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BORONATION-THALLATION, A NEW APPROACH TO THE SYNTHESIS OF INDOLES HAVING ARYL AND/OR A HETEROARYL SUBSTITUENT AT THE 4-POSITION[1]

Masanori Somei,* Hirokuni Amari, and Yoshihiko Makita
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920, Japan

A new coupling reaction for unsymmetrical biaryls was developed and applied successfully to the syntheses of 4-arylindoles. Photoreaction of 4-halogenoindoles also proved to be a useful method for preparing 4-substituted indoles. An alternative method for synthesizing 4-(3-pyridyl)-3-indolecarbaldehyde is also reported.

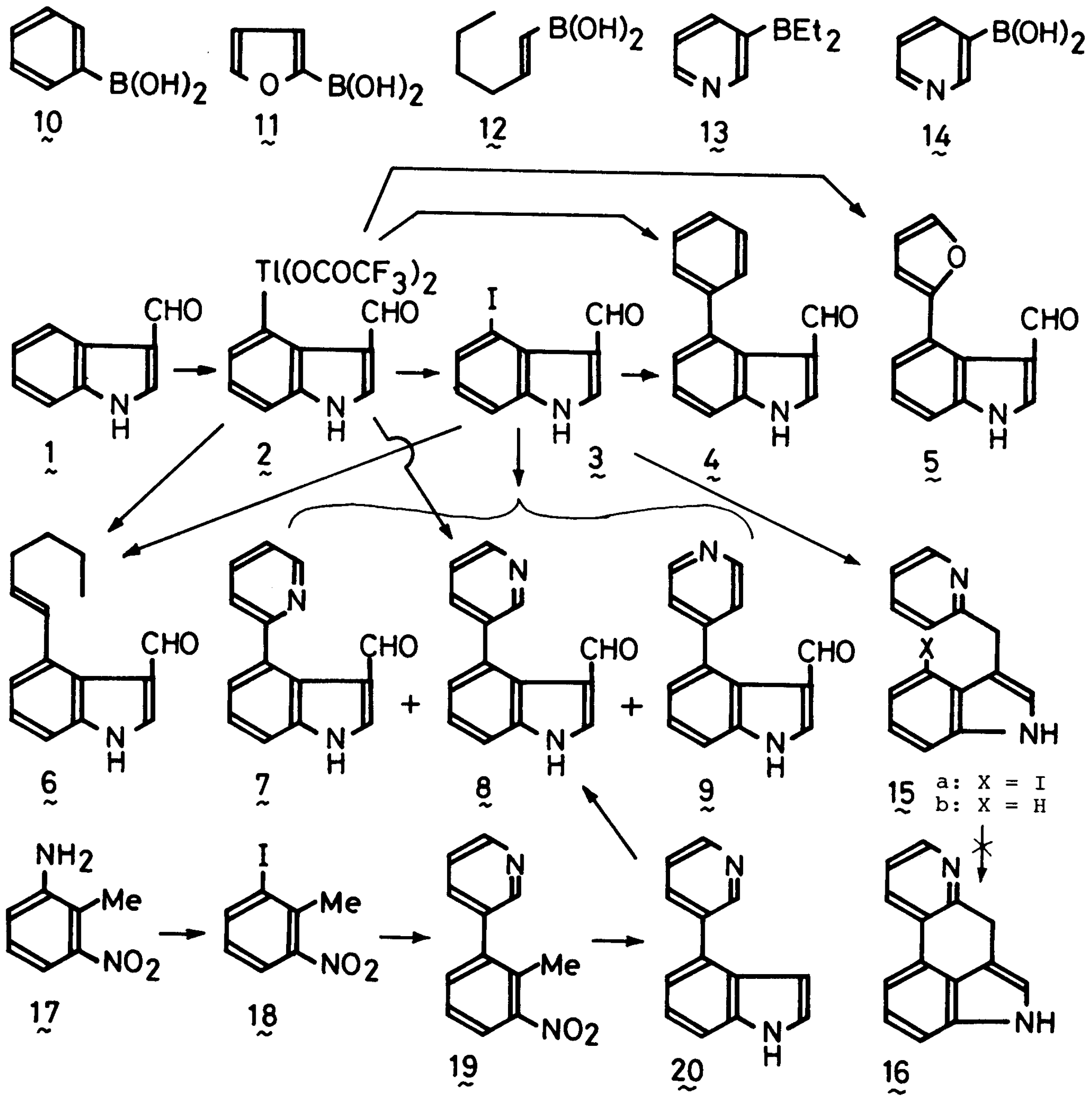
KEYWORDS ——— boronation-thallation; unsymmetrical coupling; 4-substituted indole; boronic acid; thallium compound; photoreaction; 4-(3-pyridyl)indole; titanium (III) chloride; thallation-palladation

