

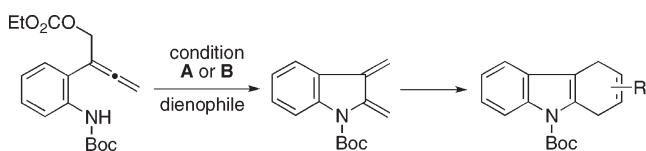
Generation of *N*-(*tert*-Butoxycarbonyl)indole-2,3-quinodimethane and Its [4+2]-Type Cycloaddition

Fuyuhiko Inagaki, Masaya Mizutani, Norikazu Kuroda, and Chisato Mukai*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192 (Japan)

cmukai@kenroku.kanazawa-u.ac.jp

Received June 22, 2009

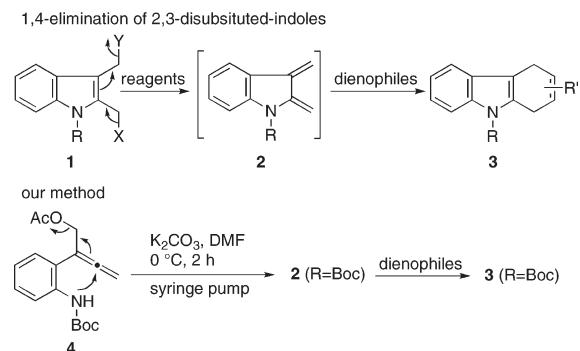


condition A : 0.2 equiv. of K_2CO_3 , toluene reflux
condition B : 5 mol % of $Pd_2(dba)_3$, toluene reflux

The two conditions for the preparation of the reactive *N*-(*tert*-butoxycarbonyl)indole-2,3-quinodimethane intermediate were developed by the reaction of the *N*-(*tert*-butoxycarbonyl)-2-(1-ethoxycarbonyloxymethyl)aniline with K_2CO_3 or $Pd_2(dba)_3$ in refluxing toluene. The resulting *N*-(*tert*-butoxycarbonyl)indole-2,3-quinodimethane was captured by several alkenyl and alkynyl dienophiles to provide the corresponding tetrahydro- and dihydrocarbazole derivatives.

The indole-2,3-quinodimethane **2**¹ is well-known to be a powerful enophile for the [4+2]-type cycloaddition reaction, which produces tetrahydro- and dihydrocarbazoles and their related compounds **3**. Almost all of the procedures^{1,2} for the in situ generation of this reactive indole-2,3-quinodimethane **2** involve the 1,4-elimination-type or its related reactions of the

SCHEME 1. Generation of Indole-2,3-quinodimethanes



starting indole derivatives **1**³ possessing suitable substituents at the C₂- and/or C₃-positions except for several alternatives.⁴

Recent efforts in this laboratory⁵ developed a novel procedure for the facile preparation of the reactive indole-2,3-quinodimethane intermediates **2** (R = Boc) by the intramolecular base-catalyzed S_N2' -type reaction of the 2-(1-acetoxymethyl)aniline derivatives **4** (Scheme 1). The produced indole-2,3-quinodimethane intermediates **2** (R = Boc) were captured by dienophiles to afford the corresponding tetrahydro- and dihydrocarbazole derivatives **3** (R = Boc), the chemical yields of which, however, depended on the property of the dienophiles. If the dienophiles are unstable under basic conditions, this ring-closing reaction produces **3** (R = Boc) in poor yields accompanied by the formation of significant amounts of the known dimer of **2**⁶ (R = Boc, see compound **7** in Table 1). Our continuous interest in this field prompted us to optimize the reaction conditions aiming at improvement of the chemical yields of the cycloadducts in order to make our method more useful. This paper provides the alternative conditions for the in situ generation of the indole-2,3-quinodimethane, which led to the better results of the [4+2]-type cycloaddition of **2**, when compared to the previously reported ones.

In a previous study,⁵ the tetrahydrocarbazole derivative **6b**⁵ could be synthesized in 93% yield when **4** was treated with dimethyl fumarate in the presence of 3 equiv of K_2CO_3 at 0 °C for 2 h, whereas dimethyl maleate was shown to be an unsuitable dienophile in this [4+2] cycloaddition with **2** (R = Boc) to give the cyclized product **6a**⁵ in a poor yield (7%) along with the known dimer **7**,⁶ in 85% yield, which should have occurred from the dimerization of **2**. Thus, at the beginning of this research, several leaving groups instead of the acetoxy group of **4** and some types of bases were evaluated by using dimethyl maleate as a dienophile, thereby we finally determined the conditions consisting of the combination of ethyl carbonate and a catalytic amount of K_2CO_3 . As a result, a solution of **5** and dimethyl maleate in toluene was refluxed (condition A) in the presence of 0.2 equiv of K_2CO_3 for 1 h to afford **6a** in 82% yield and its isomer **6b** (4%) together with the dimer **7** (13%) (Table 1,

*To whom correspondence should be addressed. Phone: +81-76-234-4411. Fax: +81-76-234-4410.

