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A NEW VERSATILE SYNTHESIS OF 4-NITROINDOLES

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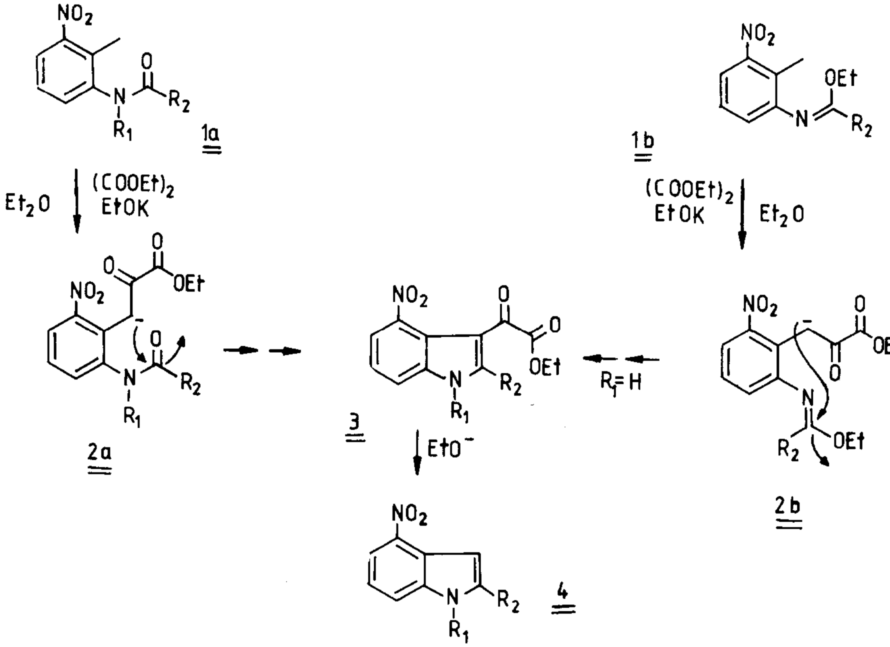
Summary: A variety of substituted 4-nitroindoles are prepared from the corresponding 3-nitro-*o*-toluidines or their iminoether derivatives by treatment with alkoxide/oxalic ester in various solvents.

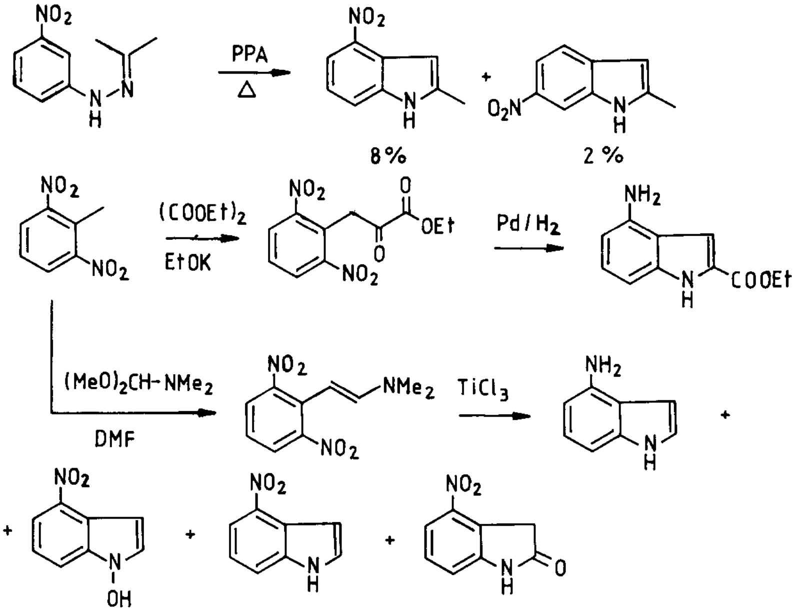
Simple indoles, substituted in 4-position (*e.g.* 4-aminoindole and 4-formylindole) are of considerable interest as starting materials in the synthesis of many natural products and drugs[1] and in current synthetic approaches[2,3] to teleocidin A[4] and related potent tumour promotors, 4-nitroindole is an important starting material.

We have now, as outlined in Scheme 1, developed a convenient synthetic route (two variants) to a variety of substituted 4-nitroindoles, which hitherto have been rather difficult to obtain. Thus the Fischer cyclization[5] results in an isomeric mixture in a very low yield and the Reissert[6] and the Batcho/Leimgruber[7,8] procedures (and modifications thereof[9,10]) encompass a reduction step which do suffer from drawbacks such as complex product patterns (Scheme 2).



SCHEME 1

The new procedure involves the formation of an intermediate nitrophenyl-pyruvic ester anion (2a or 2b) by action of alkoxide/oxalic ester on the corresponding starting materials (1a or 1b)[11]. Many of these anions turn out to be sufficiently nucleophilic to attack the intramolecularly present electrophile (i.e. the amide or the iminoether function), and hence resulting in a 4-nitro-3-indolyl oxoacetic ester (3). The latter, which in one instance has been isolated, will under the conditions used (i.e. equimolar amounts of alkoxide) eliminate oxalic ester and eventually give the 4-nitroindole derivative (4)[12].

