Regioselective Synthesis of Substituted Carbazoles, Bicarbazoles, and Clausine C

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ABSTRACT: Substituted carbazoles are efficiently constructed from 3-trifluoro-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 carbazoles, show exciting activities for the treatment of cancers. 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). Elliptinium acetate contains a carbazole core structure. It is a DNA intercalator and a potent topoisomerase II inhibitor that is used to treat breast cancer. 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.

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 and continues to be an active area of research now.

There are many dozens of distinct approaches to carbazole synthesis, and comprehensive reviews have been written on this topic. 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, 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.

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.

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. We recently found that substituted indolines and indoles can be prepared from N-butynyl-3-amino-2-pyrones in the presence of base. In this manuscript, we describe how alkyne-tethered 3-anilido-2-pyrones (10) undergo intramolecular cycloadditions, presumably giving intermediates 11, which rapidly lose CO2 to form substituted carbazoles 12 (Scheme 1, bottom).

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

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Figure 1. Biologically active carbazoles.
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 (R3) were tolerated. Carbazoles bearing phenyl groups at C4 (12b and 12c) were formed in good yields. The alkyne may also contain an sp3-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 alkyld 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., R1). 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 biaryl 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).

Biaryl lacking C2-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 oxidation12 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-acetylene24 and 3,5-dibromo-2-pyrone25 to give compound 10p. Removal of the TMS protecting group...
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%. Bromo-carbazole 12q was converted into clausine C in good yield. Overall, this is a five-step synthesis of clausine C from 26 in 48.5% yield, which compares well with previous strategies.

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.

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