The idea of directly introducing aromatic and heteroaromatic compounds into the 4-position of the indole nucleus opens a new chemistry in the field of 4-substituted indoles.[2] From this viewpoint, we have extensively examined the reactions of 4-halogenoindoles[3] with aryl halides and/or halogeno-pyridine derivatives under Ullmann,[4] Heck,[5] and thallation-palladation[6] reaction conditions, but the desired 4-substituted indoles were produced only in poor yields. Now, we report a versatile synthesis method, which can be designated as boronation-thallation, for synthesizing 4-substituted indoles.

The boronation-thallation method is a boronation version of the thallation-palladation method.[6] It consists of the reaction of aryl thallium compounds with boronic acid derivatives in the presence of a catalytic amount of palladium salt. It tolerates air and moisture. Thus, (3-formylindol-4-yl)thallium bis-trifluoroacetate (2), readily available in 77% yield[7] from 3-indolecarbaldehyde (1), reacted with benzeneboronic acid (10) in the presence of a catalytic amount of palladium acetate in dimethylformamide at 120°C for 1 h to give 60% yield of 4-phenyl-3-indolecarbaldehyde (4, mp 164.5-165.5°C). Under similar reaction conditions, 2-furylboronic acid (11)[8] and (*E*)-1-hexen-1-ylboronic acid (12)[9] afforded 4-(2-furyl)-3-indolecarbaldehyde (5, mp 105.0-106.0°C) and 4-(*E*-1-hexen-1-yl)-3-indolecarbaldehyde (6, mp 99.0-101.0°C) in 57% and 33% yields, respectively. These results clearly indicate that the boronation-thallation method is superior to the alternative reactions of halogen compounds. Thus, when 4-iodo-3-indolecarbaldehyde (3)[10] reacted with 10 and 1-hexene according to the Suzuki[11] and Heck methods, respectively, 4 and 6 were produced in the respective yields of 48% and 12%.

A similar trend was observed in the reactions of diethyl(3-pyridyl)borane (13) with 2 and 3. Under Terashima's reaction conditions,[12] compound (3) afforded the desired 4-(3-pyridyl)-3-indolecarbaldehyde (8, mp 190.0-191.0°C) in only 0.3% yield. The reaction of 13 with thallium compound (2) afforded 8 in eight times as much yield (2.4%) as Terashima's method. Although the yield of 8 is still not satisfactory, it should be noted that only a 3-pyridyl derivative was produced regioselectively. The boronation-thallation reaction of 2 with 14 is now being studied.

The photochemical reaction of 3 also proved to be a useful method to meet our end. Thus, irradiation of 3 with a 450W high pressure mercury lamp in benzene or furan in the presence of a trace amount of pyridine afforded 4 and 5 in 60% and 64% yields, respectively. Irradiation of 3 in pyridine non-regioselectively afforded three possible isomers, 4-(2-pyridyl)- (7, mp 185.0-186.0°C), 4-(3-pyridyl)- (8), and 4-(4-pyridyl)-3-indolecarbaldehyde (9, mp 285.0-288.0°C) in 30%, 19%, and 9% yields, respectively. Irradiation of the compound (15a, mp 167.0-168.0°C), prepared from 3 in two steps in 63% overall yield, afforded only dehalogenated compound (15b) without any detectable amount of formation of the desired compound (16).



