

**REACTIONS OF 3-FORMYLINDOLE *N,N*-DIMETHYLHYDRAZONES WITH DIENOPHILES.
A STEREOSPECIFIC ADDITION**

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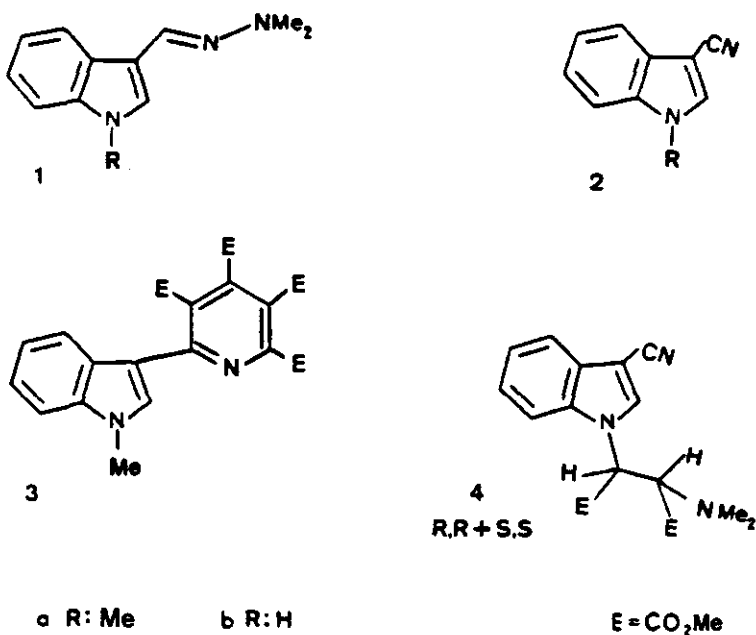
Abstract - 3-Formyl-1-methylindole *N,N*-dimethylhydrazone (**1a**) and 3-formylindole *N,N*-dimethylhydrazone (**1b**) react with methyl propiolate to give 3-cyano-1-methylindole (**2a**) and 3-cyanoindole (**2b**) respectively. When dimethyl acetylenedicarboxylate was used as a reagent the hydrazone (**1a**) afforded the nitrile (**2a**) and the pyridine (**3**) but in the reaction of the hydrazone (**1b**) an enantiomeric mixture of *R,R* and *S,S* dimethyl 1-(3-cyano-1-indolyl)-2-dimethylamino-succinates (**4**) were obtained and their structures confirmed by X-ray single crystal analysis.

Although it has been reported that 1-aza-1,3-butadiene systems are appropriate substrates for Diels-Alder reactions,¹ no [4+2] cycloadducts were obtained in our previous works^{2,3} on the reactivity of the 2-formylthiophene, 2-formyl-1-methylpyrrole, benzaldehyde, and 2-formylfuran *N,N*-dimethylhydrazones towards dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate (MP). Nevertheless the varied reactivities of these compounds and its dependence on the type of heterocyclic ring attached to the hydrazone group,²⁻⁴ prompt us to extend this study to 3-formylindole *N,N*-dimethylhydrazones (**1**).

The reaction of the hydrazone (**1a**) with DMAD afforded the nitrile (**2a**) (27%), the pyridine (**3**) (8%) and dimethyl 2-dimethylaminomaleate (26%). The formation of the nitrile and the amino diester can be explained

in a similar way as we reported in our previous work.² The formation of the pyridine (3) by reaction of the hydrazone (1a) with DMAD shows a second example of this particular reactivity of the hydrazone group towards acetylenic esters that we reported by the first time for 3-formyl-1-methylpyrrole *N,N*-dimethylhydrazone when methyl propiolate was used as a reagent.³ In the reaction of the hydrazone (1a) with MP the nitrile (2a) (75%) and methyl *E*-3-dimethylaminoacrylate (48%) were obtained.

