REARRANGEMENTS OF N-UREIDOPYRROLES: A CASE OF MONONUCLEAR HETEROCYCLIC REARRANGEMENT INVOLVING AN AROMATIC HETEROCYCLE AS CARBON-NITROGEN-NITROGEN SEQUENCE

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Abstract - The rearrangement, under basic conditions, of the N-ureidopyrroles (8) directly led to the pyrrolylalkenes (14). The reaction was explained in terms of initial mononuclear heterocyclic rearrangement leading to the pyrrolo[1,2-c][1,2,3]-triazoles (12) followed by their decomposition to the final products under the reaction conditions. Attempts to thermally rearrange compound (8b) only gave products of decomposition of the ureido moiety.

The mononuclear heterocyclic rearrangements (mhr) represented by the general Scheme 1→2[1] have shown to be a versatile tool to synthesize heterocyclic systems. This is especially due to the availability of several sequences in the XYZ side chain.[2]

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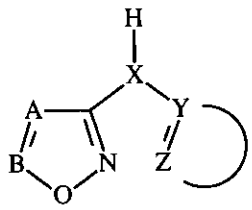
When the side chains are incorporated in an aromatic or heteroaromatic ring the mhr leads to condensed heterocyclic systems. Thus annelation to the Y-Z bond gives rise to the rearrangement 3→4.[3,4]



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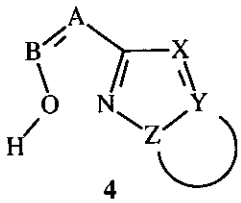

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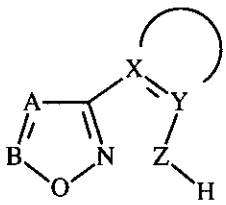

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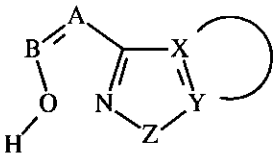

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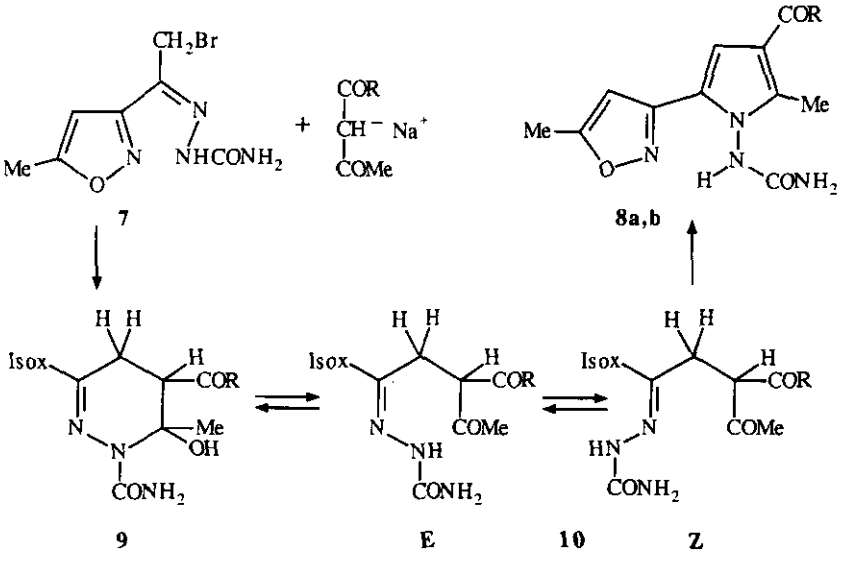
Annelation to X-Y bond, instead, originates the condensed heterocycles (6) by rearrangement of 5. Examples of this type of rearrangement are represented by 1,2,4-oxadiazole derivatives bearing as side chains aromatic or heteroaromatic C-amino moieties which play the role of CCN sequence.[5-7] While C-amino heterocycles (CCN sequence) originate condensed pyrazole systems, N-amino heterocycles (CNN sequence) should give rise to condensed 1,2,3-triazole derivatives. Considering that pyrrolotriazole derivatives have shown herbicide activity[8] and in connection with our studies on polycondensed nitrogen heterocycles[3] with potential biological activity,[9] we became interested in the synthesis of 1H-pyrrolo[1,2-c][1,2,3]triazoles by mhr using as starting material the isoxazolyl-N-ureidopyrroles (8), in which the 3-position of the isoxazole ring bears a side chain with a CNN sequence where the C-N bond is part of a pyrrole nucleus. This approach to the polycondensed system should allow the isolation of derivatives with a 10 π-electron conjugated system whereas the syntheses reported so far always produced non-aromatic derivatives.[10-15]

