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A General Carbazole Synthesis via Stitching of Indole−Ynones with Nitromethanes: Application to Total Synthesis of Carbazomycin A, Calothrixin B, and Staurosporinone

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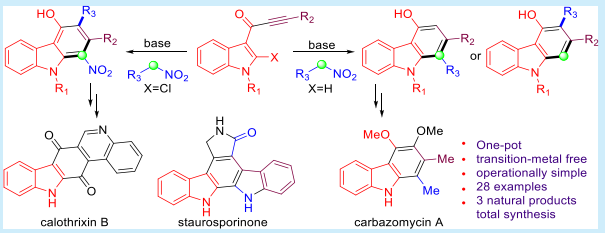
Supporting Information

ABSTRACT: A new, one-pot domino benzannulation reaction between indole-3-ynones and various nitromethane derivatives has been explored for a general entry to diversely functionalized carbazole frameworks (28 examples). The scope of this new benzannulation has been extended to variants like 2-chloroindole-3-ynones to eventuate in chemo-differentiated 1,2,3,4-tetrasubstituted carbazoles with retention of the nitro group. The efficacy of this strategy has been demonstrated through concise total synthesis of natural products, viz. carbazomycin A, calothrixin B, and staurosporinone (K252c).



Carbazoles are nitrogen-containing heterotricyclic motifs often found embedded in diverse natural products and pharmaceuticals of varying complexity and display a broad range of bioactivities such as anticancer, antipsychotic, antimicrobial, antibiotic, anti-inflammatory, and antioxidative, to name a few.[1] Additionally, carbazole based platforms serve as useful building blocks in the design of organic materials due to their hole-transporting, light-emitting, photoconductive, and photorefractive properties, Figure 1.[2] Due to the increasing importance of carbazole-based natural products and the emerging potential applications of functionalized carbazoles as materials, newer synthetic methods for their acquisition continue to be developed.[1−4] Apart from the classical reactions such as Fisher−Borsche synthesis, Graebe−Ullmann thermolysis, Cadogan reductive cyclization, and Knolker's Fe-complex mediated route, methods involving transition-metal-mediated cyclizations and insertions on diverse substrates have also been developed.[3] However, a strategy that employs indole templates as a launch pad toward carbazoles through a benzannulation tactic has gained increasing traction in recent years because of its ready access to the vast indole molecular bank. A few examples from this repertoire are captured in Scheme 1.[4]

The methods available for the construction of carbazoles, though plenty and serviceable, often entail multistep endeavors, use of precious metal catalysts (Pt, Au, Ag, Pd, etc.), and harsh reaction conditions and at times have limited functional group maneuverability.[3,4] Thus, there are opportunities for devising alternate, one-pot approaches from readily

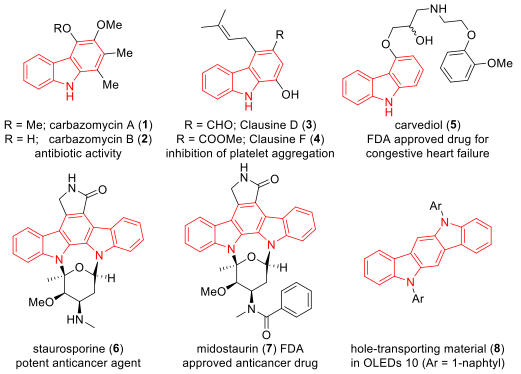
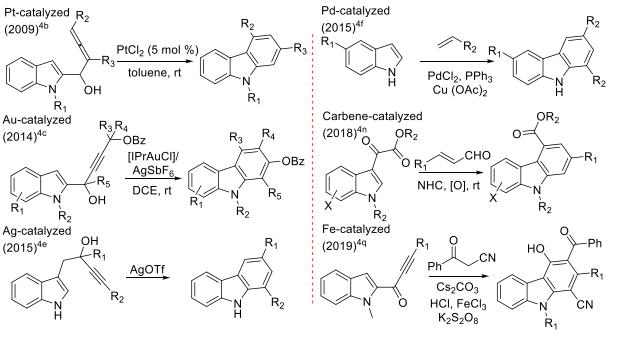


Figure 1. Prototypical carbazole natural products and pharmaceuticals.