More interesting results were found in the reaction of the hydrazone (1b) with DMAD. In addition to dimethyl 2-dimethylaminomaleate a solid compound (45.7%), mp 160 °C, was obtained, whose elemental analysis showed it was a 1:1 adduct of formula $C_{17}H_{19}N_3O_4$. The most relevant signals in the 1H -nmr were a pair of doublets at 4.2 and 5.4 (J 11 Hz) and three singlets at 3.8 (3H), 3.7 (3H), and 2.2 (6H) probably from the esters and the dimethylamino group. A band at 2225 cm^{-1} in the ir spectrum was indicative of the conversion of the hydrazone group into a cyano group in a similar way as we reported for other dimethylhydrazones.² This showed that the nmr signal assigned to the dimethylamino could not be the initial group of the hydrazone, but must have migrated elsewhere. The ^{13}C -nmr spectrum support the assignment made by 1H -nmr with signals at 41.7 ($N(CH_3)_2$), 51.8 and 53.1 ($2 \times OCH_3$). Two further signals appeared in this region at 57.4 and 66.6 (DEPT $2 \times CH$) showing that the doublets in the 1H -nmr at 4.2 and 5.4 were due to a pair of vicinal aliphatic hydrogens. At lower field the signals at 87.5 and 115.4 were assigned to the $=C-C\equiv N$. In the aromatic region five CH groups and two quaternary carbons were definitively conclusive for the assignment of the structure of the adduct as the dimethyl 1-(3-cyano-1-indolyl)-2-dimethylaminosuccinate (4).



As we have found no precedent for the reaction sequence leading to this structure, unambiguous confirmation was obtained by single crystal X-ray analysis. The X-ray analysis showed that an enantiomeric mixture of R,R and S,S succinates was obtained (R,R showed in Figure 1). The coupling constant 11 Hz found in ^1H -nmr is in agreement with the torsional angle (-179.4°) for the H-C-C-H of the succinate moiety.

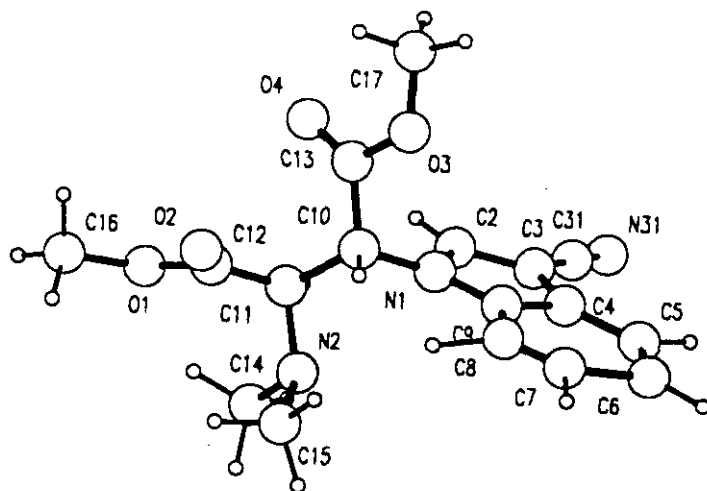
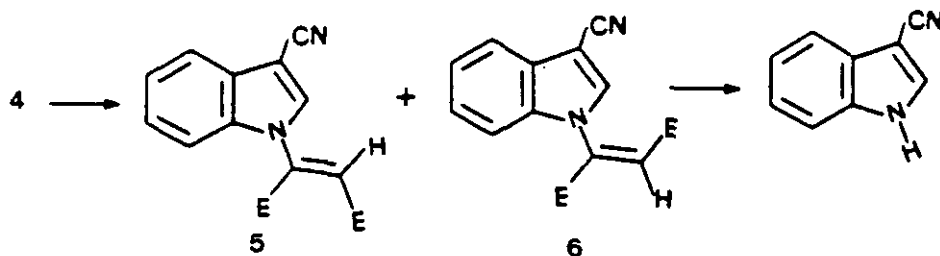


Figure 1

The formation of the succinate (**4**) (R,R + S,S) may be explained by a cis addition, of the cyanoindole (**2b**) to dimethyl 2-dimethylaminomaleate, both products formed in the reaction of the hydrazone (**1b**) with DMAD. By the other hand the observed regioselectivity of this addition is probably determined by an initial hydrogen bond between the acidic hydrogen of the cyanoindole and the dimethylamino group of the maleate ester. Nevertheless an attempt to prove this possibility failed when we tried to react the cyanoindole (**2b**) and dimethyl 2-dimethylaminomaleate in toluene at room temperature.

