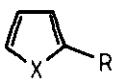
STUDIES ON DIMETHYLHYDRAZONES OF HETEROARYL ALDEHYDES. THE REACTIVITY OF 2-FORMYLFURAN, 2-FORMYLTHIOPHENE AND 1-METHYL-2-FORMYLPYRROLE N,N-DIMETHYLHYDRAZONES WITH METHYL PROPIOLATE AND DIETHYL AZODICARBOXYLATE

Belén Abarca*, Rafael Ballesteros, Eugenia González, Pedro Sancho, José Sepúlveda, and Concepción Soriano

Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, Avda. Blasco Ibañez 13, 46010-Valencia, Spain

Abstract- The title hydrazones react with methyl propiolate giving the new 2-heteroarylpyridines (4,5 and 6).The reaction with diethyl azodicarboxylate gives 1:1 Michael adducts except with formylthiophene hydrazone that gives the compound (14) a novel type of 1:1 adduct.

Several reports from this laboratory have described[1] cycloaddition reactions of vinyl derivatives of five-membered heterocycles under a variety of reaction conditions. The presence of a nitrogen atom in the diene system showed new possibilities of synthesis of heterocyclic compounds when the reactivity of the hydrazones (1, 2, and 3) was studied towards dimethyl acetylenedicarboxylate (DMAD).[2] In this work we have studied the reactivity of the mentioned compounds, with methyl propiolate (MP) and diethyl azodicarboxylate (DEAD).



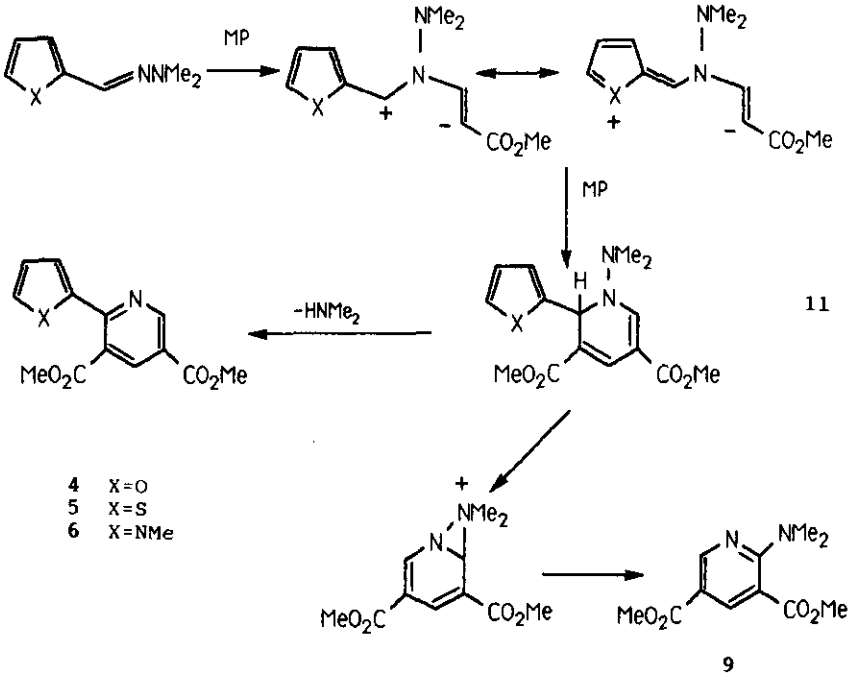
1 X=O,R=-CH=NNMe$_2$
2 X=S,R=-CH=NNMe$_2$
3 X=NMe,R=-CH=NNMe$_2$
7 X=S,R=-CN
8 X=NMe,R=-CN

Reactions of the hydrazones (1, 2, and 3) with MP were slower than those with DMAD. The reactions were accompanied by polymer formation. The reaction mixtures were very difficult to handle. After careful chromatographic purification, it was possible to characterize the different compounds formed in each case.
With the hydrazone (1) no Diels-Alder cycloadduct to the furan ring was formed. A surprising compound was isolated in low yield. The elemental analysis gave

the formula $C_{13}H_{11}NO_5$. The ^{13}C nmr showed clearly the presence of two methyl ester groups (δ 167.72, 164.66, 52.57 and 52.33 ppm), accompanied by nine aromatic carbon signals, and the absence of the dimethylamino group. The ^1H nmr showed five signals in the aromatic region integrating for one proton each, two coupled doublets at δ 9.20 and 8.40 with coupling constant of 2 Hz (characteristic pattern for a 2,3,5-trisubstituted pyridine), two doublets at δ 7.55 (J=1.5 Hz) and 7.20 (J=3.5 Hz) and a double doublet at δ 6.55 (J=1.5, 3.5 Hz), which agree well with those expected for a monosubstituted furan. All these data are consistent with 2-(2-furyl)-3,5-dimethoxycarbonylpyridine (**4**).