(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 cited therein.

(2) 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) Jakiwicz, 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.

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

(4) Fuwa and Sasaki very recently reported a new method for the generation of the indole-2,3-quinodimethane based on the intramolecular Heck reaction. (a) Fuwa, H.; Sasaki, M. *Chem. Commun.* **2007**, 2876–2878. (b) Fuwa, H.; Tako, T.; Ebine, M.; Sasaki, M. *Chem. Lett.* **2008**, 37, 904–905.

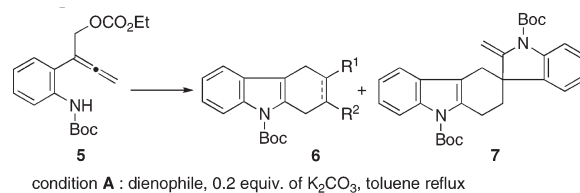
(5) Kuroda, N.; Takahashi, Y.; Yoshinaga, K.; Mukai, C. *Org. Lett.* **2006**, *8*, 1843–1845.

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

entry 1). Significant improvement in the chemical yield of **6a** was attained. Compound **6b** was also obtained in a yield as high as that of the previous one (entry 2). Although methyl acrylate provided **6c**⁵ in a moderate yield under the previous conditions, condition A afforded **6c** with a much better yield (91%) (entry 3). Additionally, two typical olefinic dienophiles, acrylonitrile and methyl vinyl ketone, reacted under condition A to yield both of the corresponding cycloadducts **6d**⁴ and **6e**⁴ in satisfactory yields (entries 4 and 5), although DMAP was used instead of K₂CO₃ in the case of **6d**. The acetylenic dienophiles were also found to be suitable substrates under condition A. In fact, dimethyl acetylenedicarboxylate furnished **6f**⁵ in a fairly improved yield (93%) (entry 6). It should be noted that a significant improvement was recorded for the cycloaddition with methyl propiolate to produce **6g**⁵ in 70% yield (entry 7), whereas **6g** was only obtained in 8% yield under the previous conditions. Consequently, it became clear that condition A can be applied to not only the olefinic dienophiles **6a–e**, but also the acetylenic ones **6f,g** with almost total suppression of the formation of the dimer **7**. Contrary to our prediction, *N*-phenylmaleimide, which produced **6h**⁵ in 87% yield under the previous conditions, gave an intractable mixture under condition A. Changing the base from K₂CO₃ to DMAP produced **6h** in 34% yield along with the dimer **7** (23%) (entry 8). Electron-rich olefins are generally regarded as an ineffective counterpart in the intermolecular [4+2] cycloaddition of **2**.² In fact, the capture of **2** with olefins possessing an electron-donating group such as ethyl vinyl ether, vinyl acetate, and styrene under the previous conditions led to failure and the exclusive formation of the dimer **7** was observed. When styrene reacted with **5** under condition A, however, the desired cycloadduct **6i** could be isolated in 40% yield along with **7** (11%).

Our efforts then turned to investigating the [4+2] cycloaddition of the indolo-2,3-quinodimethane **2** with quinone derivatives. Treatment of the carbonate **5** with *p*-quinone under condition A unexpectedly gave an intractable mixture. No improvement could be realized by changing the base. 1,4-Naphthoquinone also did not furnish any desired products. Allyl carbonate groups were well-known to produce the corresponding (π -allyl)palladium complex⁷ when treated with a palladium(0) catalyst. We tentatively assumed that treatment of **5** with a palladium(0) catalyst would result in the formation of the vinylidene(π -allyl)palladium complex **8**,⁸ that might collapse to the indole-2,3-quinodimethane **2** and/or its related palladium complexes **9** and **10**⁹ via the intramolecular attack of the nitrogen atom under nearly neutral conditions, in which both the base-sensitive *p*-quinone and 1,4-naphthoquinone must be tolerable (Scheme 2). Thus, a solution of **5** and *p*-quinone in toluene was heated under reflux for 10 min in the presence of 5 mol % of Pd₂(dba)₃ (condition B) to produce the cycloadduct **6j** in 40% yield (Table 2, entry 1). Similar treatment of **5** with 1,4-naphthoquinone provided **6k** in 70% yield (entry 2). These results are in sharp contrast to the fact that neither **6j** nor **6k**

