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SYNTHESIS OF (3-INDOLYL)HETEROAROMATICS BY SUZUKI-MIYAURA COUPLING AND THEIR INHIBITORY ACTIVITY IN LIPID PEROXIDATION

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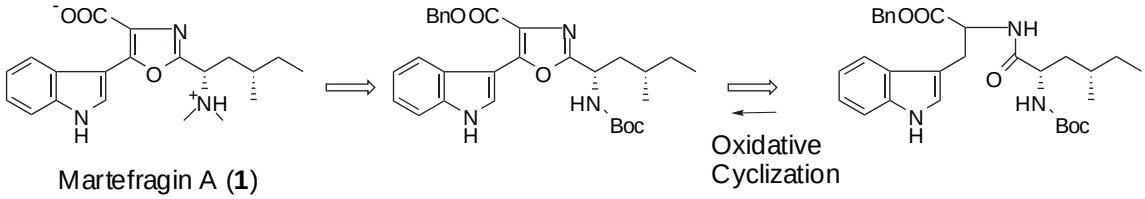
Abstract - A variety of (3-indolyl)heteroaromatic compounds were synthesized by Suzuki-Miyaura coupling of 3-indolylboronic acid and halogenated heteroaromatics. 2-(3-Indolyl)thiophene showed potent inhibitory activity against lipid peroxidation by rat liver microsome.

Martefragin A (**1**) is an indole alkaloid isolated from a sea algae, *Martensia fragilis* Harvey, collected at Toyama Bay in Japan.[1] Since **1** showed potent inhibitory activity against lipid peroxidation (30-fold more potent inhibitor than α-tocopherol) by rat liver microsome, it was expected to be a new lead compound in the development of anti-oxidant drugs. We have already reported the first asymmetric total synthesis of **1** and its stereoisomers. This total synthesis allowed us to determine the absolute stereochemistry of the natural product, as shown in Scheme 1.[2]

Scheme 1



An efficient method for synthesizing analogs of martefragin A using a solid-phase synthesis was also developed and some analogs were found to be more potent inhibitors than the natural product.[3] A preliminary study on the structure-activity relationship showed that the presence of an indole ring is essential for its biological activity.[4] Therefore, we turned our attention to the effect of heteroaromatics connected to the C3 position of indole. Using the same procedure for the synthesis of martefragin A, thiazole and imidazole analogs of martefragin A were prepared and both showed potent activities. To investigate the effects of structurally diverse heteroaromatic rings, a new strategy for synthesizing (3-indolyl)heteroaromatics was required. We report here a Suzuki-Miyaura coupling reaction of 3-indoleboronic acid with halogenated heteroaromatic compounds.

Coupling reactions at the 3-position of indoles were widely studied using 3-indolylzinc derivatives by Sakamoto[5] and Bosch.[6] Stille coupling reactions of 3-tributylstannylindole and halo aromatics or 3-iodo-indole with tributylstannylimidazole derivatives were also studied by Ortar[7] and Hibino.[8] The introduction

of simple phenyl and alkenyl groups at the C2 and C3 positions of indole by Suzuki-Miyaura coupling has been reported recently.[9,10] In the synthesis of an indole alkaloid, topsentin, Ohta used Suzuki-Miyaura coupling, and a 3-(3-indolyl)imidazole derivative was obtained in 79% yield using *N*-silylated 3-indolylboronic acid and a protected 3-bromoimidazole derivative.[11] Interestingly, the reverse combination of bromide and boronic acid gave the same product in only 7% yield.

We chose Ohta's protocol to construct a library of indole substituted heteroaromatics, since a wide variety of halogenated heteroaromatic compounds are available commercially (Scheme 2).