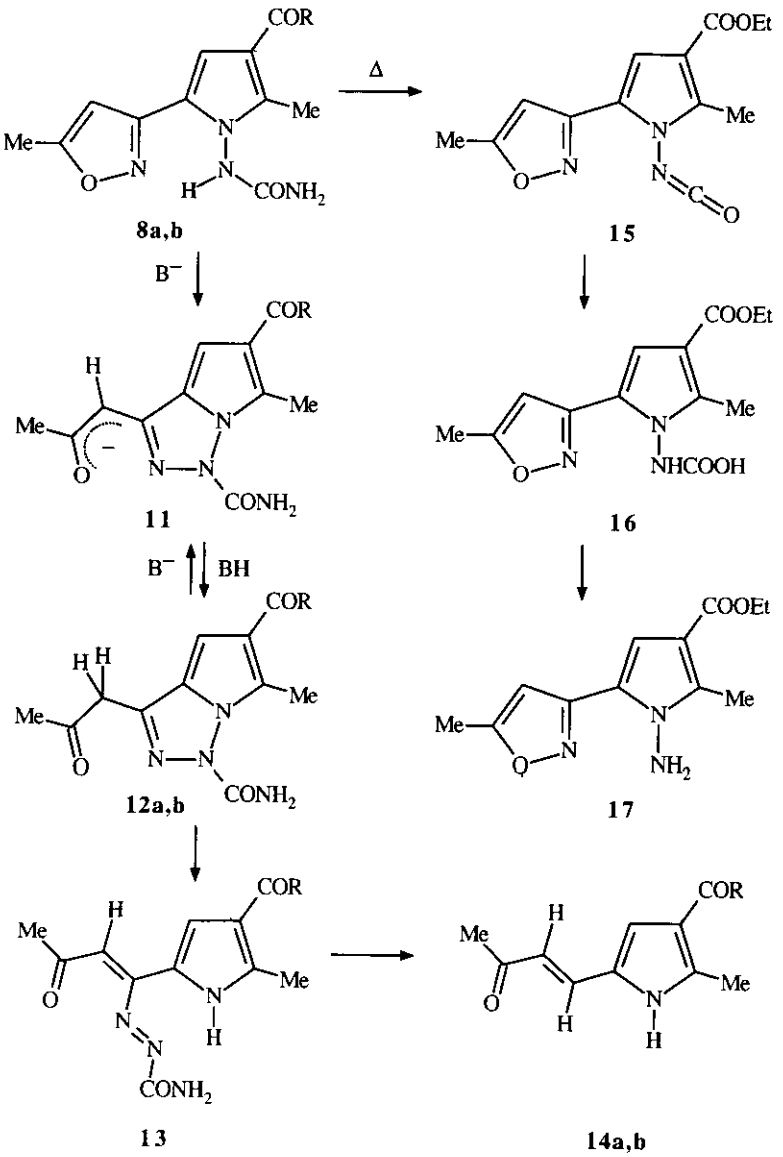
Thus reaction of the semicarbazone of the bromoacetylisoxazole (7) with the sodium salts of ethyl acetoacetate or acetylacetone directly led, in high yields, to the N-ureidopyrroles (8a,b) through the intermediacy of the carbinolamines of type (9) that undergo ring opening to 10, E to Z isomerization and ring closure processes.[16]



