Tetrahedron Letters,Vol.25,No.3,pp 285-288,1983
Printed in Great Britain

0040-4039/84 $3.00+ .00

BENZ[c,d]INDOLES - I. THE USE OF TERT-BUTOXY-BIS(DIMETHYLAMINO)METHANE AS CONDENSATION REAGENT.

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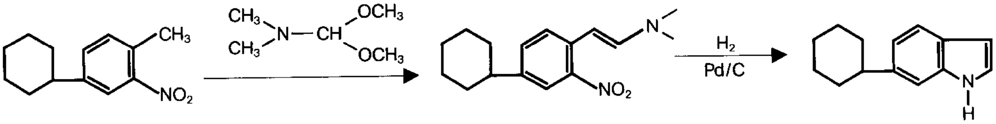
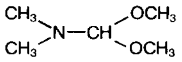
Summary: A simple and efficient route to benz[c,d]indoles is the reaction of nitrotetralins with Bredereck's reagent and reduction of the condensation product to the corresponding annelated indole.

In connection with another project [1)] we were faced with the problem of synthesizing 6-substituted indoles. We decided to use Leimgruber's [2)] indole synthesis as a versatile route to e.g. 6-cyclohexylindole.



Under the drastic conditions used with N,N-dimethylformamide dimethyl acetal (1) (140-170°, 1-2 days) the yield was rather low. In contrast to this sluggish reaction, the condensation with tert-butoxy-bis(dimethylamino)methane [3,4)] (2) was achieved under mild conditions, (60-80°, 1-2 days).



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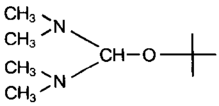
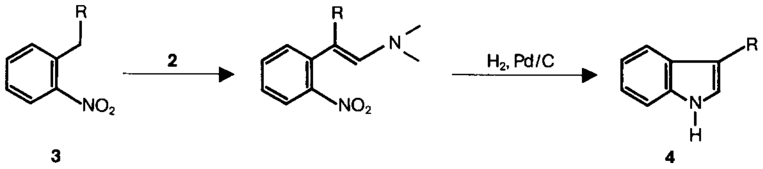


2

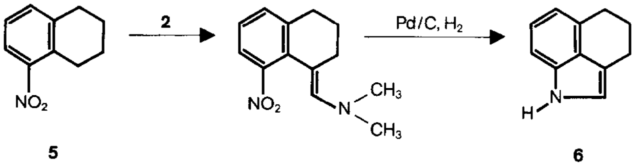
The difference in the reactivity between the two reagents is believed to be due to facilitated dissociation of 2 as compared to 1, with concomitant greater alkoxide concentration; at the same time, the deprotonation of the C-H substrate is increased by the larger basicity of the tertiary butoxide ion.

It should be possible to apply this reaction sequence to other alkylnitrobenzenes (e.g. 3 -> 4).



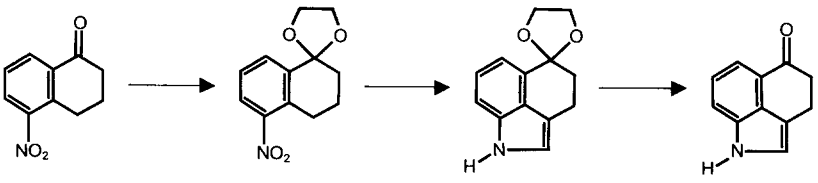
Although this indole synthesis has been known since 1971 [2c], only nitrotoluenes are known as C-H-acidic components; even the reaction with ethylnitrobenzene (3 R = methyl) is not reported in the literature. Indeed, when 2 g of ethylnitrobenzene were dissolved in 10 ml tert-butoxy-bis(dimethylamino)methane and heated for 18 hrs at 100°, a product was formed which was freed from volatile components in vacuo, dissolved in toluene and hydrogenated with Pd/C 10 % for 18 hrs. The final product isolated in 52 % yield was identical with 3-methylindole (skatole), in all respects.

More interesting was the reaction of nitrotetralin 5 [5] with an excess of 2 which again functioned as solvent and reagent.



The same conditions as above afforded after filtration of the product through silica gel with methylene chloride the desired 1,3,4,5-tetrahydrobenz[c,d]indole (6) [6] in 40 % yield over both steps.

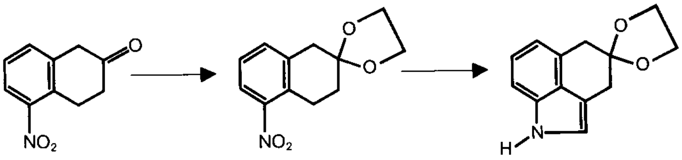
In the same manner functionalized nitrotetralins can be brought to reaction. An expedient, simple and high yielding synthesis of the so called Uhle ketone 10 7) is as follows:



7 8 9 10

The keto group of 5-nitro-1-tetralone (7) 8) is quantitatively protected with ethylene glycol to give 1,1-ethylendioxy-5-nitro-1,2,3,4-tetrahydronaphthalene (8) (m.p. 122- 123°) which yields under the usual conditions (10 hrs, 90°; then Pd/C toluene) the tetracyclic compound 9 in 45 %. The intermediate enamino ketone was not isolated because of its rapid hydrolysis on silica gel to the corresponding aldehyde. To prepare an analytical pure sample of the acetol 9, (m.p. 160-162°, the raw material contains a small amount of deprotected ketone 10), it was chromatographed on silica gel with methylene chloride. Deketalisation of the crude product in tetrahydrofuran/water with a few drops of 2n HCl yielded the desired ketone 10 which was identical with an authentic sample 9).

Finally 5-nitro-2-oxo-1,2,3,4-tetrahydronaphthalene (11) 10) was converted into the corresponding tricyclic indole 12 (m.p. 194-195°) by the same sequence of steps.



11 12

It seems likely from the examples described here, that other ring systems, e.g. tetracyclic compounds which are ubiquitous in nature, can be synthesized by this method.

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9) F.C.Uhle, J.Am.Chem.Soc. 71, 761 (1949).

10) Prepared in ca. 70 % yield by conventional 1,2-keto group transposition from 5-nitro-1,3,4,5-tetrahydrobenz[c,d]indole.

(Received in Germany 14 October 1983)