ORGANIC LETTERS

2005
Vol. 7, No. 26
5793−5796

A New Entry to the Synthesis of 2,3-Disubstituted Indoles

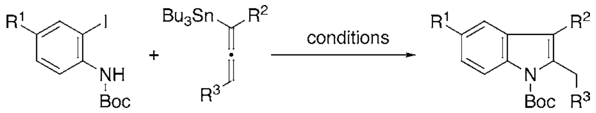
Chisato Mukai* and Yukie Takahashi

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 September 10, 2005

ABSTRACT



Conditions i : $Pd_2(dba)_3$, TFP, CuI, TBAC, DMF, rt
Conditions ii : (i) $Pd_2(dba)_3$, TFP, CuI, TBAC, DMF, rt; (ii) TBAF, 0 °C

The Stille coupling of *N*-acyl-2-iodoanilines with the 1-(tributylstannyl)-1-substituted allenes affected the successive one-step formation of the 2-methyl-3-substituted indoles. Alternatively, the other type of 2-alkyl-3-substituted indoles could be synthesized in a one-pot operation, which consists of the Stille coupling reaction with the 1-(tributylstannyl)-1,3-disubstituted allenes, followed by TBAF treatment. This procedure could be applied to the synthesis of indomethacin.

The indole skeleton is one of the most attractive frameworks with a wide range of biological and pharmacological activities.[1] This physiologically important nucleus is abundantly found in therapeutic agents[2] as well as in natural products. Many protocols for the synthesis of the indole nucleus,[3] not to mention the classical Fisher indole synthesis,[4] have already been reported. The recent progress in the metal-catalyzed construction of the indole skeleton[5] has achieved remarkable improvement regarding efficiency and functional group compatibility. In particular, the palladium-catalyzed ring-closing reaction of the 2-alkynylaniline derivatives[5,6] was widely investigated and has efficiently produced 2-substituted indoles, whereas the plausible 3-indolylpalladium intermediates, formed in situ from the 2-alkynylaniline derivatives, were further transformed into more useful 2,3-disubstituted indoles when additional RX species (R = alkyl, aryl, alkenyl; X = halide, OTf, etc.) or carbon monoxide existed in the reaction vessel. In addition, these indole derivatives were directly prepared by the palladium-catalyzed intermolecular coupling reaction of 2-haloaniline derivatives with terminal or internal alkyne counterparts[5,7] under heating conditions.

We envisaged that the palladium(0)-catalyzed coupling reaction of the *N*-acyl-2-iodoanilines with a suitable allenylstannane counterpart would afford the corresponding 2-allenylanilines, the nitrogen functionality of which might

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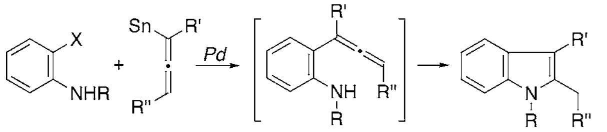
10.1021/ol052179u CCC: $30.25

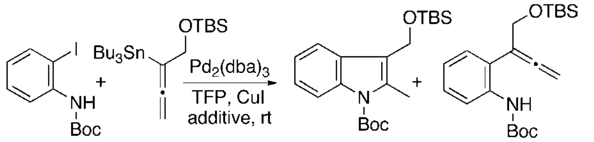
make the sp-hybridized carbon center of the allenyl moiety slightly electron-deficient due to the inductive effect of the electron-deficient *N*-acyl moiety through the benzene ring. The activated sp-hybridized center would hopefully be attacked by the nitrogen functionality in a formal endo-mode manner[8] with aid of the palladium catalyst and/or weak bases leading to the indole frameworks (Scheme 1). On the basis of these considerations, we investigated the coupling reaction of the *N*-acyl-2-iodoanilines with the allenylstannanes. This letter describes the preliminary results of (i) a novel and efficient protocol for preparing 2,3-disubstituted indoles by taking advantage of the Stille coupling reaction,[9] followed by the formal endo-mode ring-closing reaction[8] in a one-pot process, and (ii) its application to the synthesis of indomethacin.

