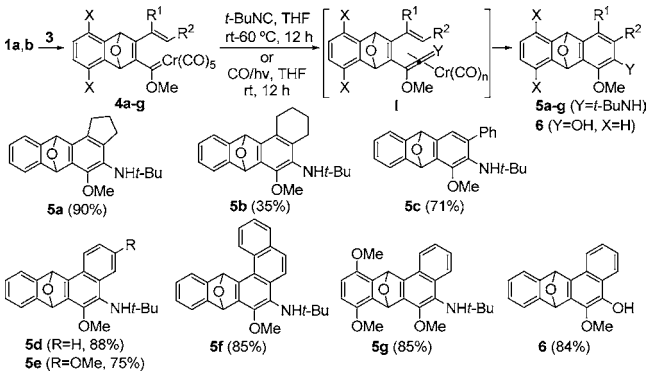
Table 1. [4 + 2] Cycloaddition of Akynyl Fischer Carbenes **3** and Isobenzofurans **2**



entry	X	carbene	M	R	product	yield (%)[a]
1	H	**3a**	Cr	1-cyclopentenyl	**4a**	72
2	H	**3b**	Cr	1-cyclohexenyl	**4b**	*b*
3	H	**3c**	Cr	(*E*)-CH=CHPH	**4c**	*c*
4	H	**3d**	Cr	Ph	**4d**	85
5	H	**3e**	Cr	*p*-$MeOC_6H_4$	**4e**	75
6	H	**3f**	Cr	1-naphthyl	**4f**	64
7	OMe	**3d**	Cr	Ph	**4g**	81
8	H	**3g**	Cr	*p*-ClC_6H_4	**4h**	70
9	H	**3h**	Cr	*t*-Bu	**4i**	60
10	H	**3i**	W	Ph	**4j**	74

[a] Isolated yields after SiO_2 chromatography (hexanes/EtOAc 5:1). [b] Not isolated; see below and Scheme 3. [c] Not purified; decomposes in SiO_2.

Scheme 2. [4 + 2] Cycloaddition/Benzannulation Sequence from Fischer Carbenes **3**, Isobenzofurans **2**, and *t*-BuNC or CO



(4) Barluenga, J.; Fenández-Rodriguez, M. A.; Aguilar, E. *Org. Lett.* **2002**, *4*, 3659−3662.
(5) Rohr, J.; Thiericke, R. *Nat. Prod. Rep.* **1992**, *9*, 104−137.
(6) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093−2135.
(7) Warrener, R. N.; Hammer, B. C.; Russell, R. A. *J. Chem. Soc., Chem. Commun.* **1981**, 942−943.

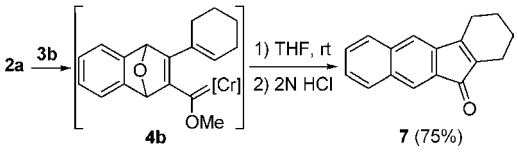
(8) The anthraquinone unit is part of a large group of naturally occurring compounds with a number of different biological properties specially antitumor activity. See: Tietze, L. F.; Gericke, K. M.; Schuberth, I. *Eur. J. Org. Chem.* **2007**, 4563−4577 and references therein.

protocol was followed to access cycloadducts **5b**−**g**. Thus, 3,6-di(pyridin-2′-yl) *s*-tetrazine was added to a solution of epoxynaphthalenes **1** and stirred at room temperature for 30 min to generate isobenzofurans **2** (see Scheme 1). Then, carbene complexes **3** were added at room temperature, and the mixture was stirred for 2−24 h. When the cycloaddition reaction was complete (according to TLC), *tert*-butylisocyanide was added to the mixture at room temperature, and the mixture was stirred for 1 min and then heated at 60 °C (for complexes **3c**−**e**) or stirred at room temperature (for complexes **3a,b,f**) for 12 h. Finally, the solvent was removed, and the products **5** were purified by flash chromatography on silica gel (hexanes/EtOAc, 10:1)

Therefore, excellent yields were reached for the whole sequence regardless of whether an alkenyl (compounds **5a**−**c**) or an aryl (compounds **5d**−**g**) group participates in the benzannulation step. In the same way, the benzannulation reaction in the presence of carbon monoxide was undertaken. Cycloadduct **4d**, generated from epoxynaphthalene **1a** and phenylalkynylcarbene **3d**, evolved under a carbon monoxide atmosphere (rt, *hν*, 12 h) to furnish dihydrotetraphene **6** (84% yield), with high and orthogonal oxygen functionalization.

