

Regioselective Synthesis of 4,6,7-Trisubstituted Benzofurans from Furfural Imines and Nonheteroatom Stabilized Alkynylcarbene Complexes

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Group 6 Fischer carbene complexes, discovered in 1964,¹ have demonstrated in the past decades high versatility for the synthesis of carbo- and heterocycles as well as open chain compounds.² Conversely, their nonheteroatom stabilized counterparts, first reported by Casey in 1973,³ have received much less attention mainly due to their low stability, particularly those having hydrogen at the C α carbon.^{4,5} On the basis of this fact, we and others realized that alkynyl carbenes would be much more promising from a synthetic point of view. It was reported that alkynyl carbenes of groups 6 and 7 behave as carbenoids in the homocoupling reaction (dimerization)⁶ as well as in the cross-coupling reaction with methoxyfuran.⁷ However, cyclization reactions of this class of metal carbenes are restricted to an isolated intramolecular cyclopropanation reported by Casey.^{6b}

On the basis of the structural correspondence with α,β -unsaturated (alkoxy)carbene complexes, we decided to investigate the potential of nonstabilized alkynyl carbenes as a three-carbon synthon in carbocyclization reactions. We report herein a new and highly regioselective benzannulation reaction via the [3+3] carbocyclization of group 6 alkynylcarbene complexes **3** and furan-2-carbaldehyde imines **4**, wherein the carbene ligand behaves as 1,3-dipole species **I** (Figure 1).⁸ This benzannulation methodology would represent a useful alternative to the well established annulation of the furan ring. In this sense, the protocol reported here would overcome the use of a pre-existing arene ring with the appropriate substitution pattern, not always easily accessible for the benzofuran synthesis. In spite of its importance for the construction of functionalized six-membered rings, this type of carbocyclization is rather uncommon in the literature due primarily to the lack of appropriate pairs of C₃ synthons.⁹

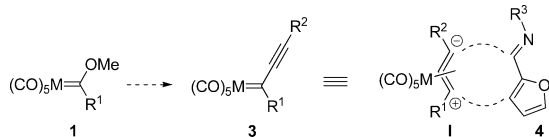


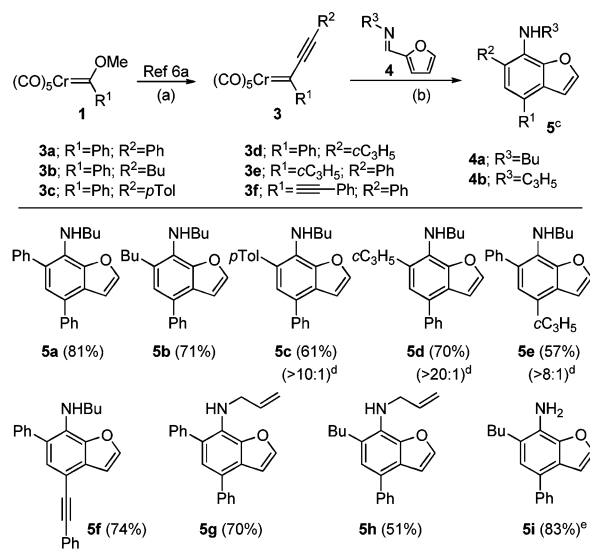
Figure 1. [3+3] Carbocyclization of nonstabilized alkynyl carbenes.

Interestingly, the reaction could be carried out in a one-pot manner starting from the corresponding (methoxy)carbene complex, thus avoiding handling of the rather unstable (alkynyl)carbene complex. Therefore, the yields given throughout this study are referred to as (methoxy)carbenes **1**. The protocol simply consists of the generation of the nonstabilized metal carbene **3** by methoxyacetylide exchange of the oxygen-stabilized carbene **1** (see ref 6a and Supporting Information) followed by the addition of the substrate **4** (Table 1).

Thus, 2-furaldehyde imine **4a** ($R^3 = \text{Bu}$) was added to a blue-colored solution of chromium alkynyl carbene **3a–f** in THF at -80°C and allowed to warm up until disappearance of the blue color

(see Supporting Information). Removal of the solvents and chromatographic purification afforded benzofurans **5a–h**¹⁰ in moderate to good overall yields. The reaction was found to be regioselective affording a single or major (compounds **5c–e**; >8:1) regioisomer (see Table 1). Interestingly, taking advantage of the versatile access to metal carbenes **3**, either regioisomer of **5** would be readily available by simply exchanging their substituents R^1/R^2 . In this way, both regioisomers **5d** and **5e** were efficiently synthesized from carbenes **3d** ($R^1 = \text{Ph}$; $R^2 = c\text{C}_3\text{H}_5$) and **3e** ($R^1 = c\text{C}_3\text{H}_5$; $R^2 = \text{Ph}$), respectively. Moreover, starting from the cross-conjugated diynyl carbene **3f** ($R^1 = \text{Ph}-\text{C}\equiv\text{C}$) permits attachment of the alkynyl functionality at the C-4 of the benzofuran **5f**. In the same way, the 2-furaldehyde imine **4b** ($R^3 = \text{allyl}$) afforded the cycloadducts **5g,h**, as single regioisomers, upon reaction with carbenes **3a,b** under the standard protocol. In turn, **5h** underwent efficient Pd-catalyzed *N*-allyl cleavage to provide the *N*-unsubstituted 7-aminobenzofuran **5i**.¹¹

