

# Generation and Trapping of Isobenzofuran Intermediates Formed in the Coupling of Fischer Carbene Complexes and *o*-Alkynylbenzoyl Derivatives

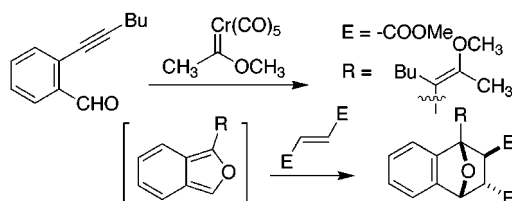
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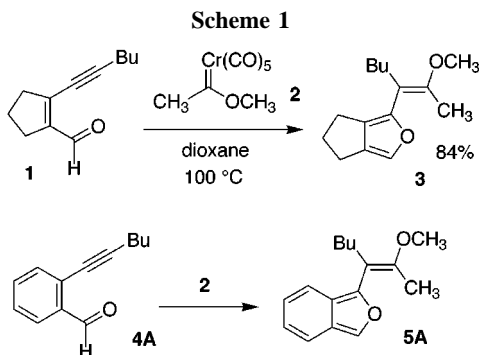
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## ABSTRACT



The coupling of *o*-alkynylbenzoyl derivatives with carbene complexes has been investigated. The reaction initially affords isobenzofuran derivatives, which convert to alkylidene-phthalan derivatives or can be trapped by various dienophiles to afford benzo-oxanorbornene derivatives.

Recently, the synthesis of furans (e.g., **3**, Scheme 1) through the coupling of Fischer carbene complexes (**2**) with enyne-



aldehydes (**1**) or ketones was reported.<sup>1</sup> In this Letter, the effect of replacing the central alkene functionality with an aromatic ring will be examined. If the coupling of *o*-

alkynylbenzaldehyde derivative **4A** with carbene complex **2** follows the same course as the reaction of aldehyde **1** and complex **2**, isobenzofuran **5A** will be produced. Although isobenzofurans are unstable, they have been proven to be very useful synthetic intermediates.<sup>2</sup>

(1) Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, *63*, 4563–4564.

(2) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1999**, *73*, 1–96.

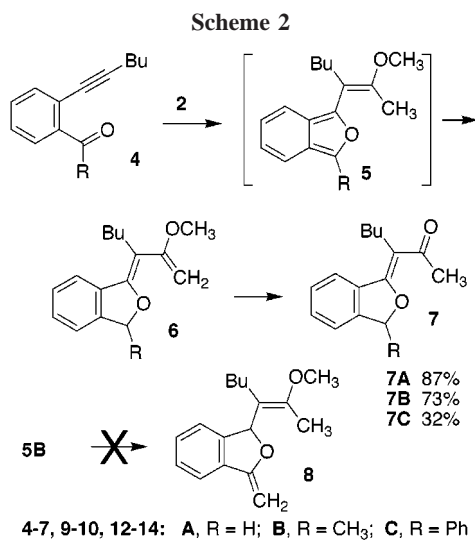
(3) This compound was a single isomer; the *E*–*Z* configuration for this compound could not be reliably assigned. The depicted configuration has been suggested (see Supporting Information for a discussion).

(4) The most notable feature is two singlets at  $\delta$  4.3 and 4.2, which are consistent with the alkene protons in a 1,1-disubstituted enol ether. See methoxypropene in the following: Pouchert, C. J.; Behnke, J. *The Aldrich Library of <sup>13</sup>C NMR and <sup>1</sup>H NMR Spectra*; Aldrich Chemical: Milwaukee, WI, 1992; Vol. 1, p 334A.

(5) For a theoretical discussion of the interconversion of isobenzofurans and alkylidene-phthalans, see: Friedrichsen, W. *Struct. Chem.* **1999**, *10*, 47–51.

(6) (a) The stereochemical assignment was based on the coupling constant of 5.5 Hz between the  $H_A$  and  $H_B$ , which is expected to be nearly 0 Hz in the opposite stereoisomer. Yamaguchi, Y.; Yamada, H.; Hayakawa, H.; Kenematsu, K. *J. Org. Chem.* **1987**, *52*, 2040–2046. (b) Chromium carbene-alkyne coupling affords *E* enol ethers. McCallum, J. S.; Kunng, F. A.; Gilberton, S. R.; Wulff, W. D. *Organometallics* **1988**, *7*, 2346–2360.