It should be noted that the cycloadduct **5b**, derived from the alkynylcarbene **3b** (R = 1-cyclohexenyl) and the isobenzofuran **2a**, was isolated in only 35% yield after column chromatography.[9] In this particular case, the pentannulation reaction of the dienylcarbene precursor (see Figure 1, via A) was the major reaction pathway, affording the cyclopentadienone adduct **7** (see the structure in Scheme 3) as a

Scheme 3. Pentannulation Reaction to Compound **7**

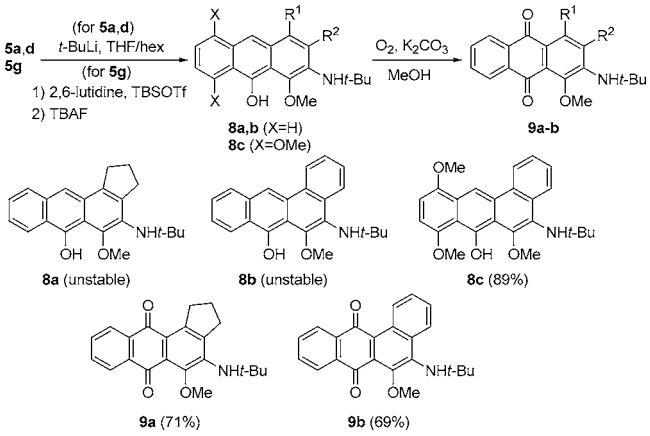


yellow solid in 49% yield. In fact, stirring at room temperature a THF solution of **2a** and **3b** in the absence of isocyanide led exclusively, after aqueous acid hydrolysis, to compound **7** (75% yield) via the carbene intermediate **4b** (Scheme 3) (see Supporting Information).

Since compounds **5** potentially contain the skeleton of anthraquinone, the transformation of the ether bridge to the quinone function was next attempted (Scheme 4). First, the ether bridge could be selectively cleaved to afford the hydroxy derivatives **8a**−**c** by basic treatment of **5a,d** (X = H; *t*-BuLi, THF/hexane) and **5g** (X = OMe; (i) 2,6-lutidine, TBSOTf, (ii) TBAF).[10] Although alcohols **8a,b** were found

(9) The benzannulation reaction using tungsten carbenes was found less efficient. Thus, attempts to improve the yield of compound **5b** using the corresponding tungsten enynylcarbene were unsuccesful.

Scheme 4. Synthesis of Phenols **8** and Quinones **9** from Benzannulated Products **5**



to be rather unstable, rapid purification of **8b** allowed for complete NMR characterization. The structure of the *O*-silyl precursor of **8c** was confirmed by NOESY experiments (NOE involving both H's of the bay-region; *t*-BuSi-OMe; *t*-BuN-OMe) (see Supporting Information). The transformation of the latter structure to the quinone moiety was undertaken on compounds **8a,b**, which yielded **9a,b** by oxidation with O_2/K_2CO_3 in methanol.[11,12] The oxidation step was effected without purification of alcohols **8**, the overall yield from **5** being 69−71%.

In conclusion, we have demonstrated that alkynyl Fischer carbenes **3** behave as excellent dienophiles in [4 + 2] cycloaddition reactions toward isobenzofurans **2**. Significantly, the resulting carbene cycloadducts are suitable precursors for the benzannulation reaction, making thus easily accessible a number of highly susbtituted polycyclic structures having the anthraquinone framework. In addition the whole two-step process is conducted in a one-pot fashion from commercially available 1,4-dihydro-1,4-epoxynaphthalenes. The protocol described herein should find application in the total synthesis of some members and derivatives of the angucyclinone family.

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Supporting Information Available: Experimental procedures and charaterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Unfortunately these standard oxidation conditions were not effective in the case of the dimethoxy derivative **8c**.