

A Novel Generation of
Indole-2,3-quinodimethanes

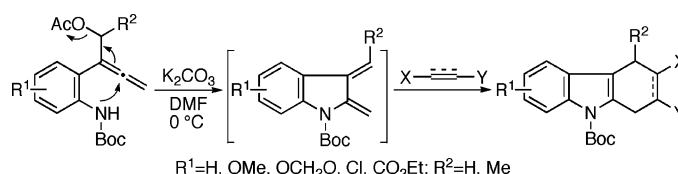
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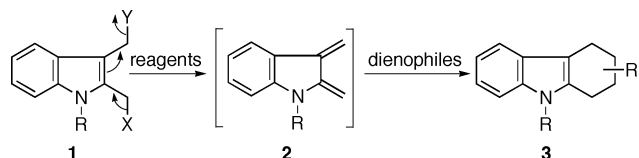
ABSTRACT



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*-quinodimethane² 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

Scheme 1



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

Recent efforts in this laboratory⁵ 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

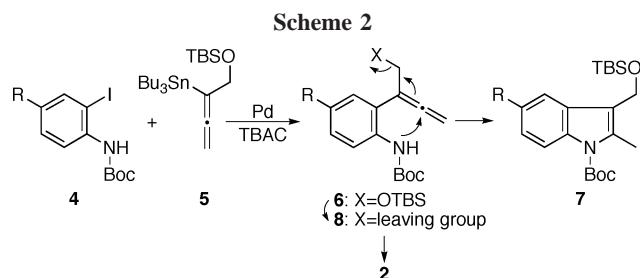
(1) (a) Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35–41. (b) Pindur, U.; Erfanian-Abdoust, H. *Chem. Rev.* **1989**, *89*, 1681–1689 and references therein.

(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.

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(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}

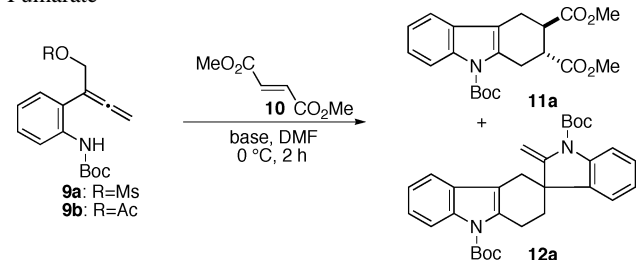
(5) Mukai, C. Takahashi, Y. *Org. Lett.* **2005**, *7*, 5793–5796.



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

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



entry	substrate	R	base (3 equiv)	carbazole 11a (%)	dimer 12a (%)
1	9a	Ms	K ₂ CO ₃	76	13
2	9a	Ms	CS ₂ CO ₃	81	13
3	9a	Ms	NaH	77	10
4	9b	Ac	K ₂ CO ₃	87	
5	9b	Ac	CS ₂ CO ₃	84	
6	9b	Ac	K ₂ CO ₃ ^a	93	
7	9b	Ac	CS ₂ CO ₃ ^a	84	

^a Reaction was carried out using a syringe pump.

10 in DMF was treated with K₂CO₃ 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). Cs₂CO₃ 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 CH₂Cl₂, 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

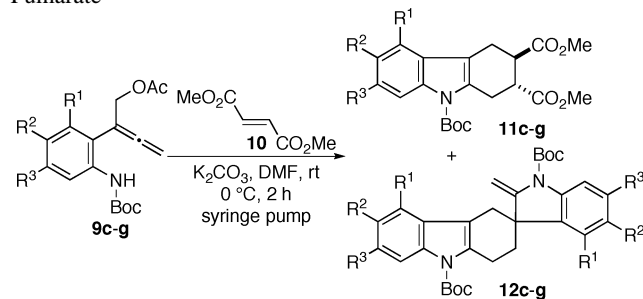
(6) Compounds **9a,b** were prepared from **6** (R = H) by the successive desilylation and acylation. The details are described in the Supporting Information.

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

instability⁸ 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 pump⁹ (entry 6). Thus, the allenyl acetate group was shown to be a suitable functionality for our purpose.

Our next step was to determine the electronic effect of the substituent on the benzene ring of the allenylanilines¹⁰ in the above procedure. These results are summarized in Table 2. The allenylanilines **9c,d**, having a methoxy group,

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 ₂ O–		11e (54)	
4	9f	H	CO ₂ Et	H	11f (69)	12f (25)
5	9g	H	Cl	H	11g (56)	<i>a</i>

^a A trace of **12g** was detected.

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

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

(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 K₂CO₃ (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 NH₄Cl and extracted with Et₂O. 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

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

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 regioisomers¹³ (entry 3). The

(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 compound⁷ and obtained as a mixture of the 2- and 3-methoxycarbonyl derivatives in the ratio of 4:1.

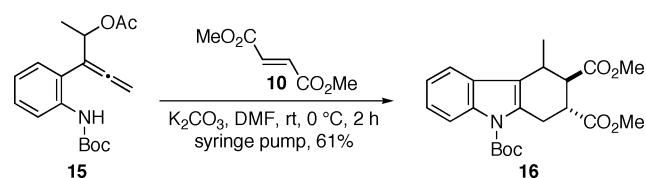
(14) Compound **14e** was obtained as a mixture of the 2- and 3-methoxycarbonyldihydrocarbazole derivatives. The ratio of the two isomers (4:1) was determined by the conversion of **14e** into **14c** under hydrogenation conditions.

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

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 reactivity¹² toward the indole-2,3-quinodimethane, the same as **13a**, to afford the dihydrocarbazole 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

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 conditions⁹ with dimethyl fumarate (**10**) to produce the desired carbazole derivative **16** as a mixture of two diastereoisomers¹⁵ 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.

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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 ¹H and ¹³C 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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