Scheme 1



The Stille coupling reaction[9] of *N*-(*tert*-butoxycarbonyl)-2-iodoaniline (**1a**) under standard conditions was first investigated. Treatment of **1a** with **2**[10,11] in DMF in the presence of 3 mol % of Pd$_2$(dba)$_3$,[12] tri-2-furylphosphine (TFP, 24 mol %), and CuI (10 mol %) at room temperature for 2 h afforded the normal Stille coupling product **4a** in 96% yield (conditions A) (Table 1, entry 1). When the reaction was performed in the presence of LiCl (3 equiv), the distribution of the products drastically changed and the desired indole derivative **3a** could be isolated in 56% yield along with **4a** in 18% yield (entry 2).[13] Interestingly, other lithium halides such as LiBr and LiI exclusively produced **4a** instead of **3a** (entries 3 and 4). These results suggested that the chloride anion might be the most favorable additive for the efficient construction of **3a**. Thus, we evaluated four additional chloride species (entries 5−8). As a result, three chlorides provided **3a** as the major product (entries 6−8). In particular, tetra-*n*-butylammonium chloride (TBAC) was found to be the most effective for our purpose and led to the exclusive formation of **3a** in 84% yield (conditions B) (entry 7).[14] Thus, it turned out that the allene derivative **4a** and 1-(*tert*-butoxycarbonyl)-3-(*tert*-butyldimethylsiloxy)-methyl-2-methylindole (**3a)** can be selectively prepared by the reaction of **1a** with **2** by proper choice of conditions (with or without TBAC). TFP was found to be superior to the other ligands examined, although Ph$_3$As worked as well as TFP (72%).

Table 1. Palladium(0)-Catalyzed Coupling Reaction of **1a** with **2**[a]



1a **2** **3a** **4a**

entry	additive (3 equiv)	solvent	time (h)	**3a** (%)	**4a** (%)
1		DMF	2		96
2	LiCl	DMF	0.5	56	18
3	LiBr	DMF	1		52
4	LiI	DMF	1		64
5	KCl	DMF	7		53
6	Et$_4$NCl	DMF	2	46	12
7	Bu$_4$NCl	DMF	2.5	84	
8	BnEt$_3$NCl	DMF	1	24	20
9	K$_2$CO$_3$[b]	DMF	9	29	

[a] Reactions were carried out with aniline **1a**, allene **2**, Pd$_2$(dba)$_3$ (3 mol %), TFP (24 mol %), CuI (10 mol %), and additive (3 equiv). [b] 1.2 equiv of K$_2$CO$_3$ was used.

Our next step was to determine the electronic effect of the substituent on the benzene ring in the above procedures (Table 2). A mixture of **1b**, having a methoxy group, and **2** was used along with the palladium-catalyzed coupling conditions in the absence of TBAC (conditions A) to afford the allene **4b** in 90% yield, while the indole derivative **3b** was obtained in 65% yield when exposed to the palladium catalyst in the presence of TBAC (conditions B). The nitro compound **1c** unexpectedly gave the indole derivative **3c** in

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(8) Upon treatment with NaH at room temperature, *N*-(*tert*-butoxycarbonyl)-2-(1-phenylsulfonylpropa-1,2-dien-1-yl)aniline underwent the endo-mode ring-closing reaction to furnish the corresponding indole derivative in a high yield. Mukai, C.; Kobayashi, M.; Kubota, S.; Takahashi, Y.; Kitagaki, S. *J. Org. Chem*. **2004**, *69*, 2128−2136.

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(10) We chose 1-(*tert*-butyldimethylsiloxy)-2-(tributylstannyl)-2,3-butadiene (**2**) as the first allene for this investigation, because the expected indole derivatives would possess a hydroxymethyl functionality at the C$_3$-position, which must be useful for further elaborations such as the carbon homologation reaction, if the reaction proceeded as planned.