To account for the formation of compound (**4**), we assume that the furfural dimethylhydrazone initiates the nucleophilic attack by the imino nitrogen to the most electrophilic position in MP, leading to a zwitterionic intermediate which undergoes a 1,4-dipolar cycloaddition with another molecule of MP. Elimination of dimethylamine gives aromatization, producing the pyridine ring, (Scheme I).

To the best of our knowledge, this is the first example of synthesis of a pyridine from an aldehyde dimethylhydrazone. The closest analogy found in the literature is the reaction of acetone N,N-dimethylhydrazone with DMAD giving a dihydropyridine.[3]



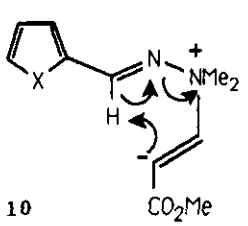
Scheme I

The 2-thienyldimethylhydrazone (2) reacted hardly with MP to give the pyridine (5) in 16% yield and the nitrile (7) as a major compound. Also the reaction of 1-methyl-2-pyrrolyldimethylhydrazone (3) with MP gave a pyridine compound (6) in 7% yield as well as the cyano compound (8). No Michael adduct was found, but another compound was isolated in very low yield. Analysis gave a molecular formula $C_{11}H_{14}N_2O_4$ and the ^1H nmr and ^{13}C nmr data suggested the structure (9) for this compound (see the experimental sections).

The formation of the nitriles could be explained by the attack of the dimethylamino nitrogen to yield zwitterion (10), which undergo N-N$^+$ bond fission, via a cyclic transition state, in a similar way as we reported in the reactions with DMAD.[2] The pyridines (4,5,and 6) could be formed if the reaction goes by attack on the imino nitrogen as we discuss above. Compound (9) should formed also by the attack of the imino nitrogen when the intermediate (11) undergoes a intramolecular Michael addition with elimination of methylpyrrole and aromatization (Scheme 1).

In connection with this research, we also report the behaviour of the dimethyl hydrazones (1, 2, and 3) to DEAD as dienophile. Unexpected results are obtained. In the reaction of the furfural hydrazone (1), two compounds were isolated, the diethyl hydrazodicarboxylate and a compound with molecular formula $C_{13}H_{20}N_4O_5$. The ^1H nmr and the ^{13}C nmr data suggested this product to be the Michael adduct (12). Potts and Walsh[4] have also found Michael adducts in the reaction of the furfural hydrazone with some quinones.

The 1-methyl-2-pyrrolyl aldehyde dimethylhydrazone (3) reacted easily with DEAD to give the Michael adduct (13) in a moderate yield (63%). The reaction with 2-thienylhydrazone (2) needed harder conditions, and gave a mixture of two compounds, one being identified as the well known diethyl hydrazodicarboxylate. The elemental analysis of the other was compatible with a 1:1 adduct. The ir spectrum of the compound showed absortions at 3350, 1750 and 1740 cm^{-1} indicating the presence of one NH group and two nonequivalent carbonyl groups.



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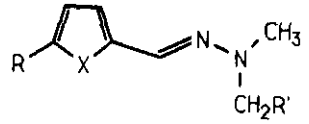

12 X=O;R=-N(CO$_2$Et)-NH(CO$_2$Et);R'=H
13 X=NMe;R=-N(CO$_2$Et)-NH(CO$_2$Et);R'=H
14 X=S;R=H;R'=-N(CO$_2$Et)-NH(CO$_2$Et)

The ^{1}H and ^{13}C nmr spectra furnished a conclusive evidence that the isolated adduct was the compound (14), with a characteristic signal at δ 72.0 ppm due to the $N-CH_2-N$ group. Although tertiary amines react giving similar adducts[5] no examples are known for N,N-dimethylhydrazones. The mechanism generally described for this reaction, involves an initial coordination of the tertiary amine nitrogen with the electrophilic azo group. The resulting ion pair can then produce the structure actually formed by an ylide rearrangement. Another reasonable explanation would involve an initial single electron transfer from tertiary nitrogen to azo ester forming two ion radicals. Transfer of a hydrogen atom from the readily accessible methyl group would then afford two charged species which could easily unite to form the observed product.[5g] Both mechanisms would explain our result.

