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A new procedure for the preparation of 2-vinylindoles and their [4+2] cycloaddition reaction

Yaseen Ali Mosa Mohamed, Fuyuhiko Inagaki, Ryohei Takahashi, Chisato Mukai *

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

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ABSTRACT

A new approach for the synthesis of 2-vinylindole derivatives by 5-*exo* mode cyclization of 2-(3-silyloxymethylallenyl)anilines was developed. The starting allenylanilines were easily prepared by the Stille coupling of *o*-iodoaniline and allenylstannanes. The formed 2-vinylindole derivatives were transformed into several carbazole derivatives via the [4+2] cycloaddition reaction with suitable dienophiles.

1. Introduction

In our previous studies, we developed a new procedure for the generation of the reactive indole-2,3-quinodimethane intermediates **2** from the allenylanilines **1** via the S_N2'-type reaction in the 5-*endo*-type manner (Fig. 1).[1] This method was entirely different from the well-known ones[2] that took advantage of the 1,4-elimination-type or related reactions of the 2,3-disubstituted indole derivatives. The indole-2,3-quinodimethane intermediates **2** were successively captured by several dienophiles in the same reaction vessel to afford the tetrahydro- and dihydrocarbazole derivatives **3**.

We envisaged that the similar S_N2'-type reaction of allenylanilines **4** via the 5-*exo* mode ring-closing reaction would furnish the 2-vinylindole derivatives **5**,[3] which are known to be a useful component for the syntheses of some drugs[4] and natural products.[5] We now describe a new entry for the preparation of 2-vinylindole frameworks and their [4+2] cycloaddition leading to an alternative method for the construction of the carbazole derivatives **6**.

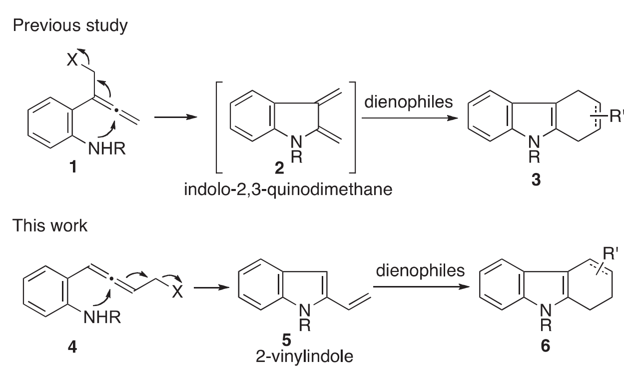

Fig. 1. Formation of carbazole derivatives based on S_N2' cyclization and Diels–Alder reaction.

2. Results and discussion

At the beginning of this project, the Stille coupling reaction[6] of the *N*-(*tert*-butoxycarbonyl)-2-iodoaniline (**7**) and 3-(*tert*-butyldimethylsilyloxymethyl)-1-(tributylstannyl)allene derivatives **8** was conducted for the preparation of the *N*-(*tert*-butoxycarbonyl)-2-{3-(*tert*-butyldimethylsilyloxymethyl)allenyl} aniline derivatives **9**. According to a previous procedure,[1,7] **7** was treated with allenylstannane **8a**[8] in DMF in the presence of 3 mol % of $Pd_2(dba)_3$, tri-2-furylphosphine (TFP, 24 mol %), and CuI (10 mol %) at room temperature for 2 h to produce the allenylaniline derivative **9a** in 79% yield (Table 1, entry 1). Other allenylstannanes **8b–d** (R^1=Me, Et, CH_2OBn: R^2=H) gave the corresponding allenylanilines **9b–d** in good yields (entries 2–4). The tetrasubstituted derivatives **9e,f** (R^1=CH_2OBn: R^2=Bu, $(CH_2)_4OPMB$) were produced in moderate yields from **7** and the tetrasubstituted allenylstannanes **8e,f** (entries 5 and 6).

* Corresponding author. Tel.: +81 76 234 4411; fax: +81 76 234 4410; e-mail address: cmukai@kenroku.kanazawa-u.ac.jp (C. Mukai).