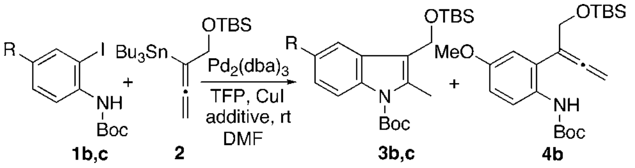
(11) All allenes used in this study were prepared by the method of Marshall, see: (a) Marshall, J. A.; Wang, X.-j. *J. Org. Chem*. **1992**, *57*, 1242−1252. (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem*. **1999**, *64*, 8214−8219. (c) Williams, D. R.; Mi, L.; Mullins, R. J.; Stites, R. E. *Tetrahedron Lett*. **2002**, *43*, 4841−4844.

(12) Several other palladium catalysts were screened, but no catalysts could exceed the result of Pd$_2$(dba)$_3$.

(13) When 10 equiv of LiCl was added to the reaction mixture (3.5 h at room temperature), **3a** was obtained in 67% yield as the sole product.

(14) When *N*-acetyl-2-iodoaniline was exposed to conditions A or B, the corresponding allenyl derivative or indole derivative was selectively formed in the respective yields of 80% and 70%, although a higher reaction temperature (50 °C) was necessary under conditions A.

Table 2. Palladium(0)-Catalyzed Coupling Reaction of **1b,c** with **2**[a]



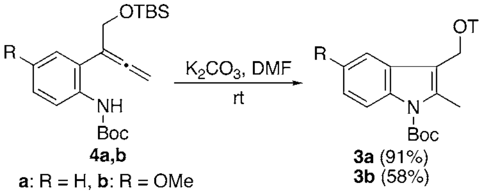
entry	substrate	R	additive (3 equiv)	time (h)	**3** (%)	**4** (%)
1	**1b**	OMe		3[b]		**4b** (90)
2	**1b**	OMe	TBAC	4	**3b** (65)	
3	**1c**	NO$_2$		3	**3c** (65)	
4	**1c**	NO$_2$	TBAC	3[b]	**3c** (72)	

[a] Reactions were carried out with aniline **1**, allene **2**, Pd$_2$(dba)$_3$ (3 mol %), TFP (24 mol %), and CuI (10 mol %) in the presence or absence of TBAC (3 equiv). [b] A reaction mixture was heated at 50 °C.

65% as the sole product under conditions A (entry 3). Conditions B exclusively produced **3c** in a higher yield (72%) (entry 4).

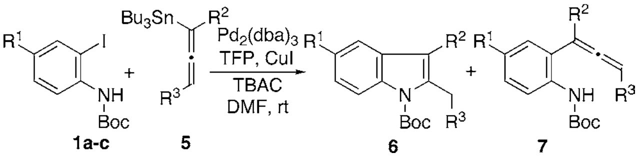
Upon exposure to conditions B, **4a** was easily converted to **3a** in 77% yield. The transformation of **4a** into **3a** (70%) was also realized under conditions B omitting CuI and TFP. However, no reaction took place with TBAC alone in DMF, and a decomposition was observed when treated with Pd$_2$(dba)$_3$ in DMF. The allenylanilines **4a**,**b** could be simply converted into **3a**,**b**[15] by treatment with K$_2$CO$_3$ (Scheme 2).

Scheme 2



To extend the scope of this newly developed method, several allenylstannanes **5**[11] were used for conditions B with **1a**−**c** (Table 3). By analogy to the reaction of **1a** with **2**, the reaction between the 1-(tributylstannyl)-1-substituted allenes **5a**−**c** and **1a** directly afforded **6a**−**c** (Table 3, entries 1−3), although the yields were somewhat lower compared to that of **3a**. When the 1-(tributylstannyl)-1,3-disubstituted allene **5d** and **1a** were exposed to conditions B, the coupling product **7d**, instead of **6d**, was obtained in a high yield (entry 4). A similar behavior was observed in the reaction of **1b** with **5d** (entry 5). Other 1-(tributylstannyl)-1,3-disubstituted allenes **5e**,**f** as well as 1-(tributylstannyl)-3-substituted allene **5g** gave **7g**−**i** (entries 7−9) except for the reaction of the nitro compound **1c** with **5d**, which produced the indole derivative **6f** in 71% yield as the sole isolatable product (entry 6).

