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BORONATION-THALLATION, A NEW APPROACH TO THE SYNTHESIS OF INDOLES
HAVING ARYL AND/OR A HETEROARYL SUBSTITUENT AT THE 4-POSITION¹⁾

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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

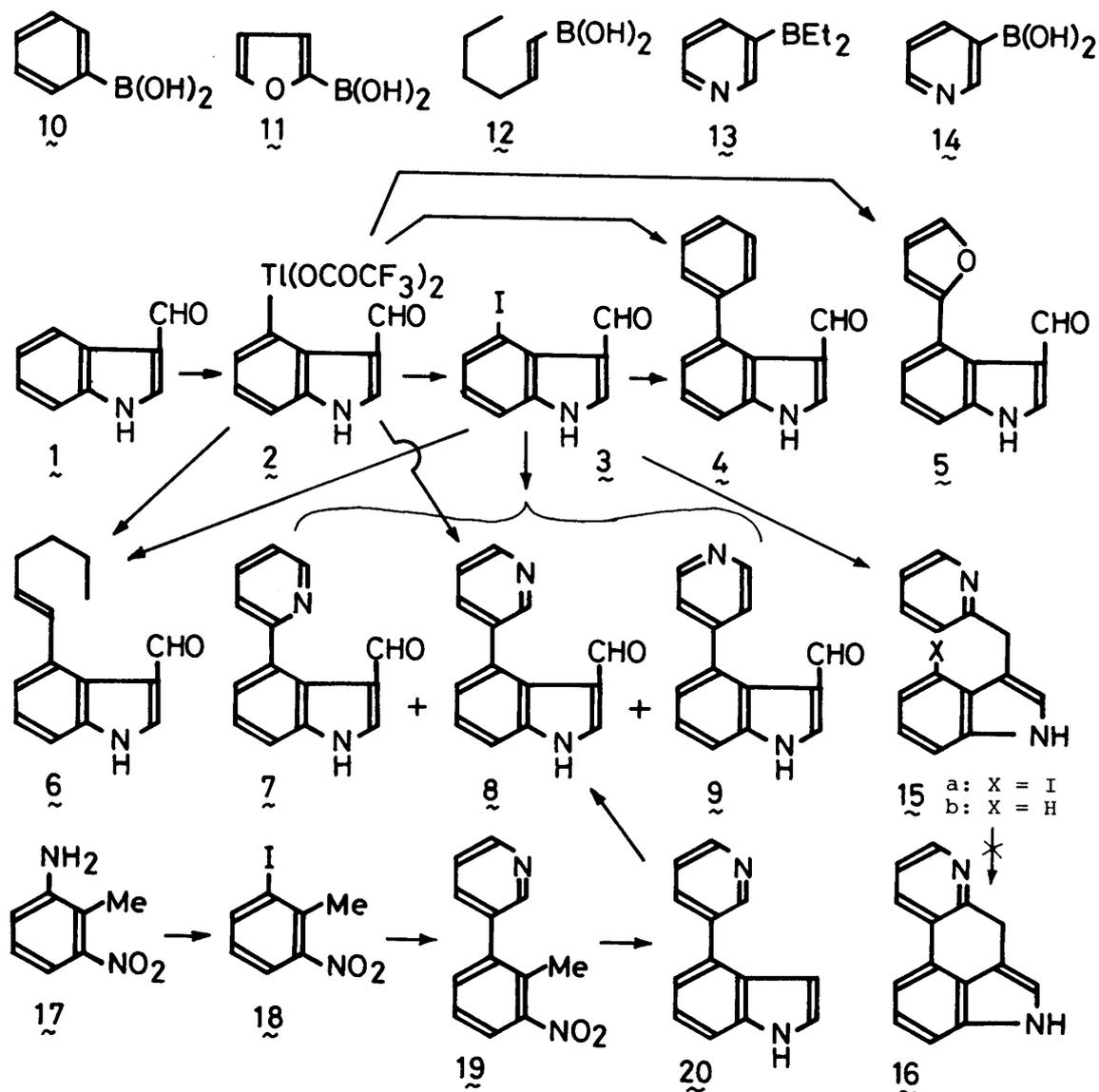
The idea of directly introducing aromatic and heteroaromatic compounds into the 4-position of the indole nucleus opens a new chemistry in the field of 4-substituted indoles.²⁾ From this viewpoint, we have extensively examined the reactions of 4-halogenoindoles³⁾ with aryl halides and/or halogeno-pyridine derivatives under Ullmann,⁴⁾ Heck,⁵⁾ and thallation-palladation⁶⁾ 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% yield⁷⁾ 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 Suzuki¹¹⁾ 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.

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