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A NEW ENTRY FOR PREPARATION OF 2-SUBSTITUTED AZAINDOLES†

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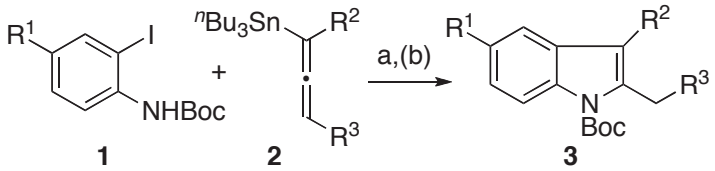
Abstract – A series of 2-substituted 5-, 6- and 7-azaindoles were synthesized from iodo-*N*-(*tert*-butoxycarbonyl)aminopyridines via the corresponding allenyl derivatives.

Recently, we reported a novel method for the one-step synthesis of 2-methyl-3-substituted indoles **3** (R^3=H) under the typical Stille conditions[1] in the presence of tetrabutylammonium chloride (TBAC) that effected the coupling reaction between *N*-acyl-2-iodoanilines **1** and the 1-(tributylstannyl)-1-substituted allenes **2**, followed by the formal endo-mode cyclization of the resulting allenyl species.[2] An alternative one-pot procedure including a successive Stille reaction (with or without TBAC) and a subsequent TBAF treatment resulted in the efficient formation of the other types of 2-alkyl-3-substituted indoles (Scheme 1). This method could successfully be applied to the synthesis of indomethacin.



a) $Pd_2(dba)_3$ (3 mol%), TFP (24 mol%). CuI (10 mol%), TBAC (3 equiv.), DMF, rt; b) TBAF (3 eq.), THF, 0 °C.

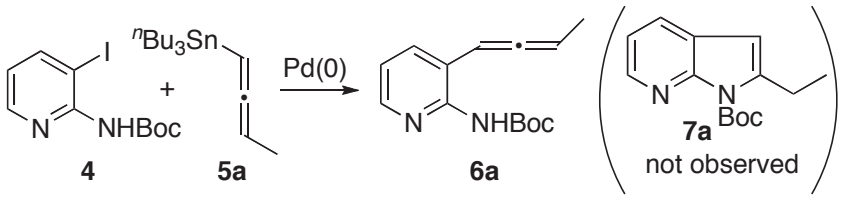
Scheme 1. Palladium(0)-catalyzed Coupling Reaction of **1** with **2**

The azaindole frameworks,[3] a bioisostere of indole, are involved as a core framework in various natural products and pharmaceuticals.[4] We describe here a new synthetic protocol for the preparation of

† This paper is dedicated to Emeritus Professor Akira Suzuki on the occasion of his 80th birthday.

2-substituted azaindole derivatives based on the our own newly developed method for the construction of the indole skeleton.

At the beginning of this program, synthesis of 2-substituted 7-azaindole was examined (Table 1). According to the previously established conditions, which directly led *N*-acylanilines to the corresponding indole derivatives, 2-aminopyridine derivative **4** was treated with **5a**[5] in DMF in the presence of 3 mol % $Pd_2(dba)_3$, tri-2-furylphosphine (TFP, 24 mol %), CuI (10 mol %), and TBAC (3 equiv) at room temperature (condition A) for 60 h to afford unexpectedly a complex mixture (entry 1). When the reaction was carried out in the absence of TBAC (condition B), the Stille coupling product **6a** was obtained in 86% yield (entry 2). Changing the solvent from DMF to THF decreased the chemical yield of **6a** (entry 3). Treatment of **6a** with TBAF in THF gave 7-azaindole **7a** in 58% yield as expected (Scheme 2).

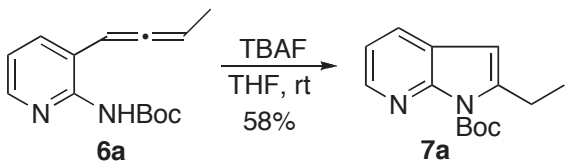


4 **5a** **6a**

entry	condition[a]	time (h)	**6a** (%)
1[b]	A	60	-
2	B	18	86
3	B[c]	14	52

[a]Condition A: $Pd_2(dba)_3$ (3 mol%), TFP (24 mol%), CuI (10 mol%), TBAC (3 equiv.), DMF, rt. Condition B: $Pd_2(dba)_3$ (3 mol%), TFP (24 mol%), CuI (10 mol%), DMF, rt. [b]Complex mixture was obtained. [c]THF was used under the same condition.