Scheme 1. Illustrative Recent Approaches to Carbazoles from Indole Templates



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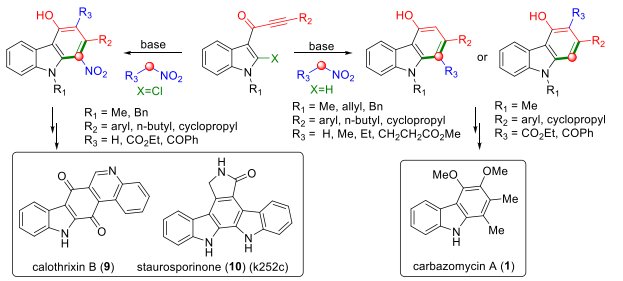
accessible indole precursors to access diversely functionalized carbazoles which are efficient and operationally simple.

In the past few years, ynones have emerged as valuable and widely sought building blocks to construct a variety of aromatic, heterocyclic, and carbocyclic compounds through multiple bond-forming processes.[5,6] Recently, our group has demonstrated a one-pot process for the efficient assembly of highly functionalized spirooxindoles[6a,b] and naphthalenes[6c] by harnessing a strategically embedded ynone moiety.[6] Further tactical advances[6c] have led to a general, one-pot synthesis of functionalized carbazoles through a domino benzannulation of indole-3-ynones/2-chloro-indole-3-ynones with diverse nitromethane(s); in this process, the later serves as a one carbon domino linker through a tandem Michael addition−iminium ion cyclization protocol, Scheme 2. In addition, many examples

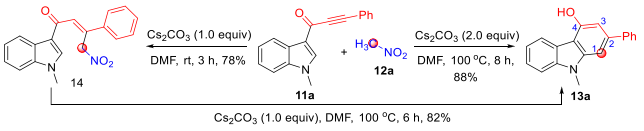
Scheme 2. Present Work on Carbazoles and Synthesis of Natural Products



(28) of diverse carbazole framework acquisition in one-pot, concise total syntheses of three complex bioactive carbazole natural products, viz. carbazomycin A **1**[3a,c,7] calothrixin B[8] **9**, and staurosporinone[9] **10**, of high contemporary interest are described.

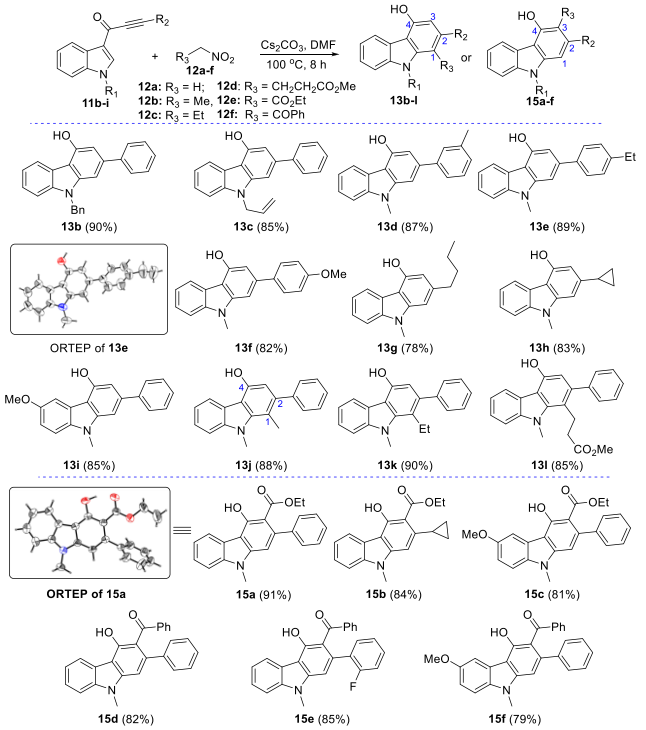
To begin, a reaction between indole-3-ynone **11a** [1-(1-methyl-1*H*-indol-3-yl)-3-phenylprop-2-yn-1-one, prepared in two routine steps from commercial indole-3-carboxaldehyde (Supporting Information, SI)] with nitromethane **12a** under optimized conditions [Cs_2CO_3 (2.0 equiv), DMF, 100 °C, 8 h, see the SI] delivered carbazole **13a** in 88% yield with substitution at the 2 and 4 positions, Scheme 3. When the reaction was performed under ambient conditions, only the Michael addition product **14** was observed, which further converted to the carbazole **13a**.