Table 3. Palladium(0)-Catalyzed Coupling Reaction of **1** with **5**[a]

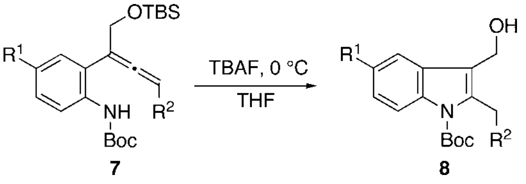


entry	allene	R^1	R^2	R^3	time (h)	**6** (%)	**7** (%)
1	**5a**	H	CH$_2$OPMB	H	5.5	**6a** (65)	
2	**5b**	H	(CH$_2$)$_2$OTBS	H	4	**6b** (57)	
3	**5c**	H	C$_6$H$_{13}$	H	0.5	**6c** (46)	
4	**5d**	H	CH$_2$OTBS	Me	3		**7d** (94)
5	**5d**	OMe	CH$_2$OTBS	Me	1[b]		**7e** (59)
6	**5d**	NO$_2$	CH$_2$OTBS	Me	6[b]	**6f** (71)	
7	**5e**	H	CH$_2$OTBS	Pr	3		**7g** (94)
8	**5f**	H	C$_7$H$_{15}$	Me	6		**7h** (57)
9	**5g**	H	H	C$_5$H$_{11}$	0.5		**7i** (62)

[a] Reactions were carried out with aniline **1**, allene **5**, Pd$_2$(dba)$_3$ (3 mol %), TFP (24 mol %), CuI (10 mol %), and TBAC (3 equiv). [b] The reaction mixture was heated at 50 °C.

According to the procedure in Scheme 2, the transformation of **7d** into **6d** was carried out with the aid of K$_2$CO$_3$, but **6d** was obtained in a low yield (25%). Therefore, an alternative and more efficient condition for the transformation of **7** into the corresponding indole derivatives was necessary in order to make this procedure a more significant one. After screening several conditions, we reached the conclusion that TBAF was the best base for this objective. Thus, treatment of **7d** with 3 equiv of TBAF in THF at 0 °C effected the ring closure accompanied by the concomitant desilylation to furnish **8d** in 62% yield (Table 4, entry 1). Similarly, **7e**,**g** afforded **8e**,**g** in respective yields of 83% and 70% (entries 2 and 3).[16] The hydroxymethyl compound (desilylated-**7d**) could also be converted into **8d** in 82% yield.

Table 4. Conversion of Allenes **7d,e,g** into Indoles **8d,e,g**[a]



entry	**7**	R^1	R^2	time (h)	**8** (%)
1	**7d**	H	Me	0.5	**8d** (62)
2	**7e**	OMe	Me	1	**8e** (83)
3	**7g**	H	Pr	0.5	**8g** (70)

[a] Reactions were carried out with allene **7** and TBAF (3 equiv) at 0 °C.

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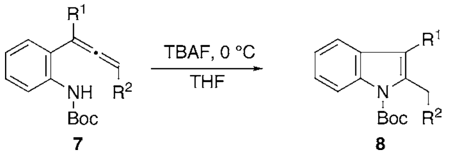
(15) Treatment of the *N*-acetyl congener of **4a** with K$_2$CO$_3$ effected the ring-closing reaction to produce the *N*-acetyl congener of **3a** in 49% yield.

(16) Compound **4a** could be converted into 1-(*tert*-butoxycarbonyl)-3-hydroxymethyl-2-methylindole (desilylated-**3a**) in 66% yield by exposure to TBAF.

This condition was shown to be applicable to other allenes. Indeed, the allenes **7h**,**i**, which lack a (*tert*-butyldimethylsiloxy)methyl functionality on the allenyl moiety, produced the corresponding indole derivatives **8h**,**i** using the TBAF treatment conditions (Table 5).

