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First Inverse Electron-Demand Diels–Alder Methodology of 3-Chloroindoles and Methyl Coumalate to Carbazoles

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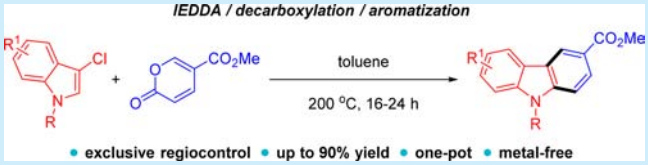
Supporting Information

ABSTRACT: The first successful inverse electron-demand Diels–Alder has been demonstrated with the 2-pyrone methyl coumalate in conjunction with substituted indoles. Utilizing 1-alkyl-3-chloroindoles as the electron-rich dienophile efficiently generates carbazoles without the need for additional metal catalysts. Through a thermal, one-pot Diels–Alder/decarboxylation/elimination domino sequence, access to a class of 3-methylcarbazoles is rapidly generated with exclusive regiocontrol in up to 90% yield.



The [4 + 2] cycloaddition has become a venerable strategy in synthetic routes to create sophisticated frameworks. Of utmost importance in achieving regioselectivity is synchronizing the electronics of the diene and dienophile. Contrary to the normal electron-demand (NED) Diels–Alder reaction, the inverse electron-demand Diels–Alder reaction (IEDDA) couples an electron-poor diene with an electron-rich dienophile and has been popularly incorporated into synthetic routes.[1] The Diels–Alder reaction has been a central initial reaction in domino sequences,[2] especially with azadienes toward complex heterocycles.[3]

Indoles are widely recognized as valuable synthons both as the diene and dienophile in Diels–Alder transformations[4] toward higher order alkaloids. In the former respect, vinyl-substituted indoles on the 2- or 3-position have been prepared as practical synthetic dienes.[4a,5] On the other hand, the 2,3-double bond of the indole was a dienophile in the first example of a removable tether in an intramolecular NED reaction by Kraus after activation with electron-withdrawing substituents.[6] The electron-rich nature of the 2,3-olefin on the indole appears to be an ideal dienophile; however, the capacity of indoles as dienophiles in the IEDDA is a greater challenge compared to enamines since it requires breaking the aromaticity of the heterocycle. Pioneering work by Sietz demonstrated that 7-azaindole is an effective dienophile with 1,2,4,5-tetrazine,[7] after which researchers pursued reactive dienes for the IEDDA. Snyder was an early proponent who explored the scope with azadienes;[1b] more recently, the approach has been incorporated into syntheses of complex heterocycles,[1d,8] including key steps to strychnine.[9] However, the nucleophilicity of the 3-position sometimes interferes with the desired IEDDA reaction[10] and the scope in many cases is limited to intramolecular reactions.

In the context of pyrone and indole Diels–Alder reactions, only fused pyrano[3,4-*b*]indoles have been utilized as dienes;[11] however, electron-deficient pyrones with indoles in an IEDDA reaction are absent from the literature. Although azadienes are highly effective in many instances, Snyder's early work acknowledged that methyl coumalate was unreactive toward substituted indoles under his reaction conditions.[10] However, methyl coumalate has emerged as a versatile springboard for diversification[12] and can easily be obtained through the dimerization of natural-occurring malic acid.[13] 2-Pyrones have been examined as dienes, primarily to further manipulate the bicyclo[2.2.2]octene adduct.[14] Interest in green aromatic compounds has resulted in precedent to regioselectively generate functionalized aromatics through an IEDDA/decarboxylation/elimination cascade from methyl coumalate.[12a]

We endeavored to develop a general approach to extend the applicability of indoles as dienophiles in the IEDDA reaction. We will present a novel regioselective annulation methodology featuring an IEDDA between 3-chloroindoles and the 2-pyrone methyl coumalate to generate natural and synthetic carbazoles, which is the first report between the two specified Diels–Alder components.

Carbazoles are a class of aromatic alkaloids[15] with expansive applications from materials science[16] to natural products with antiviral, antimalarial, and antitumor activity.[15b,17] The vast majority of biologically active carbazoles are isolated from plants of the family Rutaceae[15b] and generally arise from the 3-methylcarbazole scaffold. Elaborated derivatives possess oxygenated substituents or higher oxidation states at the 3-position (Figure 1). Attaining **1**–**4** and related targets remains an attractive area of research achieved via a range of disparate synthetic routes (Scheme 1).[18] Metal catalysts are common among the pathways, which are challenging to completely remove and are detrimental for further biological studies. In particular, the Itami and Lei protocol depends on the interaction of multiple metals, with some in greater than stoichiometric amounts.[18e]

