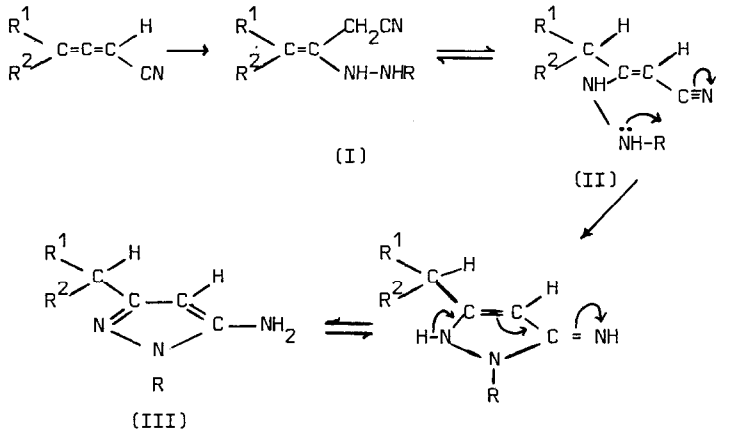
Tetrahedron Letters No. 42, pp 3743 - 3746, 1977. Pergamon Press. Printed in Great Britain.

N-PHENYLPYRAZOLES AND 3H-INDOLES FROM ALLENIC NITRILES. A NOVEL FISCHER-INDOLE REACTION.

By Stephen R. Landor*, Phyllis D. Landor, Zacharias T. Fomum and George M. Mpango, Department of Chemistry, University of Exeter, Exeter EX4 4QD, Makerere University, Kampala, and University of Yaounde, Cameroon.

(Received in UK 17 August 1977; accepted for publication 2 September 1977)

Michael addition of hydrazine (R=H) to allenic nitriles followed by nucleophilic ring closure by attack of the second amine group on the carbon of the nitrile has recently been shown to give quantitative yields of 5-substituted 3-aminopyrazoles (III, (R=H).[1]



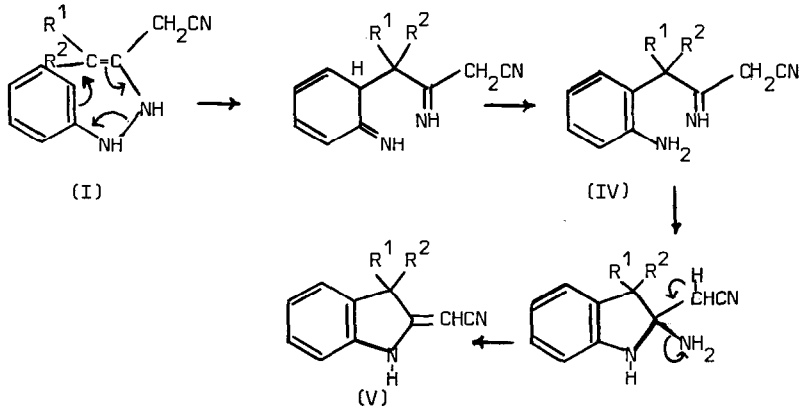
Scheme 1

Neither the unconjugated adduct (I, R=H) nor the conjugated adduct (II, R=H) have been isolated as cyclisation takes place spontaneously under

* Present Address: Department of Chemistry, University of Lagos, Lagos, Nigeria.

the reaction conditions employed. We now report that substituted hydrazines e.g. phenylhydrazine (R=Ph) at controlled temperatures give first unconjugated and then the conjugated adduct (II, R=Ph) which can be isolated in quantitative yield. On heating the conjugated adduct (II) (R^1 = Me, R^2 = Et) at 60° for 15 min 1-phenyl-5-amino-3-(2'-butyl)pyrazole was formed as the main product containing less than 5% of an impurity, later shown to be the 3H-indole. However, if redistilled phenylhydrazine and 4-methylhexa-2,4-diene-nitrile are mixed at room temperature and then heated to 80°, an exothermic reaction is initiated with the temperature rising to 185°. The product consists of approximately equal quantities of the pyrazole (III, R^1 = Me, R^2 = Et) and a new compound m/e 198 (M^+, $C_{13}H_{17}N_2$ requires 198) which was identified as 3-ethyl-3-methyl-2-(cyanomethylene)-3H-indole(V)[2], m.p. 65°; this showed the characteristically shielded enaminic proton at τ 6.12 and the exchangeable hydrogen on the nitrogen well downfield at τ 0.6. Overlapping quartets for the methylene of the ethyl group may be due to either the E or Z isomer.* As the conjugated adduct (II) yields only pyrazole (III) it is reasonable to assume that unconjugated adduct (I) gives rise to the 3H-indole the formation of which may be rationalised in the following way. The unconjugated adduct undergoes a [3,3] sigmatropic rearrangement, followed by prototropic rearrangement to the substituted aniline (IV) which cyclises by nucleophilic addition to the imine and eliminates ammonia to give the 3H-indole (V) (see Scheme 2).

