CONDENSED HETEROAROMATIC RING SYSTEMS. XXIII.[1]
A CONCISE SYNTHESIS OF HIPPADINE

Takao Sakamoto,*[a] Akito Yasuhara,[a] Yoshinori Kondo,[a] and Hiroshi Yamanaka[b]

a) Pharmaceutical Institute, Tohoku University, Aobayama, Aoba-ku, Sendai 980, Japan; b) Department of Education, Yamagata University, 1-4-12, Koshirakawa-cho, Yamagata 990, Japan

Abstract–Hippadine, a pyrrolophenanthridine alkaloid, was synthesized in 39% overall yield of three steps using the palladium-catalyzed cross-coupling reaction of 2,6-dibromoaniline with (*Z*)-1-tributylstannyl-2-ethoxyethene as a key step.

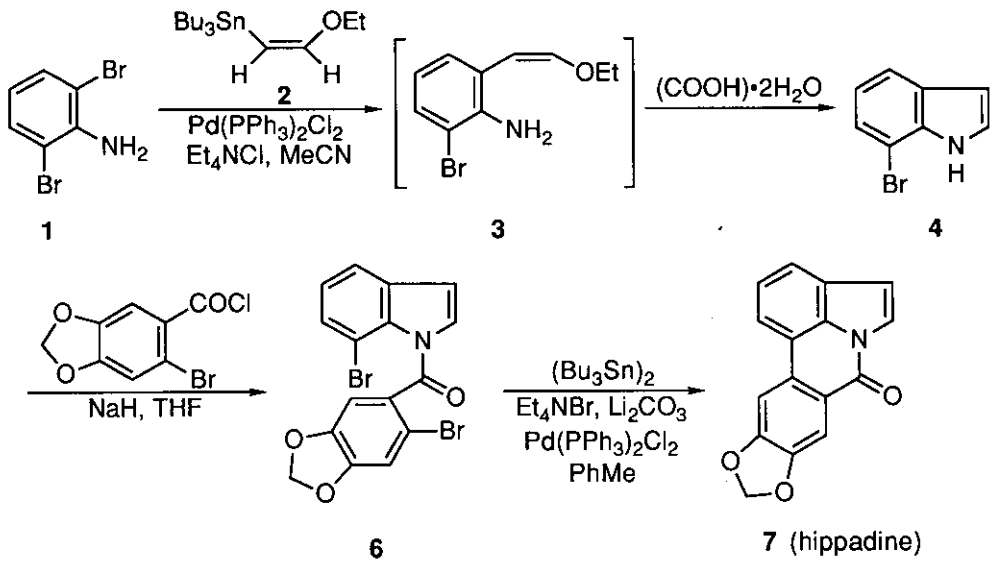
Previously, we reported that the palladium-catalyzed reaction of aryl halides with (*Z*)-1-tributylstannyl-2-ethoxyethene yielded (*Z*)-2-ethoxyethenylarenes which are arylacetaldehyde equivalent derivatives.[2,3] Application of the palladium-catalyzed reaction to *ortho*-substituted haloaromatics made the construction of various condensed heterocycles possible. Especially, pyrrole ring-fused heterocycles such as indole,[3] pyrrolopyridine,[1] and pyrrolopyrimidine[4] were easily synthesized by this methodology.

Utilizing the indole formation as a key reaction, we report here a concise synthesis of hippadine, a pyrrolophenanthridine alkaloid isolated from *Crinum* species (*Amaryllidaceae*).[5]

The palladium-catalyzed reaction of commercially available 2,6-dibromoaniline (**1**) with (*Z*)-1-tributylstannyl-2-ethoxyethene (**2**) under the reported conditions[2,3] followed by cyclization of the coupling product (**3**) with oxalic acid gave 7-bromoindole (**4**) in 96% yield. To the best of our

knowledge, this reaction is the simplest and most high yield synthetic method of 7-bromoindole from the commercially available material at present.

The *N*-acylation of **4** with 2-bromo-3,4-methylenedioxybenzoyl chloride gave the 1-benzoylated indole (**6**) in 72% yield, which was cyclized to hippadine under Stille's conditions[6] in 68% yield. The overall yield from the commercially available starting material (**1**) was 39%.



