THE ANOMALOUS STILLE REACTION OF 5-STANNYLIMIDAZOLE WITH 3-IODOINDOLE

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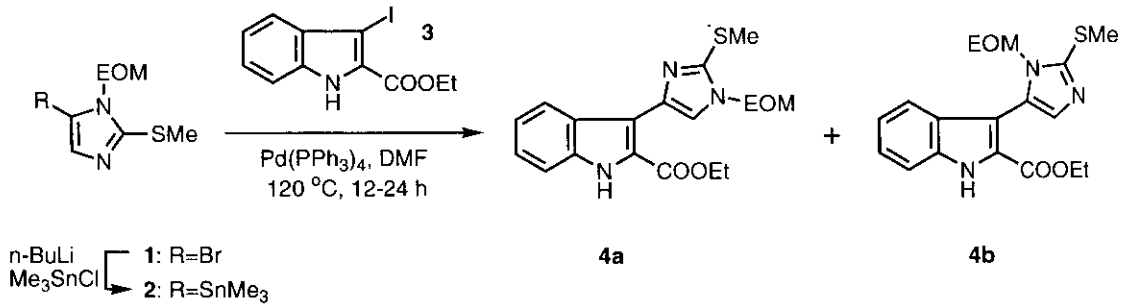
Abstract — Palladium(0)-catalyzed cross-coupling reaction of 5-stannylimidazole with 3-iodoindole gave two products including unexpected *cine* substitution.

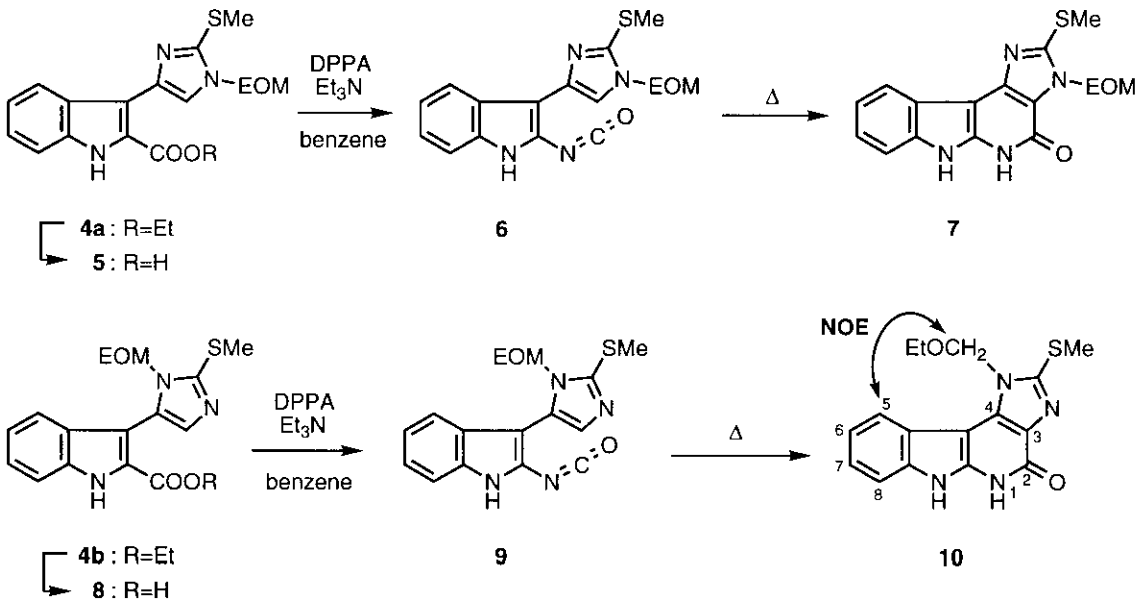
Palladium(0)-mediated coupling reaction of organotin compounds with halides or triflates (Stille reaction) has emerged in recent years as a powerful method for the stereoselective and chemoselective formation of carbon-carbon bonds including heterocycles.[1] One of the limitations of this method that has recently been reported is in the tendency of certain α-substituted olefinic stannane to undergo *cine* substitution.[2] To date, *cine*-substitution of aryl- and/or heteroarylstannane has not yet been reported. Here, we describe the first example of *cine* substitution of heteroarylstannane.