Table 1. Palladium(0)-Catalyzed Coupling Reaction of **4** with **5a**

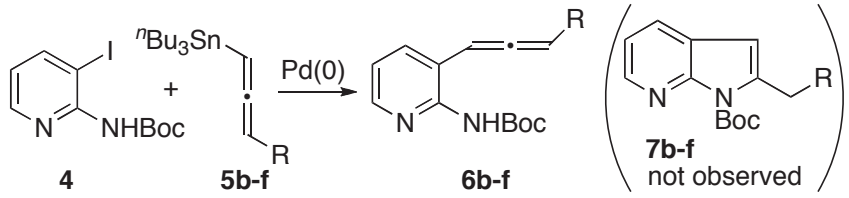


6a **7a**

Scheme 2. Conversion of **6a** into **7a**

Compound **4** was exposed to other allenes **5b-f** in the presence of a palladium catalyst providing the corresponding Stille coupling products **6b-f** in satisfactory yields as summarized in Table 2. As can be seen in Table 2, the condition without TBAC (condition B) consistently produced the allenyl derivatives **6b-f** (entries 1-5), whereas the condition with TBAC (condition A) was again found not to be effective for

our purpose (entries 6-10). This was not the case in the reaction of **1** with **2** where the condition with TBAC generally afforded indole frameworks directly and the Stille coupling products were obtained

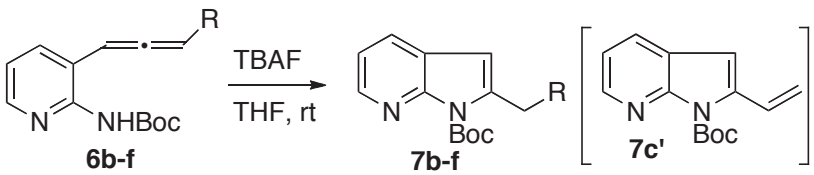


4 **5b-f** **6b-f**

entry	allene	R	condition[a]	time (h)	product and yield (%)
1	**5b**	H	B	3	**6b** (91)
2	**5c**	CH_2OTBS	B	4	**6c** (67)
3	**5d**	$^nC_5H_{11}$	B	5	**6d** (88)
4	**5e**	$(CH_2)_2Ph$	B	16	**6e** (81)
5	**5f**	^{i}Pr	B	3	**6f** (85)
6	**5b**	H	A	12	-
7	**5c**	CH_2OTBS	A	2	-
8	**5d**	$^nC_5H_{11}$	A	7	**6c** (48)[b]
9	**5e**	$(CH_2)_2Ph$	A	12	-
10	**5f**	^{i}Pr	A	4	**6f** (42)

[a]Condition A: $Pd_2(dba)_3$ (3 mol%), TFP (24 mol%), CuI (10 mol%), TBAC (3 equiv.), DMF, rt. Condition B: $Pd_2(dba)_3$ (3 mol%), TFP (24 mol%), CuI (10 mol%), DMF, rt. [b]Aminopyridine **4** was recovered in 36 % yield.

Table 2. Palladium(0)-Catalyzed Coupling Reaction of **4** with **5b-f**



6b-f **7b-f** **7c'**

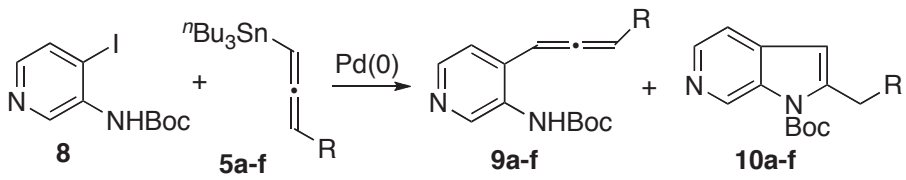
entry	substrate	R	time (h)	**7** (%)
1	**6b**	H	1	**7b** (69)
2	**6c**	CH_2OTBS	3	-[a]
3	**6d**	$^nC_5H_{11}$	4	**7d** (74)
4	**6e**	$(CH_2)_2Ph$	4	**7e** (37)[b]
5	**6f**	^{i}Pr	4	**7f** (68)

[a]**7c'** was obtained in 67% yields. [b]**6e** was recovered in 50% yield.

