FIVE-STEP SYNTHESIS OF 4-ALKYLINDOLES

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A facile introduction of carbon nucleophiles to the singlet oxygen adducts, derived from 1-acyl-1,2-dihydropyridine derivatives was reported two years ago in this symposium.

This reaction was extended to N-methoxycarbonylpyrrole 1. 1 in a dichloromethane solution was photooxygenated in an oxygen atmosphere at -78° using methylene blue as a sensitizer. The endoperoxide obtained here was stable at only low temperature, and when warmed at room temperature, the singlet oxygen came out rapidly, and the endoperoxide went back to 1. Therefore, after photooxygenation, the endoperoxide was directly reacted with various nucleophiles, such as trimethylsilyl enol ethers, vinyl ethers, N-methylpyrrole, and indole, in the presence of stannous chloride, while the reaction mixture remained cool. Condensation reaction took place quite readily, and 2-substituted pyrrole derivatives were obtained as major products in good yield, accompanied by the formation of 2,2'-bipyrrole derivatives and/or 2,2'-disubstituted 3-pyrrolines in a small amount.

When one of the pyrrole derivatives obtained above, N-methoxycarbonyl-2-pyrrolyl-crotonaldehyde 2, was treated with stannic chloride, N-methoxycarbonylindole was obtained in a good yield, and this knowledge was successfully extended to the synthesis of 4-alkylindoles. 2 was converted to the corresponding unsaturated ketones by Grignard reaction, followed by oxidation with pyridinium chlorochromate. Treatment of these unsaturated ketone derivatives with stannic chloride under ice cooling for 10-20 min gave similarly 4-alkylindole derivatives in ca. 40-50% yield and cleavage of N-methoxycarbonyl group was readily achieved with dilute alkali at room temperature. Now, the synthesis of 4-alkylindoles with or without oxygen function in the alkyl side chain, was achieved in five steps from 1. 4-(2-oxo-4-butyl)indole thus synthesized, was converted to 4-(3-methyl-2-butenyl)-indole 3, with methylmagnesium iodide, followed by treatment with p-toluenesulfonic acid. 4-(3-Methyl-2-butenyl)tryptophan, which can be derived from 3 is an important precursor in the biogenesis of ergot alkaloid.