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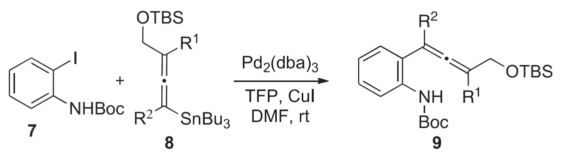
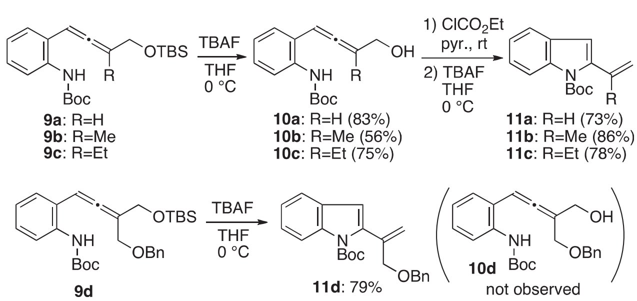
Table 1
Stille coupling of *o*-iodoaniline **7** and allenylstannanes **8**



Entry	Allene	R^1	R^2	Time (h)	Product	Yield (%)
1	**8a**	H	H	2	**9a**	79
2	**8b**	Me	H	3	**9b**	90
3	**8c**	Et	H	5	**9c**	78
4	**8d**	CH_2OBn	H	4	**9d**	88
5	**8e**	CH_2OBn	Bu	12	**9e**	49
6[a]	**8f**	CH_2OBn	$(CH_2)_4OPMB$	6	**9f**	50

[a] The reaction was heated at 70 °C.

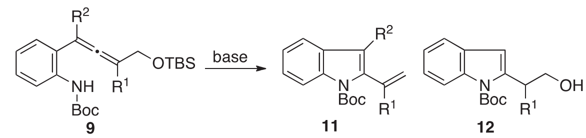
With the required allenylanilines **9** in hand, the ring-closing reaction for the construction of 2-vinylindole derivatives **11** was examined (Scheme 1). After removing the TBS group of the 1,3-disubstituted allene derivative **9a** with TBAF in THF at 0 °C, the resulting **10a** (83%) was successfully converted into *N*-(*tert*-butoxycarbonyl)-2-vinylindole (**11a**) in 73% yield by ethoxycarbonylation followed by TBAF treatment. The 1,1,3-trisubstituted allene derivatives **9b** and **9c** having a methyl or ethyl group on the vinyl position also provided the corresponding 2-vinylindole derivatives **11b** and **11c** in good yields. TBAF treatment of the 1,1,3-trisubstituted allene derivative **9d** directly and unexpectedly produced the 2-vinylindole derivative **11d** in 79% yield. This was in sharp contrast to the cases in which the desilylated products **10a–c** were obtained upon exposure of **9a–c** to TBAF.



Scheme 1. Formation of 2-vinylindoles **11**.

Based on the direct conversion of the allenylaniline **9d** to 2-vinylindole **11d**, we reinvestigated the one-step conversion of allenylanilines **9** into **11** (Table 2). Treatment of the allenylaniline **9a** with TBAF in THF at room temperature (not at 0 °C) afforded the desired 2-vinylindole derivative **11a** in 83% yield (entry 1).[9] At a higher temperature (45 °C), *N*-(*tert*-butoxycarbonyl)-2-(2-hydroxy-1-alkylethyl)indole derivatives **12b,c** were obtained instead of **11b,c** (entries 2 and 3). On the other hand, the tetrasubstituted allene derivatives **9e,f** were converted to the desired 2-vinyl-3-substituted indole derivatives **11e** (62%) and **11f** (73%) at 0 °C (entries 4 and 5). K_2CO_3 was used as a base for the formation of the indole derivatives from the allenylanilines in previous papers.[1,7] Thus, K_2CO_3 was again found to be a suitable base for the transformation of the allenylanilines **9b,c** to 2-vinylindoles **11b,c**. In fact, **11b,c** were obtained in satisfactory yields when **9b,c** were reacted with K_2CO_3 in DMF at rather higher reaction temperatures (85–110 °C)(entries 6–8).[10]