EXPERIMENTAL

Mps were determined on a Kofler heated stage and are uncorrected. Column chromatography was performed on Merck silica gel. Plc was on plates 20x20 cm, of Merck silica gel 60 PF_{254}. Hplc was performed on a Waters instrument, using a semipreparative silica Porasil column, eluting with a mixture of hexane and ethyl acetate. ^{1}H and ^{13}C spectra were recorded using a Bruker WP-80 or AC-200. Ir were determined with a Perkin-Elmer 843 spectrophotometer.

Reaction of furfural N,N-dimethylhydrazone with methyl propiolate.- To a solution of hydrazone (1) (0.8 g, 5 mmol) in chloroform (10 ml), a solution of methyl propiolate (1.38 g, 14.4 mmol) in chloroform (10 ml) was added dropwise. The mixture was heated at reflux for 54 h, and then was cooled. The solvent was evaporated and the residue was purified by column chromatography (eluent; hexane with increasing amounts of ethyl acetate). The first fraction eluted was starting hydrazone (0.22 g). The second one was trimethyl 1,3,5-benzenetricarboxylate (0.07 g, 2 %). The following fraction was 2-(2-furyl)-3,5-dimethoxycarbonylpyridine (4) (0.15 g,10 %). mp 78-80°C (hexane). Found: C,59.60; H,4.16; N,5.06: $C_{13}H_{11}NO_5$ requires C,59.77; H,4.21; N,5.36. ^{1}HNmr $\delta(CDCl_3)$ 9.20(1H, d, J=2 Hz); 8.40(1H, d, J=2 Hz); 7.55(1H, d, J=1.5 Hz); 7.20(1H, d, J=3.5 Hz); 6.55(1H, dd, J=1.5, 3.5 Hz); 3.92(3H, s), 3.90(3H, s).^{13}CNmr $\delta(CDCl_3)$ 167.72 (s), 164.66(s), 151.59(d), 149.21(s), 144.97(d), 137.89(d), 134.43(s), 124.83(s), 123.28(s),

113.66(d), 112.31(d), 52.57(q), 52.33(q). Ir $\nu_{max.}$(CCl_4) 3000, 2950, 1730 cm^{-1}.

Reaction of 2-formylthiophene N,N-dimethylhydrazone with methyl propiolate.- A solution of the hydrazone (2) (1 g, 6.5 mmol) and methyl propiolate (2.1 g, 26 mmol) in dichloromethane (25 ml) was heated in a sealed tube at 150°C during 15 days. Evaporation gave crude product (3.1 g), which was purified by column chromatography (eluent; hexane and increasing amounts of ethyl acetate). The first fraction was 2-thienylcarbonitrile (7) (140 mg, 20 %). The second fraction was a mixture, which was separated by hplc (eluent; hexane:ethyl acetate= 1:1). First fraction eluted was trimethyl 1,3,5-benzenetricarboxylate (860 mg, 14 %). The second product eluted was 2-(2-thienyl)-3,5-dimethoxycarbonylpyridine (5) as an oil (300 mg, 16 %) (retention time 16 min). Found: C,56.60; H,4.07; N,5.30: $C_{13}H_{11}NO_4S$ requires C,56.31; H,3.97; N,5.05. ^{1}HNmr δ ($CDCl_3$) 9.10(1H, d, J=2 Hz); 8.40(1H, d, J=2 Hz); 7.60-7.30(2H, m); 7.05(1H, dd, J=4, 5 Hz); 4.00 (3H, s); 3.90(3H, s). Ir ν_{max} (CCl_4) 1720, 1240, 700 cm^{-1}.

