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A CONVENIENT SYNTHETIC APPROACH TO 4-SUBSTITUTED INDOLES[1]

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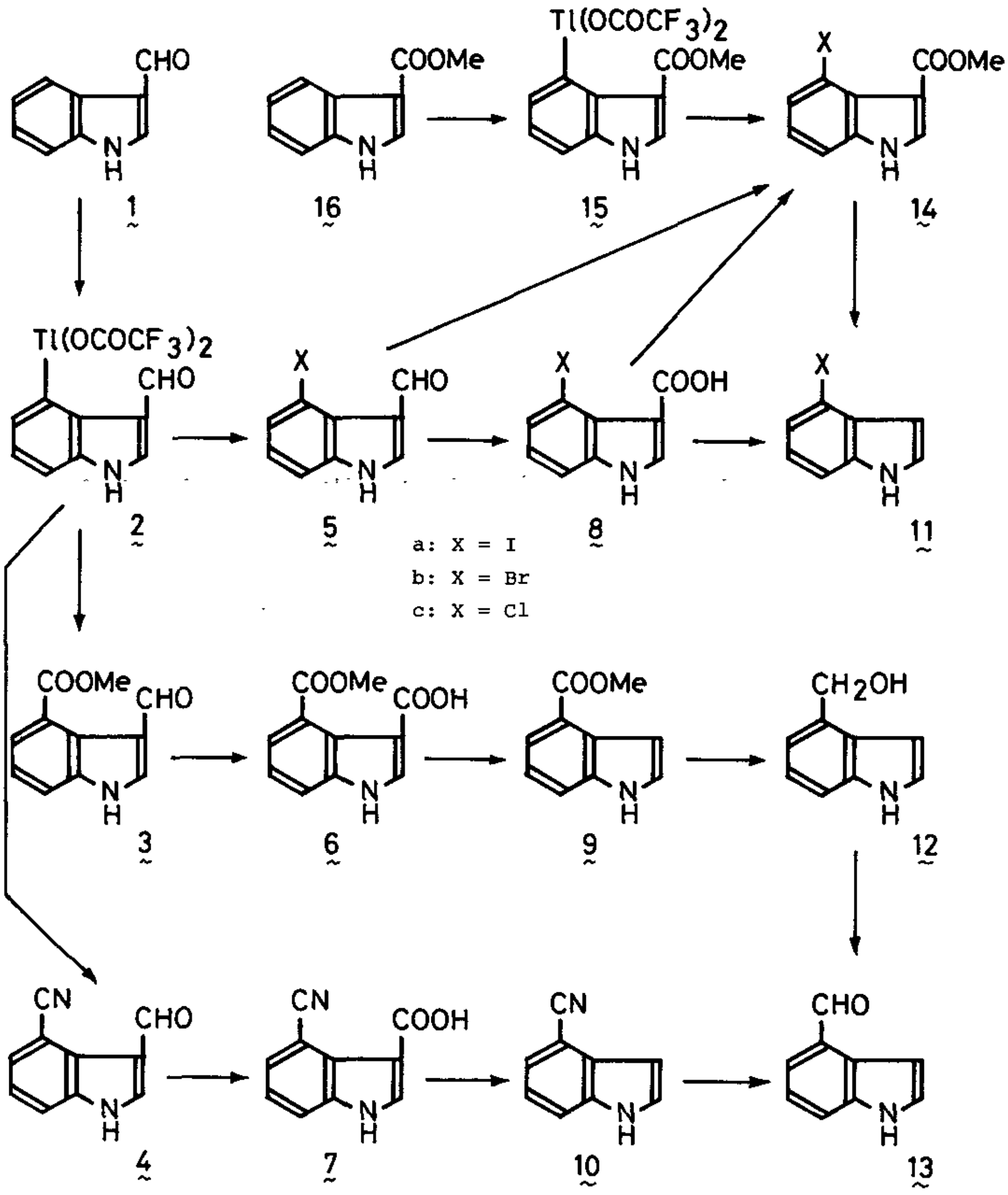
Abstract ——— A simple and practical synthetic method for 4-halogenoindoles, 4-indolecarbaldehyde, 4-cyanoindole, and 4-methoxycarbonylindole is elaborated.

