Unexpected [4+2] Cycloaddition through Chromium Non-Heteroatom-Stabilized Alkynyl Carbene Complexes. Regioselective Access to Substituted 6-Azaindoles

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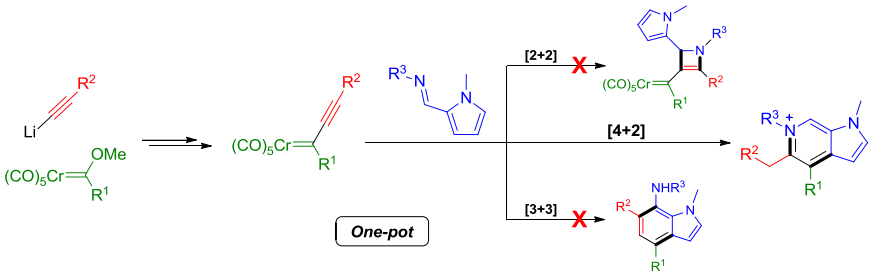


ABSTRACT: A formal [4+2] heterocycloaddition of non-heteroatom-stabilized alkynyl carbene complexes and iminopyrroles is described. The reaction implies a totally regioselective synthesis of 6-azaindole derivatives through the formation of the pyridine ring. The mechanism of the reaction has been explored in terms of density functional theory calculations showing preference for [4+2] instead of the [2+2] or [3+3] cycloadditions observed with other imines. The structure of the products also shows an unusual connectivity pattern from carbene complexes.

Group VI Fischer carbene complexes, discovered in 1964,[1] have demonstrated their high versatility as tools for carbo- and heterocyclizations.[2] Among them, different examples of [4+2] formal cycloadditions have been reported.[3] This reactivity has usually been observed in α,β-unsaturated carbene complexes acting as dienophiles through their double or triple bond. However, to the best of our knowledge, no examples have been reported to date of participation of group VI carbene complexes through formal [4+2] cycloadditions involving the $C_{carbene}$ and C_{α} positions. Additionally, after poor applications for decades,[4] non-heteroatom-stabilized carbene complexes, first reported by Casey in 1973,[5] have been a particular object of attention, since a new methodology for their synthesis has been established in our group.[6,7] Following this methodology, in addition to open chain compounds,[8] [2+1],[9] [2+2],[10] [3+3][11] and [4+3][12] carbo- and heterocycloadditions have also been achieved (Figure 1). However, no examples of formal [4+2] cycloadditions have been reported to date.

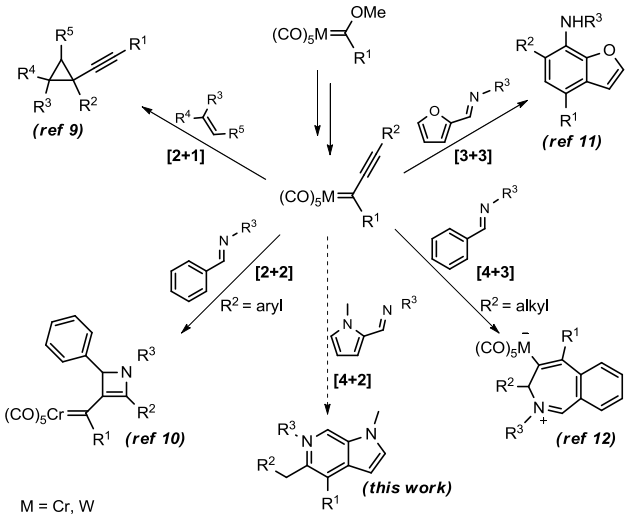


Figure 1. Formal carbo- and heterocycloadditions of Group VI non-heteroatom-stabilized alkynyl carbene complexes.

On the other hand, azaindole derivatives represent a family of compounds of an increasing interest due to their potential pharmacological activity[13] and applicability as synthetic key intermediates.[14] Synthetic approaches to these compounds usually require having the corresponding prefunctionalized pyridines, which are not always easily accessible.[15] However, for the alternative strategy *via* construction of the pyridine ring, scarce examples have been reported.[16]

In this work, we report a mild and regioselective synthesis of substituted 6-azaindole derivatives, through the formation of the pyridine ring, in the reaction of 2-iminopyrroles and *in situ* synthesized non-heteroatom-stabilized alkynyl carbene complexes. Iminopyrroles showed an unexpected reactivity pattern compared to their furfural analogues (Figure 2).[11b] Additionally, this procedure represents the first formal [4+2] cycloaddition of group VI non-heteroatom-stabilized carbene complexes and the first example of Fischer type or non-heteroatom-stabilized group VI carbene complexes acting as a C-2 building block through their $C_{carbene}$ and C_{α} positions.

