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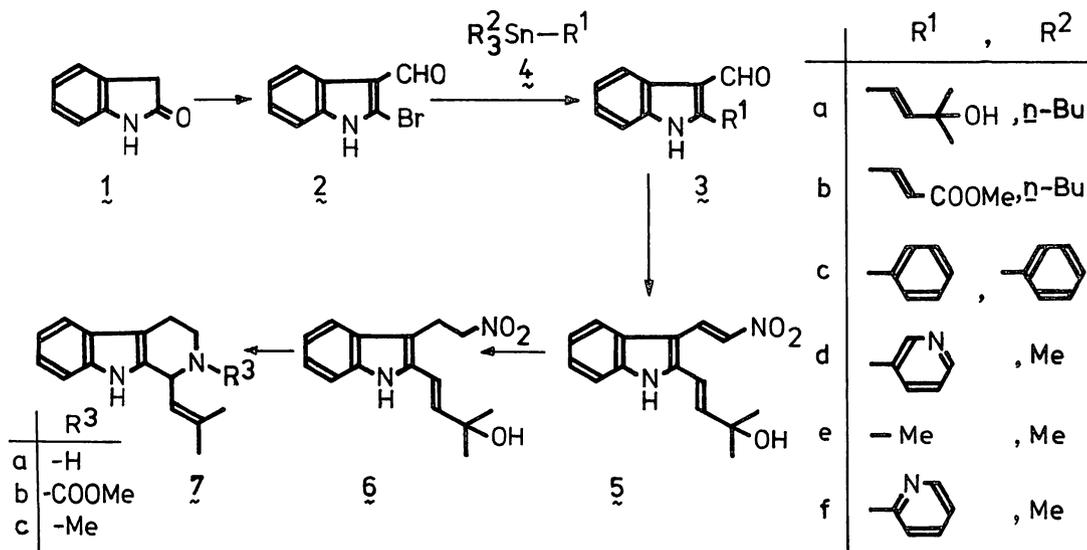
A CONVENIENT SYNTHETIC METHOD OF 2-SUBSTITUTED INDOLES AND ITS APPLICATION FOR THE SYNTHESIS OF NATURAL ALKALOID, BORRERINE¹

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Abstract ——— A simple synthetic method of 2-substituted indoles is developed. Total synthesis of natural alkaloid, borrerine, is also reported.

In this communication, we describe a versatile two step synthetic method which can provide synthetically useful 2-substituted indoles, and its application for the synthesis of natural alkaloid, borrerine (7c).²

Commercially available 2-oxindole (1) led to 2-bromo-3-indolecarboxaldehyde (2) in 77% yield according to Schulte's procedure.³ In order to introduce a carbon side chain directly into the 2-position of 2, improved Heck reaction^{4a,b} seemed to be promising among various palladium catalyzed cross coupling reactions.^{4a-d} However,



the Heck reaction of 2 with 2-methyl-3-buten-2-ol produced the desired 2-(3-hydroxy-3-methyl-1-buten-1-yl)-3-indolecarboxaldehyde (3a, mp 190.5-193°C) in poor yield and the yield could not be increased above 15% under various reaction conditions. On the other hand, modified Stille's reaction^{4c} was found to meet our end. Thus, 3a was obtained in 87% yield by the reaction of 2 with (3-hydroxy-3-methyl-1-buten-1-yl)tributyltin (4a)⁵ in the presence of tetra-*n*-butylammonium chloride and a catalytic amount of palladium acetate. Similarly, the reaction of 2 with tin reagents, such as 4b,⁶ 4c, 4d,⁷ 4e, and 4f,⁷ afforded 3b (mp 261-262°C), 3c (mp 260.5-263°C), 3d (mp 246-246.5°C), 3e (mp 207-208.5°C), and 3f (mp 226-227°C) in 67%, 68%, 38%, 39%, and 5% yields, respectively. An attempt to improve the yield of 3f is currently under investigation.

With the desired building blocks (3a-f) for various 2-substituted indoles in hand, we next tried a total synthesis of borrerine (7c).² First, 3a was converted to 5 (mp 246-247°C) in 86% yield by the reaction with nitromethane in the presence of ammonium acetate. Subsequent reduction of 5 with sodium borohydride in methanol afforded 6 (mp 122-123°C) in 80% yield. Next, our reductive amino cyclization method⁸ (refluxing with zinc in methanolic hydrochloric acid) was successfully applied to 6 affording 7a (mp 162-164°C, lit.^{2b} mp 158-159°C) in 50% yield. Treatment of 7a with methyl chloroformate gave 85% yield of 7b (mp 188.5-189°C, lit.^{2b} mp 180-181°C), which finally led to borrerine (7c, mp 107-108°C, lit.^{2b} mp 102-103°C) in 70% yield by the reduction with lithium aluminum hydride in anhydrous tetrahydrofuran. Spectral data of 7c were identical with those of borrerine which was synthesized by Sakai and co-workers.^{2b,9}

Biological evaluations of new compounds and the total synthesis of other related natural alkaloids are currently in progress.

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9. Mixed melting point of 7c and borrerine showed no depression. Borrerine and 7c melted once at about 57-59°C and gradually solidified, and then finally melted at 107-108°C.

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