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A SIMPLE SYNTHESIS OF 7-SUBSTITUTED 1-ACETYL-2,3-DIHYDROINDOLES¹

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Abstract ——— 7-Cyano-, 7-hydroxy-, 7-methoxycarbonyl-, 7-methyl-, 7-nitro-, and 7-phenyl-1-acetyl-2,3-dihydroindoles are prepared in two steps (or one pot) from 1-acetyl-2,3-dihydroindole.

Although 7-substituted 1-acetyl-2,3-dihydroindoles are suitable building blocks for the synthesis of biologically interesting indole alkaloids² having a substituent at the 7-position, they are available only through a laborious multistep route. We now wish to describe a simple synthesis method for them utilizing (1-acetyl-2,3-dihydroindol-7-yl)thallium bis(trifluoroacetate) (2), readily available from 1-acetyl-2,3-dihydroindole (1) as reported previously.³

We first applied our stannation-thallation (tin-thall) reaction⁴ for obtaining 7-alkyl and 7-aryl substituted compounds. Treatment of 2 with tetramethyltin in the presence of a catalytic amount of palladium acetate (Pd(OAc)₂) in N,N-dimethylformamide (DMF) at 120°C for 4 h afforded 1-acetyl-2,3-dihydro-7-methylindole⁵ (3, mp 89-90°C) and 1 in 32% and 45% yields, respectively. Similarly, 1-acetyl-2,3-dihydro-7-phenylindole (4, mp 125.5-126°C) was prepared in 35% yield together with 63% yield of 1 by the reaction of 2 with tetraphenyltin.

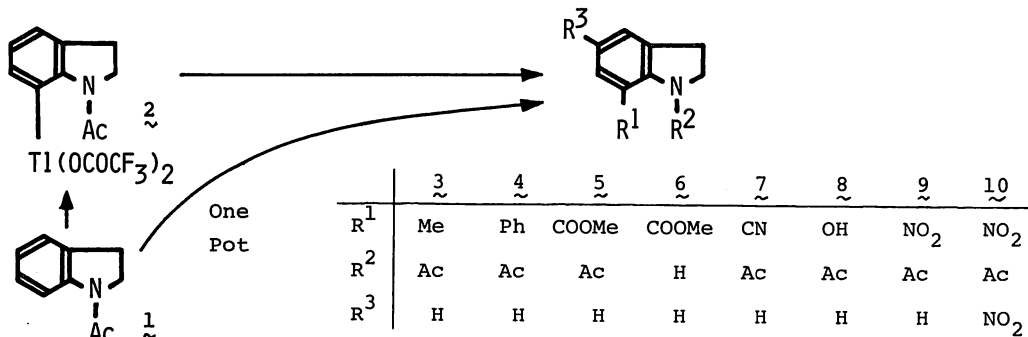
Introduction of methoxycarbonyl group into the 7-position under the usual reaction conditions^{6a,b} was not satisfactory. Thus, the reaction of 2 with carbon monoxide in the presence of a catalytic amount of Pd(OAc)₂ in methanol at 80°C for 3 h, followed by the treatment with ethereal diazomethane, afforded methyl 1-acetyl-2,3-dihydroindole-7-carboxylate (5, mp 103-104°C) and 1 in 27% and 44% yields, respectively. Interestingly, addition of chromium hexacarbonyl to the above reaction medium was newly found to improve the yield of the desired product (5) remarkably. Using one molar equivalent of chromium hexacarbonyl, 5 was obtained in 52% yield together with methyl 2,3-dihydroindole-7-carboxylate (6, mp 69-69.5°C) and 1 in 11% and 23%

yields, respectively.

1-Acetyl-2,3-dihydroindole-7-carbonitrile (2, mp 133.5-134°C, lit.⁷ mp 124°C) could be produced in 69% yield by the reaction of 2 with five molar equivalents of cuprous cyanide^{6b,c} in DMF at 120°C for 6 h. On the other hand, our phenol synthesis method⁸ from thallium compound was successfully applied to 2 and its reaction with cupric sulfate pentahydrate in DMF-H₂O (1:1, v/v) at 125°C for 6 h afforded 1-acetyl-2,3-dihydro-7-hydroxyindole (8, mp 114.5-115°C; lit.⁹ mp 112-114°C) in 62% yield. One pot synthesis of 8 from 1 could be readily carried out in 42% overall yield by the initial thallation with thallium tris(trifluoroacetate), followed by the reaction with cupric sulfate pentahydrate.

Conversion of carbon-thallium bond to carbon-nitrogen bond is reported by the reaction with sodium nitrite.¹⁰ However, the attempted nitration of 2 according to the reported method¹⁰ gave 1-acetyl-2,3-dihydro-7-nitroindole (9, mp 163-164°C) in poor yield (3-26%) under various reaction conditions in addition to variable yields (0-26%) of 1-acetyl-2,3-dihydro-5,7-dinitroindole (10, mp 217-218°C, lit.¹¹ mp 210-212°C). Although Taylor¹² and Uemura¹⁰ reported that the reaction of thallium compounds with nitronium ion could not change the carbon-thallium bond to a carbon-nitrogen bond, we expected that the addition of cupric (or cuprous) ion would alter the reaction to the desired direction. Based on this idea, we finally found a new method which produced the desired mononitro compound (9) selectively. Thus, treatment of 2 with two molar equivalents of cupric nitrate trihydrate in DMF-acetic anhydride (1:1, v/v) at 80°C for 5 h afforded 46% yield of 9 without any detectable amount of 10. Generalization of this reaction is now in progress.

In conclusion, various 7-substituted 2,3-dihydroindoles are easily available utilizing 2 as a common synthetic intermediate, though optimum reaction conditions are not made. Since the isolation of 2 is not necessary and one pot operation is possible,^{3d} the present method should find considerable application in organic synthesis.



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