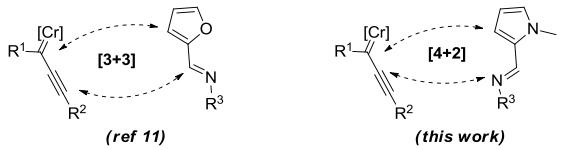
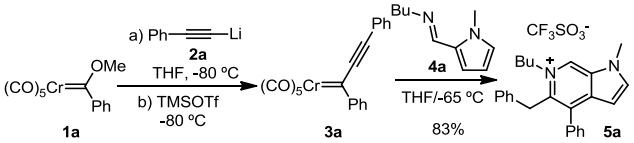


Figure 2. Connectivity pattern in the synthesis of 6-azaindole derivatives.

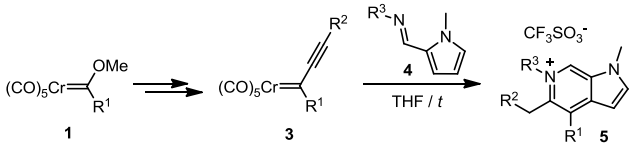
Thus, alkynylcarbene **3a** was previously generated from alkoxycarbene **1a** after a sequential low temperature (-80 ºC) addition of the corresponding lithium acetylide **2a** and trimethylsilyltriflate. Then, two equivalents of *N*-methylpyrroloimine **4a** were added and the mixture allowed a reaction at -65 ºC. After several hours of reaction, a solution colour change informed us of the disappearance of the non-heteroatom-stabilized carbene complex **3a** (colour changes from deep blue to red) and a few drops of water were added. Finally, solvents were removed under reduced pressure and the residue was purified by a chromatographic column. Following this procedure, 6-azaindolinium salt **5a** was obtained, in an 83% overall yield, from alkoxycarbene **1a** (Scheme 1). The structure of 6-azaindolinium **5a** was determined by mono and bidimensional NMR experiments.

Scheme 1. Synthesis of 6-azaindolinium 5a.



With this result in hand, we decided to investigate the scope and regioselectivity of the reaction starting from different, *in situ* synthesized, non-heteroatom-stabilized alkynyl carbene complexes. After performing several reactions, we made the observation that a change in the substitution pattern of the substrates requires deep control in the temperature of the reaction, which is crucial for the formation of the corresponding 6-azaindole derivatives (Table 1).

Table 1. [4+2] 6-Azaindolinium Synthesis from Non-Heteroatom-Stabilized Carbene Complexes 3.



compound	R^1	R^2	R^3	*t* (ºC)	yield (%)[a]
5a	Ph	Ph	Bu	-65	83
5b	Ph	*p*-Tol	Bu	-65	76
5c	*p*-Tol	Ph	Bu	-55	80
5d	Ph	Bu	Bu	-65	51
5e	*c*-C_3H_5	Ph	Bu	-45	43
5f	PhC≡C-	Ph	Bu	-70	92
5g	Ph	Ph	$-CH_2-CH=CH_2$	-60	81
5h	PhC≡C-	Ph	$-CH_2-CH=CH_2$	-65	68

[a] Overall yield from alkoxycarbenes **1**.

The structure of the compounds and the regiochemistry of the reaction were unambiguously determined by X-ray diffraction analysis performed on a monocrystal of compound **5b**[17] (Figure 3).

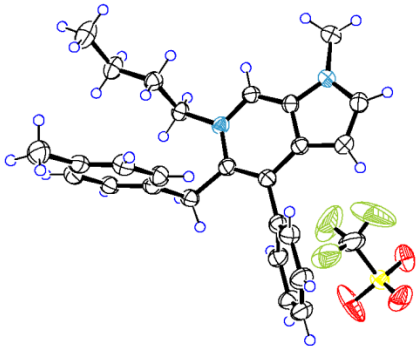


Figure 3. Ortep view for azaindolinium **5b**. Thermal ellipsoids at the 50% level.

