SYNTHESES OF 7-SUBSTITUTED INDOLES[1]

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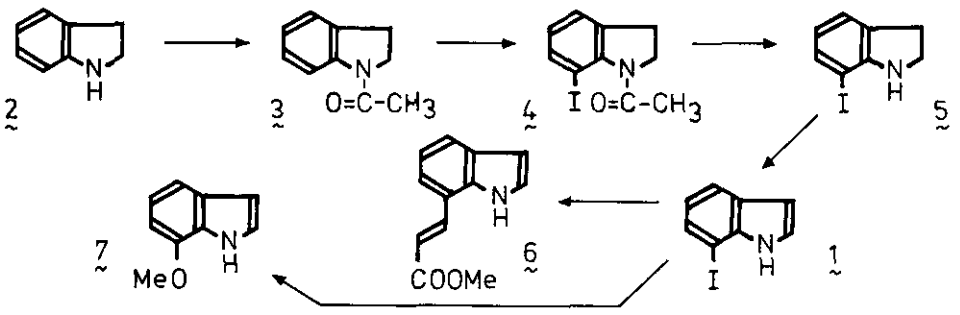
Abstract ——— A facile synthetic method for 7-iodoindole was established. Its versatility for the syntheses of 7-substituted indoles was shown by leading it to 7-methoxyindole and methyl 3-(indol-7-yl)acrylate.

There are many biologically interesting indole derivatives carrying substituents at the 7-position.[2] However, their syntheses remain untouched due to the lack of the efficient and general synthetic method for 7-substituted indoles. In this paper, we describe a reliable and simple synthetic method for 7-iodoindole (1) which should be a common and the simplest building block for various 7-substituted indoles. 1-Acetylindoline (3), prepared quantitatively by refluxing indoline (2) in acetic anhydride, was thallated with 1.6 mol eq. of thallium tris-trifluoroacetate in trifluoroacetic acid.[3] After evaporation of the solvent, the residue was directly iodinated with aq. potassium iodide to give 1-acetyl-7-iodoindoline (4, mp 128.0-128.5°C) in 74% yield together with 5% yield of 1-acetyl-5-iodoindoline (mp 142.5-143.5°C). When the acetyl group of 3 was substituted for methoxycarbonyl group, the expected 7-substituted indole could not be obtained. Alkaline hydrolysis of 4 gave 7-iodoindoline (5, oil) in 84% yield. After considerable efforts,[4] treatment of 5 with oxygen in the presence of a catalytic amount of salcomine[5] in methanol was found to produce the desired 7-iodoindole (1, mp 55.0-56.0°C) cleanly in 77% yield. The versatility of 1 was proved by the following reactions. When 1 was subjected to Heck reaction[6] using methyl acrylate as an olefin component, methyl 3-(indol-7-yl)-acrylate (6, mp 96.0-96.5°C) was produced in 91% yield. It should be noted that neither compound (4) nor (5) underwent Heck reaction successfully under various reaction conditions. Furthermore, 7-methoxyindole (7, oil) was obtained by the treatment of 1 with sodium methoxide in N,N-dimethylformamide in the presence of

copper iodide.[7]

The structures of 6 and 7 were unequivocally established by the alternative syntheses using improved Leimgruber-Batcho method[8] starting from 3-methyl-2-nitrobenzoic acid and 3-hydroxy-2-nitrotoluene, respectively.

In conclusion, 7-iodoindole is now readily available from indoline in four steps with an overall yield of 48%. Syntheses of various 7-substituted indoles and natural alkaloids are currently in progress.



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