Scheme 3. Probing Experiment



Encouraged by this outcome, we proceeded to demonstrate the generality and scope of this tandem benzannulation employing eight variations of *N*-protected indole-3-ynones **11b−i** with nitromethane under the optimized conditions to furnish diverse carbazoles **13b−i**, respectively, in one-pot operation and in good yields, Scheme 4. To amplify the scope further, compatibility of the reaction for alkyl-substituted nitromethanes (**12b−d**) with indole-3-ynone (**11a**) was investigated to successfully deliver the corresponding 1,2,4-trisubstituted carbazoles **13j−l**, respectively, with an additional

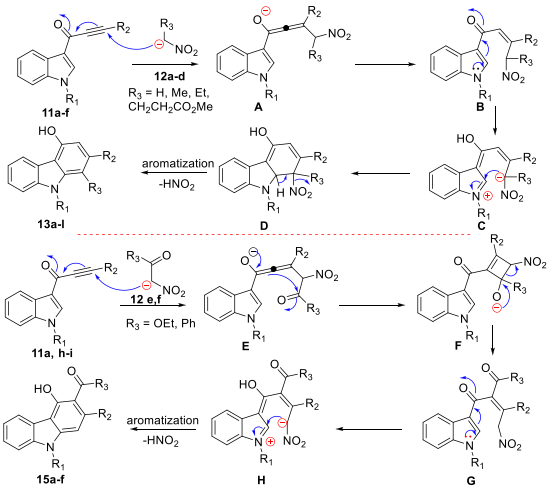
Scheme 4. Diverse Carbazoles from Indole-3-ynones and Nitromethanes



substitution on the newly formed phenyl ring at the much desired 1-position. The formation of carbazoles **13a−l** was secured through consistent and complementary spectral data and single-crystal X-ray structure determination on **13e**, Scheme 4. However, when ethyl nitroacetate **12e** or benzoylnitromethane **12f** was deployed as a reaction partner with ynones **11a**/**11h−j**, a welcome deviation[6c] in the reaction pathway was encountered to smoothly deliver carbazoles **15a−f**, respectively, and the structures were unambiguously secured through a single-crystal X-ray structure determination of **15a**, Scheme 4.

Possible reaction mechanisms for these tandem processes leading to carbazoles are depicted in Scheme 5 and have precedence.[5,6] Michael addition of nitromethane-derived anion

Scheme 5. Possible Reaction Mechanism



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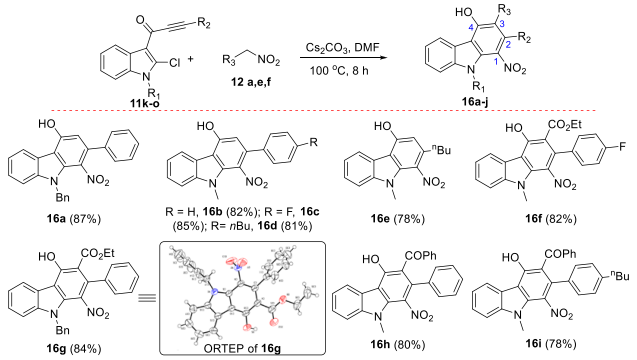
12a−d to ynones **11a−j** affords intermediate **A**, which tautomerizes to cyclic enaminoketone **B** and further rearranges to an iminium ion **C**. Intramolecular carbanion capture in iminium cation **C** and ejection of nitro group in **D**, driven by aromatization, eventuates in the corresponding carbazoles **13a−l**. On the other hand, in the case of doubly activated carbonyl bearing nitromethanes **12e,f** leading to **15a−f**, the initial Michael adduct **E**, through intramolecular Aldol-type addition, forms a strained cyclobutane intermediate **F**, Scheme 5. A retro-nitroaldol process involving C−C bond cleavage in **F** leads to intermediate **G**. Further generation of an iminium ion **H**, C−C bond formation through intramolecular charge collapse, ejection of the nitro group, and concomitant aromatization delivers **15a−f**, Scheme 5. A distinctive feature of this new carbazole synthesis is that the nitro group of nitromethanes **12a−f** functions as a sacrificial activator that vanishes after delivery.[10]