Coupling of *o*-alkynylbenzaldehyde derivative **4A** and methylcarbene complex **2** in refluxing dioxane afforded either enol ether **6A** or the corresponding ketone **7A** (Scheme 2).



The ketone<sup>3</sup> was the exclusive product of the reaction after purification using silica gel; however, the <sup>1</sup>H NMR spectrum of the crude product after filtration through Celite was consistent with that of enol ether **6A**.<sup>4</sup> A similar reaction was observed in the coupling of alkynylacetophenone derivative **4B** with carbene complex **2**. A likely mechanism in these reactions is the formation of isobenzofuran derivative **5A** followed by a net 1,7-hydrogen shift<sup>5</sup> followed by hydrolysis. In the case of **5B**, none of the 1,5-hydrogen shift isomer **8** was observed. Coupling of phenyl ketone **4C** with the carbene complex afforded a crude product (red oil) consistent with the isobenzofuran structure **5C** (accompanied by the corresponding phenyl-Cr(CO)<sub>3</sub> complex); however, attempts to purify **4C** by chromatography resulted in only ketone **7C**.

The reaction process was also examined in the presence of a dienophile, dimethyl fumarate (Scheme 3). The coupling of alkynylbenzaldehyde **4A**, carbene complex **2**, and dimethyl fumarate (~1:1:1 ratio) led to the three-component coupling product **9A**<sup>6</sup> in 54% yield. Ring-opened product **10** was observed after exposure to mild acids.<sup>7</sup> Formation of compound **9A** occurs through generation of isobenzofuran **5A**, followed by Diels-Alder reaction with dimethyl fumarate to afford adduct **9A**. Use of a large excess of dimethyl fumarate led to a considerable quantity of alkene cyclopropanation product **11**.<sup>8</sup> The reaction employing acetyl analogue

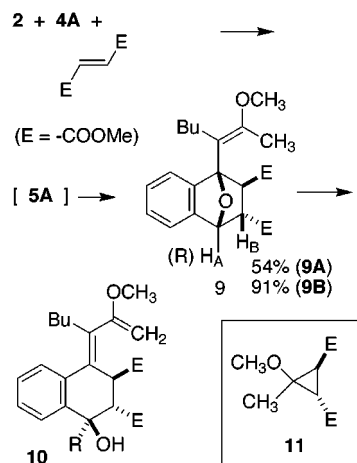
(7) Compound **10** (or the corresponding ketone) was observed if the chloroform NMR sample was kept at room temperature for >12 h or if the silica gel purification was conducted too slowly.

(8) Wienand, A.; Reissig, H.-U. *Organometallics* **1990**, *9*, 3133–3142.

(9) For efficient deoxygenation using chromium(0) species, see: Wulff, W. D.; Kaesler, R. W.; Peterson, G. A.; Tang, P.-C. *J. Am. Chem. Soc.* **1985**, *107*, 1060–1062.

(10) High endo selectivity is observed for coupling of free isobenzofurans and *N*-methylmaleimide. Tobia, D.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 2611–2614. The endo configuration is suggested on the basis of the chemical shifts of H<sub>A</sub> and H<sub>B</sub> at >4 ppm.

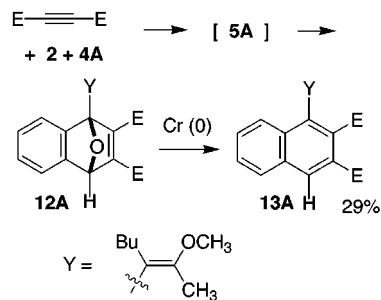
**Scheme 3**



**4B** proceeded similarly to afford a 6:1 ratio of cycloadducts **9B** in 91% yield.

A very complex reaction mixture resulted when the dienophile trap was switched to dimethyl acetylenedicarboxylate (Scheme 4). The major product was naphthalene

