SYNTHESIS OF INDOLE AND RELATED COMPOUNDS FROM HALO-NITROAROMATICS

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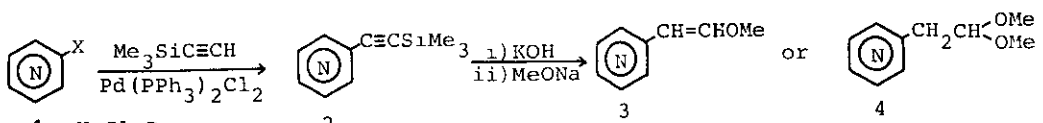
Abstract——5,7-Dimethyl-6-azaindole was synthesized by treatment of 3-amino-2,6-dimethyl-4-pyridineacetaldehyde diethyl acetal with hydrochloric acid in boiling ethanol. According to the similar manner, indole and ethyl 4-indolecarboxylate were obtained from the corresponding 2-aminophenylacetaldehyde derivatives in satisfactory yields. The starting materials were easily prepared by palladium-catalyzed cross-coupling reaction of o-halonitroaromatics with trimethylsilylacetylene followed by the reaction with sodium ethoxide and catalytic reduction of the o-nitro group.

As reported previously[1] various chloro- and bromo-N-heteroaromatics (1) such as 2-chloropyridine, 2-chloroquinoline, 3-bromopyridine, or 3-bromoquinoline, reacted with trimethylsilylacetylene by catalytic action of dichlorobis(triphenylphosphine)palladium in triethylamine. The resulting trimethylsilylethynyl-N-heteroaromatics (2) are convertible to the corresponding enol ethers (3) or acetaldehyde acetals (4) by the reaction with sodium methoxide in boiling methanol.[2] As an extension of this investigation, in the present paper, we describe a facile synthesis of indole derivatives from appropriate o-halonitroaromatics.

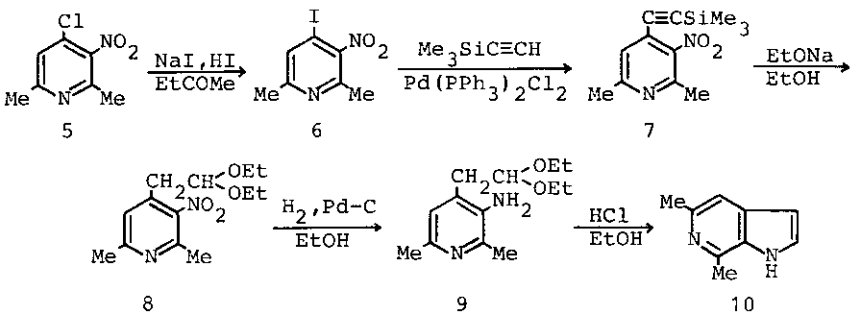


1 X=Cl,Br 2 3 4

Scheme 1

Firstly, the synthesis of 5,7-dimethyl-6-azaindole (10) as a representative of aza-indoles, from 4-chloro-2,6-dimethyl-3-nitropyridine (5)[3] was examined. When 4-iodo-2,6-dimethyl-3-nitropyridine (6), mp 149-150°C, obtained by the trans-halogenation of 5 with sodium iodide in 2-butanone was allowed to react with trimethyl-

silylacetylene under the reported conditions,[1] 2,6-dimethyl-3-nitro-4-(2-trimethylsilylethynyl)pyridine (7) was obtained in 63 % yield. Treatment with sodium ethoxide in boiling ethanol transformed 7 smoothly into 2,6-dimethyl-3-nitro-4-pyridineacetaldehyde diethyl acetal (8), bp 105-107°C (2 mmHg), in 64 % yield. Catalytic hydrogenation over palladium-charcoal and subsequent hydrolysis of the resultant aminopyridineacetaldehyde diethyl acetal (9) with ethanolic hydrochloric acid gave 5,7-dimethyl-6-azaindole (10), mp 138-139°C, in 68 % yield.

