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Letter

Regioselective Synthesis of Substituted Carbazoles, Bicarbazoles, and Clausine C

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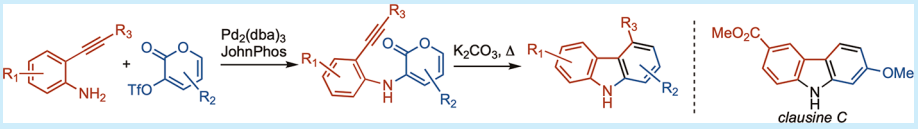

ABSTRACT: Substituted carbazoles are efficiently constructed from 3-triflato-2-pyrones and alkynyl anilines. Multiple substituents are tolerated on the carbazole, and complete control of regiochemistry is observed. Complicated and sterically congested substitution patterns are produced. This strategy is also used to prepare substituted bicarbazoles and related biaryls. Finally, the method was showcased in a synthesis of the carbazole natural product clausine C.

Heterocycles represent privileged structures among medicinal compounds. Carbazoles, especially naturally occurring carbaozles, show exciting activities for the treatment of cancers.[1] For example, in 1965, Chakraborty discovered the first carbazole natural product, murrayafoline A, from the tree *Murraya koenigii*; murrayafoline A has antibiotic and antitumor properties (Figure 1).[2] Elliptinium acetate contains a carbazole

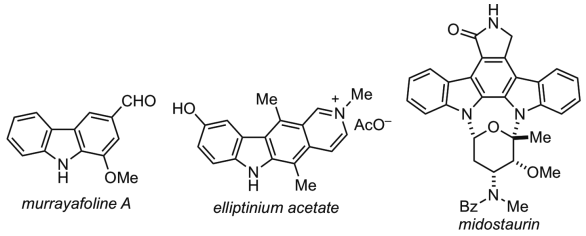

Figure 1. Biologically active carbazoles.

core structure. It is a DNA intercalator and a potent topoisomerase II inhibitor that is used to treat breast cancer.[3] Elliptinium acetate is based on the structure of the carbazole natural product ellipticine. Finally, midostaurin, an analogue of staurosporine, is a carbazole used to treat leukemia.[4]

Considering that carbazoles have potent biological activities, it is perhaps unsurprising that chemists have developed many methods for their construction. In fact, the discovery of methods capable of constructing substituted carbazoles began in the late 19th century[5] and continues to be an active area of research now.[6]

There are many dozens of distinct approaches to carbazole synthesis, and comprehensive reviews have been written on this topic.[7] A theme that pervades the synthesis of substituted carbazoles is the requirement for control of regiochemistry when the fused tricyclic system is created. One general method for carbazole synthesis involves the cyclization of diphenylamines **1** to form substituted carbazoles **2**. In the absence of directing groups,[8] the cyclization of molecules **1** tends to give C−C bond formation at the least hindered carbon atoms. For example, cyclization of **3** gives **4** as the major regioisomer, and only trace amounts of **5** are formed.[9]

A second general method for carbazole synthesis involves the cyclization (C−N bond formation) of 2-aminobiphenyls (**6**). Again, selective formation of a single desired regioisomer can be a problem. As an example, subjection of **7** to photochemical conditions gave regioisomers **8** and **9** without selectivity.[10]

Our group has become interested in methods for heterocycle synthesis that do not depend on sterically directed regioselective outcomes. Specifically, we are investigating cyclizations where the substitution pattern of the starting material directly leads to substitution in the product.[11] We recently found that substituted indolines and indoles can be prepared from *N*-butynyl-3-amino-2-pyrones in the presence of base.[12] In this manuscript, we describe how alkyne-tethered 3-anilido-2-pyrones (**10**) undergo intramolecular cycloadditions, presumably giving intermediates **11**, which rapidly lose CO_2 to form substituted carbazoles **12** (Scheme 1, bottom).[13] The reaction is high yielding, tolerates a wide variety of substitution, and is completely regioselective. Moreover, the method can be used to produce bicarbazoles, related biaryls, and the substituted carbazole natural product, clausine C.

The starting materials for our carbazole synthesis were prepared from simple 3-hydroxy-2-pyrones (**13**, Scheme 2).[14]

