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# A Novel Generation of Indole-2,3-quinodimethanes

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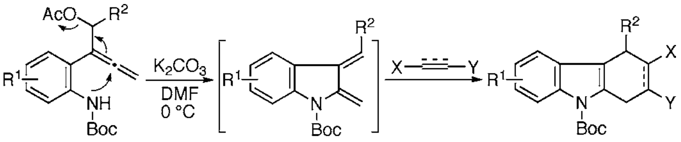
## ABSTRACT

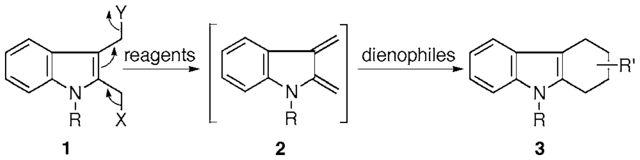


$R^1$=H, OMe, $OCH_2O$, Cl, $CO_2Et$; $R^2$=H, Me

**A novel and efficient procedure for the generation of the reactive indole-2,3-quinodimethane intermediates from the allenylanilines is described. The indole-2,3-quinodimethane intermediates were captured by several dienophiles to afford the corresponding tetrahydro- and dihydrocarbazole derivatives. This method is significantly different from the previously reported ones, which involve the 1,4-elimination or its related reactions of the indole derivatives that possess suitable substituents at both the C-2 and C-3 positions.**

The 2,3-bis(methylene)-2,3-dihydroindole system, the so-called indole-2,3-quinodimethane **2**,[1] is a kind of *o*-quinodimethane[2] and well-known to be a powerful diene in the Diels−Alder reaction resulting in the efficient formation of tetrahydro- and dihydrocarbazoles and their related compounds **3**. As described in Scheme 1, almost all of the procedures[1,3] hitherto reported for in situ generation of this reactive indole-2,3-quinodimethane **2** take advantage of the 1,4-elimination-type or related reactions of the 2,3-disubstituted indole derivatives **1**.[4]

**Scheme 1**



Recent efforts in this laboratory[5] disclosed a one-step preparation of the 2,3-disubstituted indoles **7** by the Stille coupling reaction of the *N*-(*tert*-butoxycarbonyl)-2-iodoanilines **4** with the 1-(*tert*-butyldimethylsiloxy)methyl-1-(tributylstannyl)allenes **5** via the 2-allenylanilines **6** (Scheme 2). When this ring-closing reaction was carried out in the absence of tetra-*n*-butylammonium chloride (TBAC), the allenyl derivatives **6** could be isolated in high yields. Therefore, we postulated that adjustment of the siloxy functionality of **6** with a suitable leaving group (e.g., compound **8**), followed by the intramolecular $S_N2'$ reaction by the nitrogen functionality, as depicted in Scheme 2, would lead to the novel generation of the indole-2,3-quinodimethane **2**, which should react with dienophiles already present in the reaction vessel. This letter describes a new and efficient synthesis of the indole-2,3-quinodimethane, which results

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[1] (a) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35−41. (b) Pindur, U.; Erfanian-Abdoust, H. *Chem. Rev.* **1989**, *89*, 1681−1689 and references therein.

[2] (a) Oppolzer, W. *Synthesis* **1978**, 793−802. (b) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873−2889. (c) Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proc. Int.* **1991**, *23*, 237−272. (d) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199−3246.

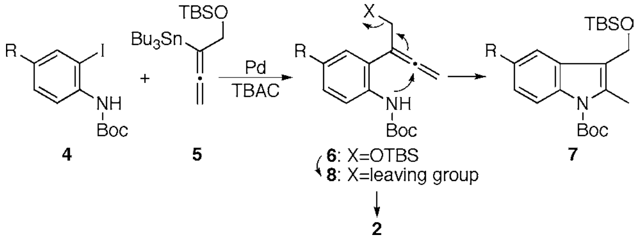
[3] For recent references, see: (a) Vice, S. F.; Nandin de Carvalho, H.; Taylor, N. G.; Dmitrienko, G. I. *Tetrahedron Lett.* **1989**, *30*, 7289−7292. (b) Fray, E. B.; Moody, C. J.; Shah, P. *Tetrahedron* **1992**, *49*, 439−450. (c) Rao, M. V. B.; Satyanarayana, J.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1995**, *36*, 3385−3388. (d) Ciganek, E.; Schubert, E. M. *J. Org. Chem.* **1995**, *60*, 4629−4634. (e) Jakiwczyk, O. M.; Nielsen, K. E.; Nandin de Carvalho, H.; Dmitrienko, G. I. *Tetrahedron Lett.* **1997**, *38*, 6541−6544. (f) Laronze, M.; Sapi, J. *Tetrahedron Lett.* **2002**, *43*, 7925−7928.