TABLE 1. Base-Catalyzed Reaction of Allenylanilines **5** with Dienophiles



entry	dienophile	time (h)	carbazole 6 (%)	previous results (%)
1		1	 6a (86), ^a 7 (13)	6a (7) 7 (85)
2		2.5	 6b (93)	6b (93)
3		3	 6c (91) ^b	6c (52) 7 (30)
4		1	 6d (82), ^{c,d} 7 (14)	
5		1	 6e (82), ^e 7 (trace)	
6		1.5	 6f (93)	6f (48) 7 (17)
7		2	 6g (70) ^f	6g (8) 7 (76)
8		9	 6h (34) ^d , 7 (23%)	6h (87)
9		9	 6i (40) ^g , 7 (11)	

could be prepared under the previous conditions or condition A. Other successful examples under condition B are summarized in Table 2. Methyl acrylate and methyl vinyl ketone afforded the corresponding cycloadducts **6c,e** in reasonable yields (entries 3 and 4). *N*-Phenylmaleimide furnished the cycloadduct **6h** in a much better yield than that under condition A (entry 5).

Table 3 shows the reactions under condition B, the chemical yields of which did not exceed those obtained

(7) (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140–145. (b) Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257–276.

(8) (a) Mandal, A. K.; Schneckloth, J. S. Jr.; Crews, C. M. *Org. Lett.* **2005**, *7*, 3645–3648. (b) Schneckloth, J. S. Jr.; Pucheault, M.; Crew, C. M. *Eur. J. Org. Chem.* **2007**, 40–43.

(9) Yoshida, H.; Nakano, S.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Org. Lett.* **2006**, *8*, 4157–4159.

SCHEME 2. Pd(0)-Catalyzed Generation of Indole-2,3-quinodimethane Derivatives

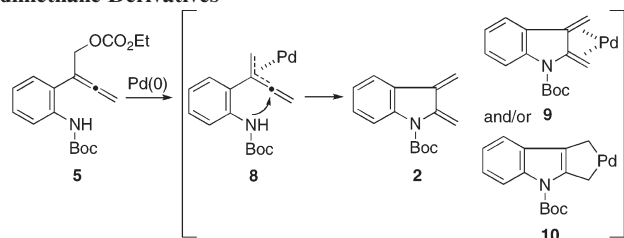
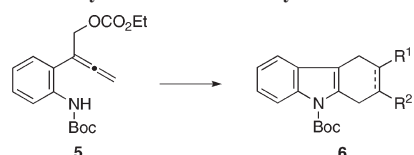


TABLE 2. Pd-Catalyzed Reaction of Allenylanilines 5 with Dienophiles



condition B : dienophile, 5 mol % of Pd₂(dba)₃, toluene reflux

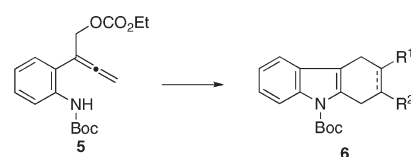
entry	dienophile	product (%)		
1				6c (71) ^a
4		6e (74), ^b 7 (trace)		
5		6h (94)		

^aA mixture of the 2-CO₂Me and 3-CO₂Me derivatives (53:18) was obtained. ^bA mixture of the 2-COMe and 3-COMe derivatives (59:15) was obtained.

under condition A. In the cases of dimethyl acetylenedicarboxylate and methyl propiolate, the palladium-catalyzed trimerization¹⁰ proceeded (entries 4 and 5). In particular the trimethoxycarbonylbenzene derivatives were obtained in a 77% total yield and any other products derived from **5** could not be observed in the reaction mixture (entry 5).

In summary, we have developed two alternative conditions for the preparation of carbazole derivatives via the reactive indolo-2,3-quinodimethane intermediate, which was generated in situ by the reaction of the 2-(1-ethoxycarbonyloxy-methyl allenyl)aniline with K₂CO₃ or Pd₂(dba)₃ in refluxing

TABLE 3. Pd-Catalyzed Reaction of Allenylanilines 5 with Other Dienophiles



condition B : dienophile, 5 mol % of Pd₂(dba)₃, toluene reflux

entry	dienophile	product (%)
1		6a (8), ^a 7 (34)
2		6b (43), 7 (53)
3		6d (37), ^b 7 (trace)
4		6f (9) 11 (7)
5		 12 (29) 13 (48)
6		6i (2), ^c 7 (67)

^aA mixture of **6a** and **6b** (6:2) was obtained. ^bA mixture of 2-CN and 3-CN derivatives (28:9) was obtained. ^c3-Ph derivative was obtained.

toluene. Thus, exposure of the allenylanilines and a proper dienophile to one of the three conditions (the present two conditions and the previously reported one) would provide the desired carbazole derivatives in reasonable yields.