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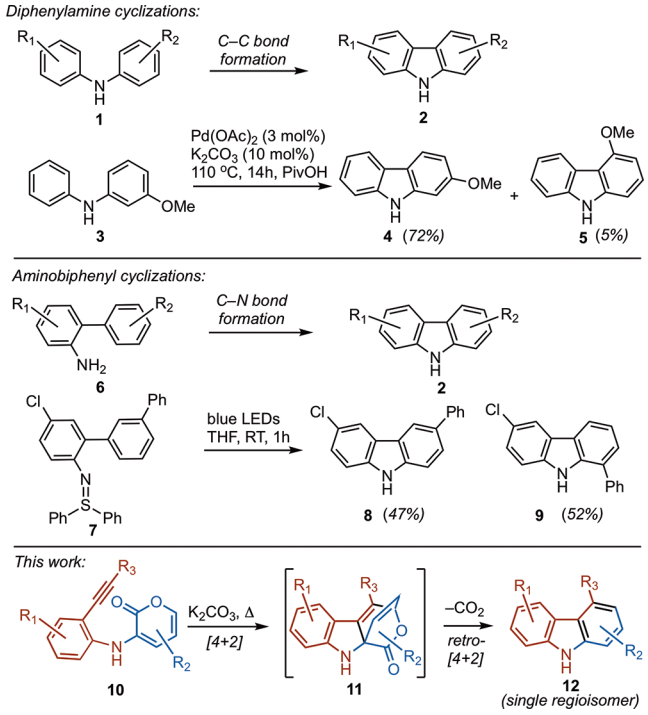
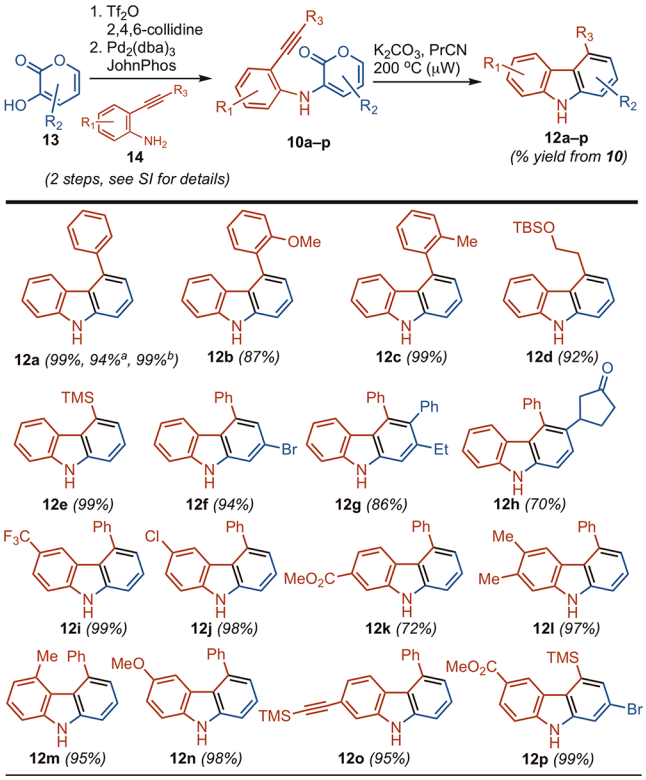
Scheme 1. Carbazole Syntheses



Scheme 2. Scope of the Carbazole Synthesis



[a]200 °C, 4 h, oil bath heating. [b]Reaction performed on a 1 mmol scale.

Triflation of **13** followed by C−N bond formation with alkynyl aniline **14** gave key substrate **10**.[15]

Gratifyingly, microwave heating of **10a** in the presence of base gave the substituted carbazole **12a** in high yield.[16] This transformation could also be conveniently conducted with conventional oil-bath heating to give **12a** in excellent yield. Moreover, the reaction was performed on a large scale (1 mmol) with no decrease in isolated yield.

Additional substrates were evaluated to investigate the tolerance of the reaction to substitution. A wide variety of alkyne substituents (R_3) were tolerated. Carbazoles bearing phenyl groups at C4 (**12b** and **12c**) were formed in good yields. The alkyne may also contain an sp^3-hybridized carbon, and **12d** was prepared in high chemical yield. Silyl substitution was also tolerated, and **12e** was formed in good yield.

The pyrone may contain additional substituents; 2-bromo-4-phenylcarbazole **12f** and 2,3,4-trisubstituted carbazole **12g** were efficiently prepared. The pyrone could contain additional alkyl substituents, and cyclopentanone-substituted carbazole **12h** was prepared in high yield. Note that these carbazoles would be particularly difficult to make by the cyclization of the corresponding diphenylamines (e.g., Scheme 1, top).

Substitution was well tolerated on the phenyl ring of substrate **10** (i.e., R_1). Electron withdrawing trifluoromethyl (**12i**), halogen (**12j**), and carbomethoxy groups (**12k**) were all compatible with the reaction. Carbazoles bearing electron donating groups were also successfully prepared in high yield by this method. Specifically, dimethyl- (**12l**), methyl- (**12m**), and methoxy-substituted (**12n**) carbazoles were all formed. Carbazole **12o** was prepared from the corresponding substrate with two different alkyne groups; only the alkyne proximal to the pyrone undergoes cycloaddition. Finally, carbazole **12p** was made from the corresponding starting material with substitution on the alkyne, phenyl, and pyrone functional groups.

Sterically hindered biaryl molecules are important for modern materials applications, pharmaceuticals, and as ligands for catalysis.[17] Bicarbazole natural products are well-known.[18] The carbazole synthesis was used in the preparation of bicarbazoles and related molecules (Scheme 3). Alkyne **15** was dimerized using the Glaser method to give diyne **16**.[19] Treatment with the standard conditions induced tandem pericyclic cascades and produced bicarbazole **17** in excellent yield. Starting materials bearing additional substitution were also tolerated, and they gave more hindered bicarbazoles. Specifically, alkyne **18** was dimerized to give **19**. The pericyclic cascade gave substituted bicarbazole **20**. Such biaryls that have multiple substituents surrounding the biaryl axis are typically chiral molecules, with slow racemization rates at RT.[20] Bicarbazole **20** displayed chemical shift inequivalent geminal methylene protons, suggesting that the molecule has slow rotation about the biaryl bond (i.e., atropisomerism).