[4] The formation of the indole-2,3-quinodimethane by the sulfur dioxide extrusion of the thieno[3,4-*b*]indole dioxide was also reported.[3a]

[5] Mukai, C. Takahashi, Y. *Org. Lett.* **2005**, *7*, 5793−5796.

10.1021/ol060418n CCC: $33.50

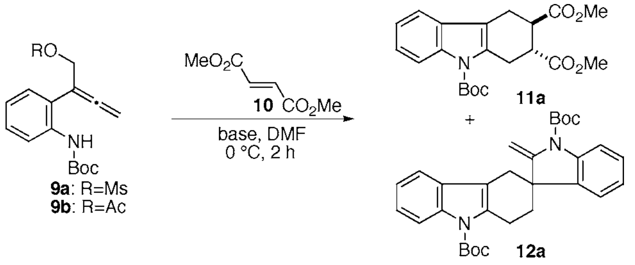
**Scheme 2**



from the simultaneous construction of both the indole nucleus and a 2,3-bis(methylene) functionality by a one-pot synthesis.

Our initial evaluation of this proposed methodology was carried out using the mesylate **9a**[6] and dimethyl fumarate (**10**) under basic conditions (Table 1). A solution of **9a** and **10** in DMF was treated with $K_2CO_3$ at 0 °C for 2 h to afford the desired tetrahydrocarbazole derivative **11a** in 76% yield along with the known dimer **12a**[7] of the indole-2,3-quinodimethane intermediate in 13% yield (entry 1). $Cs_2CO_3$ in DMF provided a slightly better result (81% yield) than the other bases (entry 2). Similarly, NaH effected the formation of the indole-2,3-quinodimethane to produce **11a** in 77% yield (entry 3). Other solvents, such as DMSO, THF, benzene, and $CH_2Cl_2$, were more ineffective than DMF. Although the simultaneous formation of the indole-2,3-quinodimethane intermediate and the [4 + 2] cycloaddition could be achieved, the reliable reproducibility of this transformation was not realized, presumably due to the instability[8] of the mesylate **9a**. Therefore, we next examined the reactivity of the corresponding acetate **9b**,[6] which is more stable and easier to handle than the mesylate **9a**. Treatment of **9b** with the two carbonates afforded the desired product **11a** in high yields without the formation of the dimer **12a** (entries 4 and 5). Furthermore, the better result was obtained when the reaction was performed using a syringe pump[9] (entry 6). Thus, the allenyl acetate group was shown to be a suitable functionality for our purpose.

**Table 1.** Reaction of Allenylanilines **9a**,**b** with Dimethyl Fumarate

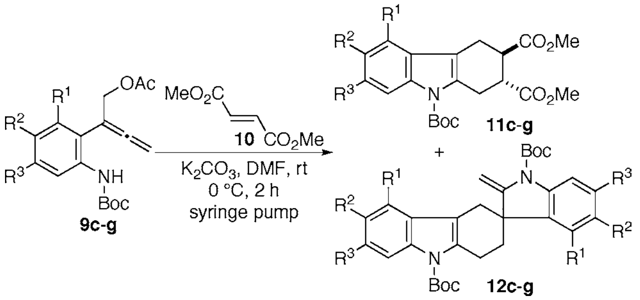


| entry | substrate | R | base (3 equiv) | carbazole **11a** (%) | dimer **12a** (%) |
|---|---|---|---|---|---|
| 1 | **9a** | Ms | $K_2CO_3$ | 76 | 13 |
| 2 | **9a** | Ms | $Cs_2CO_3$ | 81 | 13 |
| 3 | **9a** | Ms | NaH | 77 | 10 |
| 4 | **9b** | Ac | $K_2CO_3$ | 87 | |
| 5 | **9b** | Ac | $Cs_2CO_3$ | 84 | |
| 6 | **9b** | Ac | $K_2CO_3$ [a] | 93 | |
| 7 | **9b** | Ac | $Cs_2CO_3$ [a] | 84 | |

[a] Reaction was carried out using a syringe pump.