Table 1. One-Pot Synthesis of Benzofurans **5** from Fischer Carbene Complexes **1** via Nonheteroatom Stabilized Carbene Complexes **3**



a) $R^2 = \text{Li}$, 2, THF, -80°C , 2) TMSOTf, -80°C

b) THF, -80°C and slow warm-up

c) Overall yield from carbene **1**

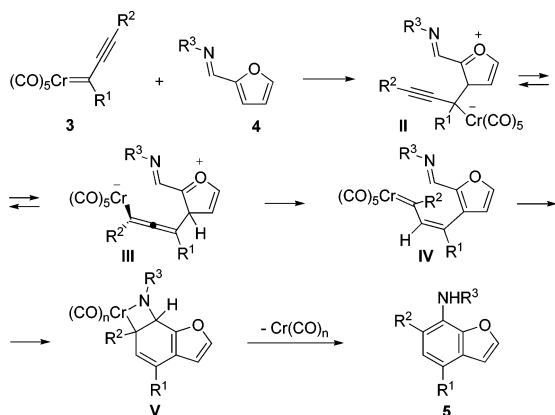
d) Regioisomeric ratio

e) Obtained by deprotection of **5h**; *N,N*-Dimethylbarbituric acid, Pd(PPh₃)₄, CH₂Cl₂, 40°C

A mechanistic proposal for the formation of the benzofuran skeleton **5** from alkynyl carbenes **3** is outlined in Scheme 1. Thus, the [3+3] cyclization process would be initiated by the nucleophilic 1,2-addition of the furan C-3 to the nonstabilized carbene complex **3** to form the intermediate Csp³-propargyl metalate **II**. This

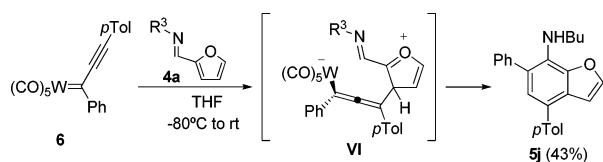
intermediate might equilibrate to the more stable Csp²-allenyl metalate **III** which could evolve to the nonheteroatom stabilized alkenyl carbene intermediate **IV** by proton transfer. Finally, a [2+2] intramolecular cyclization (intermediate metallazacyclobutane **V**) followed by Cr–H_β elimination and reductive metal elimination would account for the formation of **5**.

Scheme 1. Mechanistic Proposal for the Formation of Benzofurans **5a–h**



We have also made a single test to evaluate the influence of the metal on the regioselectivity of the reaction (Scheme 2). Fortunately, when the tungsten carbene **6**, formed from the corresponding tungsten (methoxy)carbene complex, reacted with 2-furaldehyde imine **4a** under the standard reaction conditions, the benzofuran derivative **5j** was obtained in 43% yield along with minor amounts of its regioisomer **5c** (**5j**/**5c** > 20:1). In this case, the process should involve the intermediate **VI**, analogous to **III** (Scheme 1), by conjugate addition of the imine to the carbene. Therefore the regioselectivity found with chromium carbenes can be reversed by simply using a metal with higher steric demand, like tungsten, which makes more difficult the 1,2-addition and directs the process through the 1,4-addition pathway.¹²

Scheme 2. Reverse Regioselectivity with Tungsten Carbene Complex **6**



In conclusion, presented here is the first synthetic application of group 6 nonheteroatom stabilized carbene complexes in carbocyclization reactions. Specifically, a facile and regioselective entry into substituted benzofurans is achieved by the [3+3] benzoannulation reaction of 2-furaldehyde imines and metal alkynylcarbene complexes. Moreover, this work features access to *N*-unsubstituted 7-aminobenzofurans, a heterocyclic motif found in compounds with antitumor activity. It should be noted that the procedure reported herein involves the construction of the arene ring, while most general methods to synthesize the benzofuran ring are based on the annulation of the furan ring onto a preexisting arene nucleus.^{13,14} Due the simplicity of the reaction and the readily availability of the starting materials, this benzoannulation reaction seems amenable for selectively accessing other classes of polycyclic structures.

Finally, this work reveals that these apparently elusive alkynylcarbene complexes can be easily handled and might be synthetically useful.

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Supporting Information Available: Data for **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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