Table 5. Conversion of Allenes **7h,i** into Indoles **8h,i**[a]

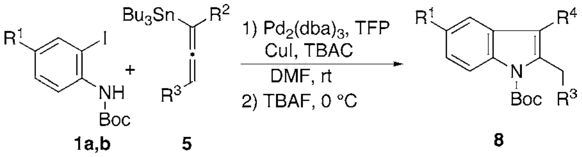


entry	**7**	R^1	R^2	time (h)	**8** (%)
1	**7h**	C_7H_{15}	Me	0.5	**8h** (82)
2	**7i**	H	C_5H_{11}	1	**8i** (54)

[a] Reactions were carried out with allene **7** and TBAF (3 equiv) at 0 °C.

More efficiently and conveniently, the successive two-step treatment of the compounds **1a**,**b** with the allenes **5d**−**g** under conditions B and TBAF[17] made possible the one-pot synthesis of the indole frameworks **8d**,**e**,**g**−**i** (Table 6).

Table 6. One-Pot Preparation of Indoles **8**

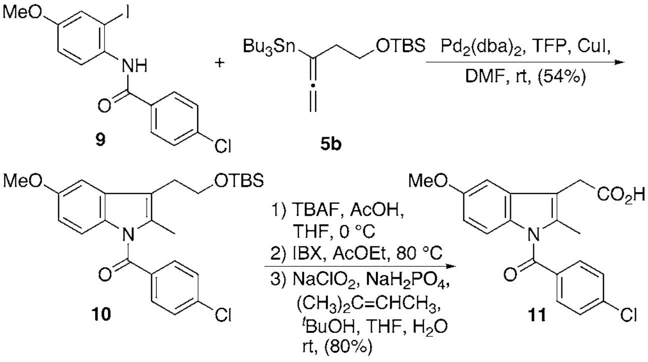


entry	**5**	R^1	R^2	R^3	**8** (%)	R^4
1	**5d**	H	CH_2OTBS	Me	**8d** (70)	CH_2OH
2	**5d**	OMe	CH_2OTBS	Me	**8e** (72)[a]	CH_2OH
3	**5e**	H	CH_2OTBS	Pr	**8g** (69)	CH_2OH
4	**5f**	H	C_7H_{15}	Me	**8h** (56)	C_7H_{15}
5	**5g**	H	H	C_5H_{11}	**8i** (54)	H

[a] Coupling reaction was carried out at 50 °C.

The final phase in this investigation involves the application of this methodology to the synthesis of indomethacin (**11**),[18] an antiinflammatory, nonsteroid agent having an indole nucleus. The *N*-acyl-2-iodoaniline **9**[19] was reacted with **5b**[11] under conditions B and directly produced **10** in 54% yield, which was subsequently transformed into indomethacin (**11**) in an 80% overall yield by the three-step conversion as shown in Scheme 3.

Scheme 3



In summary, we have developed a novel one-step procedure for the synthesis of 2-methyl-3-substituted indoles by taking advantage of the Stille coupling reaction of *N*-acyl-2-iodoanilines with the 1-(tributylstannyl)-1-substituted allenes. Alternatively, the other several 2,3-disubstituted indoles (involving the 2-monosubstituted indole) could be synthesized in a one-pot process, which consists of the Stille coupling reaction of the *N*-acyl-2-iodoanilines with the 1-(tributylstannyl)-1,3-disubstituted allenes (or 1-(tributylstannyl)-3-substituted allene), followed by TBAF treatment. In addition, this procedure could be successfully applied to the preparation of indomethacin. Further application of this method to the synthesis of not only the bioactive compounds but also natural products having the indole skeleton as a core framework will be reported in due course.

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 procedures for synthesis of allenylstannanes, indoles, and 2-allenylanilines, and characterization data for all new compounds. ^{1}H and ^{13}C NMR spectra for compounds **2**, **4a**,**b**, **5b**,**c**,**e**, **6b**,**c**, **7d**,**e**,**h**,**i**, and **8d**,**e**,**g**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] The use of TBAF in place of TBAC in the palladium-catalyzed coupling reaction (conditions B) was unfortunately found to be fruitless.

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[19] Prepared by the condensation of 2-iodo-4-methoxyaniline with 4-chlorobenzoyl chloride in 81% yield under the conventional conditions.