a: R = OEt; b: R = Me

The structure of compounds (8) was confirmed by elemental analysis and spectral data. In fact the ir spectra showed strong and broad absorptions at 3440-3380 cm^{-1} and 3300-3200 cm^{-1} due to the NH_2 and NH stretchings. The ^1H nmr spectra showed the pyrrole H-4 at δ 6.90-7.05, the isoxazole H-4 at δ 6.47-6.52, the NH_2 and NH at δ 6.30 and δ 9.38-9.39 respectively. The rearrangement of isoxazolyl-N-ureidopyrroles (8a,b) was carried out in refluxing DMF with potassium t-butoxide as the base to afford a single product which showed in the mass spectrum a parent peak 71 daltons below the values expected for the 1H-pyrrolo[1,2-c][1,2,3]triazoles (M^+=292 for 12a and M^+=262 for 12b). The ^1H nmr spectra showed a broad exchangeable singlet at δ 11.87-11.92 for a NH proton, a doublet (J=2.0 Hz) at δ 6.84-6.99 which became a singlet upon exchange with deuterium oxide,

typical of a pyrrole β proton, an AB system quartet (ν_A δ 7.34 and ν_B δ 6.48, J=16.2 Hz) typical of a trans CH=CH group and signals compatible with two methyl and one ethoxy groups in the case of derivative a and three methyl groups in the case of derivative b. The ^{13}C nmr spectra



a: R = OEt; b: R = Me

showed three doublets at ca 117, 121 and 133 ppm due to the pyrrole C-4 and to the ethylene carbon atoms respectively, five singlets compatible with the presence of two carbonyl groups, two quaternary pyrrole α carbons and one quaternary pyrrole β carbon. The ir spectra beside the NH stretchings at 3240-3200 cm^{-1} showed two carbonyl absorptions in the range 1695-1620 cm^{-1}. On the basis of these data the product was assigned the structure trans-acetylpyrrolylethenes (14a,b).

The formation of compounds (14) was explained in terms of rearrangement of the anion of the ureido moiety of 8 by intramolecular nucleophilic attack to the isoxazole nitrogen. The resulting intermediate (11) can isomerize to the azocarbonyl structure (13) which, under the reaction conditions, decomposes to the final product. With the aim to isolate the 1H-pyrrolotriazole intermediate (12) or the azoacyl derivative (13) the reaction was repeated under a wide range of temperature (20 - 100°C) but only unreacted starting material was recovered.

Since 1,2,4-oxadiazole derivatives bearing a semicarbazone side chain in some instances gave thermally induced mhr products,[17] we attempted a thermal rearrangement although the isoxazole nucleus is less prone than the oxadiazole system. Thermal rearrangement of compound (8a) failed. In this case only decomposition of the ureido moiety was observed and derivatives (16) and (17) were isolated. Their formation probably goes through the intermediate isocyanate (15).[18]

Therefore the isolation of compounds (14) is indicative of the occurrency of the mhr under basic conditions. However the pyrrolotriazoles (12) undergo, in the same basic conditions, ready N-N bond rupture brought about either by the electron withdrawing effect of the β-carbonyl group of the pyrrole ring or by the conjugation with the acetonyl anion. The failure of the thermal rearrangement is consistent with the low nucleophilicity of the ureido NH.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary apparatus; ir

spectra were determined in bromoform with a Jasco FT/IR 5300 spectrophotometer; ^{1}H and ^{13}C nmr spectra were measured at 250 and 62.8 Mz respectively in $(CD_3)_2SO$ solution using a Bruker AC-E series 250 Mz spectrometer (TMS as internal reference); mass spectra were obtained with a JEOL JMS-01 SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 Kv accelerating voltage. Column chromatography was performed with Merk silica gel 230-400 mesh ASTM.

Preparation of 3-ethoxycarbonyl- and 3-acetyl-2-methyl-5-(5-methylisoxazol-3-yl)-1-ureidopyrroles (8a,b).