Table 3. Conversion of **6** into **7**

under the condition without TBAC. Cyclization of allenylaminopyridine derivative **6b** with TBAF gave 2-methyl-7-azaindole (**7b**) in 69% yield (Table 3, entry 1). In the reaction of **6c,** 2-vinyl-7-azaindole (**7c'**) (67%) was obtained instead of **7c** (entry 2).[6] 2-Hexyl- and 2-isobutyl-7-azaindoles **7d**,**f** were synthesized from **6d**,**f** in 74% and 68% yield, respectively (entries 3,5). In the case of **6e**, the corresponding cyclized product **7e** was obtained in a rather low yield along with the recovery of the starting material (50% yield)(entry 4). Thus, it was shown that the palladium-catalyzed coupling reaction of 2-aminopyridines with 3-substituted allenylstannanes, followed by base treatment results in the production of the corresponding 2-substituted-7-azaindoles.

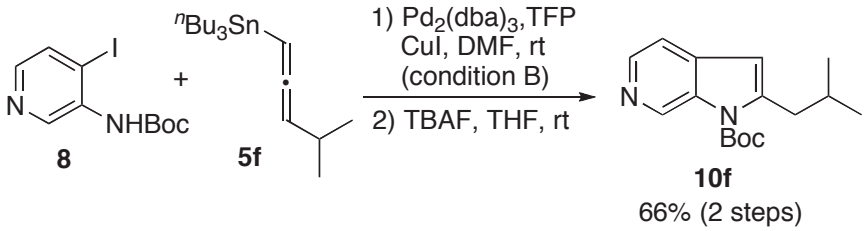
Our efforts were then directed toward synthesis of 6-azaindoles. Treatment of 3-amino-4-iodopyridine derivative **8** with 1,2-butadienyltributylstannane (**5a**) in the presence of $Pd_2(dba)_3$, TFP, and CuI in DMF at room temperature (condition B), however, afforded neither allenylpyridine **9a** nor 6-azaindole **10a** (Table 4, entry 1). In contrast to the conversion of **4** into **7**, the condition with TBAC (condition A) worked well in this case providing directly 2-ethyl-6-azaindole (**10a**) in 82% yield (entry 2). Other 6-azaindoles **10b-f** possessing Me, $(CH_2)_2OTBS$, and hexyl substituents at the C_2-position were easily prepared in high yields under the condition A (entries 3-5). In the case of tributyl(5-phenyl-1,2-pentadienyl)stannane (**5e**), 6-azaindole derivative **10e** was isolated in a moderate yield (entry 6). The condition with TBAC (condition A) was not useful for the preparation of **10f**. In fact, a mixture of **10f** and the allenyl derivative **9f** was obtained in 31% yield when exposed to condition A (entry 7).



entry	allene	R	condition[a]	time (h)	product and yield (%)
1	**5a**	Me	B	18	-
2	**5a**	Me	A	2	**10a** (82)
3	**5b**	H	A	2	**10b** (92)
4	**5c**	CH_2OTBS	A	8	**10c** (85)
5	**5d**	$^n C_5H_{11}$	A	12	**10d** (83)
6	**5e**	$(CH_2)_2Ph$	A	3.5	**10e** (50)
7	**5f**	^{i}Pr	A	4	**9f**/**10f** (31)[b]

[a]Condition A: $Pd_2(dba)_3$ (3 mol%), TFP (24 mol%), CuI (10 mol%), TBAC (3 equiv.), DMF, rt. Condition B: $Pd_2(dba)_3$ (3 mol%), TFP (24 mol%), CuI (10 mol%), DMF, rt. [b]Product was a 1:1 mixture of **9f**/**10f**.

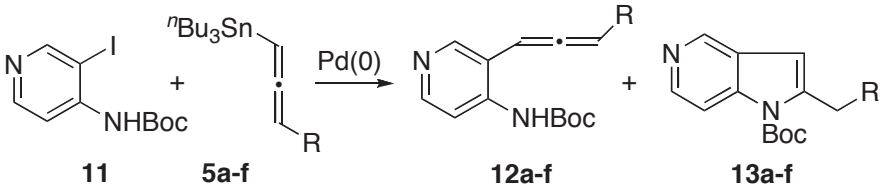
Table 4. Palladium(0)-Catalyzed Coupling Reaction of **8** with **5a-f**



Scheme 3. Synthesis of **10f** from **8** and **5f** via 2 steps

An efficient synthesis of 2-isobutyl-6-azaindole (**10f**) (66%) was accomplished by using condition B, followed by base treatment as shown in Scheme 3.