Our next step was to determine the electronic effect of the substituent on the benzene ring of the allenylanilines[10] in the above procedure. These results are summarized in Table 2. The allenylanilines **9c**,**d**, having a methoxy group, provided the corresponding tetrahydrocarbazole **11c**,**d** in the respective yields of 81 and 79% (entries 1 and 2). Similarly, the methylenedioxy derivative **11e** was obtained in 54% yield without the formation of the dimer **12e** (entry 3). The electron-withdrawing groups, such as the ethoxycarbonyl and chloro groups, seemed not to disturb the production of the indole-2,3-quinodimethane intermediate, but the formation of the dimers increased (entries 4 and 5). In particular, a significant amount of the dimer **12f** was observed when the ethoxycarbonyl derivative **9f** was exposed to the reaction conditions (entry 4).[11]

**Table 2.** Reaction of Allenylanilines **9c**−**g** with Dimethyl Fumarate



| entry | substrate | $R^1$ | $R^2$ | $R^3$ | carbazole **11** (%) | dimer **12** (%) |
|---|---|---|---|---|---|---|
| 1 | **9c** | OMe | H | H | **11c** (81) | |
| 2 | **9d** | H | OMe | H | **11d** (79) | |
| 3 | **9e** | H | $-OCH_2O-$ | | **11e** (54) | |
| 4 | **9f** | H | $CO_2Et$ | H | **11f** (69) | **12f** (25) |
| 5 | **9g** | H | Cl | H | **11g** (56) | *a* |

[a] A trace of **12g** was detected.

Our efforts then turned to investigating the [4 + 2] cycloaddition of the indole-2,3-quinodimethane with several

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(6) Compounds **9a**,**b** were prepared from **6** (R = H) by the successive desilylation and acylation. The details are described in the Supporting Information.

(7) Marinelli, E. R. *Tetrahedron Lett.* **1982**, *23*, 2745−2748.

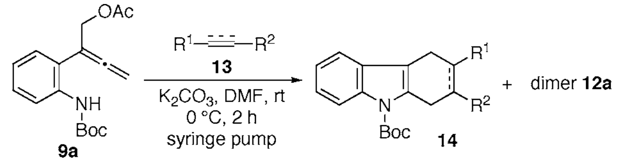
(8) The mesylate **9a** spontaneously collapsed when kept in the solvent at room temperature.

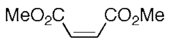
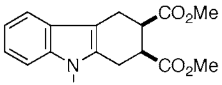
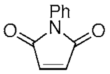
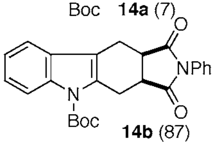
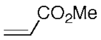
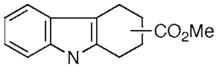
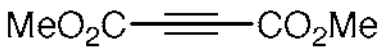
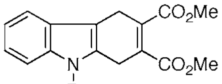
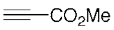
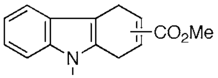
(9) **Typical procedure.** To a suspension of the dienophile (0.30 mmol) and $K_2CO_3$ (0.30 mmol) in DMF (1.0 mL) was added at 0 °C a solution of **9** (0.30 mmol) in DMF (1.0 mL) over a period of 2 h using a syringe pump under a nitrogen atmosphere. The reaction mixture was diluted with saturated aqueous $NH_4Cl$ and extracted with $Et_2O$. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with AcOEt−hexane to afford the [4 + 2] cycloaddition products.