4-Halogenoindoles,[2] 4-indolecarbaldehyde,[3] 4-cyanoindole,[2b,4] and 4-alkoxycarbonylindoles[3c,5] are useful building blocks for the construction of natural alkaloids having 4-substituted indole nucleus. However, they are still not readily available, though much efforts have been paid on their syntheses. In this communication, we wish to describe a simple and practical synthetic method for these building blocks. We have already established an experimental procedure for the synthesis of (3-formylindol-4-yl)thallium bis-trifluoroacetate (2) starting from 3-indolecarbaldehyde (1) in 100-200g scale.[6] Now, we have found that the thallium compound (2) can be used as a common intermediate for the syntheses of above mentioned building blocks. Thus, carbonylation of 2 in methanol[7] in the presence of a catalytic amount of palladium acetate afforded methyl 3-formyl-4-indolecarboxylate (3) in 54% yield. Cyanation of 2 with cuprous cyanide[8] in refluxing N,N-dimethylformamide produced 4-cyano-3-indolecarbaldehyde (4) in 53% yield. Preparation of 4-halogeno-3-indolecarbaldehydes (5a-c) was carried out by the reaction of 2 with appropriate halogenating reagents according to our reported procedure.[2a]

Since 4-substituted indoles having no substituent at the 3-position are sometimes needed, we next tried to get them utilizing above mentioned readily accessible compounds, 3, 4, and 5a-c. Direct decarbonylation of 5a by treatment with either acids or bases were unsuccessful. Therefore, various oxidative reagents were examined on 5a as a representative substrate with an aim to obtain the corresponding 4-iodo-3-indolecarboxylic acid (8a) but all attempts[9] ended in failure. Finally, oxidation with sodium chlorite in the presence of 2-methyl-2-butene[10] was found to work well



a: X = I
b: X = Br
c: X = Cl

and 5a was converted to 8a in 73% yield. Under similar reaction conditions, methyl 3-formyl-4-indolecarboxylate (3), 4-cyano- (4), 4-bromo- (5b), and 4-chloro-3-indolecarbaldehyde (5c) were successfully transformed to the corresponding carboxylic acids, 6, 7, 8b, and 8c, in 77%, 90%, 86%, and 93% yields, respectively. Treatment of 8a with ethereal diazomethane afforded methyl 4-iodo-3-indolecarboxylate (14a) in quantitative yield, although direct conversion of 5a to 14a using manganese dioxide and sodium cyanide in methanol[11] proceeded in only 24% yield. Based upon these results, when the sodium chlorite oxidation reaction was carried out and followed by treatment with ethereal diazomethane, one pot syntheses of methyl 4-halogeno-3-indolecarboxylates (14a, b,[12] c[12]) was realized in 78%, 81%, and 93% yields, respectively. These compounds were identical with the authentic samples prepared from methyl 3-indolecarboxylate (16) *via* (3-methoxycarbonylindol-4-yl)-thallium bis-trifluoroacetate (15) and were easily led to the corresponding 4-halogenoindoles (11a-c) in high yields according to the reported alkaline hydrolysis reaction.[2a]

Decarboxylation of 4-substituted-3-indolecarboxylic acids were readily attained simply by heating them in pyridine. Under the reaction condition, 6, 7, and 8a afforded the expected 4-substituted indoles, 9, 10, and 11a, in 99%, 90%, and 89% yields, respectively. Subsequent reduction[13] of 4-cyanoindole (10) with diisobutylaluminum hydride produced 4-indolecarbaldehyde (13) in 62% yield.

Since interconversion[3,4,5] among 9, 4-hydroxymethylindole[14] (12), and 13 are well established, various simple 4-substituted indoles (3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14) became now readily available from 3-formylindole (1) in hundreds gram scale.

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