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A CONVENIENT ROUTE TO 4-ALKYLAMINOMETHYLINDOLE DERIVATIVES[1]

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A facile four step synthesis of 4-[N,N-disubstituted]aminomethylindoles 5a-5c from 2-methyl-5-nitroisoquinolinium iodide 1 was described. In the course of the conversion, the mechanism of Hofmann degradation reaction of 2-substituted 2-methyl-5-nitroisoquinolinium salts 3a-3d was discussed.

4-Substituted indoles have not been readily accessible as yet, though much efforts have been paid to elaborate their syntheses.[2] We wish to report a facile and convenient four step synthesis of 4-alkylaminomethylindole derivatives 5a-5c starting from 2-methyl-5-nitroisoquinolinium salt 1.

2-Methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline 2 was obtained in 98% yield by the reduction of 1 with excess $NaBH_4$ in MeOH at room temperature. Treatment of 2 with propargyl bromide, allyl bromide, benzyl bromide, or methyl iodide in benzene gave the corresponding quaternary salts 3a-3d, each in quantitative yield. These salts underwent Hofmann degradation by the action of n-BuLi to afford 2-[N,N-disubstituted]aminomethyl-6-nitrostyrenes 4a-4d in reasonable yields as shown in Table I. The o-nitrostyrene derivatives 4a-4c were easily converted to the corresponding 4-substituted indoles by the treatment with refluxing triethylphosphite.[3]

Hofmann degradation reaction: n-BuLi in hexane (0.7 ml, 3.65 mol equiv) was added to a stirred solution of 3b (101 mg) and DABCO[4] (123 mg, 3.40 mol equiv) in abs. THF-HMPT[4] (3:1, v/v, 4 ml) at room temperature under argon atmosphere. After stirring for 2.5 hr, water was added and the whole was extracted with benzene, washed with water, dried over Na_2SO_4, and evaporated in vacuo to leave an oil. The residue was subjected to preparative thin layer chromatography on silica gel using CH_2Cl_2-hexane (1:1, v/v) to afford 4b [oil, IR (KBr): 3086, 1643, 1531, 1359 cm^{-1}, Mass m/e: 232 (M^+), NMR (CCl_4, δ): 2.13 (3H,s), 2.95 (2H,d,J=6 Hz), 3.43 (2H,s), 5.11 (1H,d,J=17 Hz), 5.35 (1H,d,J=11 Hz), 4.83-6.13 (3H,m), 6.78 (1H,d.d,J=11 and 17 Hz),

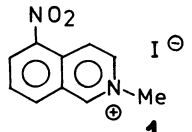
7.21 (1H,d,J=7 Hz), 7.35-7.66 (2H,m)] in 54% yield.

Formation of indoles: A solution of 4a (40 mg) in TEP[4] (1 ml) was refluxed for 1.5 hr under nitrogen atmosphere. After evaporation of TEP in vacuo, the residue was subjected to preparative thin layer chromatography on silica gel using MeOH-CH_2Cl_2 (1:99, v/v) to afford 5a [mp 69-70°, IR (KBr): 3250, 2086 cm^{-1}, Mass m/e: 198 (M^+), NMR (CCl_4,δ): 2.10 (1H,t,J=2 Hz), 2.33 (3H,s), 3.23 (2H,d,J=2 Hz), 3.76 (2H,s), 6.56 (1H,t,J=3 Hz), 6.80-7.13 (4H,m), 7.93 (1H,br.s,NH)] in 28% yield in addition to minor unknown products.

In the case of 3a, Hofmann degradation was carried out without using DABCO and even by the action of 10% NaOH in acetone at room temperature for 2.5 hr, 4a was obtained in 26% yield. On the other hand, 4b, 4c, and 4d were obtained in 38%, 6%, and 0% yield, respectively, in the absence of DABCO.

As the basicity of the methylene group on the N-substituents increases, yields of 4 decrease and more powerful base is required. These observations would appear to be best accomodated by the formation of carboanion, attached α to nitrogen on the N-substituents, which then abstracts C_4-H intramolecularly to form Hofmann degradation products.

Further transformation of 5 into pyrrolo[4,3,2-de]isoquinolinium salts is currently under investigation.



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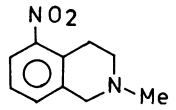

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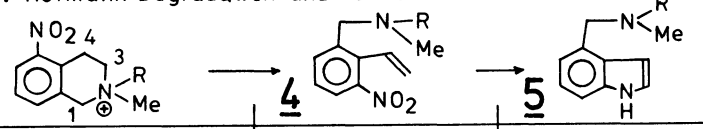
Table I. Hofmann Degradation and Formation of Indoles*



3	4	5
a) R = $-CH_2-C\equiv CH$	Yield, 69 %	Yield, 28 %
b) $-CH_2-CH=CH_2$	53 %	32 %
c) $-CH_2-Ph$	24 %	32 %
d) $-CH_3$	4 %	not tried

* Optimization of yields has not been made.

References and Notes

1) This report is part VII of a series entitled "The Chemistry of Indoles." Part VI: M.Somei, K.Hashiba, F.Yamada, T.Maekawa, T.Kimata, and C.Kaneko, This journal, 1245(1978).
2) a: Preparation of cycloalkanon[c,d]indoles; T.Nagasaka and S.Ohki, Chem. Pharm. Bull., 25, 3023 (1977) and references cited therein. b: Fries type reaction; O.Yonemitsu and S.Naruto, Chem. Pharm. Bull., 20, 2272 (1972), M.Somei and M.Natsume, Tetrahedron Letters, 2451 (1973). c: Various 4-substituted indoles; D.E.Ames and O.Ribein, J. Chem. Soc., perkin I, 1073 (1976), H.Plieninger, M. Hobel und V.Liede, Chem. Ber., 96, 1618 (1963) and references cited therein.
3) J.I.G.Cadgan, W.M.Cameron, R.K.Mackie, and R.J.G.Searle, J. Chem. Soc., 4831 (1965). Poor results were obtained in the conversion of o-nitrostyrenes into indoles having no substituents at the 2-position.
4) DABCO: 1,4-diazabicyclo[2.2.2]octane, HMPT: hexamethylphosphoric triamide, TEP: triethylphosphite.

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