THE REACTIVITY OF 2-FORMYLTHIOPHENE, 1-METHYL-2-FORMYLPYRROLE, BENZALDEHYDE AND 2-FORMYLFURANE N,N -DIMETHYLHYDRAZONES WITH DIMETHYL ACETYLENEDICARBOXYLATE

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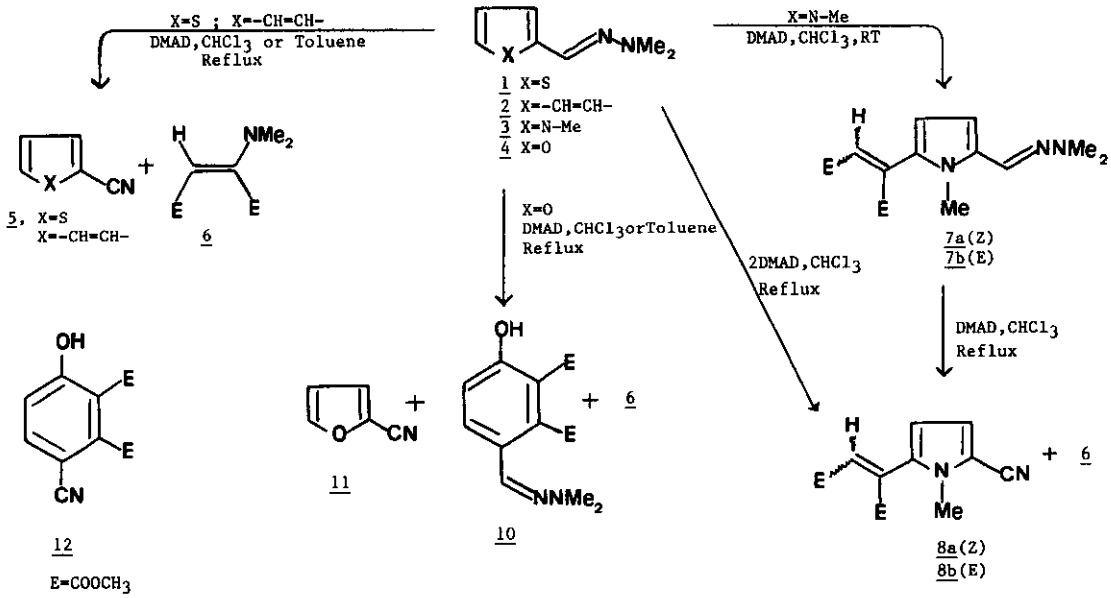
Abstract- N,N-Dimethylhydrazones derived from 2-formylthiophene, benzaldehyde, and 1-methyl-2-formylpyrrole react with dimethyl acetylenedicarboxylate (DMAD), giving the corresponding nitriles. The reaction with furfural N,N-dimethylhydrazone takes place via the intermediacy of a Diels-Alder adduct with the furan ring.

It has been shown recently[1] that although 1-aza-1,3-dienes are reluctant to participate in Diels-Alder reactions, these systems with an appropriate substitution can react with electron-poor dienophiles affording the corresponding cycloadducts. Looking at this new possibility of synthesis of heterocycles and as an extension of our studies on the reactivity, as 1,3-dienes, of five membered heterocyclic compounds bearing olefinic substituents,[2] we have prepared the N,N-dimethylhydrazones 1, 2, 3, and 4 and we have studied their reactivity with DMAD.

The reaction of the N,N-dimethylhydrazone 1 with DMAD was carried out in chloroform or toluene at reflux temperature affording 2-thienylnitrile 5 and another compound identified as the aminodiester 6 by spectroscopic analysis.[3] No Diels-Alder cycloaddition compounds were found in the crude mixture.

The same reaction with benzaldehyde N,N-dimethylhydrazone 2 gave the corresponding nitrile.

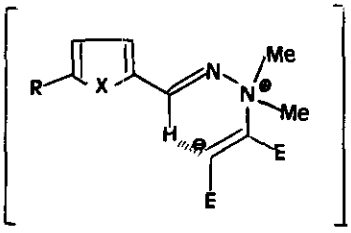
When the hydrazone 3 in chloroform was mixed with DMAD at room temperature, the Michael addition reaction took place and the adducts 7a and 7b, from attack at C_5, could be isolated with good yields. The same reaction with two moles of DMAD at reflux temperature afforded a mixture of the E/Z isomers 8a and 8b, that could be separated chromatographically. Here again the aminoester 6 was isolated from the reaction mixture.



Hydrazones have the well-known capacity to react with electrophilic reagents at either of the three nucleophilic centers, the amino nitrogen, the imino nitrogen and the imino carbon.[4] However when α,β-unsaturated N,N-dimethylhydrazones react with electron-poor dienophiles giving cycloadditon compounds[1], the mechanism of the reaction involve the initial attack of the C_4 to the electrophile, because of the reversed polarity of these 1-amino-1-aza-1,3 -diene systems.

Our experiments with the N,N-dimethylhydrazones 1, 2, and 3 ,have shown that these compounds react with DMAD by the amino nitrogen and afford nitriles as a

result of the elimination of the aminodiester 6 through a six membered intermediate 9.



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Although many methods are described for the synthesis of nitriles from aldehyde hydrazones as starting materials,[5] the acetylenic esters were never used as reagents for this conversion, so the present work provides a new route for the synthesis of these compounds.

In complete contrast with the hydrazones 1, 2, and 3, the 2-formylfuran N,N-dimethylhydrazone 4 reacts with DMAD in chloroform at reflux temperature to give a major compound 10 through a Diels-Alder cycloaddition to the furan ring in a similar way as it has been reported by Potts [6] in the reaction with maleic anhydride. Small amounts of 2-furylcarbonitrile 11 and the aminodiester 6 were isolated as a result of a competing reaction of the dimethylhydrazone group. Nevertheless, it was not possible to detect any amount of the corresponding nitrile 12.