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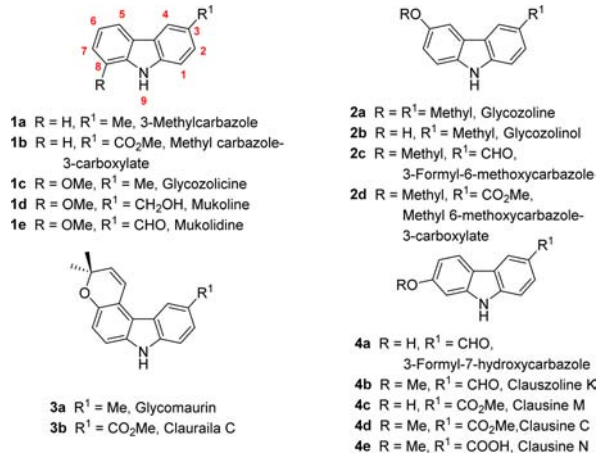
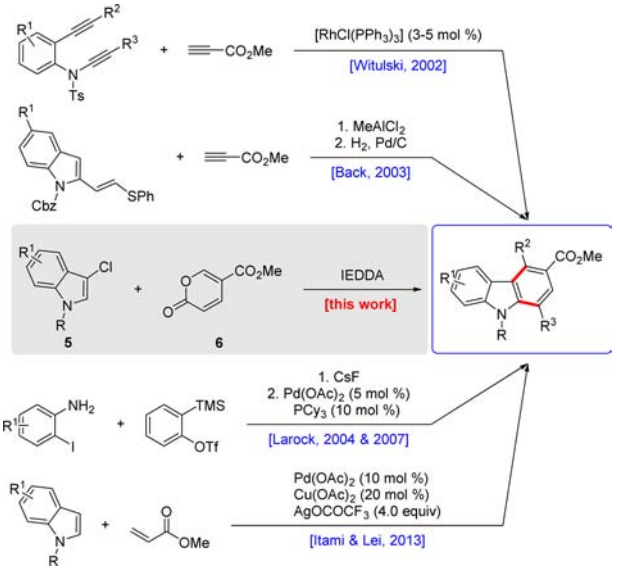


Figure 1. Naturally occurring 3-methylcarbazole and derivatives accessible through present methodology.

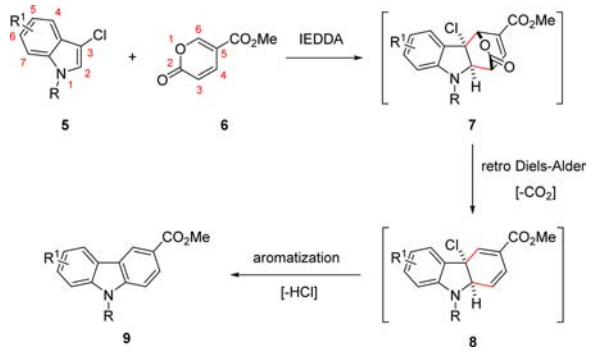
Scheme 1. General Approaches to Targeted Carbazoles[18]



Furthermore, highly substituted aromatics or advanced precursors necessitate multistep syntheses and can lead to regioisomeric mixtures as described in the Witulski route,[18a] which complicates purification. Our proposed methodology targets the 3-methylcarbazole family from which biological activity arises, where the methyl coumalate ester functionality exactly maps onto the carbazole 3-position and makes it an ideal platform to directly construct the basic skeleton. We envisioned that functionalizing the indole with a leaving group would lead to the IEDDA-initiated cascade reaction to aromatize and reveal carbazoles without metal catalysts while simultaneously allowing flexibility for analogue development.

In our earlier work, the Diels–Alder/decarboxylation/elimination sequence with ketal dienophiles positioned a methoxy group to facilitate aromatization and eliminated the need for an oxidation catalyst.[12a] With a benzofuran dienophile, a biphenyl system was generated since the phenol-like intermediate functioned as a good leaving group in the adduct.[12a] Considering the precedent for ring-opening with benzofurans, we decided to add a good leaving group on the indole 3-position to prevent analogous ring-opening (Scheme 2).

Scheme 2. Proposed Mechanism to Carbazoles



The leaving group would similarly keep the reaction metal free since thermal conditions would induce elimination from **8** because it is one step away from carbazoles. We selected halides as the leaving group because they have the advantage of easy introduction to the indole 3-position. Furthermore, they are electronegative, neutral species, which enables the indole to maintain its unidirectional dipole and favor the high IEDDA regioselectivity. Although 3-bromoindoles were initially attempted with **6** at 200 °C in toluene, only a complex mixture resulted. Subsequently, 3-chloroindoles were subjected to the reaction conditions, but only trace amounts of carbazole were observed, along with insoluble tar formation. The difficulties led us to consider adding an electron-donating protecting group on the indole 1-position to attenuate tar formation yet uphold the electronics of the IEDDA.