To a mixture of sodium ethoxide (0.14 g, 20 mmol) in ethanol (30 ml) and ethyl acetoacetate or acetylacetone (20 mmol), the semicarbazone of the 3-bromoacetyl-5-methylisoxazole[19] (0.52 g, 20 mmol) was added in small portions with stirring and cooling (ice bath). After 30 min the mixture was acidified with ethanolic hydrogen chloride and refluxed for 15 min. After cooling the resultant solution was poured onto crushed ice. The solid precipitate was filtered off, air dried and recrystallized from ethanol.

Compound (8a) (R=OEt) (yield 85%), mp 270°C; ir: 3440, 3300 and 3260 (NH_2 and NH), 1690 and 1670 (CO) cm^{-1}; ^{1}H nmr δ: 1.28 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 2.37 (3H, s, pyrrole CH_3), 2.42 (3H, d, J=0.7 Hz, isoxazole CH_3), 4.21 (2H, q, J=7.0 Hz, $\underline{CH_2}CH_3$), 6.30 (2H, s, exchangeable NH_2), 6.52 (1H, d, J=0.7 Hz, isoxazole CH), 6.90 (1H, s, pyrrole CH), 9.38 (1H, s, exchangeable NH); ^{13}C nmr δ: 10.32 (q), 11.65 (q), 14.33 (q), 59.18 (t), 100.35 (d), 109.34 (d), 109.84 (s), 121.18 (s), 140.43 (s), 154.33 (s), 156.93 (s), 163.81 (s), 168.71 (s); ms m/z: M^+= 292. Anal. Calcd for $C_{13}H_{16}N_4O_4$: C, 53.42; H, 5.52; N, 19.17. Found: C, 53.40; H, 5.50; N, 19.21.

Compound (8b) (R=Me) (yield 80%), mp > 300°C; ir: 3380, 3260 and 3200 (NH_2 and NH), 1670 and 1640 (CO) cm^{-1}; ^{1}H nmr δ: 2.35 (3H, s, pyrrole CH_3), 2.37 (3H, s, $COCH_3$), 2.42 (3H, d, J=0.7 Hz, isoxazole CH_3), 6.30 (2H, s, exchangeable NH_2), 6.47 (1H, d, J=0.7 Hz, isoxazole CH), 7.05 (1H, s, pyrrole CH), 9.39 (1H, s, exchangeable NH); ^{13}C nmr δ: 10.58 (q), 11.62

(q), 28.13 (q), 100.30 (d), 110.09 (d), 118.74 (s), 121.74 (s), 139.40 (s), 154.37 (s), 156.84 (s), 168.68 (s), 193.54 (s); ms m/z: M^+= 262. Anal. Calcd for $C_{12}H_{14}N_4O_3$: C, 54.95; H, 5.38; N, 21.37. Found: C, 54.88; H, 5.40; N, 21.34.

Rearrangement of Compounds (8a,b) under Basic Conditions: trans-1-Acetyl-2-(3-ethoxycarbonyl- and 3-acetyl-2-methylpyrrol-5-yl)ethene (14a,b).

A solution of compounds (8a,b) (20 mmol) and potassium t-butoxide (0.22 g, 20 mmol) in anhydrous DMF (10 ml) was refluxed until the tlc showed no starting material (15 min). After cooling the solution was poured onto crushed ice and the pH was adjusted to ca 7 with acetic acid. The solid precipitate was filtered off, air dried and purified by chromatography using dichloromethane:ethyl acetate 2:1 as eluant.

Compound (14a) (R=OEt) (yield 85%), mp 145°C (ethanol); ir: 3210 (NH), 1695 and 1655 (CO) cm^{-1}; ^1H nmr δ: 1.25 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 2.23 (3H, s, CH_3), 2.46 (3H, s, CH_3), 4.16 (2H, q, J=7.0 Hz, $\underline{CH_2}CH_3$), 6.46 (1H, d, J=16.2 Hz, CH), 6.84 (1H, d, J=2.3 Hz, pyrrole H-4, singlet upon exchange with deuterium oxide), 7.35 (1H, d, J=16.2 Hz, CH), 11.87 (1H, br s, exchangeable NH); ^{13}C nmr δ: 12.97 (q), 14.34 (q), 26.82 (q), 58.99 (t), 113.26 (s), 117.04 (d), 121.57 (d), 126.64 (s), 132.86 (d), 140.22 (s), 163.96 (s), 197.21 (s); ms m/z: M^+= 221. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.12; H, 6.88; N, 6.33.