* The protons of the prochiral CH_2 of the Et group give rise to an AB quartet each line being split into further quartets by the neighbouring CH_3. The outer lines of the AB quartet being very weak only the two overlapping quartets of the inner lines are observed.



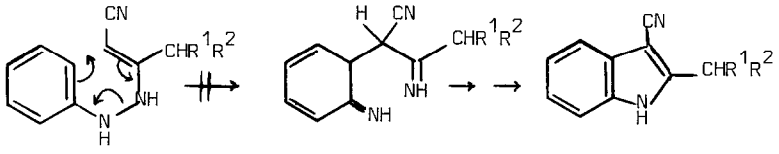
Scheme 2

The ratio of pyrazole to indole is determined by the relative rates of reaction for the prototropic rearrangement of unconjugated to conjugated adduct (I $\overset{k_1}{\rightleftharpoons}$ II) and the sigmatropic rearrangement (k_2). Attempts to even partly inhibit the prototropic rearrangement by conducting the experiment under strictly aprotic conditions in dry refluxing dichlorobenzene met with little success, as the nitrile tends to dimerise under these conditions. Furthermore proton or Lewis acids, which normally catalyse the Fischer-Indole reaction, yield pyrazole as the predominant product and therefore $k_{1cat.} \gg k_{2cat.}$ where $k_{1cat.}$ and $k_{2cat.}$ are the rates of the catalysed prototropic and sigmatropic rearrangements.

4-Ethylhexa-2,3-dienenitrile similarly gave 1-phenyl-5-amino-3-(3'-pentyl)pyrazole (59%) (III, $R_1 = R_2 = Et$), m.p. 65°, and 2-(cyanomethylene)-3,3-diethyl-3H-indole[2] (41%) (V, $R_1 = R_2 = Et$), m.p. 94°, from the mixture of reagents heated to 80°, 4-methylhepta-2,3-dienenitrile gave 1-phenyl-5-amino-3-(2'-butyl)pyrazole (61%) (III, R_1 = Me; R_2 = Pr) and 2-(cyanomethylene)-3-methyl-3-propyl-3H-indole (39%) (V, R_1 = Me; R_2 = Pr) and methyldeca-2,3-dienenitrile gave 1-phenyl-5-amino-3-(2'-octyl)pyrazole (48%) (III, R_1 = Me; R_2 = hexyl) and 2-(cyanomethylene)-3-methyl-3-hexyl-3H--indole (52%) (V, R_1 = Me; R_2 = hexyl). Hepta-2,3-dienenitrile gave only 1-

-phenyl-5-amino-3-butylpyrazole presumably because the unconjugated adduct from a 3-monoalkylcyanoallene rearranges very fast to the conjugated adduct.[3]

No trace of the product from an alternative sigmatropic rearrangements of the conjugated adduct (II), which would yield 2-(2-butyl)-3-cyanoindole (VI) was detected. Apparently the sigmatropic rearrangement which forces both aromatic and enaminic double bonds out of conjugation is now energetically considerably less favourable than the nucleophilic attack of nitrogen on the trans-nitrile.



(II) (VI)

As expected, phenylpropynenitrile gave one product, the 1,3-diphenyl-5-aminopyrazole[2], m.p. 129°, as the acetylene can only form the conjugated adduct.

1. Z. T. Fomum, P. D. Landor, S. R. Landor, and G. Mpango, Tetrahedron Lett., 1975, 1101.

2. All new compounds gave satisfactory elemental analyses and spectroscopic properties in accord with these structures.

3. During the course of this work T. Tamnefors, A. Claesson and M. Karlsson (Acta Pharm. Suec., 1975, 12, 435) reported the formation of pyrazoles from 1,4- and 1,2-additions of phenyl and methylhydrazines to an allenic ketone, 2-methyl-4,5-hexadiene-3-one. Although a possible product from the Michael adduct with phenylhydrazine, no indole was isolated. However in view of our results the rate of prototropic rearrangement of the conjugated adduct from the terminal allene would be expected to be very much greater than that of the sigmatropic rearrangement leading to an indole which, therefore, is not formed.