Biaryls lacking C_2-symmetry could also be prepared. Alkynylaminopyrone **15** was coupled with bromoalkyne **21** to give non-symmetric diyne **22**. Heating this molecule gave a tandem pericyclic cascade, and *in situ* oxidation[12] led to formation of 4-(4-indolyl)-carbazole **23**. Finally, alkyne **15** could be advanced to non-symmetric diyne **24** over four steps.[21] Treatment of **24** under our standard conditions gave non-symmetric bicarbazole **25** in excellent yield.

Clausine C is a substituted carbazole natural product originally isolated from the Asian shrub *Clausena excavata* (Scheme 4).[22] Clausine C has been prepared using several different synthetic strategies,[23] and we decided to showcase our current method in a synthesis of this target. Commercially available iodoaniline **26** underwent sequential cross-coupling reactions with TMS-acetylene[24] and 3,5-dibromo-2-pyrone[25] to give compound **10p**. Removal of the TMS protecting group

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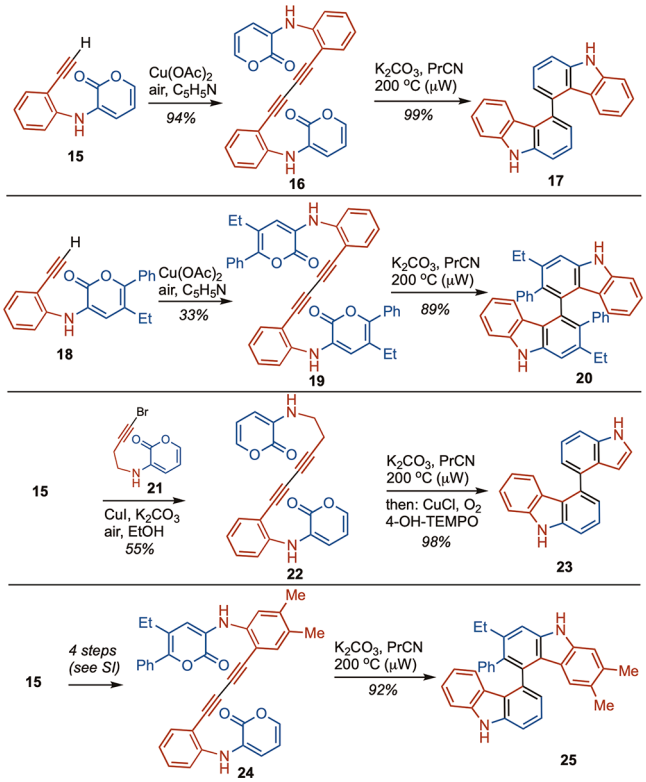
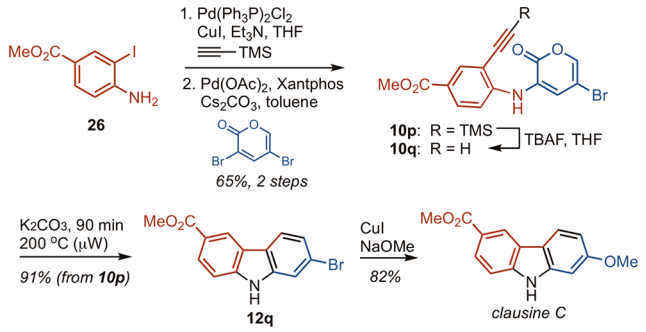
Scheme 3. Biaryl Syntheses



Scheme 4. Synthesis of Clausine C



gave key intermediate **10q** (with a trace amount of **12q**). Isolation and subjection of **10q** to our standard conditions induced smooth formation of substituted carbazole **12q** with complete control of substituent regiochemistry. The combined isolated yield of **12q** over the two steps was 91%. Bromocarbazole **12q** was converted into clausine C in good yield.[26] Overall, this is a five-step synthesis of clausine C from **26** in 48.5% yield, which compares well with previous strategies.[23,26]

In conclusion, a new regioselective carbazole synthesis has been discovered. The reaction allows for controlled substitution patterns at any carbazole position. Moreover, multiple substituents are conveniently incorporated on the carbazole framework. Symmetric and non-symmetric bicarbazoles and related molecules can be prepared using this method. Finally, we used the method in an efficient synthesis of the natural product clausine C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02449.

Experimental procedures, spectroscopic data, and depiction of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(14) All 2-pyrones used in this study were prepared according to literature precedent. See the Supporting Information for details.

(15) Compounds **10f** and **10p** were prepared from the corresponding 3-bromo-2-pyrone. See the Supporting Information for details.

(16) We believe that the base may serve to partially deprotonate **10**, leading to a more electron-rich diene. See ref 12.

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Schemes 1 and 2 were corrected on August 23, 2021.

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