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ONE STEP SYNTHESIS OF 4-METHYLAMINOMETHYLINDOLE[1]

Masanori SOMEI, Fumio YAMADA, and Chikara KANEKO
Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920

4-Methylaminomethylindole was prepared in one step in 20% yield from 2-methyl-5-nitroisoquinolinium iodide by the reaction with aqueous $TiCl_3$.

We wish to report a convenient and economical one step synthesis of 4-methylaminomethylindole 2, a useful intermediate for 4-substituted indoles,[2] from 2-methyl-5-nitroisoquinolinium iodide 1.[3]

Treatment of 1 with aqueous $TiCl_3$ in H_2O at room temperature gave 2 in varied yields depending on the reaction conditions. The effects of the amount of $TiCl_3$, the reaction time, and the solvent system on the yield of 2 are summarized in Tables I, II, and III.

Water was a solvent of choice and the reaction proceeded very fast (7 min). Since the methylaminomethylindole 2 was sensitive to acids, the longer the reaction time, the poorer the yield of 2. The mechanism shown in chart I is proposed for this reaction. $TiCl_3$ is known to reduce nitroarenes to the corresponding amines[4] under the condition, and hence expected to reduce the nitro group of 1. Concomitant reduction of the 1,2-immonium function of 1 may then result in generation of an intermediate 3. The latter may be hydrolyzed under the condition to give another intermediate 4, which would cyclize to the final product 2.[3]

Table I. Effect of The Relative Ratio of $TiCl_3$ to 1 *

Entry	Mol Equiv of $TiCl_3$	Yield of 2 (%)	Reaction Time (min)
1	3.5	1	5
2	7.0	5	7
3	7.7	20	7
4	8.7	4	7

* The reactions were carried out at room temperature (19°C).

Table II. Effect of The Reaction Time*

Entry	Reaction Time (min)	Yield of 2 (%)	Room Temperature (°C)
5	3	14	18
6	5	16	20
3	7	20	19
7	10	8	18

* 7.7 Mol equiv of $TiCl_3$ was used.

Table III. Effect of The Solvent Systems*

Entry	Solvent System	Yield of 2 (%)
3	H_2O	20
8	H_2O-MeOH (2:1, v/v)	13
9	H_2O-THF (2:1, v/v)	4

* Reaction time was kept constant for 7 min and 7.7 mol equiv of $TiCl_3$ was used at room temperature (19°C).

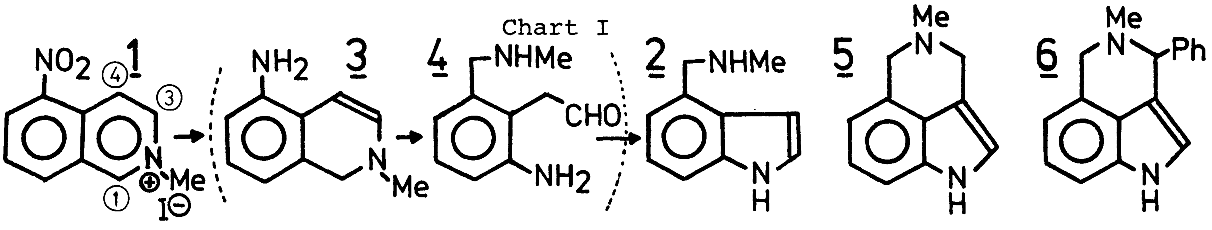

Chart I

The compound 2 was further converted to 4-methyl-1,3,4,5-tetrahydropyrrolo-[4,3,2-de]isoquinoline 5[5] (yield 11%) and 4-methyl-3-phenyl-1,3,4,5-tetrahydro-pyrrolo[4,3,2-de]isoquinoline 6[6] (yield 31%) by the reaction with HCHO-AcOH and benzaldehyde-AcOH, respectively.

Although the yield of 2 is still not satisfactory (20%), the present one step procedure provides a valuable synthetic method for 4-substituted indoles which are not readily accessible by the known synthetic routes.[2]

The reaction of 1 with stannous chloride is currently under investigation.

Typical Experiment

To a stirred solution of 1 (160 mg) in H_2O (2 ml) was added an aqueous $TiCl_3$ solution (16%, 2.5 ml, 7.7 mol equiv). After stirring for 7 min at room temperature, the reaction mixture was basified by adding aqueous 2N-NaOH solution and extracted with MeOH-CH_2Cl_2 (5:95, v/v). The extract was washed with sat. NaCl solution, dried over Na_2SO_4, and evaporated to leave an oil, which was subjected to preparative thin layer chromatography on Al_2O_3 using MeOH-CH_2Cl_2 (3:97, v/v) as an eluent giving 2 in 20% yield (16 mg).

References and Notes

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