

Catalytic Synthesis of 3-Substituted Indoles using CO as Building Block and Supported Rhodium as Catalyst

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Summary Under hydroformylation conditions, using supported rhodium as catalyst, 2-nitrostyrene is directly converted into skatole in *ca.* 70% yield, by a reaction involving formation of 2-(*o*-nitrophenyl)propionaldehyde by homogeneous catalysis, reduction of the nitro-group by heterogeneous catalysis, then ring closure and thermal dehydration.

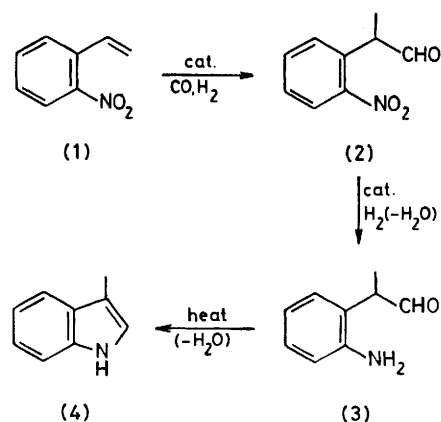
MANY 3-substituted indoles have a biological function,¹ either as biochemical intermediates (auxin, tryptophan, tryptamine, serotonin) or as natural drugs (gramine, bufotenine, psilocine).

A large number of syntheses of the indole ring have been reported.² The most widely used, due to Fischer, involves an acid-catalysed cyclization of an arylhydrazine.³

Our interest in the hydroformylation of substituted styrenes⁴ prompted us to explore a novel catalytic route to 3-substituted indoles, which should result in a practicable synthetic method, since the starting styrenes are now readily available.^{4,5}

Our results in hydroformylating 2-nitrostyrene are reported here. The expected reaction pathway to skatole can be summarized as in the Scheme, and we wished to discover a method that would lead to highly selective formation of the branched-chain aldehyde (2), and a catalyst which would be able to perform the hydroformylation and nitro-group reduction in one step.

The hydroformylation of styrene derivatives with rhodium complexes is well known to show a high selectivity for formation of branched-chain rather than terminal aldehydes, because of the strong orienting effect of the aromatic ring. Hence we have compared some rhodium



SCHEME.

complexes and precursors. Whatever the conditions, even under high pressure and at high temperatures, the complexes RhCl(PPh₃)₃ and RhCl(CO)(PPh₃)₂ lead to a low conversion of 2-nitrostyrene. Clusters such Rh₄(CO)₁₂ and Rh₆(CO)₁₆ are quite ineffective. In previous work we had found that the most active catalysts were produced *in situ* from supported rhodium precursors such as Rh/Al₂O₃ and Rh/C. With Rh/C, at 80 °C and under a pressure of 160 atm [*p*(CO) = *p*(H₂)] in benzene, (1) is completely converted within 1–2 h into the 2-nitroaldehyde (2) (*ca.* 60%), other expected products (3) (5%) and (4) (5%), and a by-product (*ca.* 28%) (g.l.c. analysis), which was identified as 2-aminoacetophenone on the basis of m.s. and n.m.r. data.

These results suggested that supported rhodium should be a convenient catalytic precursor for skatole synthesis, in that it is both selective for formation of the branched-chain aldehyde and able to promote nitro-group reduction. Higher temperatures did lead to the conversion of (2) and (3) into (4). At 160 °C (1) was converted directly into (4) in *ca.* 70% yield, together with a polymeric mixture arising from 2-aminoacetophenone, which can react thermally with aldehydes, as shown by separate experiments.

Unsuccessful attempts were made to reduce the yield of 2-aminoacetophenone, and we are not yet able to explain how it is formed. Investigations are in progress to discover if it is a Wacker-like reaction product or the result of oxygen transfer from the nitro-group to the double bond at the rhodium surface. The reaction of a mixture of styrene and nitrobenzene under the hydroformylation conditions leads to recovery of nitrobenzene unchanged, whereas the styrene is converted into aldehydes. Analogous results were obtained from 3- and 4-nitrostyrene, which gave only nitroaldehydes. These surprising results suggest

that two conditions must be satisfied for both oxygen insertion and NO₂ reduction: the double bond should be *ortho* to the nitro-group, and the double bond should be co-ordinated.

Additional results support the reaction pathway suggested. Heating of the 2-nitroaldehyde (2) in benzene solution in the presence of Rh/C under hydrogen pressure gives pure skatole and the expected amount of water (3 mol per mol), and similarly the 2-aminoaldehyde (3) leads to (4) and water.

Our results indicate the following conclusions. (i) Under severe hydroformylation conditions supported rhodium can act as a reservoir of rhodium carbonyl complexes and as a mass contact able to activate molecular hydrogen, and (ii) a catalytic route to 3-substituted indoles from 2-nitrostyrenes and carbon monoxide is available.

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¹ L. F. Fieser and M. Fieser, 'Organic Chemistry,' Rheinhold, New York, 1956, p. 508.

² R. M. Acheson, 'An Introduction to the Chemistry of Heterocyclic Compounds,' Interscience, New York, 1960, p. 142.

³ For a review see B. Robinson, *Chem. Rev.*, 1963, **63**, 373.

⁴ R. Lai and E. Ucciani, *J. Mol. Catal.*, 1978, **4**, 401.

⁵ R. Bross and M. Anteunis, *Synth. Commun.*, 1976, **6**, 53.