Scheme 1

A synthesis of hippadine was reported by some groups.[7-10] For example, recent Snieckus's synthesis from *N*-acetylindoline (5 steps, 24% overall yield) used palladium-catalyzed arylation of 7-iodo-*N*-acetylindoline with a benzeneboric acid derivative as a key reaction.

EXPERIMENTAL

7-Bromoindole (4)

A mixture of 2,6-dibromoaniline (1.00 g, 4 mmol), (*Z*)-1-tributylstannyl-2-ethoxyethene (**2**) (1.44 g, 4 mmol), $Pd(PPh_3)_2Cl_2$ (0.16 g, 0.23 mmol), Et_4NCl (0.66 g, 4 mmol), and MeCN (20 ml) was refluxed for 4 h. To the reaction mixture was added $(COOH)_2 \cdot 2H_2O$ (200 mg) and the mixture was

refluxed for 3 h. After removal of the solvent, the residue was purified by silica gel column chromatography using hexane/CH_2Cl_2 (1:1) to give colorless needles which were recrystallized from hexane. mp 44°C. Lit.,[11] mp 45-45.5°C. 60 MHz ^{1}H-Nmr ($CDCl_3$) δ (ppm): 4.2-4.4 (1H, br), 6.5-7.4 (5H, m).

7-Bromo-1-(2-bromo-4,5-methylenedioxybenzoyl)indole (6)

A mixture of 2-bromo-4,5-methylenedioxybenzoic acid (0.86 g, 3.3 mmol) and $SOCl_2$ (5 ml, 70 mmol) was refluxed for 1 h. After evaporation of the $SOCl_2$, the residue (**5**) was dissolved in THF (10 ml). A THF (5 ml) solution of **4** (0.59 g, 3 mmol) was dropwise added to a THF suspension of 60% NaH (0.14 g, 3.6 mmol), and the mixture was stirred at room temperature for 0.5 h. To this mixture was added the THF solution of **5** described above, and the whole mixture was stirred at room temperature for 3 h. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$, and the $CHCl_3$ was evaporated. The residue was purified by silica gel column chromatography using hexane/CH_2Cl_2 (1:1) to give colorless needles which were recrystallized from acetone. mp 125-126°C. Ir ν (KBr) cm^{-1}: 1714. 300 MHz ^{1}H-Nmr ($CDCl_3$) δ (ppm): 6.10 (2H, s), 6.60 (1H, d, *J*=3.7 Hz), 7.06 (1H, s), 7.11 (1H, d, *J*=3.7 Hz), 7.14 (1H, s), 7.18 (1H, dd, *J*=7.7, 7.7 Hz), 7.56 (1H, d, *J*=7.7 Hz), 7.58 (1H, d, *J*=7.7 Hz). Ms *m/z*: 423 (M^+). *Anal.* Calcd for $C_{16}H_9NO_3Br_2$: C, 45.42; H, 2.14; Br, 37.77; N, 3.31. Found: C, 45.33; H, 2.29; Br, 37.70; N, 3.31.

Hippadine (7)

A mixture of **6** (0.50g, 1.46 mmol), $(Bu_3Sn)_2$ (0.67 g, 1.46 mmol), Bu_4NBr (0.71 g, 2.19 mmol), Li_2CO_3 (0.11 g, 1.46 mmol), $Pd(PPh_3)Cl_2$ (50 mg, 0.07 mmol), and toluene (20 ml) was refluxed for 12 h. After removal of the solvent, the residue was purified by silica gel column chromatography using CH_2Cl_2 as an eluent to give pale yellow needles, which were recrystallized from hexane-acetone. mp 215-217°C. Lit.,[8] mp 217-218°C. Ir ν ($CHCl_3$) cm^{-1}: 1675. 300 MHz ^{1}H-Nmr ($CDCl_3$) δ (ppm): 6.17 (2H, s), 6.90 (1H, d, *J*=3.7 Hz), 7.48 (1H, dd, *J*=7.7, 7.7 Hz), 7.66 (1H, s), 7.76 (1H, d, *J*=7.3 Hz), 7.92 (1H, d, *J*=7.3 Hz), 7.98 (1H, s), 8.05 (1H, d, *J*=3.7 Hz). Ms *m/z*: 263 (M^+). *Anal.* Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 72.78; H, 3.52; N, 5.29.

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