Compound (14b) (R=Me) (yield 92%), mp 215°C (ethanol); ir: 3240 (NH), 1655 and 1620 (CO) cm^{-1}; ^1H nmr δ: 2.24 (3H, s, CH_3), 2.31 (3H, s, CH_3), 2.46 (3H, s, CH_3), 6.48 (1H, d, J=16.2 Hz, CH), 6.99 (1H, d, J=2.3 Hz, pyrrole H-4, singlet upon exchange with deuterium oxide), 7.34 (1H, d, J=16.2 Hz, CH), 11.92 (1H, br s, exchangeable NH); ^{13}C nmr δ: 13.54 (q), 26.81 (q), 28.18 (q), 117.60 (d), 121.46 (d), 122.38 (s), 126.20 (s), 132.79 (d), 139.53 (s), 193.30 (s), 197.10 (s); ms m/z: M^+= 191. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.12; H, 6.78; N, 7.32.

Attempts to rearrange compounds (8a,b) under the same basic medium at room temperature for several days, at 50°C and 100°C for 6 h failed. In all

cases unreacted starting material was quantitatively recovered.

Thermolysis of Compound (8a).

Compound (8a) (1.17 g, 4 mmol) was heated in an oil bath at 280°C for 2 h. After cooling the solid was dissolved in dichloromethane and chromatographed using dichloromethane:ethyl acetate 4:1 as eluant. The first product eluted was 1-amino-3-ethoxycarbonyl-2-methyl-5-(5-methyl-isoxazol-3-yl)pyrrole (17) (0.45 g, yield 45%), mp 94°C (ethanol); ir: 3340, 3280 and 3120 (NH_2 and NH), 1680 (broad CO) cm^{-1}; ^1H nmr δ: 1.26 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.42 (3H, s, CH_3), 2.50 (3H, s, CH_3), 4.18 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$), 6.00 (2H, s, exchangeable NH_2), 6.72 (1H, s, CH), 6.84 (1H, s, CH); ^{13}C nmr δ: 11.64 (q), 11.72 (q), 14.33 (q), 58.91 (t), 100.94 (d), 108.87 (s), 108.87 (d), 121.16 (s), 138.89 (s), 155.39 (s), 163.94 (s), 168.43 (s); ms m/z: M^+= 249. Anal. Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.89; H, 6.09; N, 16.76.

The second product eluted was [3-ethoxycarbonyl-2-methyl-5-(5-methylisoxazol-3-yl)-pyrrol-1-yl]carbamic acid (16) (0.41 g, yield 35%) mp 268°C (ethanol); ir: 3260 (broad NH and OH), 1700 and 1670 (CO) cm^{-1}; ^1H nmr δ: 1.30 (3H, t, J=7.1 Hz, $CH_2C\underline{H}_3$), 2.32 (3H, s, CH_3), 2.52 (3H, s, CH_3), 4.21 (2H, q, J=7.1 Hz, $C\underline{H}_2CH_3$), 5.98 (1H, s, CH), 6.70 (1H, s, CH), 8.78 (1H, s, exchangeable OH), 9.86 (1H, br s, exchangeable NH); ^{13}C nmr δ: 10.22 (q), 11.63 (q), 14.33 (q), 59.25 (t), 100.41 (d), 110.00 (d), 122.15 (s), 122.32 (s), 140.44 (s), 154.11 (s), 155.06 (s), 163.68 (s), 168.62 (s); ms m/z: M^+= 293. Anal. Calcd for $C_{13}H_{15}N_3O_5$: C, 53.24; H, 5.16; N, 14.33. Found: C, 53.30; H, 5.10; N, 14.22.

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