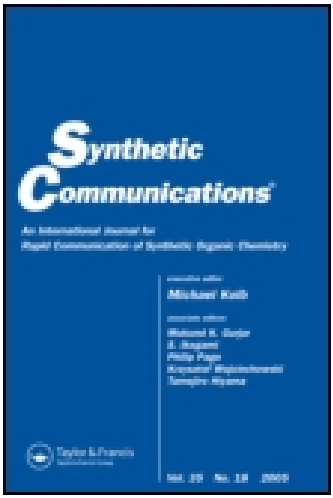

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New Methods of Preparation of Some Polyfunctional Pyrroline Derivatives

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NEW METHODS OF PREPARATION OF SOME POLYFUNCTIONAL PYRROLINE DERIVATIVES

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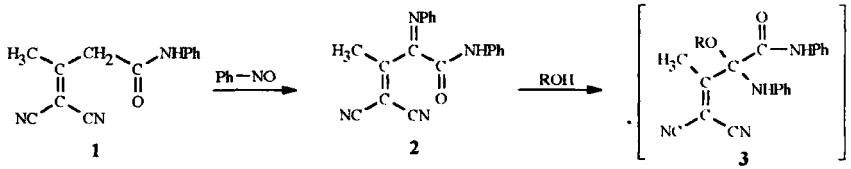
Abstract - The reaction of dicyanomethylene compound **1** with nitrosoarene yields α-imino-β-dicyanomethylidene-α,β-diketobutyric acid anilides **2.** Treatment of **2** with various nucleophiles leads to polyfunctional derivatives of pyrroline system **4-7**.

Recently[1] we have reported chemoselective cyclisation of simple Knoevenagel condensation products, in the presence of base or in acetic acid. In this paper we wish to report a novel route to synthesis of pyrroline system from dicyanomethylene compound **1** [2,3] with very active methylene group, which underwent spontaneous condensation with nitrosoarene giving α-imino-β-dicyanomethylidene-α,β-diketobutyric acid anilide **2**. (Scheme 1)

According to expectations [4,5], the polar C=N bond of the heterodien system of the compound **2** readily reacted with various nucleophiles, affording the non-isolated



Scheme 1

intermediate adducts **3**, which showed markedly high reactivity leading to heterocyclisation products **4-7** [6]. (Scheme 2)

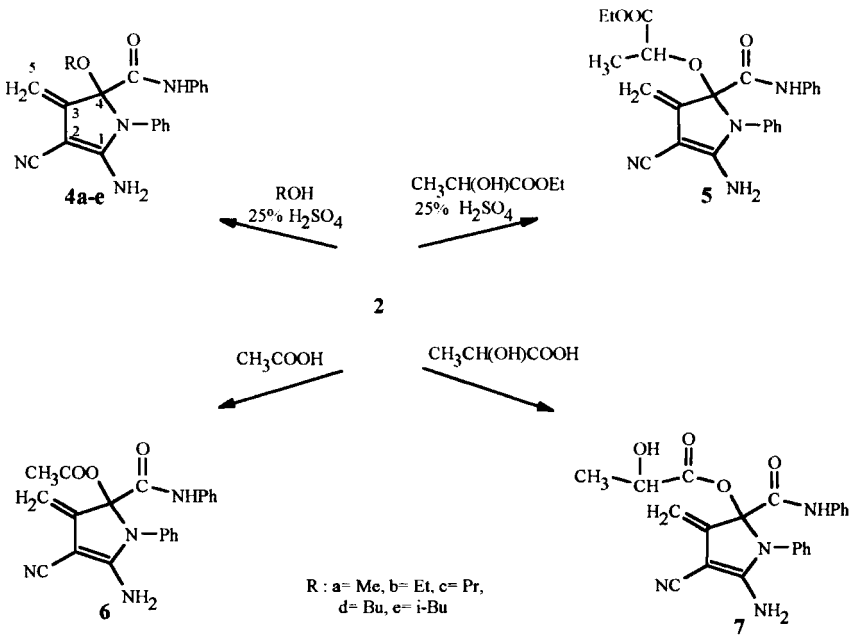
Reactions of **2** with nucleophiles:

a) **Alcohols.** Initial treatment of compound **2** with sulphuric acid and subsequently with alcohols (ethanol, methanol, propanol, butanol, i-butanol) led to the formation of 2-amino, 3-carbonitrile, 5-(ethero, carbamoyl), 4-methylidene, 1-phenylo-pyrroline derivatives **4**. Cyclisation of **3** to **4** took place between α-anilino NH-group, generated in an addition process, and one of the cyano groups, finally pyrroline system was formed.

b) **Hydroxyacids.** Analogically, after treatment of compound **2** with sulphuric acid, then lactic acid ethyl ester, 5-substituted 2-amino, 3-carbonitrile derivatives of pyrroline system **5** were isolated.

c) **Carboxyacids.** On the other hand, direct treatment of α-imino, β-dicyanomethylidene derivatives of α,β-diketobutyric acid **2** with carboxylic acids gave products **6** and **7**.