(10) Preparation and characterization of the unknown allenylanilines are described in the Supporting Information.

dienophiles. Exposure of **9a** and the *cis*-isomer of **10**, dimethyl maleate (**13a**), to the optimized conditions provided the [4 + 2] cycloadduct **14a**[12] in 7% yield, in sharp contrast to the reaction with dimethyl fumarate (**10**), and the major product was the dimer **12a** (Table 3, entry 1). The reactive *N*-phenylmaleimide (**13b**) afforded **14b**[7] in 87% yield (entry 2). The reaction with an additional olefinic dienophile, methyl acrylate (**13c**), proceeded to furnish the cycloaddition product **14c** as a mixture of two regioisomers[13] (entry 3). The acetylenic dienophile, dimethyl acetylenedicarboxylate (**13d**), produced the desired **14d** in a yield similar to that of **14c**[7] (entry 4), but methyl propiolate (**13e**) was found to have low reactivity[12] toward the indole-2,3-quinodimethane, the same as **13a**, to afford the dihydrocarbozole derivative **14e**[14] in a low yield (entry 5). Thus, the reactivities of several dienophiles toward the indole-2,3-quinodimethane, as shown in Table 3, are in accordance with those previously reported.[12]

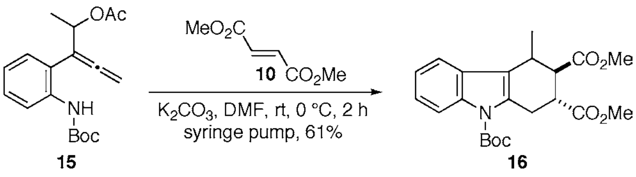
**Table 3.** Reaction of Allenylanilines **9a** with Dienophiles



| entry | dienophile **13** | carbazole **14** (%) | dimer **12a** (%) |
|---|---|---|---|
| 1 |  **13a** |  **14a** (7) | 85 |
| 2 |  **13b** |  **14b** (87) | — |
| 3 |  **13c** |  **14c** (52) | 30 |
| 4 |  **13d** |  **14d** (48) | 17 |
| 5 |  **13e** |  **14e** (8) | 76 |

Finally, the transformation of the allenylaniline derivative, which has an alkyl appendage at the allenic position, into the tetrahydrocarbazole derivative was investigated hoping to apply this newly developed methodology to the intramolecular version. As a result, compound **15**[10] was exposed to the optimized conditions[9] with dimethyl fumarate (**10**) to produce the desired carbazole derivative **16** as a mixture of two diastereoisomers[15] in 61% yield (Scheme 3).

### Scheme 3



In summary, we have developed a novel procedure for the generation of the reactive indole-2,3-quinodimethane intermediates from the allenylanilines. This method is entirely different from the previously reported ones, which were based on the 1,4-elimination or its related reactions of the indole derivatives, possessing suitable substituents at both the C-2 and C-3 positions. Determining the scope and limitations of this method as well as its application to the synthesis of natural products is now in progress.

**Acknowledgment.** This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for which we are thankful.

**Supporting Information Available:** General procedure for preparation of allenylanilines **9a−g** and **15**, characterization for data for compounds **9a−g**, **11a**,**c−g**, **12f**, **14a**,**d**,**e**, **15**, and **16**, and $^{1}H$ and $^{13}C$ NMR spectra for compounds **9b**,**d**,**e**,**g**, **12f**, and **15**. This material is available free of charge via Internet at http://pubs.acs.org.

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(11) The electron-deficient substituent on the benzene ring might decrease the reactivity of the indole-2,3-quinodimethane as a diene in the [4 + 2] cycloaddition.[1a]

(12) Pindur reported that the *N*-benzoylindole-2,3-quinodimethane, generated from 2,3-bis(bromomethyl)indole, failed to react with acrolein, diethyl maleate, or the propiolates: Haber, M.; Pindur, U. *Tetrahedron* **1991**, *47*, 1925−1936.

(13) Compound **14c** is a known compound[7] and obtained as a mixture of the 2- and 3-methoxycarbonyl derivatives in the ratio of 4:1.

(14) Compound **14e** was obtained as a mixture of the 2- and 3-methoxycarbonyldihydrocarbazole derivatives. The ratio of the two isomers (4:1) was determined by the conversion of **14e** into **14c** under hydrogenation conditions.

(15) A mixture of two isomers was obtained in the ratio of 3:2.