INTRAMOLECULAR DIELS-ALDER REACTIONS OF 2-VINYLINDOLES : A NEW APPROACH TO FUNCTIONALIZED CARBAZOLES

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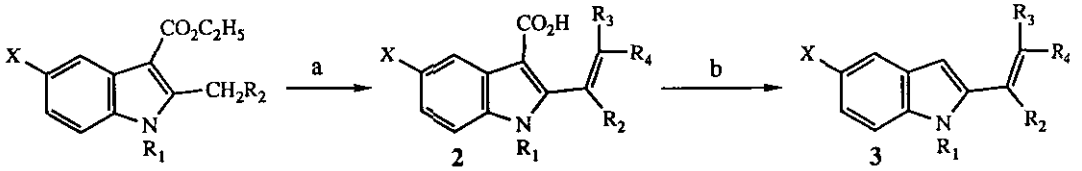
Abstract - Intramolecular Diels-Alder reactions of 2-vinylindoles are discussed. When the dienophile is appended to C2 of the 2-vinylindole, these reactions represent a novel approach to carbazole derivatives.

Recently we disclosed a simple, two step synthesis of 2-vinylindoles,[1] a class of indole derivatives which, although previously difficult to synthesize, are important intermediates for many indole derivatives, including natural products.[2] This methodology, summarized in Scheme 1, utilized 2-alkylindole-3-carboxylates (**1**) in a one pot procedure to form 2-vinylindole-3-carboxylic acids (**2**) via deprotonation of the C2 methylene, attack of the resulting stabilized anion on an aldehyde or ketone, lactonization of the resulting alkoxide, and finally "internal elimination" of the carboxylic acid to yield **2**.[3] The C3-unsubstituted 2-vinylindoles (**3**) were then readily available via thermal decarboxylation of **2**. This two pot synthesis of 2-vinylindoles resulted in moderate to excellent yields of **3** from **1** with a wide variety of substituents. As a result of the ease of this methodology, we sought to explore new uses for 2-vinylindole derivatives. In this communication, we would like to outline our preliminary discoveries concerning the use of 2-vinylindoles as 4π components in *intramolecular* Diels-Alder reactions.

Scheme 1



1
(a: X=CH_3O, R_1=CH_3, R_2=H)

a : 1) LDA, THF, -78° C; 2) R_3R_4C=O; 3) $NaOCH_3$, Δ
b : bromobenzene, reflux (156° C)

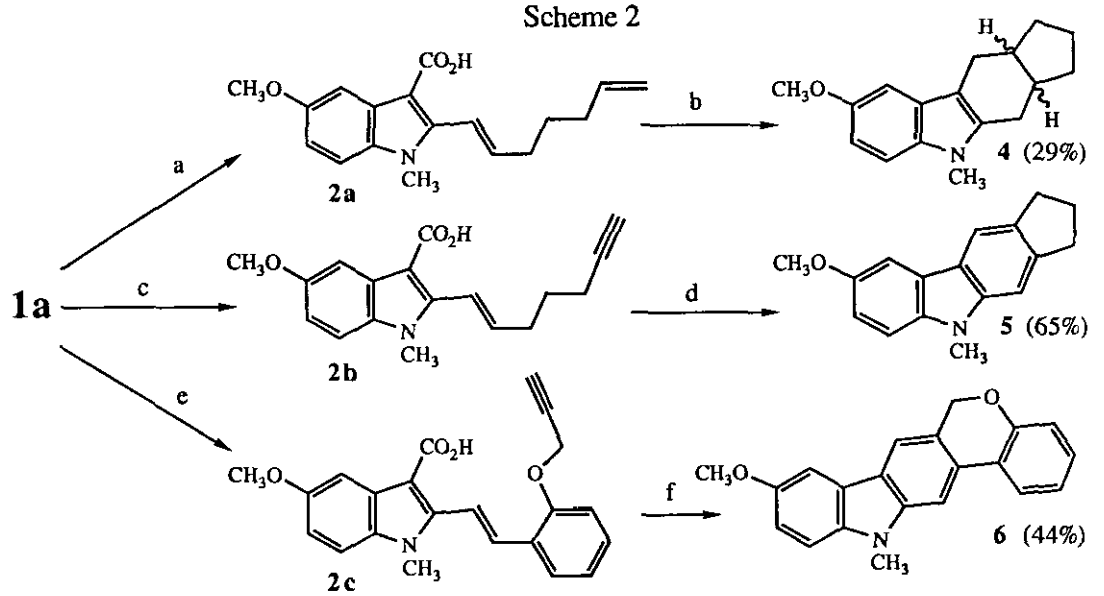
The Diels-Alder reactions of vinylindoles has been recently reviewed.[2] Because of their ease of availability, 3-vinylindoles have been a primary focus in this study, and the *intermolecular* Diels-Alder reactions of 3-vinylindoles have been shown to be a viable methodology for the synthesis of complex indole derivatives. The corresponding *intermolecular* Diels-Alder reactions of 2-vinylindoles have been less studied as a result of the difficulties surrounding the synthesis of these compounds. However, recently Pindur and co-workers have begun an extensive examination of this particular cycloaddition reaction.[4] Because of the aromatic nature of their 4π component, vinylindoles react primarily with highly activated, electron poor dienophiles in *intermolecular* Diels-Alder reactions.