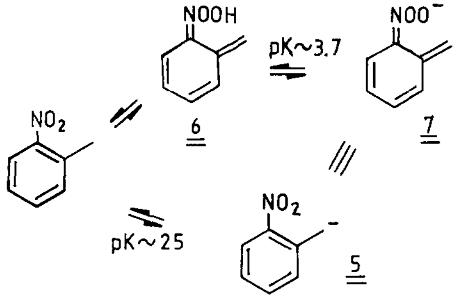


SCHEME 2

To account for the results it is assumed that the anion of the o-nitrotoluene (5) attacks the oxalic ester (cf. the Reissert reaction). The direct deprotonation of an o-nitrotoluene by alkoxide (for instance ethoxide) is, however not likely to occur since the acidities of the reactants are respectively $pK>25$ and $pK\approx17$[13], giving as a crude estimate[14] the deprotonation rate $k_f < 10^{-8}\ M^{-1}s^{-1}$.

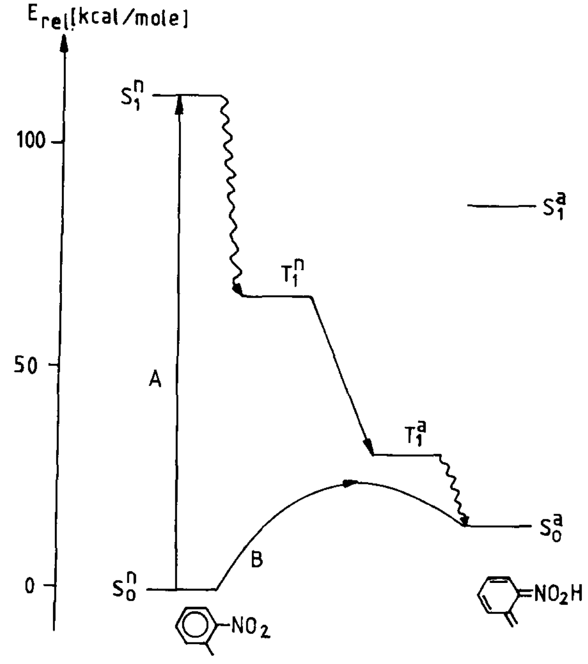
$$HA \underset{k_b}{\overset{k_f}{\rightleftharpoons}} A^- + H^+ , \qquad K_{HA} = k_f/k_b$$

It is therefore also assumed that 5 originates from deprotonation of the strongly coulored aci-nitro tautomer (6). The photochromic properties of o-nitrotoluenes leading to species like 6 are quite well investigated[14-16] and it has been shown that the acidities of the aci-nitro forms ranges from $pK \approx 2$ to $pK \approx 4$ and that their anions (e.g. 7) are identical with those formed by deprotonation of the o-nitrotoluenes with strong base (Scheme 3).



SCHEME 3

A series of CNDO calculations made by Ryaboi and Basov[17] do suggest that formation of 6 also can, in addition to the well known photochromic route, be achieved through a thermochromic route (pathways B and A respectively in the energy diagram). A quantitative interpretation is, of course, hard to make on the basis of semi-empirical MO-SCF calculations, but in combination with experimental data[18,19] the energetics of the nitro/aci-nitro tautomerism can be reasonably well described (see below).



In the energy diagram S and T are singlets and triplets, a and n refer to aci-nitro and nitro forms respectively. The only controversial assumption in the figure is the energy barrier for the $S_0^n \rightarrow S_0^a$ conversion (calculated[17] to be ca.15 kcal/mole) whereas a rough estimate based on the reaction times for the Batcho/Leimgruber reaction gives an energy of 25 kcal/mole, the barrier for the reverse reaction is determined to be[18,19] ca. 10 kcal/mole.

The reason why direct cyclizations of e.g. 1b will fail is not fully understood but the model does suggest that the corresponding anion has a methylene rotational barrier incompatible with such a reaction path-way. The barrier should be expected to be lowered by conjugation in the case of 2a and 2b.

The simplicity of the new procedure is demonstrated by the synthesis of 2-ethyl-4-nitroindole. Potassium (0.39g ; 10mmol) was dissolved in ethanol (5ml) under N_2 whereupon dry ether (50ml) was added. To this solution is added diethyl oxalate (2.92g; 20mmol) and after 5 min. stirring N-(2-methyl-3-nitrophenyl)-1-ethoxy-1-propylimine[11] (1b,R_2=Et) was added at room temperature. The mixture (deep-red within 20 min.) was refluxed 24h, whereupon the solvent was evaporated and the residue dissolved in methanol and slowly poured into ice-water (saturated with K_2CO_3) under vigorous stirring. Filtration gave the product as yellow crystals 1.33g (70%) mp 147-9°C. IR (KBr: 3315,1578,1540,1500,1473,1320,1296,1270 cm^{-1}.

Other indoles made using this procedure are listed in footnote 20.

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12. Efforts to directly convert 1 into 4 were unsuccessful in spite of application of a variety of reaction conditions.
13. This is even more accentuated in the Batcho-Leimgruber reaction where the base present is DMF-dimethyl acetal (pK≈10) and the rate of deprotonation is estimated to be $k_f \leq 10^{-15} M^{-1} s^{-1}$ (cf.ref.14).
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20. 4-nitroindole m.p.205-6°C (82%), 1-methyl-4-nitro-2-phenylindole m.p. 123-6°C (7%), 2-methyl-4-nitroindole m.p.192-4°C (65%), 1-H-2,3-dihydro-8-nitro-pyrrolo(1,2-α)indole m.p.132-3°C (35%).

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