Scheme 1

During the course of studies toward total syntheses of grossularines-1 and -2,[3,4] we required 3-imidazolylindole (**4b**) for the synthesis of a tetracyclic α-carboline framework. 5-Stannylimidazole (**2**) was prepared from 1-ethoxymethyl(EOM)-5-bromo-2-methylthioimidazole (**1**)[5] by bromine-lithium exchange reaction with n-BuLi followed by treatment with trimethyltin chloride. The cross-coupling reaction of **2** with 3-iodoindole (**3**)[6] was carried out in the presence of $Pd(PPh_3)_4$ in DMF (12 h at 120 °C) to give two coupling products. Both products were easily separated by silica gel column chromatography [EtOAc/hexane (3:7)] to give the faster moving product and the slower moving product (46 and 38%

yields based on **3**). Each compound showed similar spectral data except the melting points, and we therefore tantatively suggested that the faster moving product was 3-(4-imidazolyl)indole (**4a**) and the slower moving product was 3-(5-imidazolyl)indole (**4b**).[7] Moreover, this reaction was re-examined using the protocol [$Pd(PPh_3)_4$, 2,6-di-*tert*-butyl-4-methylphenol, i-Pr_2NEt, toluene, reflux] of Stork[2b] to produce the same two products [**4a** (13%) and **4b** (34%) yields based on **3**]. In addition, an existence of regioisomer of 5-bromoimidazole (**1**)[5] or 5-stannylimidazole (**2**)[8] has been denied in spectral data and by thin layer chromatography.



Scheme 2

For the determination of structures of **4a** and **4b**, both products independently led to tetracyclic α-carbolines as follows. Hydrolysis of esters (**4a** and **4b**) followed by Curtius rearrangement using diphenylphosphoryl azide (DPPA) yielded isocyanates (**6**: 81% and **9**: 84% from **4a** and **4b**), which were subjected to thermal electrocyclic reaction in the 2-azahexatriene system[9] involving the indole 2,3-bond in *o*-dichlorobenzene to provide tetracyclic α-carbolines (**7**: 72% and **10**: 91%)[10] (Scheme 2). In the difference nuclear Overhauser effect (NOE) experiments, when C_5-H of α-carboline (**7**) was irradiated, no NOE enhancement of the methylene group (EOM-group) was observed. On the other hand, irradiation of C_5-H of α-carboline (**10**) caused NOE enhancement (8.0%) of the methylene group (EOM-group). These results indicated that the faster moving product corresponding to α-carboline (**7**) was abnormal product, 3-(4-imidazolyl)indole (**4a**) and the slower moving product corresponding to α-carboline (**10**) was the normal product, 3-(5-imidazolyl)indole (**4b**) as initially speculated. It was demonstrated that this reaction proceeds by way of not only *ipso*-substitution but also *cine*-substitution reaction. Thus, we found anomalous Stille reaction between heteroarylstannane and heteroaryl halide.

Mechanistically, the indole-Pd^{II}-I species, derived from oxidative insertion of Pd(0) into 3-iodoindole (**3**), would be coordinated with the imidazolylstannane. For the normal *ipso*-substitution, transmetalation of this coordinated species[11] would be converted into the indole-Pd^{II}-imidazole species and then the *ipso* product (**4b**) would be obtained.[1] In contrast, this coordinated species[11] might undergo a Heck-type insertion reaction by some factors. Next step, a palldium-carbene intermadiate[2b-e] reported recently might be generated by 1,1-elimination of trimethyltin iodide from a Heck-type adduct to yield the *cine* product (**4a**) through 1,2-hydrogen shift followed by reductive elimination. It is considered that factors in order to undergo *cine* substitutions depend on an electronic and/or a steric effects of substituents of imidazole ring.[2b-e] Further studies are in progress.