While the *intramolecular* version of these cycloadditions would seem to be a particularly attractive methodology for the synthesis of functionalized indoles and natural products, there have been only two examples of this type of intramolecular cyclization found in the literature. Before 1987, the only instance of an *intramolecular* Diels-Alder reaction of a vinylindole was the elegant work of Kuehne and co-workers[5] using highly polarized, activated 2-vinylindoles formed *in situ* for the synthesis of *Aspidosperma* alkaloids. Recently, two groups have reported utilizing 3-(1H-indol-3-yl)-2-propenoates in *intramolecular* Diels-Alder reactions of 3-vinylindoles, demonstrating the utility of 3-vinylindoles in *intramolecular* Diels-Alder reactions.[6] In 1987, Blechart and co-workers[7] developed a synthesis of 2-vinylindoles for the attempted formation of appropriately tethered 2-vinylindoles for intramolecular Diels-Alder reactions. This work, however, failed to provide the necessary 2-vinylindole derivatives. In light of these reports, we wish to disclose our preliminary findings on the first examples of *intramolecular* Diels-Alder reactions of novel, unactivated 2-vinylindoles as an approach to the carbazole heterocycle. Carbazoles represent the heterocyclic backbone of a number of natural products,[8] including ellipticine (used as an anticancer medicament), and new synthetic routes to this ring system are still a focus for research.[9]

The reaction of ethyl 1,2-dimethyl-5-methoxyindole-3-carboxylate (**1a**) with 5-hexenal[10] and 5-hexynal[10] under the reaction conditions previously described[1b] afforded modest yields of the desired 2-(1,6-heptadienyl)indole-3-carboxylic acid[11] (**2a**, 37%) and 2-(hept-1-en-6-ynyl)indole-3-carboxylic acid (**2b**, 18%), respectively (Scheme 2). These procedures were not optimized for these highly reactive aldehydes, and there was difficulty in obtaining these aldehydes pure, even after careful distillation. Additionally, it should again be emphasized that these yields actually represent the sum of three distinct chemical transformations: attack of the C2 methylene anion on the aldehyde, lactonization of the resulting alkoxide,

and "internal elimination" of the carboxylic acid to yield **2**. The reaction of the anion of **1a** with 5-hexynal appeared to be especially poor as demonstrated when this reaction was quenched at -78° C, and only 43% of the desired alcohol was isolated.[1b] Heating the olefin (**2a**) in refluxing bromobenzene effected decarboxylation of **2a** (as seen via ^{1}H nmr), but no cycloaddition was detected. When the solvent was replaced by refluxing triisopropylbenzene (232° C, 18 h), the desired intramolecular Diels-Alder reaction occurred, and a 4:1 mixture of diastereomers of the expected tetrahydrocarbazole (**4**)[12] (after olefin migration for rearomatization) was isolated in 29% yield from **2a** (Scheme 2).

Scheme 2

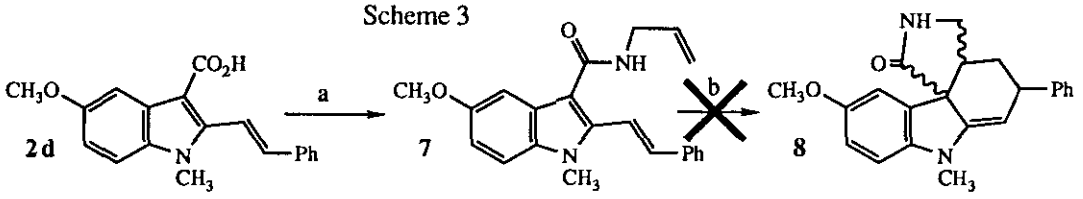


a : 1) LDA, THF, -78° C; 2) 5-hexenal; 3) $NaOCH_3/CH_3OH$, Δ
b : refluxing triisopropylbenzene (232° C), 18 h
c : 1) LDA, THF, -78° C; 2) 5-hexynal; 3) $NaOCH_3/CH_3OH$, Δ
d : refluxing nitrobenzene (210° C), 7 h
e : 1) LDA, THF, -78° C; 2) 2-(2-propynoxy)benzaldehyde; 3) $NaOCH_3/CH_3OH$, Δ
f : refluxing nitrobenzene (210° C), 3 h