The adduct (**4**) was stable and could be analyzed properly but under long contact with silica or in solvents like dichloromethane decomposed slowly but completely to a mixture of the maleate (**5**) and the fumarate (**6**) which could be resolved chromatographically. The absence of the signals for the dimethylamino group in the ^1H -nmr and new singlets at 6.3 (1H) and 7.1 (1H) from the olefinic hydrogens were characteristic of these compounds. The maleate was unstable and isomerized slowly to the fumarate. The structure of the adducts (**5**) and (**6**) was confirmed synthetically by reaction of 3-cyanoindole and DMAD in basic media. Decomposition of these compounds was also observed and 3-cyanoindole could be detected from pure samples of the fumarate (**6**) stored for a long time.



The reaction of the hydrazone (**1b**) with methyl propiolate followed a different pathway and 3-cyanoindole was isolated almost quantitatively along with methyl E-3-dimethylaminoacrylate.

The reactivity of the hydrazone (**1b**) was also studied towards dimethyl maleate, methyl vinyl ketone (reactions carried out at 100° for 20 days) and tetracyanoethylene (room temperature, 18 h). Small amounts of 3-cyanoindole were detected in all the reactions but no other compounds were identified from the complex reaction mixtures.

EXPERIMENTAL

¹H and ¹³C-nmr spectra were recorded using a Bruker-80 or AC-200. Ir spectra were determined in CCl₄ with a Perkin-Elmer 843. Melting points were determined on a kofler hot-stage apparatus and are uncorrected.

Reactions of *N,N*-dimethylhydrazones (**1a**) and (**1b**) with DMAD and MP

General procedure: A solution of the acetylenic ester (0.01 mol) in toluene (20 ml) was slowly added to the *N,N*-dimethylhydrazone⁵ (0.01 mol) in toluene (50 ml) at room temperature and stirred for 18 h. Column chromatography on Merck silica gel of the crude mixtures with increasing ratios of hexane-ethyl acetate was used for the isolation of the reaction products.

Reactions of 3-formyl-1-methylindole *N,N*-dimethylhydrazone (**1a**)

a) With DMAD

The first compound eluted with hexane-ethyl acetate (1:1) was 1-methyl-3-cyanoindole⁶ (**2a**) (27%) and then dimethyl 2-dimethylaminomaleate (25%). Further elution (ratio 1:2) afforded tetramethyl 6-(1-methylindolyl)-pyridine-2,3,4,5-tetracarboxylate (**3**) (8%), mp 140 °C (dichloromethane-hexane). **3**: Anal. Calcd for C₂₂H₂₀O₈N₂: C, 60.00; H 4.58; N 6.37. Found C 59.77; H 4.29; N 6.13. Ir ν_{\max} (CCl₄) 1717 cm⁻¹. ¹H-Nmr (CDCl₃) 3.6 (s, 3H), 3.7 (s, 3H), 3.8 (s, 6H), 3.9 (s, 3H), 7.2-7.0 (m, 3H), 7.3 (s, 1H), 8.3-8.0 (m, 1H).

^{13}C -Nmr 32.9 (q), 52.8 (3 x q), 53.1 (q), 109.4 (d), 112.6 (s), 121.3 (d), 121.4 (d), 122.5 (s), 122.8 (d), 126.0 (s), 126.7 (s), 130.9 (d), 137.2 (s), 139.6 (s), 148.4 (s), 153.4 (s), 164.8 (s), 165.5 (s), 167.2 (s).

b) With MP

The reaction was completed after 2 days and 1-methyl-3-cyanoindole⁶ (75%) and methyl 3-dimethylaminoacrylate (48%) were obtained.

Reactions of 3-formylindole *N,N*-dimethylhydrazone (**1b**)

a) With DMAD

The reaction was carried out with DMAD (0.02 mol) and the hydrazone (**1b**) (0.01 mol). Column chromatography on Merck silica gel of the crude mixture with hexane-ethyl acetate (1:1) afforded dimethyl E-3-dimethylaminomaleate (2.7%) and dimethyl 1-(3-cyano-1-indolyl)-2-dimethylaminosuccinate (**4**) (45.7%), mp 160 °C. Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_4$: C 62.01, H 6.1, N 12.72. Found: C 61.92, H 5.9, N 12.65.