From Table 1, it can be inferred that the reaction proceeds smoothly and with high versatility and total regioselectivity. Thus, in addition to aryl substituents, 6-azaindole derivatives wearing alkyl (**5d-e**) or alkynyl substituents (**5f,h**) could also be obtained, in moderate to very high overall yields, from alkoxycarbenes **1**. This methodology represents an easy access to 4,5-disubstituted 6-azaindole derivatives overcoming the requirement of a previous, and usually tedious, preparation of the pyridine ring with the appropriate substitution pattern. In addition, it is remarkable that the accessibility of both regioisomeric compounds, such as **5b** and **5c**, through a simple R^1-R^2 exchange in the carbene **3** results from the correct choice of carbene complex **1** and lithium acetylide **2**.

Next, in order to understand the mechanism of the reported reaction, we performed a computational study using Density Functional Theory (DFT) methods to calculate the reaction pathway for the formation of **5a** from non-heteroatom-stabilized carbene complex **3a** and imine **4a**. We used the metahybrid-GGA M06 functional[18] included in the Gaussi-

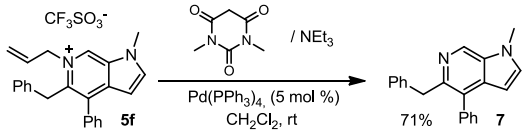
an09 program package[19] (see computational details in the Supporting Information, for a complete description of the methods). All the reported energies are free energies in solution in kcal/mol using the SMD implicit solvent methodology.[20]

The free energy profile of the reaction of formation of **5a** is shown in Figure 4. The reaction starts with the nucleophilic attack of the imine group of **4a** to the β-alkyne position of the non-heteroatom-stabilized carbene **3a**. For this step, a barrier of 20.0 kcal/mol was observed, which is easily affordable under the experimental conditions. The attack to the carbene carbon was also computed, but the energetic barrier was higher by 1.2 kcal/mol, producing an unstable intermediate **I'**, while product **I** is more stable than the starting material by 10.5 kcal/mol. Thus, the formation of **I** may be considered irreversible.

From this point, and based on previous studies,[11b] the reaction could proceed through the formation of the azetine product **6** by a [2+2] cyclization, or the seven-membered ring **II**. The difference in the reaction barriers clearly favours the formation of the seven-membered ring product (**TS-II**) by 2.6 kcal/mol with respect to the **TS-6**. This is in agreement with the lack of experimental evidence for the formation of azetines, in contrast with related reactions.[10,11b,21] From **II**, a [1,5]-H shift could occur through a barrier of 18.0 kcal/mol, irreversibly yielding the intermediate **III**. This compound is in equilibrium with the conformational isomer with the phenyl group in the apical position **III'**, which is more stable by 7.0 kcal/mol. Then, the C-N bond is broken in **TS-IV**, with a barrier of 15.0 kcal/mol, generating the allene-type intermediate **IV**. A final ring-closing reaction drives the process to the final product **V**. An alternative **TS-V'** involving a hydrogen atom migration, similarly to the reported in the [3+3] reaction with furfural imine derivatives,[11] has also been explored. However, the barrier for this process **TS-V'** is considerably higher in energy (33.3 kcal/mol), yielding exclusively the [4+2] product **V** through the competitive **TS-V**. Finally, **V** may be protonated at the Cr-C bond when water is added, yielding 6-azaindolinium derivative **5a**.

Finally, we decided to transform 6-azaindolinium compounds **5** into neutral 6-azaindoles in order to turn this work into a methodology for the formation of these valuable heterocycles. For that purpose, we put 6-azaindolinium salt **5f** under a modification[22] of the Tsuji-Trost palladium catalyzed allylation conditions (Scheme 2). Thus, treatment of compound **5f** with *N*,*N*-dimethylbarbituric acid and triethylamine, in the presence of 5 mol % of tetrakis(triphenylphosphine)palladium(0), yielded the formation of neutral 6-azaindole **7**, in a 71% yield.

Scheme 2. Transformation of 6-azaindolinium 5f into 6-azaindole 7.