The structure of **8** was confirmed unequivocally by the following synthesis procedure.11b) Thus, 6-amino-2-nitrotoluene (**17**) was converted to 2-iodo-6-nitrotoluene (**18**, mp 34.0-35.0°C) in 93% yield by the usual diazotization method. The compound (**18**) was then treated with diethyl(3-pyridyl)borane (**13**) by a modified Terashima's method12) to give 2-(3-pyridyl)-6-nitrotoluene (**19**, mp 57.0-58.0°C) in 52% yield. In contrast, 3-pyridylboronic acid (**14**) reacted with **18** under similar reaction conditions to afford **19** in 82% yield. Treatment of **19** with dimethylformamide dimethyl acetal and subsequent reduction of the resulting enamine with titanium (III) chloride in the presence of ammonium acetate13) successfully afforded 4-(3-pyridyl)indole (**20**, mp 172.0-174.0°C) in 51% yield. The Vilsmeier reaction of **20** with phosphorus oxychloride and dimethylformamide produced a 92% yield of **8**, which was identical with the samples prepared by the photo-irradiation method or the reactions of **2** and **3** with **13**.

Investigations are currently in progress to establish the scope and limitations of the boronation-thallation method.

REFERENCES AND NOTES

1) This report is presented at the 106th Annual Meeting of the Pharmaceutical Society of Japan, Chiba, April 1986. This is part XXXV of a series entitled "The Chemistry of Indoles." Part XXXIV: F. Yamada, Y. Saida, and M. Somei, Heterocycles, 24, 2619 (1986).

2) S.J. Dunsdon and J.A. Martin, Tetrahedron, 41, 2919 (1985); G. Jacques, C. Francois, and B.N. Leslie, Eur. Pat., 150139 (1985) [Chem. Abstr., 103, 19589s (1985)].

3) M. Somei, K. Kizu, M. Kunimoto, and F. Yamada, Chem. Pharm. Bull., 33, 3696 (1985); M. Somei and M. Tsuchiya, ibid., 29, 3145 (1981).

4) J. Lindley, Tetrahedron, 40, 1433 (1984); M.F. Semmelhack and L.S. Ryono, J. Am. Chem. Soc., 97, 3873 (1975); P.E. Fanta, Synthesis, 1974, 9.

5) R.F. Heck, "Organic Reactions," Vol. 27, ed. by W.G. Dauben, John Wiley and Sons, Inc., New York, 1982, p. 345.

6) M. Somei, T. Hasegawa, and C. Kaneko, Heterocycles, 20, 1983 (1983).

7) R.A. Hollins, L.A. Colnago, V.M. Salim, and M.C. Seidl, J. Heterocyclic Chem., 16, 993 (1979); M. Somei, F. Yamada, M. Kunimoto, and C. Kaneko, Heterocycles, 22, 797 (1984) and see also references 3 and 6.

8) B.P. Rogues, D. Florentin, and M. Callanquin, J. Heterocyclic Chem., 12, 195 (1975).

9) G.W. Kabalka, E.E. Gooch, and H.C. Hsu, Synth. Commun., 11, 247 (1982).

10) M. Somei and F. Yamada, Chem. Pharm. Bull., 32, 5064 (1984) and see also reference 7.

11) a) M. Miyaura, K. Yamada, and A. Suzuki, Tetrahedron Lett., 1979, 3437;
b) W.J. Thompson and J. Gaudino, J. Org. Chem., 49, 5237 (1984).

12) M. Ishikura, M. Kamada, I. Oda, and M. Terashima, Heterocycles, 23, 117 (1985); M. Ishikura, I. Oda, and M. Terashima, ibid., 23, 2375 (1985).

13) M. Somei, S. Inoue, S. Tokutake, F. Yamada, and C. Kaneko, Chem. Pharm. Bull., 29, 726 (1981); M. Somei, K. Kato, and S. Inoue, ibid., 28, 2515 (1980); M. Somei, F. Yamada, and C. Kaneko, Chem. Lett., 1979, 943.

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