Reaction of 1-methyl-2-formylpyrrole N,N-dimethylhydrazone with methyl propiolate.- A solution of the hydrazone (3) (1 g, 6.6 mmol) and methyl propiolate (0.556 g, 6.6 mmol) in chloroform (10 ml) was heated in a sealed tube at 100°C during 22 h. The solvent was evaporated and the residue was purified by column chromatography (eluent; hexane:ethyl acetate=9:1). The first fraction was 2-(1-methylpyrrolyl)carbonitrile (8) (0.14 g, 20 %);[6] the second was N-methyl-2-pyrrolyl-3,5-dimethoxycarbonylpyridine (6) as an oil (0.13 g, 7 %). ^{1}HNmr δ ($CDCl_3$) 9.00(1H, d, J=2 Hz); 8.30(1H, d, J=2 Hz); 6.70-6.55 (1H, m); 6.30-6.15 (1H, m); 6.10-5.95(1H, m); 3.80(3H, s); 3.70(3H, s); 3.65(3H, s). Ir ν_{max}(CCl_4) 2880, 1720, 1250 cm^{-1}. The following fraction was 2-dimethylamino-3,5-dimethoxycarbonylpyridine (9) (0.05 g, 3 %). mp 75°C (hexane). Found: C,55.36; H,5.69; N,11.51: $C_{11}H_{14}N_2O_4$ requires: C,55.66; H,5.88; N,11.76. ^{1}HNmr δ ($CDCl_3$) 8.77 (1H, d, J=2 Hz); 8.44(1H, d, J=2 Hz); 3.87(3H, s); 3.85(3H, s); 3.07(6H, s). ^{13}CNmr δ ($CDCl_3$) 187.16(s); 185.85(s); 159.62(s); 152.06(d); 141.79(d); 109.40 (s); 52.26(q); 51.76(q); 40.70(q). Further elution gave (E)-methyl-3-dimethylamino acrylate (0.13 g).[7]

Reaction of 2-furfural N,N-dimethylhydrazone with diethyl azodicarboxylate.- A solution of hydrazone (1) (2 g, 14 mmol) and diethyl azodicarboxylate (2.52 g,

14 mmol) in dry toluene (15 ml) was boiled for 3 h. Then the solvent was evaporated to give a crude product (5.29 g), which was purified by column chromatography (eluent; hexane:ethyl acetate=1:1). The first fraction eluted was hydrazone (1) (200 mg). The second fraction was a mixture of two products, which was separated by crystallization from CCl_4: one product was diethylhydrazodicarboxylate (440 mg); and the other was product (12) (1.2 g, 42 %). mp 77-79°C (petroleum ether, 40-60°C). Found: C,50.01; H,6.39; N,17.77; $C_{13}H_{20}N_4O_5$ requires C, 50.00; H,6.41; N,17.94. ^{1}HNmr $\delta(CCl_4)$ 7.11(1H, br s); 6.97(1H, s); 6.30-6.28(2H, m); 4.15(2H, q, J=7 Hz); 4.15(2H, q, J=7 Hz); 2.91(6H, s); 1.20(3H, t, J=7 Hz); 1.20(3H, t, J=7 Hz). ^{13}CNmr $\delta(CDCl_3)$ 156.62(s), 155.56(s), 149.16(s), 145.38(s), 122.60(d), 108.06(d), 106.69(d), 63.60(t), 62.25(t), 42.66(q), 14.40 (q), 14.40 (q), 14.31(q). Ir ν_{max} (CCl_4) 3300, 3290, 1720, 1700 cm^{-1}. Ms(%) 313 (15); 312 (100)(M^+); 239 (68)(M^+-CO_2Et).

Reaction of 1-methyl-2-formylpyrrole N,N-dimethylhydrazone with diethyl azodicarboxylate.- To a solution of hydrazone (3) (1 g, 6.6 mmol) in dichloromethane (10 ml), a solution of diethyl azodicarboxylate (1.14 g, 6.6 mmol) in dichloromethane (10 ml) was added dropwise. The mixture was stirred for 24 h at room temperature. Then the solvent was evaporated and the crude product (2.63 g) was purified by column chromatography (eluent; hexane: ethyl acetate= 1:1). The compound isolated was (13) (1.36 g,63 %). mp 105-107°C (CCl_4). Found C,51.59; H, 7.07; N,21.54: $C_{14}H_{23}N_5O_4$ requires C,51.69; H,7.07; N,21.53. ^{1}HNmr $\delta(CDCl_3)$ 7.30 (1H, s); 7.15(1H, s); 6.15-5.95(2H, m); 4.15(4H, q, J=8 Hz); 3.70(3H, s); 2.85 (6H, s); 1.29(6H, t, J=8 Hz). ^{13}CNmr $\delta(CDCl_3)$ 155.82(s), 155.69(s), 131.10(s), 128.29(d), 128.11(s), 108.50(d), 104.84(d), 63.04(t), 61.83(t), 42.82(q), 31.42 (q), 14.21(q). Ir ν_{max} (CCl_4) 3400, 3300, 3000, 1730 cm^{-1}.