Experimental Section

General Procedure for Reaction of 2-Allenylaniline 5 with K₂CO₃. To a solution of allenylaniline **5** (33.3 mg, 0.100 mmol) in toluene (1 mL) were added dienophile (1.0 mmol) and K₂CO₃ (2.8 mg, 2.0 × 10⁻² mmol) at room temperature. The reaction mixture was heated at 120 °C (oil bath temperature) until the complete disappearance of the starting material (monitored by TLC). After cooling, the reaction mixture was quenched by addition of saturated aqueous NH₄Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt gave the products.

tert-Butyl 2-Acetyl-1,2,3,4-tetrahydro-9H-carbazole-9-carboxylate and tert-Butyl 3-Acetyl-1,2,3,4-tetrahydro-9H-carbazole-9-carboxylate (6e). A mixture of 2-COMe-**6e** and 3-COMe-**6e** in the ratio of 75 to 25 was obtained as a colorless oil: IR 1720 cm⁻¹; ¹H NMR 8.12–8.10 (m, 1H), 7.40–7.37 (m, 1H), 7.26–7.19 (m, 2H), 3.30 (dd, 75/100 × 1H, J = 17.7, 5.5 Hz), 3.22 (dt,

(10) (a) Maitlis, P. M. *Acc. Chem. Res.* **1976**, *9*, 93–99. (b) tom Dieck, H.; Munz, C.; Müller, C. *J. Organomet. Chem.* **1990**, *384*, 243–255. (c) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2916.

25/100 × 1H, $J = 18.3, 3.1$ Hz), 3.12–3.07 (m, 75/100 × 1H), 3.02–2.94 (m, 25/100 × 1H), 2.92–2.89 (m, 25/100 × 1H), 2.86–2.78 (m, 2H), 2.68–2.61 (m, 75/100 × 1H), 2.31–2.21 (m, 1H), 2.279 (s, 25/100 × 3H), 2.276 (s, 75/100 × 3H), 1.88–1.75 (m, 1H), 1.670 (s, 75/100 × 9H), 1.666 (s, 25/100 × 9H); ^{13}C NMR δ 210.7, 210.2, 150.52, 150.50, 136.02, 136.00, 134.7, 133.8, 129.3, 129.2, 123.65, 123.63, 122.50, 122.47, 117.5, 117.4, 116.0, 115.5, 115.4, 115.0, 83.5, 83.4, 48.5, 47.1, 28.3, 28.2, 28.1, 27.51, 25.8, 25.3, 24.6, 23.0, 20.4; MS m/z 313 (M^+ 10.0). HRMS calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_3$ 313.1678, found 313.1671.

General Procedure for Reaction of 2-Allenylaniline 5 with $\text{Pd}_2(\text{dba})_3$. To a solution of allenylaniline **5** (33.3 mg, 0.100 mmol) in toluene (1 mL) were added dienophile (1.0 mmol) and $\text{Pd}_2(\text{dba})_3$ (4.6 mg, 5.0×10^{-3} mmol) at room temperature. The reaction mixture was heated at 120 °C (oil bath temperature) until the complete disappearance of the starting material (monitored by TLC). Chromatography of the residue with hexane–AcOEt gave the products.

tert-Butyl 7,10-Dioxo-5H-benzo[*b*]carbazole-5-carboxylate (6j). Compound **6j** was a yellow plate: mp 210–213 °C (from hexane); IR 1732, 1666 cm^{-1} ; ^1H NMR δ 8.96 (s, 1H), 8.65 (s, 1H), 8.35 (d, 1H, $J = 8.5$ Hz), 8.09 (d, 1H, $J = 7.8$ Hz), 7.60–7.56 (m, 1H), 7.47–7.42 (m, 1H), 6.96 (d, 2H, $J = 2.0$ Hz), 1.81 (s, 9H); ^{13}C NMR δ 184.90, 184.87, 150.2, 141.0, 140.2, 139.2, 138.9, 130.7, 129.7, 129.4, 127.4, 124.6, 124.0, 120.9, 118.7, 116.5, 114.9, 85.5, 28.3; MS m/z 347 (M^+ , 7.5). HRMS calcd for $\text{C}_{21}\text{H}_{17}\text{NO}_4$ 347.1158, found 347.1154.

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 grateful.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **5** and **6a–k** and characterization data for compounds **5**, **6a–d**, **6f–i**, and **6k**. This material is available free of charge via the Internet at <http://pubs.acs.org>.