ONE STEP SYNTHESIS OF 4-SUBSTITUTED INDOLES

Masanori Somei, Fumio Yamada, and Chikara Kaneko
Faculty of Pharmaceutical Sciences, Kanazawa University
Takaramachi 13-1, Kanazawa, Japan

I. 4-Methylaminomethylindole (1) was synthesized in one step in 19.6% yield from 2-methyl-5-nitroisoquinolinium iodide (2) by the reaction with aqueous $TiCl_3$. The effect of the relative amount of $TiCl_3$ to (2), the reaction time, pH, solvent systems, and the temperature on the yield of (1) was examined and the reaction mechanism was proposed.

II. Substituent at nitrogen on the isoquinoline nucleous did not alter the reaction mode and 2-benzyl-5-nitroisoquinolinium bromide was converted into 4-[benzylaminomethyl]indole in one step.

III. This novel one step reaction was successfully applied to 1-acetonyl-2-methyl-5-nitro-1,2-dihydroisoquinoline affording 4-[4-indolyl]-3-buten-2-one (3) together with (1). The scope and limitations of this one step reaction to various 1-substituted-5-nitroisoquinoline derivatives are currently under investigation.

IV. 4-[N,N-disubstituted]aminomethylindoles were prepared in relatively good yields by the reaction of (1) with alkyl or allyl halide, such as benzyl, allyl, propargyl bromide or methyl iodide in the presence of NaOH.

V. The compound (1) afforded 4-methyl-3-phenyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]-isoquinoline and 4-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-de]isoquinoline by the reaction with benzaldehyde and formaldehyde, respectively. One step procedure for obtaining pyrrolo[4,3,2-de]isoquinolines from (2) is in progress.

VI. Treatment of (1) with active MnO_2 gave 4-formylindole (4). Aldol condensation of (4) with acetone gave 4-[4-indolyl]-3-buten-2-one (3) in a good yield. This reaction constitutes two step synthesis of (4) from (2).