While the conditions needed to effect cyclization were not especially mild, this reaction is significant in that it demonstrates that the simplest version of an intramolecular Diels-Alder reaction of a 2-vinylindole is a viable reaction. Alternatively, heating the alkyne (**2b**) in refluxing nitrobenzene (210° C) for 7 hours afforded the carbazole (**5**)[13] directly in 65% isolated yield. This yield is significant in that it represents the sum of three processes: decarboxylation, cycloaddition, and oxidation (dehydrogenation). The oxidant in this reaction has not yet been identified. The relative ease and greater yield of this cycloaddition might be understood using

frontier molecular orbital theory. One would expect a smaller HOMO/LUMO energy gap between the relatively electron rich 2-vinylindole diene and the relatively electron poor alkyne (compared to an olefin) than in the case of the vinylindole and olefin. This lower energy gap should lead to increased reactivity, the need for less vigorous reaction conditions, and a higher yield. The synthesis of the dihydrobenzopyrano[4,3-b]carbazole (**6**) further demonstrated the utility of this novel approach to carbazoles. Reaction of **1a** with 2-(2-propynyloxy)benzaldehyde[14] afforded the alkyne (**2c**) in 41% yield. Heating **2c** in refluxing nitrobenzene for 3 hours afforded the fused carbazole (**6**)[15] in 44% yield via the same decarboxylation, cycloaddition, dehydrogenation route. Clearly, this methodology presents a new approach to carbazole derivatives which is complimentary to existing methods. We hope to expand the scope of this methodology in the future.

Scheme 3



a : 1) carbonyldiimidazole; 2) allylamine
b : refluxing bromobenzene (156° C), 48 h

Of note is the failed intramolecular cycloaddition of 2-vinylindole (**7**) shown in Scheme 3. Reaction of **2d**[1b] with carbonyldiimidazole followed by allylamine afforded only a low yield of the desired allyl amide (**7**, 14%) (Scheme 4). The major product of this reaction was the imidazyl amide (53%), which was unusually inert to nucleophiles. Heating **7** in refluxing bromobenzene (156° C) for 2 days regenerated only starting material (**7**) with no products seen arising from cycloaddition. While this reaction involves a sterically congested system, this approach to compounds such as **8** might represent a novel entry into these highly functionalized indole derivatives.

In conclusion, we have demonstrated that intramolecular Diels-Alder reactions of 2-vinylindoles are synthetically useful and yield novel carbazoles. We hope to continue to examine further the scope of this methodology, including the synthesis of natural products. We will examine more closely the ability to effect intramolecular Diels-Alder reactions of 3-alkynylalkyl-2-vinylindoles.

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2. For a review of the synthesis and chemistry of 2-vinylindoles, see: U. Pindur, Heterocycles, **1988**, 27, 1253.
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8. A recent example of some new carbazole natural products can be found in: M.R. TePaske, J.B. Gloer, D.T. Wicklow, and P.F. Dowd, J.Org. Chem., **1989**, 54, 4743.
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10. T.C. Adams, D.W. Combs, G.D. Daves, and F.M. Hauser, J. Org. Chem., **1981**, 46, 4582.
11. All new compounds described in this communication have been characterized by ^{1}H nmr, ^{13}C nmr, ir, lrms, and elemental analysis and/or hrms.
12. Spectral data for **4** is as follows: ^{1}H Nmr ($CDCl_3$) δ 7.11 (d, J=8.5 Hz, 1H), 6.91 (d, J=2.2 Hz, 1H), 6.78 (dd, J=2.2 and 8.5 Hz, 1H), 3.83 (s, 3H), 3.57 (s, 3H), 3.02-2.94 (m, 2H), 2.40-2.27 (m, 2H), 2.04-1.94 (m, 2H), 1.84-1.66 (m, 3H), 1.54-1.51 (m, 1H), 1.42-1.30 (m, 2H). High resolution ms calcd for $C_{17}H_{21}NO$ (M^+): 255.1624. Found: 255.1621 (0.6 ppm deviation).

13. Spectral data for **5** is as follows: mp, 135.5-136.0° C; ^{1}H nmr ($CDCl_3$) δ 7.87 (s, 1H), 7.53 (d, J=2.5 Hz, 1H), 7.25 (d, J=8.8 Hz, 1H), 7.21 (s, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 3.08 (t, J=6.9 Hz, 2H), 3.06 (t, J=6.8 Hz, 2H), 2.17 (quintet, J=7.3 Hz, 2H); ^{13}C nmr ($CDCl_3$) δ 153.3, 143.0, 141.3, 136.4, 134.8, 123.1, 121.5, 115.3, 113.8, 108.8, 104.1, 103.2, 56.2, 33.5, 32.4, 29.2, 26.5. Anal. calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.27; H, 6.70; N, 5.52.

14. A. Padwa, A. Ku, H. Ku, and A. Mazzu, J. Org. Chem., **1978**, 43, 66.

15. Spectral data for **6** is as follows: mp, 198.0-200.0° C; ^{1}H nmr ($CDCl_3$) δ 7.88 (d, J=8.7 Hz, 1H), 7.75 (s, 1H), 7.57 (s, 1H), 7.50 (d, J=2.3 Hz, 1H), 7.29-7.23 (m, 2H), 7.13-7.05 (m, 3H), 5.27 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H); ^{13}C nmr ($CDCl_3$) δ 155.1, 153.7, 141.9, 136.7, 129.1, 128.1, 124.2, 123.4, 122.8, 122.6, 122.1, 121.9, 117.6, 116.2, 115.0, 109.2, 103.2, 102.0, 69.4, 56.1, 29.2. High resolution ms calcd for $C_{21}H_{17}NO_2$ (M^+): 315.1260. Found: 315.1194 (21 ppm deviation).

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