**Scheme 4**



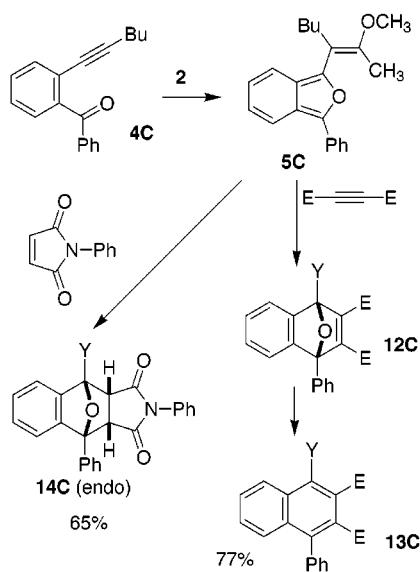
derivative **13A**, which results from a reductive deoxygenation of initial Diels-Alder adduct **12A**.<sup>9</sup> Competing coupling of the carbene complex with dimethyl acetylenedicarboxylate might account for the low yield in this case. Complex reaction mixtures were obtained from three-component couplings using ethyl acrylate or *N*-phenylmaleimide.

Since the isobenzofuran derived from benzophenone analogue **4C** appears to be fairly stable, a two-step (sequential) isobenzofuran synthesis-Diels-Alder coupling was attempted. The reaction of alkyne **4C** with carbene complex **2** for 1 h, followed by addition of *N*-phenylmaleimide resulted in endo Diels-Alder adduct **14C** (Scheme 5).<sup>10</sup> Similar coupling using dimethyl acetylenedicarboxylate afforded adduct **13C**.

(11) The exo stereochemical assignment is based on the 0 Hz coupling of H<sub>A</sub> and H<sub>B</sub> and the chemical shifts of H<sub>B</sub> and H<sub>C</sub> (~3 ppm, see ref 10).

(12) We are not aware of an isolated η<sup>5</sup>-furan-Cr(CO)<sub>3</sub> complex; however, numerous thiophene and pyrrole complexes have been reported. For a recent example, see: Loft, M. S.; Mowlem, T. J.; Widdowson, D. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 97–104 and references therein.

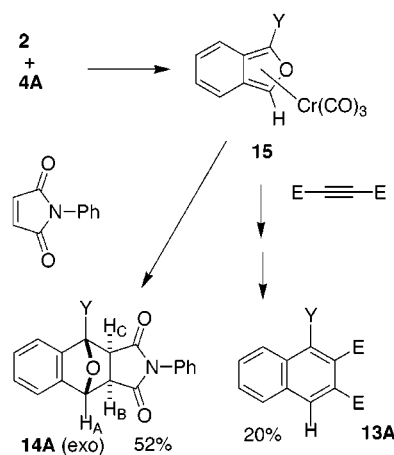
Scheme 5



Surprisingly, alkyne-aldehyde **4A** could also undergo a sequential isobenzofuran formation-Diels-Alder sequence. Thus, refluxing a mixture of alkyne **4A** and carbene complex **2** in dioxane for 0.5 h followed by addition of dimethyl acetylenedicarboxylate led to the expected Diels-Alder adduct **13A** in 20% yield, accompanied by unreacted alkyne-aldehyde and ketone **7A** (Scheme 6). A similar reaction sequence employing *N*-phenylmaleimide led to the exo<sup>11</sup> Diels-Alder adduct **14A**. A free isobenzofuran is unlikely in the reactions of **4A** based on the high exo selectivity, coupled with the substantial lifetime of the intermediate at 100 °C. The observed isobenzofurans could be stabilized by complexation to chromium,<sup>12</sup> and thus the adducts would result from an insertion-reductive elimination sequence.<sup>13</sup>

(13) The stereochemistry can be dramatically affected in metal-mediated processes. Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843-1844.

Scheme 6



In summary, isobenzofuran synthetic equivalents are readily generated from the coupling of *o*-alkynylbenzoyl derivatives with Fischer carbene complexes. The intermediates can undergo hydrogen shift processes or can be trapped through Diels-Alder reactions with electron-deficient dienophiles. Further research to define the scope of this process is currently underway in our laboratory.

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**Supporting Information Available:** Detailed descriptions of experimental procedures and characterization data for coupling products **7A-C**, **9A-B**, **13A**, **13C**, **14A**, and **14C**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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