To further augment the utilitarian aspects of our carbazole synthesis and amplify the diversity and functional group density, it was of interest to explore the reaction between 2-haloindole-3-ynones and nitromethanes. For this purpose, 2-chloroindole-3-ynones **11k−o** were identified as the readily accessible partner substrates (see the SI) for nitromethanes **12a,e,f**. The ynones **11k−o** when reacted with nitromethane **12a** under optimized conditions delivered the corresponding substituted 1-nitrocarbazoles **16a−e** in good yields, Scheme 6.

Scheme 6. Scoping Reaction of 2-Chloroindole-3-ynones with Nitromethanes

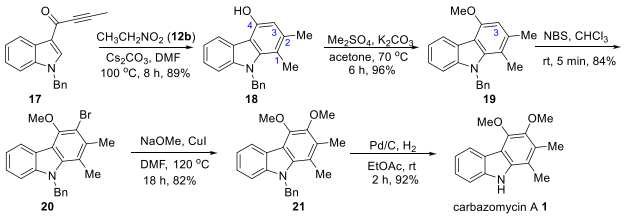


Furthermore, the β-carbonyl-substituted nitromethanes **12e,f** when reacted with ynones **11k−n** afforded the 1,2,3,4-tetrasubstituted carbazoles **16f−i**, respectively, in good yields, and their structures were unambiguously established on the basis of single-crystal X-ray analysis of **16g**, Scheme 6. Two features of this carbazole synthesis merit attention. First, all four substituents on the carbazole moiety are chemo-differentiated, and second, the presence of a 2-chloro substituent on the indole ynones alters the reaction course, and the nitro group is retained while the chlorine is eliminated to facilitate aromatization. A possible mechanism for the formation of carbazoles **16a-I** along precedented lines[5,6] is outlined in the SI.[10]

Having devised a viable new synthesis to carbazoles, it was natural to ask: How versatile and efficacious is this approach for the synthesis of diverse natural products? A credible answer to this is provided through three concise total syntheses of widely pursued, complex, carbazole-based natural product targets, viz. carbazomycin A **1**,[7] calothrixin B **9**,[8] and staurosporinone **10**.[9]

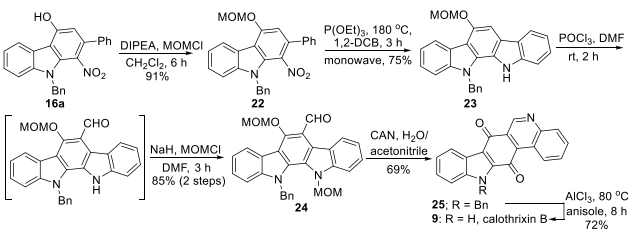
Carbazomycins, isolated from the spore-forming bacterium *Streptoverticillium*, represent the first group of antibiotics based on a carbazole scaffold and exhibit broad spectrum bioactvities.[11] These attributes, particularly the presence of the 1,2,3,4-tetrasubstituted carbazole moiety, have sustained widespread interest in their total synthesis for the past three decades.[7] Our quest toward carbazomycins, initially targeting carbazomycin A **1**, originated through reaction between indole-ynone **17** and nitroethane **12b** under optimized conditions (Cs_2CO_3, DMF, 100 °C) to afford trisubstituted carbazole **18** in good yield with the requisite 1,2-dimethyl substitution in place. Protection of the phenolic hydroxyl group as methyl ether **19**, NBS-mediated bromination to **20**, and S_NAr type reaction using NaOMe−CuI furnished the desired 1,2,3,4-tetrasubstituted carbazole **21**. Lastly, *N*-debenzylation was readily achieved through hydrogenolysis over Pd/C catalyst to furnish the natural product carbazomycin A **1** (54.1% overall yield after five steps), and its identity was confirmed through spectral comparison and single-crystal X-ray structure determination, Scheme 7.