In conclusion, we have performed a smooth and totally regioselective access to substituted 6-azaindole derivatives, valuable heterocycles, through the formation of the pyridine ring. This methodology overcomes the requirement of most synthetic procedures of a substituted pre-existing pyridine ring. On the other hand, this work represents the first example of formal [4+2] cycloaddition of group VI non-heteroatom-stabilized carbene complexes as they exhibited a differential reactivity, in their behaviour with iminopyrroles, compared with the [2+2] or [3+3] formal cycloadditions observed with their phenyl or furan analogues, respectively.

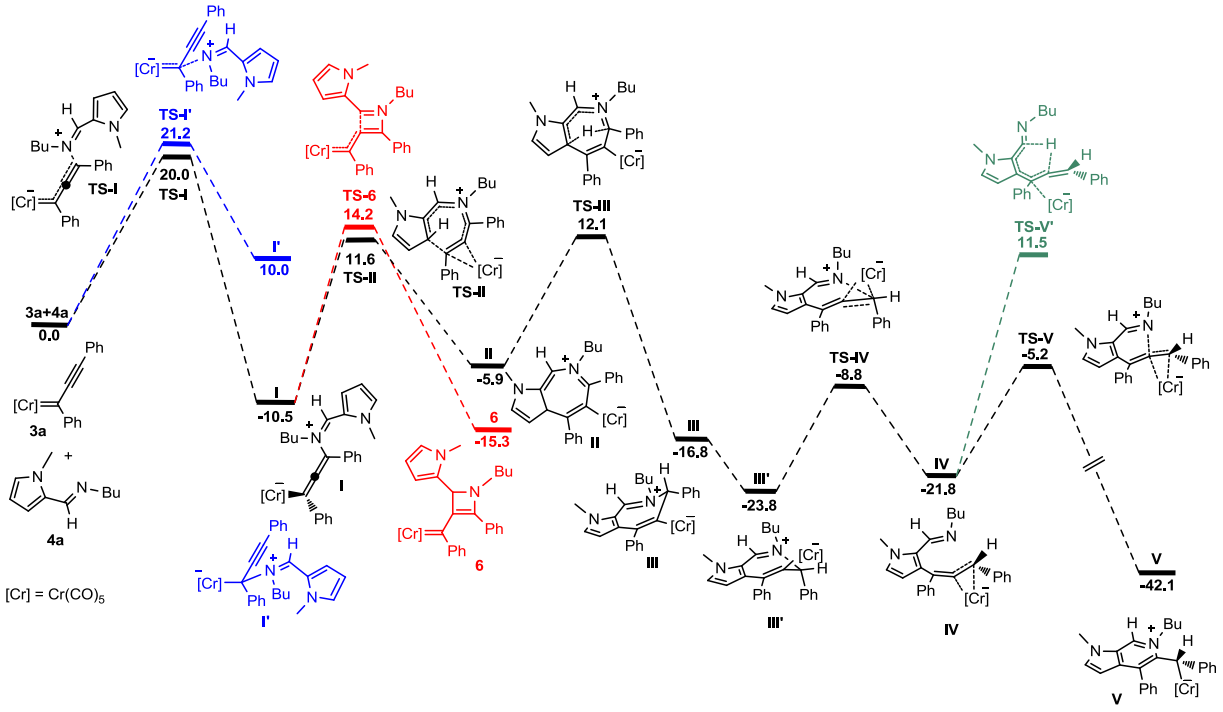


Figure 4. Computed mechanism for the formation of 6-azaindolinium **5a**. Free energies in kcal/mol relative to **3a** + **4a**.

These differences could be justified by a DFT study of the reaction mechanism. Finally, participation of these complexes, as formal dienophiles through the carbene and α positions, does not have, to the best of our knowledge, precedents in the literature for group VI carbene complexes, stabilized or not by heteroatoms.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, NMR spectra, computational details, calculated energies and Cartesian coordinates for the computed mechanism (PDF). Also includes a CIF file for the X-ray analysis of **5b**.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the Spanish Government MINECO/FEDER (CTQ-2016-76840-R and CTQ-2017-87372-P (AEI/FEDER, UE)) and Principality of Asturias (Spain, GRUPIN14-013). We also acknowledge Dr. A. L. Suárez-Sobrino for his assistance with the X-ray analysis.

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