HETEROCYCLES, Vol 27, No. 7, 1988

A CONVENIENT SYNTHETIC METHOD OF 2-SUBSTITUTED INDOLES AND ITS APPLICATION FOR THE SYNTHESIS OF NATURAL ALKALOID, BORRERINE[1]

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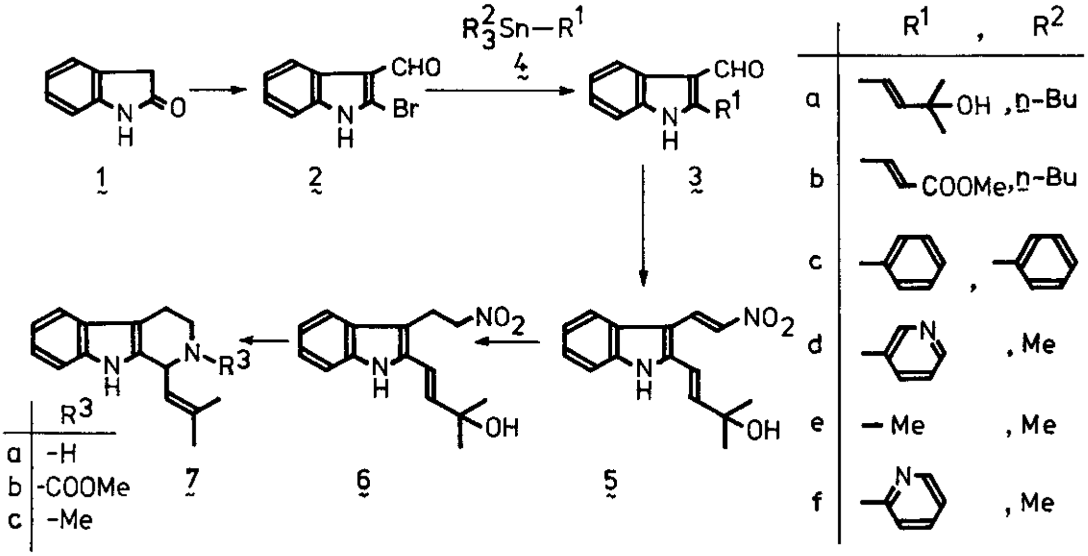
Abstract ------ A simple synthetic method of 2-substituted indoles is developed. Total synthesis of natural alkaloid, borrerine, is also reported.

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 method[8] (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.

ACKNOWLEDGEMENT

The authors express their cordial gratitude to Prof. S. Sakai, Chiba University, for kindly sending us spectral data and authentic sample of borrerine.

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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.

Received, 11th March, 1988