Structures of obtained products **4-7** were supported by their spectral data. The ir spectra of all compounds revealed the presence of one carbonyl group in the range of 1670 cm^{-1} and strong absorption of (C≡N) group at 2206 cm^{-1}. Absorption in the NH stretching vibration region appears at 3503, 3368 and 3311 cm^{-1}. The structure of five membered pyrroline ring system was strongly confirmed



Scheme 2

by the ^{1}H nmr spectra which exhibited a singlet from two protons at 4.59 ppm (**CH_2**=C), while a signal of NH_2 - two protons appeared at 4.27 ppm, as well as NH from anilide at 9.57 ppm. Moreover, the ^{1}H nmr spectra showed the aromatic protons multiplet and signals of such groups containing protons as methoxy-, ethoxy-, etc. The ^{13}C nmr spectra of compounds **4-7** revealed signals of a carbon atom in position C-1 in five membered ring in the range 147.1-149.3 ppm and C-2 in the range 135.6-136.2 ppm. Double bonded carbon atoms in position C-3 produced signals in the range 121.1-121.6 ppm, but C-5 atom of (**CH_2**=) is the source of a signal in the range 63.4-65.5 ppm, which is in good agreement with analysis of DEPT ^{13}C nmr spectrum of product **4a** [7]. Moreover, the spectra of compounds **4-7** revealed signals in the range of 71.7-75.8 ppm which are

characteristic of the quaternary C-4 carbon atom [4]. The carbonyl carbon singlets were typically positioned at 157.4 ppm and the carbon atom signal of C≡N group appeared at 115.1 ppm. Aromatic carbons were responsible for a number of signals located in the range from 119 to 138 ppm. The mass spectra of compounds **4-7** show correct molecular ions. Electron impact induced fragmentation of these compounds showed loss of the aryl isocyanate and characteristic α,β-cleavage process for heterocyclic rings. All elemental analyses of described compounds are in agreement with their proposed structures.

In conclusion, reaction of compounds **2** with various nucleophiles is a convenient method of synthesis of interesting, polyfunctional pyrroline derivatives. Further applications of this reaction are under intensive investigation.

EXPERIMENTAL

Melting points are measured on Electrothermal 1A9100 digital m. p. apparatus. Nmr spectra were recorded on Bruker AMX 500 in $CDCl_3$ solution using TMS as internal standard. Chemical shifts are reported in ppm downfield from TMS. Ir spectra were recorded on Bruker IFS 48 FT Spectrometer in KBr pellets. Ms were determined at 70 eV on Varian MAT CH-7 spectrometer and microanalyses were carried out on a Perkin-Elmer 240B apparatus.

α-Imino,β-dicyanomethylidene α,β-diketobutyric acid anilide **2**.

The method used [2] was based on condensation reaction of compound **1** (0.001 mol) with nitrosobenzene (0.001 mol) in ethanol solution at 0° C.

2: Yellow crystals, mp 128.3-130.5° C (73%); anal. calc. for $C_{19}H_{14}N_4O$: C 72.61; H 4.46; N 17.83; found C 72.50; H 4.39; N 17.88; ir (ν, cm^{-1}) 1662, 1675, 2238, 3250; ^1H nmr (δ, ppm) 2.36 (s, 3H, CH_3), 6.92-7.74 (m, 10H, 2Ph), 9.23 (s, 1H, NH).

General procedure for preparation of **4-5.**

Ethyl ether solution (15 ml) of **2** (0.001 mol) containing 15 ml of 25% sulphuric

acid was strirred for 1 h, then ethyl ether was removed. The crude product was treated with appropriate alcohol or acid derivative (0.001 mol) and stirred at room temperature for 10 h. Colourless product was purified by LSC (silicagel-chloroform) then crystallized from ethanol.

4a: Colourless crystals, mp 176.6-177.3° C (63%); anal. calc. for $C_{20}H_{18}N_4O_2$ C 69.36; H 5.20; N 16.18; found C 69.64; H 5.32; N 16.06; ir (ν, cm^{-1}) 1668, 2202, 3311, 3368, 3503; ^1H nmr (δ, ppm) 3.61 (s, 3H, CH_3), 4.27 (s, 2H, NH_2), 4.59 (s, 2H, CH_2=), 7.02-7.54 (m, 10H, 2Ph), 9.57 (s, 1H, NH); ms (m/z) 346 (78.7%), 331 (15.8%), 254 (100%), 238 (69.0%), 224 (35.5%).

4b: Colourless crystals, mp 208.7-209.5° C (87%); anal. calc. for $C_{21}H_{20}N_4O_2$ C 70.00; H 5.56; N 15.56; found C 69.73; H 5.55; N 15.47; ir (ν, cm^{-1}) 1670, 2208, 3300, 3331, 3458, ^1H nmr (δ, ppm) 1.402 (t, 3H, CH_3), 3.77 (q, 2H, CH_2), 4.30 (s, 2H, NH_2), 4.63 (s, 2H, CH_2=), 7.02-7.52 (m, 10H, 2Ph), 9.67 (s, 1H, NH); ms (m/z) 360 (42.4%), 331 (32.1%), 268 (27.0%), 240 (50.4%), 238 (100%), 224 (58.0%).