Reaction of 2-formylthiophene N,N-dimethylhydrazone with diethyl azodicarboxylate.- A solution of the hydrazone (2) (150 mg, 0.97 mmol) and diethylazodicarboxylate (169 mg, 0.97 mmol) in dry toluene (15 ml) was boiled for 15 days. Then the solvent was evaporated to give crude producte (230 mg), which was purified by column chromatography (eluent; hexane: ethyl acetate=4:1). The first fraction (100 mg) was a mixture of hydrazone (2) and diethyl azodicarboxylate. The second fraction was a mixture, which was separated by chromatotron with silica gel plate (eluent; hexane and increasing amounts of ethyl acetate). The

first product eluted was compound (14) (40 mg, 13 %). mp 83-84°C (petroleum ether). Found: C,47.63; H,5.92; N,16.92: $C_{13}H_{20}N_4O_4S$ requires C,47.56; H,6.10; N,17.07. ^{1}HNmr $\delta(CCl_4)$ 7.20(1H, s); 7.00-6.70(3H, m); 6.55(1H, br s); 4.85(2H, s); 4.20-3.60(4H, m); 2.90(3H, s); 1.15(3H, t, J=7 Hz); 1.15(3H, t, J=7 Hz). ^{13}CNmr $\delta(CDCl_3)$ 155.98(s); 155.51(s); 142.17(s); 128.57(d); 126.99(d); 125.15 (d); 124.53(d); 71.88(t); 62.67(t); 61.93(t); 35.73 (q); 14.43(q); 14.25(q). Ir ν_{max} (CCl_4) 3420, 2981, 1752, 1718 cm^{-1}. The second product was diethyl hydrazodicarboxylate (35 mg, 23 %).

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REFERENCES

1. R. A. Jones, M. T. P. Marriott, W. P. Rosenthal, and J. Sepúlveda, J.Org. Chem., 1980, 45, 4515; R. A. Jones, P. Martinez, T. Aznar, and J. Sepúlveda, Tetrahedron, 1984, 40, 4837; R. A. Jones, T. Aznar, and J. Sepúlveda, J.Chem. Soc.,Perkin Trans.I, 1984, 2541; B. Abarca, R. Ballesteros, E. Enriquez and G. Jones, Tetrahedron, 1985, 41, 2435; Ibid., 1987, 43, 269; B. Abarca, R. Ballesteros, and C. Soriano, Tetrahedron, 1987, 43, 991; M. Medio and J. Sepúlveda, Tetrahedron, 1986, 42, 6683.
2. M. E. González, P. Sancho, C. Soriano, R. Ballesteros, B. Abarca, and J. Sepúlveda, Heterocycles, 1988, 27, 1227.
3. S. F. Nelsen, J.Org.Chem., 1969, 34, 2248.
4. K. T. Potts and E. B. Walsh, J.Org.Chem., 1988, 53, 1199.
5. a) O. Diels and M. Paquin, Ber., 1913, 46, 2000; b) O. Diels and P.Pritzsche ibid., 1911, 44, 3018; c) G. W. Kenner and R. J. Stedman, J.Chem.Soc., 1952, 2089; d) H. Huisgen and F. Jakob, Liebigs Ann.Chem., 1954, 590, 37; e) E. E. Smissman and A. Makriyannis, J.Org.Chem., 1973, 38, 1652; f) H. F. Campbell, O. E. Edwards, and R. Kolk, Can.J.Chem., 1977, 55, 1372; g) R. L. Clarke, A. J. Gambino, and M. L. Heckeler, J.Org.Chem., 1978, 43, 4589.
6. Y. Tamura, M. Adachi, T. Kawasaki, H. Yasuda, and Y. Kita, J.Chem.Soc., Perkin Trans.I, 1980, 1132.
7. R. Huisgen, K. Herbig, A. Siegl, and H. Huber, Ber., 1966, 99, 2526.

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