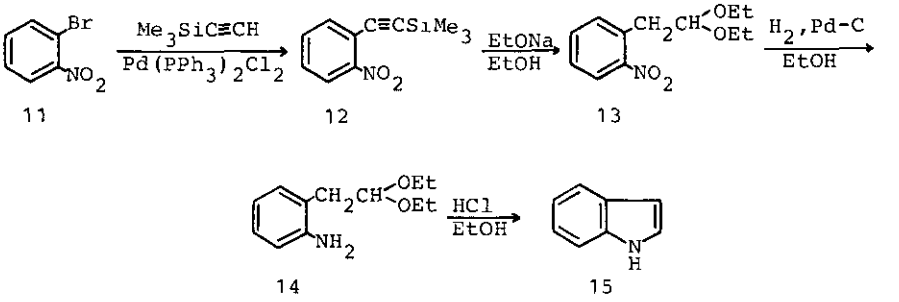


5 6 7 8 9 10

Scheme 2

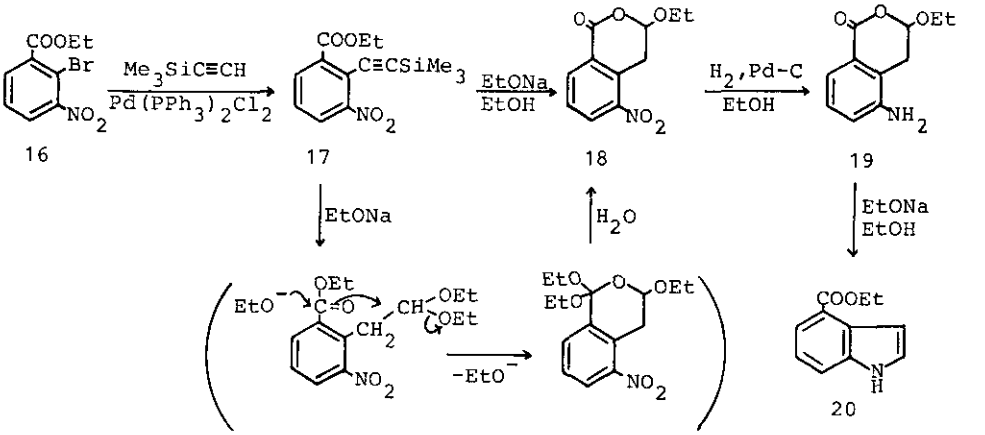
The ^{1}H-NMR spectrum of 10 is not contradicted with the expected aza-indole structure showing signals at 2.51 (3H, s), 2.66 (3H, s), 6.47 (1H, d, J=3 Hz), and 7.2-7.4 ppm (2H, m) together with a signal (9.0-9.6 ppm, 1H, br s) due to an amino proton. In order to confirm the wide applicability of this method for the preparation of aza-indole derivatives, our interest is now focussing on the synthesis of the other three kinds of aza-indoles, results of which will be reported in the following paper.

Since the method described above is apparently placed under the category of Baeyer-Jackson indole synthesis,[4] the synthesis of indole itself (15) from o-bromonitrobenzene (11) was then investigated. Namely, o-trimethylsilylethynylnitrobenzene (12) prepared by the reported method[5] from 11 was allowed to react with sodium ethoxide in ethanol to give 2-nitrophenylacetaldehyde diethyl acetal (13), bp 120-125°C (5 mmHg), which was easily reduced to 2-aminophenylacetaldehyde diethyl acetal (14), bp 90-95°C (4 mmHg) by catalytic reduction over palladium-charcoal. On treatment with conc. hydrochloric acid in ethanol, followed by neutralization of the reaction mixture with potassium carbonate, 2-aminophenylacetaldehyde underwent spontaneous dehydro-cyclization to give indole (15) which was identical with an authentic specimen in every respect. The overall yield of 15 from 11 was 34 %.



Scheme 3

Indole derivatives containing an appropriate carbon functional group at the 4-position are accepted as favorable intermediates for the synthesis of some ergot alkaloids, thus the synthesis of ethyl 4-indolecarboxylate (20) was finally examined. Ethyl 3-nitro-2-(trimethylsilylethynyl)benzoate (17) was easily obtained from ethyl 2-bromo-3-nitrobenzoate (16)[6] in 74 % yield by the similar manner to the above, but unlike the reaction of 7 and 12 with sodium ethoxide, that of 17 with the same reagent afforded a lactol ether (18), mp 94-95°C (63 %), which assumably formed through the pathway illustrated in parenthesis in Scheme 4. The spectral data[7] of 18 are satisfactory for the proposed structure.



Scheme 4

Catalytic hydrogenation of 18 over palladium-charcoal gave the corresponding amino-lactol ether (19), mp 143-144°C (85 %). Treatment of 19 with sodium ethoxide in ethanol at room temperature afforded ethyl 4-indolecarboxylate (20), mp 72-73°C[8] (75 %) as expected. The spectral data of 20[9] are also in good agreement with the value expected from the structure.

In conclusion, the efficiency of our method for the synthesis of indole derivatives depends on the synthetic availability of starting o-nitroaromatic halides.

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7. ^{1}H-NMR ($CDCl_3$) of 18: 1.20 (3H, s), 2.9-3.1 (2H, m), 3.5-4.3 (2H, m), 5.50 (1H, t, J=4 Hz), and 6.8-7.7 ppm (4H, m).
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9. ^{1}H-NMR ($CDCl_3$) of 20: 1.45 (3H, t, J=7 Hz), 4.43 (2H, q, J=7 Hz), 7.0-8.1 (5H, m), and 8.2-8.8 ppm (1H, br s).

Received, 9th March, 1984