Scheme 7. Synthesis of Antibiotic Natural Product Carbazomycin A 1



Next, we turned toward a "pseudo" carbazole alkaloid calothrixin B **9**, isolated from the cell extracts of cyanobacterial *Calothrix* species and exhibiting remarkable antiplasmodial and anticancer activity at nanomolar concentrations.[12] These attributes make **9** a promising and popular target for diversity creation and drug discovery efforts. Our carbazole synthesis appeared eminently geared for a convenient new synthesis of **9**. Toward this end, **16a** (vide supra, Scheme 6) was chosen as the starting point, and the phenolic hydroxy group was protected as MOM ether **22** to be followed by Cadogan reductive insertion of nitro group onto the adjacent phenyl ring using a monowave reactor to deliver indolocarbazole **23** quiet smoothly and efficiently. Further, Vilsmeier−Haack formylation on **23** was implemented to afford the intermediate aldehyde in which the newly installed NH group was MOM-protected to **24**, a maneuver considered necessary for further advance as noted earlier,[8g] Scheme 8. CAN mediated one-pot oxidation/hydrolysis/quinoline formation generated the phenanthridine bearing moiety **25**. Finally, $AlCl_3$-mediated *N*-

Scheme 8. Synthesis of Anti-Plasmodial and Anti-Cancer Calothrixin B 9



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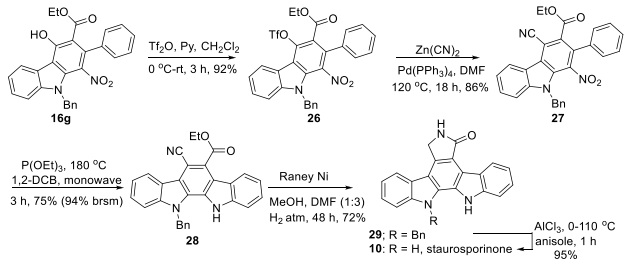
debenzylation[8g] in **25** afforded the natural product calothrixin B **9** (28.0% overall yield after six steps) with spectral data in complete agreement with the reported values.[8g]

Our last illustrative foray was targeted toward an anticancer natural product staurosporinone[13] **10**, the aglycon of potent anticancer drug candidate staurosporine[14] **6**, and FDA-approved drug midostaurin **7**.[15] These powerful indolo-carbazole alkaloids are microbial metabolites that were first isolated in 1986 from culture broths of *Nocardiopsis* sp. K-252 and *Nocardiopsis* sp. K-290 and were found to be potent inhibitors of protein kinase C.[14,15] Understandably, these indolo-carbazole natural products and, in particular, staurosporinone **10** have aroused great interest from the synthetic chemistry community,[9] and this target appeared to be a good testing bed for our carbazole methodology. Toward staurosporinone **10**, tetrasubstituted nitrocarbazole **16g** appeared fully serviceable, and the phenolic hydroxyl was converted to the corresponding triflate **26** which on further Pd-mediated coupling[16] afforded cyanated nitrocarbazole **27**. Cadogan reductive cyclization on **27** employing monowave heating delivered the pentacyclic indolo-carbazole **28** in decent yield. Raney-Ni reduction[17] of the cyano group in **28** to an amine and concomitant engagement with the adjacent ester group led to lactam **29** embodying the core structure of the natural product. Debenzylation in **29** with $AlCl_3$ in anisole delivered the target staurosporinone **10** in good yield (39% overall yield after five steps) and was found to be spectroscopically identical with the natural product, Scheme 9.

Scheme 9. Synthesis of Anti-Cancer Natural Product Staurosporinone 10



In summary, we have developed an efficient, one-pot strategy for the synthesis of carbazoles from a range of indole-3-ynones and nitromethanes. Several variants of this approach have been explored to map its scope for accessing a rich assortment of functionalized carbazoles. The potential of this new methodology has been reinforced through concise total synthesis of three diverse, bioactive carbazole alkaloids of topical interest, viz. carbazomycin A, calothrixin B, and staurosporinone.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01111.

Detailed experimental procedures and spectral data (^{1}H, ^{13}C, IR, and HRMS) for all new compounds (PDF)

Accession Codes

CCDC 1841112, 1849825−1849826, and 1891723 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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