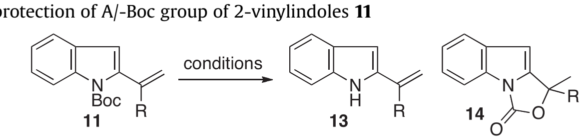
Table 2
S_N2' cyclization of 2-(4-silyloxybuta-1,2-dienyl)anilines **9**



Entry	Substrate	R^1	R^2	Base	Solvent	Temp (°C)	Time (h)	Product (%)
1	**9a**	H	H	TBAF	THF	rt	0.2	**11a** (83)
2	**9b**	Me	H	TBAF	THF	45	5	**12b** (50)
3	**9c**	Et	H	TBAF	THF	45	5	**12c** (45)
4	**9e**	CH_2OBn	Bu	TBAF	THF	0	0.5	**11e** (62)
5	**9f**	CH_2OBn	$(CH)_2OPMB$	TBAF	THF	0	0.5	**11f** (73)
6	**9b**	Me	H	K_2CO_3	DMF	110	4	**11b** (66)
7	**9b**	Me	H	K_2CO_3/ Et_2CO_3	DMF	85	4	**11b** (80)
8	**9c**	Et	H	K_2CO_3/ Et_2CO_3	DMF	95	5	**11c** (85)

By taking the [4+2] cycloaddition reaction of the 2-vinylindoles, in particular the compounds having a substituent on the vinyl position (R≠H), into account, we tried to remove a Boc group on the nitrogen atom of the indole nucleus, which should be predicted to disturb the planarity due to the nonbonding interaction with an R group. Treatment of 2-vinylindole **11b** (R=Me) with TFA in CH_2Cl_2[11] at room temperature afforded 1,1-dimethyloxazolo[3,4-*a*]indol-3(1*H*)-one (**14b**) in 76% yield (Table 3, entry 1). Similar results were observed under other acidic conditions (HCl in AcOEt,[11,12] and TMSCl, NaI in CH_3CN,[13] entries 2 and 3). In contrast to these acidic conditions, exposure to KOH in MeOH at 70 °C gave the desired 2-vinylindole derivatives **13b–d** in moderate to high yields (entries 4–6).

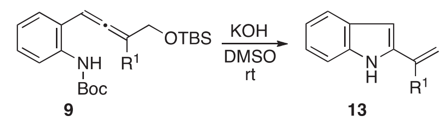
Table 3
Deprotection of A/-Boc group of 2-vinylindoles **11**



Entry	Substrate	R	Additive	Solv.	Temp	Time (h)	Product (%)
1	**11b**	Me	TFA	CH_2Cl_2	rt	1	**14b** (76)
2	**11b**	Me	HCl	AcOEt	rt	6	**14b** (45)
3	**11b**	Me	TMSCl, NaI	CH_3CN	rt	0.5	**14b** (85)
4	**11b**	Me	KOH	MeOH	70 °C	5	**13b** (92)
5	**11c**	Et	KOH	MeOH	70 °C	5	**13c** (56)
6	**11d**	CH_2OBn	KOH	MeOH	70 °C	5	**13d** (83)

The experimental results summarized in Tables 2 and 3 revealed that the one-step conversion of **9** into **11** required basic conditions, and a Boc group of **11** could also be removed by the base treatment. Thus, the direct one-step transformation of **9** into **13** would be attainable under proper basic conditions. After screening several basic conditions, we finally established the following conditions that treatment of **9a–d** with KOH in DMSO at room temperature producing the desired **13a–d** in satisfactory yields as expected (Table 4, entries 1–4).

Table 4
Formation of 2-vinylindoles **13**



Entry	Substrate	R	Time (h)	Product (%)
1	**9a**	H	0.25	**13a** (76)
2	**9b**	Me	6	**13b** (73)
3	**9c**	Et	6	**13c** (75)
4	**9d**	CH_2OBn	10	**13d** (90)