

AN INTERESTING REGIOSELECTIVITY OF PALLADATION FOR BROMOINDOLE DERIVATIVES:¹ A CONVENIENT ONE-STEP SYNTHESIS OF 4-BROMODEHYDRO-TRYPTOPHAN DERIVATIVES

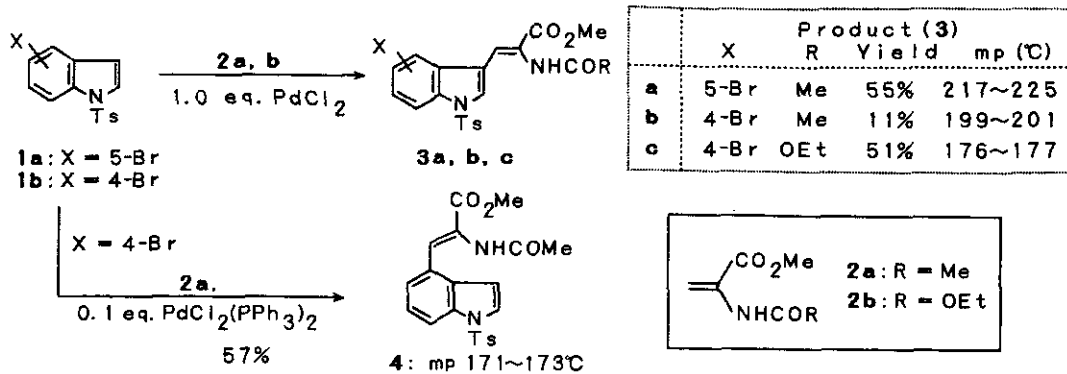
Yuusaku Yokoyama, Makio Takahashi, Yukari Kohno, Kazutaka Kataoka, Yasuko Fujikawa, and Yasuoki Murakami*

School of Pharmaceutical Sciences, Toho University,
2-2-1, Miyama, Funabashi, Chiba 274, Japan

Abstract—*N'*-Protected-*N*-tosyl-4- or 5-bromodehydrotryptophan (**3**) was obtained by the regioselective vinylation of *N*-tosyl-4- or 5-bromoindole (**1**) with *N*-protected dehydroalanine methyl ester (**2**) by the use of stoichiometric amount of PdCl₂. On the other hand, the same reaction of 4-bromoindole (**1b**) under catalytic conditions gave the 4-vinylated product (**4**).

There are several types of palladium-assisted vinylation of aromatic compounds;² one of those involves the direct palladation of aromatic hydrocarbon with Pd(II) salt to form aryl palladium σ -complex intermediate, and another involves the oxidative addition of aryl halide to Pd(0) species. The former process requires a stoichiometric amount of Pd(II) (stoichiometric condition) and the latter requires a catalytic amount of Pd(0) (catalytic condition). We have reported³ the direct vinylation at C₃-position of indoles with α,β -unsaturated carbonyl compounds by the use of stoichiometric amount of Pd(II). In the course of applying this reaction to the syntheses of dehydrotryptophan derivatives, we found an interesting regioselectivity for the palladation of 4- and 5-bromoindole derivatives under stoichiometric or catalytic condition.

5-Bromoindole (**1a**) was allowed to react with *N*-acetyldehydroalanine methyl ester (**2a**) under stoichiometric conditions⁴ to give 5-bromodehydrotryptophan⁵ (**3a**) in 55% yield. However, under catalytic conditions,⁶ the reaction did not occur at all and resulted in only recovery of the starting materials (83%). In the reaction of 4-bromoindole (**1b**), 4-bromodehydrotryptophan (**3b**) was obtained in only 17% yield under stoichiometric condition,⁴ whereas under the catalytic condition,⁶ vinylation of **1b** smoothly proceeded at the C₄-position to give the 4-vinylated products (**4**) in 57% yield,⁷ in contrast to the result of catalytic reactions of **1a**. Hedgedus et al.⁸ have reported that the compound (**3b**), which was used as the key intermediate for the total synthesis of clavicipitic acid, was prepared by three-step sequence which involved hazardous mercuration-iodination reaction of **1b** followed by the selective vinylation of the resulted 3-iodoindole with **2a**. We tried to improve the yield of 4-bromo-



dehydrotryptophan by changing the olefin from **2a** to **2b** in which the amino group was protected by an ethoxycarbonyl group. The reaction⁴ smoothly proceeded to give the desired product (**3c**)⁹ in 51% yield.¹⁰ It is quite interesting that the palladation occurred at C₃-position of 4- or 5-bromoindoles (**1a** or **1b**) under stoichiometric conditions in spite of the presence of bromine atom which had been considered as the most reactive position in the molecule. The present investigation shows that the reactive position of bromoindole towards the palladation could be controlled by changing the reaction conditions.

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REFERENCES AND NOTES

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- Reaction conditions: 1.0 eq. of PdCl₂, 4.0 eq. of AcONa, and 2.0 eq. of **2a** (or **2b**) in AcOH at 120-130°C for 2 h.
- All new compounds were identified by spectral and elemental analyses.
- Reaction conditions: 0.05 eq. of PdCl₂(PPh₃)₂, 2.0 eq. of **2a**, and 2.0 eq. of AcONa in DMF-Et₃N (1:2) at 130°C for 5 h.
- The use of PdCl₂ instead of PdCl₂(PPh₃)₂ resulted in low yield (9%) of 4-vinylated product (**4**) accompanied by starting material (83%).
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- The stereochemistry of **3c** and **4** was determined as Z-configuration on the basis of long range coupling constant of ¹H-C=C-¹³C=O (J=4 and 5 Hz) obtained by low power selective irradiation of methyl and amide protons. See M. Cutolo, V. Fiandanese, F. Naso, and O. Sciacovelli, *Tetrahedron Lett.*, 1983, **24**, 4603.
- The use of PdCl₂(PPh₃)₂ instead of PdCl₂ resulted in quantitative recovery of starting material.

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