Ir ν_{max} (CCl_4) 2225, 1733 cm^{-1} . ^1H -Nmr (CDCl_3) 2.2 (s, 6H), 3.7 (s, 3H), 3.8 (s, 3H), 4.2 (d, J 11 Hz, 1H), 5.4 (d, J 11 Hz, 1H), 7.2-7.5 (m, 3H), 7.7 (s, 1H), and 7.7-7.8 (m, 1H). ^{13}C -Nmr 41.7 (q), 51.8 (q), 53.1 (q), 57.3 (d), 66.6 (d), 87.5 (s), 110.2 (d), 115.4 (s), 119.9 (d), 122.3 (d), 124.2 (d), 127.5 (s), 134.0 (d), 135.7 (s), 168.7 (s), and 169.5 (s).

Crystal data. The structure of the succinate (**4**), was determined by X-ray diffraction. $M_r = 329.36$, orthorhombic, space group $\text{Pna}2_1$, $a = 15.8786$ (3), $b = 9.8882$ (3), $c = 22.5572$ (5) Å, $V = 3541.7$ (1) Å³, $Z = 8$, $D_x = 1.24$ Mg/m³. MoK α radiation (graphite crystal monochromator, $\lambda = 0.7103$ Å), $\mu(\text{MoK}\alpha) = 0.84$ cm⁻¹, $F(000) = 1392$, $T = 293\text{K}$. Final conventional R factor = 0.099 for 1768 'observed' reflections and 441 variables. Colorless crystal, 0.33 x 0.48 x 0.33 mm size. Nonius CAD4 single crystal diffractometer. ω - 2θ scan technique. Structure solved by direct methods using the programme SHELX86 (Sheldrick, 1985) and Fourier synthesis. The final conventional agreement factors were $R = 0.099$ and $R_w = 0.098$ for the 1768 'observed' reflections and 441 variables. Function minimized $w(F_o - F_c)^2$, $w = 1 / ({}^2(F_o) + 0.0010 F_o^2)$ with F_o from counting statistics. Maximum over error ratio in the last full matrix least-squares cycle less than 0.023. Final difference Fourier map showed no peaks higher than 0.40 e/Å nor deeper than -0.21 e/Å. Lists of structure amplitudes, anisotropic thermal parameters, H-atom parameters, distances and angles involving H atoms, H-bond distances and angles and least square-planes, data and principal torsion angles were deposited.

The succinate showed a slow decomposition after long contact with silica and solvents. In one experiment a mixture of the dimethylaminosuccinate (4) (1.66 g) in dichloromethane (50 ml) and silica (Merck 60-200 μm 10 g) was stirred for 84 h, the solvent was evaporated and the silica was extracted with methanol (Soxhlet). The crude was chromatographed with hexane-ethyl acetate (1:1). The first fraction eluted was characterized as dimethyl 3-cyano-1-indolylmaleate (5) (2.8 %). $^1\text{H-Nmr}$ (CDCl_3) 3.7 (s, 3H), 3.8 (s, 3H), 6.2 (s, 1H), and 7.0-7.7 (m, 6H). The compound was unstable and isomerized to the fumarate. Further elution gave dimethyl 3-cyano-1-indolylfumarate (6) (38 %) as yellow crystals, mp 122 °C (dichloromethane-hexane). $\text{Ir } \nu_{\text{max}}$ (KBr) 2219, 1735, 1633. $^1\text{H-Nmr}$ (CDCl_3) 3.5 (s, 3H), 3.8 (s, 3H), 7.0-7.4 (m, 4H), and 7.5-7.8 (m, 2H). $^{13}\text{C-Nmr}$ 52.3 (q), 89.3 (s), 110.8 (d), 114.6 (s), 119.8 (d), 122.8 (d), 124.6 (d), 127.0 (s), 127.4 (d), 135.2 (s), 135.6 (d), 135.8 (s), 162.4 (s), and 162.6 (s). Further elution (ratio 1:2) afforded 3-cyanoindole (5.5 %). The adducts (5) and (6) were also obtained by reaction of an equimolecular mixture of DMAD and 3-cyanoindole in acetone with K_2CO_3 .

b) With MP

Column chromatography of the crude reaction mixture with hexane-ethyl acetate (1:1) afforded methyl E-3-dimethylaminoacrylate (39.5 %). Further elution with hexane-ethyl acetate (1:2) gave 3-cyanoindole (95%).

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