Scheme 2

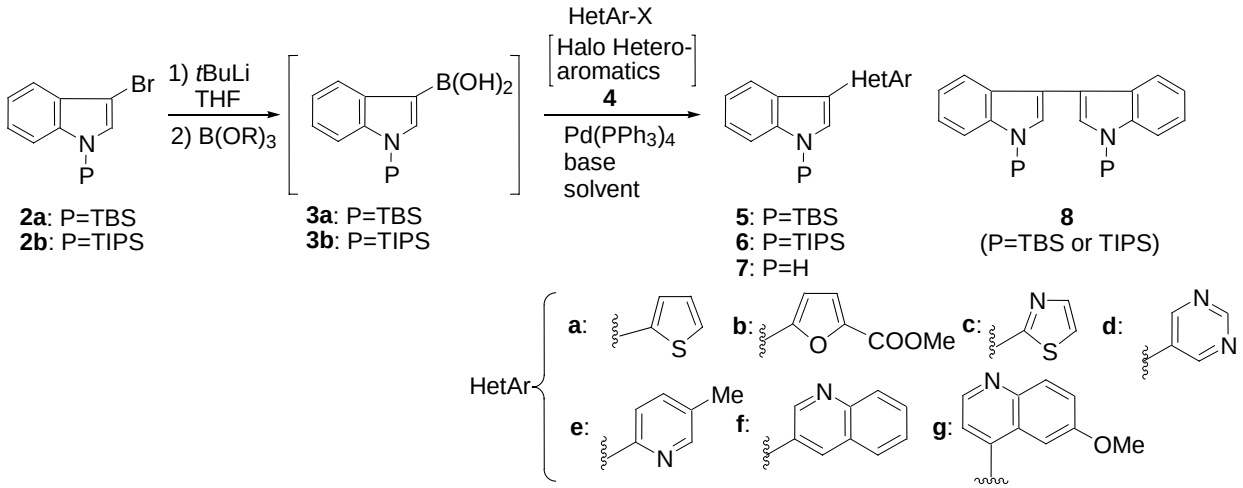
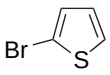
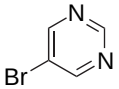
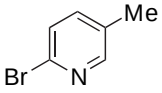
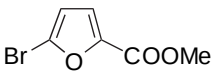
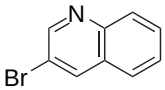
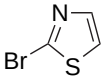
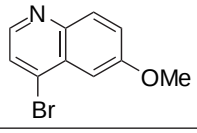


Table 1. Coupling Reactions of 3 with 4

	HetAr-X	Conditions[a]	Product (%)[c]		HetAr-X	Conditions[a]	Product (%)[c]
4a		A	**5a** (59)	**4e**		A	**5d** (61)
		B	**6a** (82)			B	**6d** (75)
		C	**6a** (86)			C	**6d** (71)
4b		A	**5a** (64)	**4f**		A	**5e** (67)
		B	**6a** (75)			B	**6e** (77)
		C	**6a** (64)			C	**6e** (76)
4c		A	**5b** (58)	**4g**		A	**5f** (71)
		B	**6b** (70)			B	**6f** (80)
		C	**6b** (69)			C	**6f** (76)
4d		A	**5c** (57)	**4h**		A	**5g** (32)
		B	**6c** (81)			B	**6g** (78)
		C	**6c** (0)[b]			C	**6g** (75)

a Condition A: **2a**, $B(OMe)_3$, $Pd(PPh_3)_4$ (5 mol%), aq. satd. Na_2CO_3, benzene-MeOH, reflux; Condition B: **2b**, $B(OiPr)_3$, $Pd(PPh_3)_4$ (3 mol%), aq. satd. Na_2CO_3, benzene-MeOH, reflux; Condition C: **2b**, $B(OiPr)_3$, $Pd(PPh_3)_4$ (3 mol%), LiOH-Na_2CO_3, aq. THF, rt, one-pot procedure. *b* **7c** was obtained in 31% yield. *c* The yields from **2**.

N-TBS-3-Bromoindole (**2a**) was prepared from indole by the standard procedure in high yield.[6,11] Lithiation of **2a** by *t*BuLi followed by reaction with trimethyl borate gave *N*-TBS-indolyl-3-boronic acid (**3a**). Although **3a** could be isolated from the crude product by precipitation, it readily decomposed to *N*-TBS-indole. Therefore, crude **3a** was used directly in the following coupling reaction. According to Ohta's

protocol, **3a** was reacted with 2 equivalents of 2-bromothiophene (**4a**) in the presence of 5 mol% of $Pd(PPh_3)_4$ and Na_2CO_3 in aqueous MeOH-benzene (Condition A, Table 1). The mixture was refluxed for 1 h to give 2-(*N*-TBS-3-indolyl)thiophene (**7a**) in 59% yield from **2a** along with bis-indole (**8**, P=TBS, 2%) and *N*-TBS-indole (16%). The coupling of **3a** with 2-iodothiophene (**4b**) slightly improved the yield. Under these conditions, brominated heteroaromatics (**4c**-**h**) were coupled with **2a**, and the results are shown in Table 1.

Several problems were observed during the reaction under Condition A. First, when the reaction was slow, a considerable amount of desilylated indoles were formed which deactivated the catalyst. Another problem was the formation of *N*-TBS-indole, which was produced by the decomposition of 3-indolylboronic acid and by protonation of 3-lithioindole. Since trimethyl borate contains a variable amount of methanol, which is difficult to remove from the reagent, we next used triisopropyl boronate.[10] The protecting group on indole was changed to a triisopropylsilyl (TIPS) group.[10] Thus, **2b** was converted to **3b** using triisopropyl borate and reacted with **4a-h**. Under these optimized conditions (Condition B) the amount of catalyst could be reduced to 3 mol%. The yields of all of the coupling products were increased.