Protecting group investigation on the 3-chloroindole commenced with silyl groups. Unfortunately, neither TMS, TBS, nor TIPS resulted in carbazole formation; rather, decomposition of the indole starting material occurred, as evidenced by ^{1}H NMR. We anticipated in situ deprotection may result with the MOM protecting group after the reaction cascade, but again only decomposition was observed. Finally, we settled on alkyl protecting groups to investigate the scope and limitations of the methodology since methyl and benzyl indoles were stable to the reaction conditions, and the latter could be deprotected to generate naturally occurring carbazoles.

Upon arriving at a good protecting group, we conducted some preliminary work with Lewis acids intending to decrease the reaction temperature. However, intractable tars resulted from 65 to 150 °C, which may have been due to indole oligomerization with Lewis acids.[19] The crude ^{1}H NMR spectra showed promising carbazole peaks, but the reactions were no longer regioselective (~1:1 ratio). The decreased regioselectivity may be ascribed to the fact that Lewis acids in IEDDA reactions tend to competitively and preferentially coordinate to the electron-rich dienophile.[1b]

We abandoned Lewis acid mediation and systematically optimized the reaction conditions for the 1-benzyl-3-chloroindole (**5a**) model system as elaborated in Table 1. The entries focus on trials with toluene as the solvent and temperatures at 200 °C based on our previous work.[12a] The tabulated ratios indicate that increasing reaction time to 16 h positively influences product formation, after which no significant increase is observed. Along the parameter of equivalents of **6** relative to **5a**, an excess of **6** promotes full conversion.

While the unconsumed **6** is largely conserved, some tars and the trimethyl 1,3,5-benzenetricarboxylate side product become

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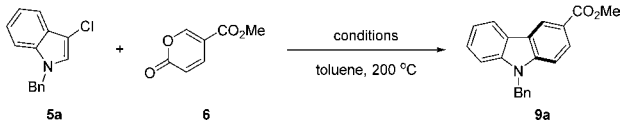
Table 1. Reaction Optimization Trials



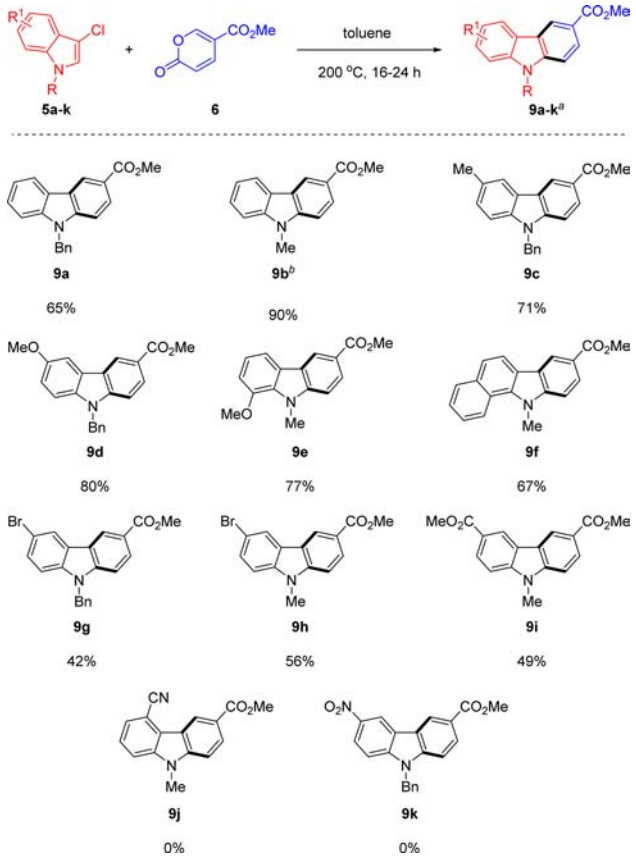
entry	time (h)	equiv **6**	concn (M)	**9a**:**5a** ratio[a]
1	6	10	0.5	1:5.5
2	16	10	0.2	1:0
3	16	6	0.1	1:0.8
4	**16**	**6**	**0.2**	**1:0**
5	16	5	0.2	1:0.1
6	16	5	0.2	1:0.1
7	16	3	neat	1:2.4
8	16	3	0.2	1:4.0
9	16	3	0.05	1:6.7
10	24	3	0.2	1:0.5
11	48	3	0.2	1:0.4

[a]Ratios determined by integration of crude ^{1}H NMR. Yields were not obtained with the exception of entry 4, which was isolated as 65%.

more pronounced as the conditions approach 10 equiv (Table 1, entries 1 and 2). Lastly, concentration plays a principal role as some solvent is essential, but altering concentration outside 0.2 M hinders the reaction outcome.