Reactions with another dienophiles are in progress.

EXPERIMENTAL

^1H and ^{13}C nmr spectra were measured for ca. 40% solutions in $CDCl_3$ using a Bruker WP-80. Ir were determined in CCl_4 with a Perkin-Elmer 843 spectrometer. Melting points are uncorrected and were determined with a Kofler hot-stage apparatus. Combustion analyses were performed at the Instituto de Quimica Bio-Orgánica of the CSIC (Barcelona).

Reaction of N,N-Dimethylhydrazones with DMAD. General Procedure.-

DMAD (0.005 mol) in chloroform or toluene (10 ml) was added at room temperature to a solution of the corresponding N,N-dimethylhydrazone (0.005 mol) in chloroform or toluene (10 ml). Then the mixture was heated at reflux temperature for

30-40 h until disappearance of the starting material. Evaporation of the solvent gave a crude product which was purified by column chromatography.

2-Formylthiophene N,N-dimethylhydrazone: Elution of the crude product (1.4 g) with hexane-ethyl acetate (5:1) gave 2-thienylcarbonitrile **5** (0.45 g, 82%) and diethyl 2-dimethylaminomaleate **6** (0.7 g).

Benzaldehyde N,N-dimethylhydrazone: Column chromatography of the crude product (1.3 g) with hexane-ethyl acetate (5:1) gave benzonitrile (0.33 g, 66%) and the adduct **6** (0.6g).

1-Methyl-2-formylpyrrole N,N-dimethylhydrazone:

a) **At room temperature**. The reaction of DMAD (0.72 g, 0.005 mol) with the hydrazone **3** (0.75 g, 0.005 mol) in chloroform (20 ml) took place at room temperature when the mixture was stirred for 3 h. Evaporation of the solvent *in vacuo* and column chromatography with hexane-ethyl acetate (4:1) gave the adduct **7b** (0.45 g, 30%) as an oil. Anal. Calc for $C_{14}H_{19}N_3O_4$: C, 57.33; H, 6.48 ; N, 14.33. Found: C, 57.29; H, 6.57; N, 14.27. Ir 1720 cm^{-1}. ^{1}H-nmr 7.1 (s, 1H), 6.75 (s, 1H), 6.0 (d, J=3Hz, 1H), 5.9 (d, J=3Hz, 1H), 3.75 (s, 3H), 3.6 (s, 6H), 2.85 (s, 6H). Further elution gave the isomer **7a** (0.42 g, 27.5%) , mp 112-113 °C (yellow needles, recrystallized from hexane); Found: C, 57.52; H, 6.78; N, 14.38. Ir 1715, 1702 cm^{-1}. ^{1}H-nmr 6.95 (s, 1H), 6.2 (d, J=4Hz, 1H), 6.0 (d, J=4Hz, 1H), 5.75(s, 1H), 3.8 (s, 3H), 3.75 (s, 3H), 3.65 (s, 3H), 2.85 (s, 6H, NMe_2).

b) **At reflux temperature**. The reaction of DMAD (1.5 g, 0.1mol) with the hydrazone **3** in chloroform (20 ml) at reflux temperature and working up as above gave a syrup which was chromatographed using hexane-ethyl acetate (9:1). The first compound eluted was the nitrile **8b** (0.28 g, 21.5%) as an oil. Anal. Calc for $C_{12}H_{12}N_2O_4$ C, 58.06 H, 4.83; N, 11.29. Found: C, 58.19; H, 4.81; N, 11.05. Ir 2220, 1720 cm^{-1}. ^{1}H-nmr 7.2 (s, 1H), 6.75 (d, J=4Hz, 1H), 6.1 (d, J=4Hz, 1H) 3.85 (s, 3H), 3.7 (s, 3H), 3.6 (s, 3H). Further elution gave the isomer **8a** (0.2 g, 15.4%), mp 102-103 °C (colorless needles, recrystallized from hexane-dichloromethane); Found: C, 57.9; H, 4.7; N, 11.08. Ir 2220,1730 cm^{-1}. 1H-nmr 6.7 (d, J=4Hz, 1H), 6.3 (d, J=4Hz, 1H), 6.1 (s, 1H), 3.8 (s, 3H), 3.75 (s, 6H).

Furfural N,N-dimethylhydrazone: Chromatography of the crude product obtained after evaporation of the solvent (1.4 g), using hexane-ethyl acetate (5:1) as an eluant gave 2-furylcarbonitrile **11** (0.034 g,). The second compound eluted was the adduct **10** (0.467 g, 35%), mp 60-61 °C (yellow needles recrystallized

from hexane). Anal. Calc for $C_{13}H_{14}N_2O_5$ C, 55.86; H, 5.66; N, 9.81. Found: C, 55.71; H, 5.71; N, 10.0. Ir 1733 cm^{-1}. ^{1}H-nmr 11-10.5 (bs, 1H), 7.75 (d, J=9Hz, 1H), 6.75 (d, J=9Hz, 1H), 6.7 (s, 1H), 3.7 (s, 6H), 2.8 (s, 6H). ^{13}C-nmr 169.2 (s), 168.7 (s), 160.7 (s), 132.4 (d), 131.9 (s) 127.2 (d), 126.2 (s), 119.2 (d), 108.8 (s), 52.6 (q), 52.0(q), 42.3 (q). Further elution gave the starting material **4** (0.26 g) and then the amino compound **6** (0.53g).

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