Next, we investigated a one-pot procedure without isolation of 3-indolylboronic acid. Thus, after the reaction of lithiated *N*-TIPS-indole with triisopropyl boronate was quenched by adding aqueous Na_2CO_3, halogenated heteroaromatic compounds and the catalyst were added to the reaction mixture (Condition C). The coupling reaction proceeded at room temperature to give the product in a yield comparable to that under Condition B. The reaction using 2-bromoimidazole gave a complex reaction mixture under all three conditions.

Scheme 3

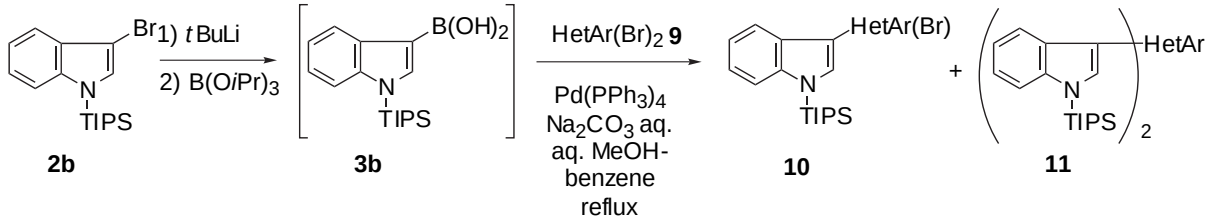
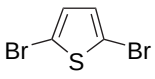
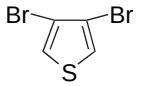
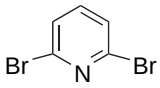


Table 2 Coupling Reaction of 3b and Dibromoheteroaromatics (9)

run	time (h)	Molar Ratio of **2b** : **9**	HetAr(Br)$_2$		Product (%) **10**	Product (%) **11**
1	1.5	1 : 2	**9a**		69	13
2	3	2.5 : 1			1	84
3	5	1 : 2	**9b**		67	5
4	25	5 : 1			8	89
5	2	1 : 2	**9c**		84	3
6	2	2.5 : 1			0	94

The coupling reaction using dibromoheteroaromatics (**9**) also proceeded under Condition B (Table 2). Depending on the ratio of **2b** and **9**, the reaction formed either mono-coupling product (**10**) or bis-coupling product (**11**).

Among the resulting (3-indolyl)heteroaromatics, **6a-6g** were desilylated by tetrabutylammonium fluoride to give **7a-7g** in high yield. The relative inhibitory activities of **7a-7g** against lipid peroxidation by rat liver microsome[1] are shown in Table 3. Except for pyrimidyl derivative (**7d**), most of the indole-substituted heteroaromatic compounds showed inhibitory activity. Among the compounds tested, 2-(3-indolyl)-thiophene (**7a**) was 2.5 times more active than the parent compound (**1**).

Table 3 Relative Inhibitory Activities of (3-Indolyl)heteroaromatics against Lipid Peroxidation by Rat Liver Microsome

	1	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**
Relative Activity	1	2.5	0.84	0.58	0.01	0.48	0.70

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REFERENCES

1. S. Takahashi, T. Matsunaga, C. Hasegawa, H. Saito, D. Fujita, F. Kiuchi and Y. Tsuda, *Chem. Pharm. Bull.*, 1998, **46**, 1527.
2. A. Nishida, M. Fuwa, Y. Fujikawa, E. Nakahata, A. Furuno and M. Nakagawa, *Tetrahedron Lett.*, 1998, **39**, 5983.
3. A. Nishida, F. Mihoko, S. Naruto, Y. Sugano, H. Saito and M. Nakagawa, *Tetrahedron Lett.*, 2000, **41**, 4791.
4. Unpublished results.
5. T. Sakamoto, T. Kondo, N. Takazawa and H. Yamanaka, *Tetrahedron Lett.*, 1993, **34**, 5955.
6. M. Amat, A. Hadida and J. Bosch, *Tetrahedron Lett.*, 1994, **35**, 793.
7. P. G. Ciattini, E. Morera and G. Ortar, *Tetrahedron Lett.*, 1994, **35**, 2405.
8. T. Choshi, S. Yamada, E. Sugino, T. Kuwada and S. Hibino, *Synlett*, 1995, 147.
9. Y. Liu and G. W. Gribble, *Tetrahedron Lett.*, 2000, **41**, 8717.
10. R. S. Hoerrner, D. Askin, R. P. Volante and P. J. Reider, *Tetrahedron Lett.*, 1998, **39**, 3455.
11. I. Kawasaki, H. Katsuma, Y. Nakayama, M. Yamashita and S. Ohta, *Heterocycles*, 1998, **48**, 1887.