ACKNOWLEDGMENT

We would like to thank Professors K. Fukumoto and T. Sakamoto (Pharmaceutical Institute, Tohoku University) for helpful suggestions. This work was supported in part by a Grant-in-Aid for Encouragement of Young Scientists (No. 07772122 to T. C.) for the Ministry of Education, Science, Sports and Culture of Japan.

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5. 5-Bromoimidazole (**1**) was prepared from imidazole as follows. Ethoxymethyl chloride (EOMCl) was added to a solution of imidazole in benzene to gave the *N*-EOM-imidazole (87%, bp 84-86 °C/4 torr). This compound was treated with n-BuLi followed by addition of MeSSMe to produce

the *N*-EOM-2-methylthioimidazole (87%, bp 130-132 °C/9 torr), which was brominated with NBS in CCl_4 to yield 5-bromoimidazole (**1**) [44%, bp 125-127 °C/3.5 torr; ^{1}H-NMR (acetone-d_6): δ 1.13 (3H, t, *J*=7 Hz), 2.53 (3H, s), 3.50 (2H, q, *J*=7 Hz), 5.23 (2H, s), 6.89 (1H, s, C_4-H)]. All new compounds provided satisfactory spectral and analytical data.

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7. Compound (**4a**): mp 120-124 °C (Et_2O-hexane); IR (KBr): 3053, 1709 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.13 (3H, t, *J*=7 Hz), 1.30 (3H, t, *J*=7 Hz), 2.64 (3H, s), 3.45 (2H, q, *J*=7 Hz), 4.26 (2H, q, *J*=7 Hz), 5.19 (2H, s), 6.85-7.41 (3H, m), 7.85 (1H, s), 8.40-8.69 (1H, m), 9.53 (1H, br s); *m/z* 359 (M^+).

   Compound (**4b**): mp 167-168 °C (Et_2O); IR (KBr): 3055, 1706 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, t, *J*=7 Hz), 1.21 (3H, t, *J*=7 Hz), 2.65 (3H, s), 3.16 (2H, q, *J*=7 Hz), 4.30 (2H, q, *J*=7 Hz), 5.22 (2H, s), 6.83-7.66 (4H, m), 7.11 (1H, s), 10.99 (1H, br s); *m/z* 359 (M^+).

8. Compound (**2**): ^{1}H-NMR (acetone-d_6): δ 0.22 (9H, s), 1.14 (3H, t, *J*=7 Hz), 2.54 (3H, s), 3.44 (2H, q, *J*=7 Hz), 5.28 (2H, s), 7.00 (1H, s, C_4-H).

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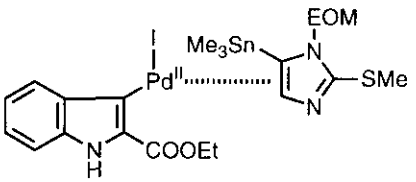
10. Compound (**7**): mp 263-265 °C (decomp) (MeOH); IR (KBr): 3109 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.09 (3H, t, *J*=8 Hz), 2.82 (3H, s), 3.58 (2H, q, *J*=8 Hz), 5.83 (2H, s), 7.14-7.17 (2H, m), 7.45-7.49 (1H, m), 7.93-7.98 (1H, m); *m/z* 328 (M^+).

    Compound (**10**): mp 269-270 °C (decomp) (MeOH); IR (KBr): 3110 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.13 (3H, t, *J*=8 Hz), 2.72 (3H, s), 3.66 (2H, q, *J*=8 Hz), 5.82 (2H, s), 7.13 (1H, t, *J*=8 Hz), 7.18 (1H, t, *J*=8 Hz), 7.47 (1H, d, *J*=8 Hz), 7.96 (1H, d, *J*=8 Hz), 8.53 (1H, s); *m/z* 328 (M^+).

11.



Received, 12th September, 1997