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BENZ[c,d]INDOLES - II. SYNTHESIS BY THE SAEGUSA CYCLIZATION

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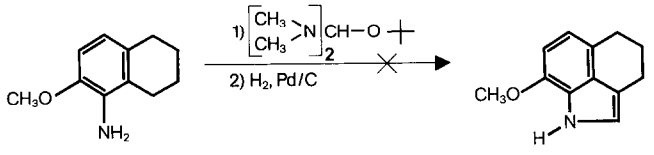
Summary: A convenient synthesis of substituted benz[c,d]indoles is described. The method consists in cyclization of bicyclic isonitriles with strong bases such as LDA to the corresponding tricyclic compound.

In the preceding paper [1] we described a method for an efficient synthesis of indoles and benz[c,d]indoles. Unfortunately, the reaction sequence could not be applied to methoxy substituted nitroaromatics such as the tetralone 1 - for reasons which we do not fully understand. **)

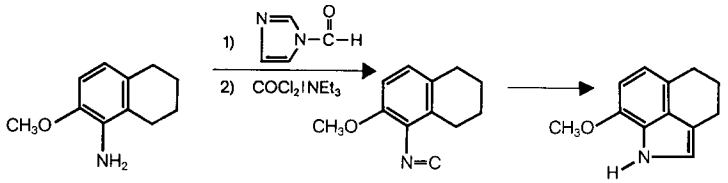


1

In searching for an alternative, we also tested the method introduced by Saegusa [2]; the indole ring is constructed by ring closure of the ortho-tolyl isocyanide.

**) Perhaps, the methoxy substituent, strongly activated by the nitro group, is cleaved to the phenol which is expected to be totally unreactive.

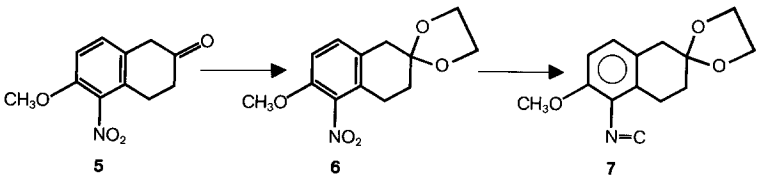
As a first example, we tried the synthesis of 8-methoxy-1,3,4,5-tetrahydrobenz[c,d]indole (4) from the readily accessible 5-amino-6-methoxy tetralin [3] (2), the amino group of which had to be transformed to an isonitrile group. This can be done in practically quantitative yield by reaction with N-formylimidazole and dehydration with phosgene/triethylamine [4].



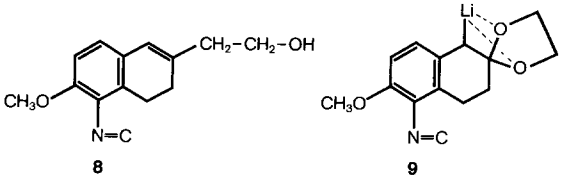
2 3 4

A useful second method, especially for larger batches, consists in the reaction of aniline under phase transfer conditions with 50 % KOH/methylene chloride / chloroform [5]. Probably in this case the reactive species is the dichlorocarbene. If a solution of the isonitrile 3 in diglyme is added dropwise to a solution of LDA (prepared in situ from butyllithium and diisopropylamine; argon, 1/2 hr, -70°) kept for a short time at -70°, slowly heated up to -15°, and after 1 hr quenched with pH 7 buffer solution, 4 is obtained in a 30 % yield.

This ring closure should also be applicable to tetralins with additional functional groups, such as 6-methoxy-5-nitro-2-tetralone [7] (5).



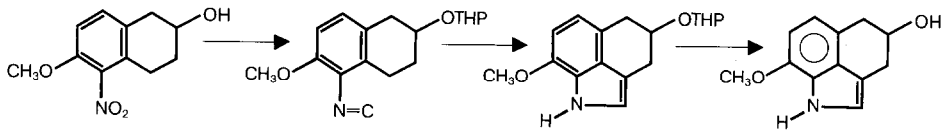
5 6 7



8 9

Conversion from the nitrotetralin 6 with a protected keto group to the isonitrile 7 was facile - but attempted cyclisation under the above mentioned conditions mainly led to recovery of starting material. Only a small amount of a product could be isolated whose physical data were in agreement with structure 8.

The synthesis was successful when the tetrahydropyranyl protected tetralol derivative 11 was employed: 2-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene[8] is acetylated in acetic anhydride with cat. amounts of sulfuric acid and then nitrated with $Cu(NO_3)_2 \cdot 2H_2O$ to the isomeric 5 and 7-substituted nitroderivatives, which can be separated from each other by simple column chromatography. The acetoxy group of the 5-NO_2-isomer is cleaved and the alcohol 10 protected as the tetrahydropyranyl ether.