4c: Colourless crystals, mp 177.8-178.6° C (73%); anal. calc. for $C_{22}H_{22}N_4O_2$ C 70.59; H 5.88; N 14.97; found C 70.26; H 5.87; N 15.17; ir (ν, cm^{-1}) 1647, 2209, 3304, 3310, 3405; ^1H nmr (δ, ppm) 1.03 (t, 3H, CH_3), 1.78 (m, 2H, CH_2), 3.66 (t, 2H, CH_2), 4.28 (s, 2H, NH_2), 4.64 (s, 2H, CH_2=), 7.02-7.53 (m, 10H, 2Ph), 9.66 (s, 1H. NH); ms (m/z) 374 (34.6%), 331 (29.6%), 238 (100%), 224 (43.8%).

4d: Colourless crystals, mp 144.4-145.4° C (69%); anal. calc. for $C_{23}H_{24}N_4O_2$ C 71.13; H 6.18; N 14.43; found C 71.06; H 6.11; N 14.62; ir (ν, cm^{-1}) 1654, 2205, 2282, 3438; ^1H nmr (δ, ppm) 0.97 (t, 3H, CH_3), 1.36-2.17 (m, 4H, CH_2-CH_2), 3.69 (t, 2H, CH_2), 4.63 (s, 2H, NH_2), 4.76 (s, 2H, CH_2=), 7.02-7.58 (m, 10H, 2Ph), 9.74 (s, 1H, NH); ms (m/z) 388 (26.5%), 331 (41.0), 238 (100%), 224 (59.8%).

4e: Colourless crystals, mp 191.4-192.4° C (79%); anal. calc. for $C_{23}H_{24}N_4O_2$ C 71.13; H 6.18; N 14.43; found C 71.21; H 6.06; N 14.44; ir (ν, cm^{-1}) 1654, 2206, 3193, 3434; ^1H nmr (δ, ppm) 1.01 (d, 6H, $2CH_3$), 2.04 (m, 1H, CH), 3.46 (d, 2H, CH_2), 4.32 (s, 2H, NH_2), 4.64 (s, 2H, CH_2=), 7.01-7.52 (m, 10H, 2Ph), 9.60 (s, 1H, NH); ms (m/z) 388 (10.3%), 330 (90.6%), 238 (100%), 224 (97.3%).

5: Colourless crystals, mp 198.3-199.7° C (65%); anal. calc. for $C_{24}H_{24}N_4O_4$ C 66.67; H 5.56; N 12.96; found C 66.84; H 5.40; N 12.83; ir (ν, cm^{-1}) 1670, 1729, 2208, 3259, 3332, 3459; ^1H nmr (δ, ppm) 1.28 (t, 3H, CH_3), 1.60 (m, 1H, CH), 2.20 (d, 3H, CH_3), 2.66 (q, 2H, CH_2), 4.29 (s, 2H, NH_2), 4.83 (s, 2H, CH_2=), 7.06-7.59 (m, 10H, Ph), 9.02 (s, 1H, NH); ms (m/z) 432 (3.9%), 360 (57.0%), 331 (58.2%), 268 (100%), 240 (98.0%), 238 (100%), 224 (97.2%).

An analogous procedure was applied for compounds **6,7** but ethyl ether solution of **2** was treated with appropriate acid.

6: Colourless crystals, mp 199.7-201.5° C (92%); anal. calc. for $C_{21}H_{18}N_4O_3$ C 67.38; H 4.81; N 14.97; found C 67.07; H 5.01; N 15.09; ir (ν, cm^{-1}) 1671, 1715, 2209, 3302, 3318, 3465; ^1H nmr (δ, ppm) 2.05 (s, 3H, CH_3), 5.15 (s, 2H, NH_2), 6.21 (s, 2H, CH_2=), 7.01-7.52 (m, 10H, 2Ph), 9.09 (s, 1H, NH); ms (m/z) 374 (64.7%), 331 (15.5%), 315 (23.3%), 240 (100%), 238 (41.3%), 222 (36.2%).

7: Colourless crystals, mp 180.8-182.0° C (76%); anal. calc. for $C_{22}H_{20}N_4O_4$ C 65.35; H 4.95; N 13.86; found C 65.56; H 4.23; N 13.47; ir (ν, cm^{-1}) 1671, 1725, 2209, 3329, 3401, 3514; ^1H nmr (δ, ppm) 1.56 (t, 3H, CH_3), 2.79 (s, 1H, OH), 4.35 (s, 2H, NH_2), 4.48 (m, 1H, CH), 5.35 (s, 2H, CH_2=), 7.06-7.57 (m, 10H, 2Ph), 9.71 (s, 1H, NH); ms (m/z) 404 (28.0%), 332 (25.3%), 315 (24.2%), 240 (100%), 213 (60.1%).

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