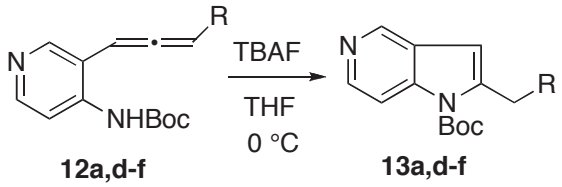
2-Substitued-5-azaindoles were our final target compounds in this investigation. By taking into account the aforementioned two conditions A and B (condition with or without TBAC), we attempted the conversion of 3-iodo-4-aminopyridine derivative **11** into the targeted compounds. Treatment of **11** with allenylstannane **5a** under condition A gave no desired products at all. Instead, the formation of 3-allenyl-4-aminopyridine derivative **12a** was observed in 80% yield under condition B (Table 5, entry 1). Condition A was found to be effective for the direct synthesis of 2-methyl-5-azaindole derivative **13b** in a satisfactory yield (entry 2). 2-Silyloxyethyl congener **13c** was also directly formed under condition A, but



entry	allene	R	condition[a]	time (h)	product and yield (%)
1	**5a**	Me	B	6	**12a** (80)
2	**5b**	H	A	2	**13b** (86)
3	**5c**	CH_2OTBS	A	19	**13c** (31)[b]
4	**5d**	$^nC_5H_{11}$	B	12	**12d** (80)
5	**5e**	$(CH_2)_2Ph$	B	24	**12e** (62)[c]
6	**5f**	^{i}Pr	B	16	**12f** (86)

[a]Condition A: $Pd_2(dba)_3$ (3 mol%), TFP (24 mol%), CuI (10 mol%), TBAC (3 equiv.), DMF, rt. Condition B: $Pd_2(dba)_3$ (3 mol%), TFP (24 mol%), CuI (10 mol%), DMF, rt. [b]Reaction was carried out at room temperature for 16 h, then 80 °C for 3 h. [c]**11** was recovered in 28% yield.

Table 5. Palladium(0)-Catalyzed Coupling Reaction of **11** with **5a-f**



12a,d-f **13a,d-f**

entry	substrate	R	time (h)	product and yield (%)
1	**12a**	Me	1.5	**13a** (78)
2	**12d**	$^{n}C_5H_{11}$	5	**13d** (66)[a]
3	**12e**	$(CH_2)_2Ph$	2	**13e** (80)
4	**12f**	^{i}Pr	3	**13f** (98)

[a]**12d** was recovered in 18% yield.

Table 6. Conversion of **12** into **13**

the chemical yield was rather low (entries 3). Allenylstannanes **5d-f** having *n*-pentyl, phenethyl, and *i*-propyl groups on the R position reacted with **11** under condition B to give the corresponding 3-allenyl-4-aminopyridine derivatives **12d-f** in good yields (entry 4-6). Cyclization of **12a**,**d-f** with TBAF treatment proceeded without any difficulty to provide the 2-substituted-5-azaindoles **13a**,**d-f** in satisfactory yields. The results are summarized in Table 6.

In summary, we have developed a new procedure for the synthesis of 2-substituted-7-azaindoles on the basis of successive Stille coupling of 2-amino-3-iodopyridines with the 1-(tributylstannyl)-3-substituted allenes, followed by cyclization of the resulting allenyl derivatives with TBAF treatment. 2-Substituted-6-azaindoles could be directly synthesized in a one-pot process under the palladium-catalyzed condition with TBAC. Synthesis of 2-substituted-5-azaindoles could be achieved by a proper choice of reaction conditions (with or without TBAC/base treatment). These results (formation of allene and/or azaindole) would reflect the electronic property of the amino functionality of the starting pyridine derivatives. Thus, we could add an alternative method for the preparation of 2-substituted-5-, 6-, and 7-azaindoles.

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6. Compound **7c** (23%) was isolated after heating a solution of **6c** in DMF at 80 °C for 3 h.