10 11 12 13

2-(2-Tetrahydropyranyloxy)-6-methoxy-5-nitro-1,2,3,4-tetrahydronaphthalene is then converted into the isonitrile 11 which when treated with LDA in diglyme at -70° produce a red solution which was held at -70° for 1/2 hr and then warmed to -20° for 1 1/2 hr. Conventional work-up provides 4-(2-tetrahydropyranyloxy)-8-methoxy-1,3,4,5-tetrahydro-benz[c,d]indole (12) in ca. 50 % yield. The alcohol 13 is quantitatively obtained through cleavage of the protecting group.

An application of the strategy described here to the synthesis of 14-methoxy-dihydrolysergic acid will be reported in due course.[9]

Some Physical Data of the Products

3 m.p. 69-70°, ^{1}H-NMR ($CDCl_3$) δ 1,6-2,0 (m, 4H); 2,6-2,9 (m, 4H); 3,87 (s, 3H); 6,7/7,02 (d, J = 9 Hz). I.R. (CH_2CL_2): 1500, 1580, 1610, 2130, 2950 cm^{-1}. 4 m.p. 71-72°, ^{1}H-NMR ($CDCl_3$) δ 1,9-2,2 (m, 2H); 2,8-3,0 (m, 4H); 3,98 (s, 3H); 6,6/6,8 (d, J = 8 Hz), 6,85

(m, 1H); 8,0 (broad N-H). I.R. (CH_2Cl_2): 1530, 2950, 3480 cm^{-1}. 5 m.p. 90-93°, ^{1}H-NMR ($CDCl_3$) δ 2,4-3,1 (m, 4H); 3,65 (s, 2H); 3,9 (s, 3H); 6,91/7,2 (d, J = 8Hz). I.R. (CH_2Cl_2): 1600, 1640, 1730 cm^{-1}. 6 m.p. 162-163°, ^{1}H-NMR ($CDCl_3$) δ 1,95 (t, 2H); 2,85-3,1 (m, 4H); 3,9 (s, 3H); 4,0 (s, 4H); 6,78 (s, 1H); 7,56 (s, 1H). I.R. (CH_2Cl_2): 1540, 1625, 2950 cm^{-1}. 7 m.p. 151-152°, ^{1}H-NMR ($CDCl_3$) δ 2,0 (t, 2H); 2,9-3,2 (m, 4H); 3,9 (s, 4H); 4,0 (s, 4H); 6,76/7,04 (d, J = 9 Hz). I.R. (CH_2Cl_2): 1510, 2160, 3000 cm^{-1}. 8 m.p. oil, ^{1}H-NMR ($CDCl_3$) δ 2,1 (broad O-H); 2,5 (t, 2H); 2,09 (t, 2H); 3,9 (s, 3H); 3,99 (s, 4H); 5,5 (s, 1H); 6,72/6,93 (d, J = 8 Hz). I.R. (CH_2Cl_2): 1660, 2150, 3500 cm^{-1}. 10 m.p. 111-113°, ^{1}H-NMR ($CDCl_3$) δ 1,6-2,1 (m, 3H); 2,5-3,2 (m, 4H); 3,85 (s, 3H); 4,15 (m, 1H); 6,82/7,16 (d, J = 8 Hz). I.R. (CH_2Cl_2): 1530, 2940, 3600 cm^{-1}. 11 m.p. 80-81°, ^{1}H-NMR ($CDCl_3$) δ 1,4-2,3 (m, 8H); 2,5-4,3 (m, 7H); 4,0 (s, 3H); 4,7-4,9 (m, 1H); 6,7/7,04 (dm, J = 9 Hz). I.R. (CH_2Cl_2): 1500, 2150, 2950 cm^{-1}. 12 m.p. 150-152°, ^{1}H-NMR ($CDCl_3$) δ 1,4-2,0 (m, 6H); 2,7-3,7 (m, 5H); 3,92 (s, 3H); 4,1-4,45 (m, 1H); 4,8-4,95 (m, 1H); 6,55/6,85 (d, J = 8 Hz); 8,0 (broad, N-H). I.R. (Nujol): 1450, 1510, 3350 cm^{-1}. 13 m.p. 96-98°, ^{1}H-NMR ($CDCl_3$) δ 2,7-3,2 (m, 4H); 3,83 (s, 3H); 4,2-4,5 (m, 1H); 6,5/6,7 (3H, J = 7 Hz); 8,35 (broad, N-H). I.R. (CH_2Cl_2): 1520, 2900, 3475, 3600cm^{-1}.

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