After optimizing the reaction conditions according to the model system to generate **9a** in 65% yield, we turned toward exploring the scope to determine the methodology's generalizability (Scheme 3). We commenced with 1-methylindole **5b** since similar 9-alkylcarbazoles display antiviral activity.[15e] The conditions cleanly afforded **9b** in 90% yield, after which we strived to enhance the electronics and favor the IEDDA more strongly with electron-donating substituents on the indole 5- or 7-position. As expected, the domino sequence furnished **9c** in 71% yield, which is higher than the corresponding model system **9a**. By predisposing the reaction with a more electron-rich methoxy group, the yields increased to 80% and 77% of **9d** and **9e**, respectively, as single regioisomers. Encouraged by the results, we extended the π-system of the carbazole with indole **5f** and discovered a route to tetracyclic analogs of methyl 3-carbomethoxy-11*H*-benzo[*a*]carbazole with **9f** in 67% yield. Our initial success fueled the investigation to incorporate halogenated substituents as a convenient moiety for potential cross-coupling to further functionalize the resultant carbazole. Halogens are slightly deactivating overall but have characteristics between strictly electron-withdrawing and electron-donating groups. While we were able to obtain the desired 9-benzylcarbazole **9g**, the 42% yield was lower than the parent carbazole **9a** during the standard reaction time frame. More electron-deficient indoles tend to react more slowly and require longer reaction time, but we did not extend the time beyond 24 h from an efficiency perspective. However, an improved yield of 56% resulted after reverting to the corresponding 9-methylcarbazole **9h**. Although it seems counterintuitive to add an electron-withdrawing group on the initial indole moiety, we surmised that the ester functionality was mild enough to mitigate the donating effect of the nitrogen on the dienophile. Our prediction was rewarded when we arrived at carbazole **9i** in 49% yield, again with complete regiocontrol. Unfortunately, the cyano- and nitro- substitutents (**9j** and **9k**) were too highly deactivating to allow the reaction to proceed; however, their nonreactivity confirms the critical importance of effectively matching the electronics of the diene and dienophile.

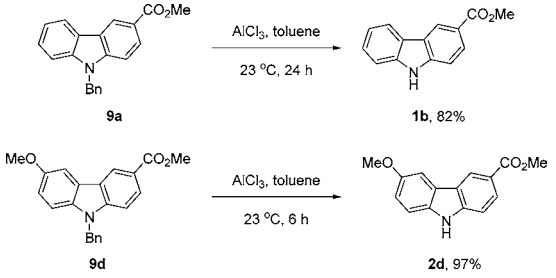
Scheme 3. Scope and Limitations of Methodology[a]



[a]The reactions are performed with **5a**–**k** (1 equiv) and **6** (6 equiv) at 200 °C in a sealed tube with toluene (0.2 M). All yields are isolated. Reaction time was 24 h for **9f**–**i**. [b]Acetonitrile was used as the solvent.

With a number of successful carbazoles achievable through our methodology, all that remained toward synthesizing naturally occurring carbazoles was a trivial deprotection, presented in Scheme 4. By slightly modifying the literature

Scheme 4. Final Deprotection Step in Synthesis to Naturally Occurring Carbazoles[a]



[a]The reactions are performed with **9a** or **9d** (1 equiv) and $AlCl_3$ (6 equiv) with toluene (0.1 M) at the specified reaction conditions. All yields are isolated.

conditions,[20] benzyl deprotection with aluminum trichloride at room temperature readily afforded the biologically active carbazoles **1b** and **2d** in 82% and 97% isolated yields, respectively, which matched the characterization data previously reported in the literature.[21]

Although we only physically synthesized two naturally occurring carbazoles, we believe our methodology capably

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provides the key step to a formal synthesis of all the carbazoles cited in Figure 1[22] after straightforward manipulation of the oxidation states.[23]

In summary, we have documented the first instance of substituted indoles as dienophiles in an IEDDA reaction with the 2-pyrone, methyl coumalate. The metal-free IEDDA/decarboxylation/elimination reaction sequence promoted solely by thermal conditions occurs in good to excellent yields with complete regioselectivity. The key that led to the reaction's success was utilizing 1-alkyl-3-chloroindoles as the dienophile which did not disrupt the inherent electron-rich nature of the indole. The chloride substituent offers the additional trifold advantages of being facilely installed, being a good leaving group to prevent ring-opening of the Diels–Alder adduct, and rendering metal catalysts unnecessary by stimulating aromatization. The methodology allows rapid entry to the carbazole backbone and has been instrumental in the synthesis or formal synthesis of biologically active targets. Overall, our discovery to combine indole dienophiles with electron-deficient pyrones in an IEDDA has established a strategy for the synthetic community to access targeted complex alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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