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Three-Component Spiro Heterocyclization of 1*H*-Pyrrole-2,3-diones with Malononitrile and Pyrazolones. Crystal and Molecular Structure of a Spiro[pyrano[2,3-*c*]-pyrazole-4,3′-pyrrole]

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Abstract—5-Phenyl-1*H*-pyrrole-2,3-diones reacted with malononitrile and 1*H*-pyrazole-5(4*H*)-ones to give substituted 6-amino-5-cyano-2′-oxo-5′-phenyl-1′,2′-dihydro-1*H*-spiro[pyrano[2,3-*c*]pyrazole-4,3′-pyrroles]. The crystal and molecular structures of ethyl 6-amino-1,1′-dibenzyl-5-cyano-3-methyl-2′-oxo-5′-phenyl-1′,2′-dihydro-1*H*-spiro[pyrano[2,3-*c*]pyrazole-4,3′-pyrrole]-4′-carboxylate were determined by X-ray analysis.

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We previously showed that three-component reactions of 1*H*-pyrrole-2,3-diones with malononitrile and six-membered carbocyclic [1, 2] and heterocyclic enols [3] involve initial condensation of the ketone carbonyl group (C^3=O) of the pyrroledione with the methylene group of malononitrile, followed by nucleophilic addition of the β-CH and OH groups of the enol to the C^3 atom and cyano group. In order to extend the scope of this spiro heterocyclization in the present work we used as heterocyclic enols 1*H*-pyrazole-5(4*H*)-ones. In this case we expected formation of pyrano[2,3-*c*]pyrazole ring system which is known to constitute the base fragment of a number of biologically active compounds exhibiting antimicrobial [4, 5], anti-inflammatory [5–7], cytotoxic [5, 8], antitubercular [9], and other kinds of activity.

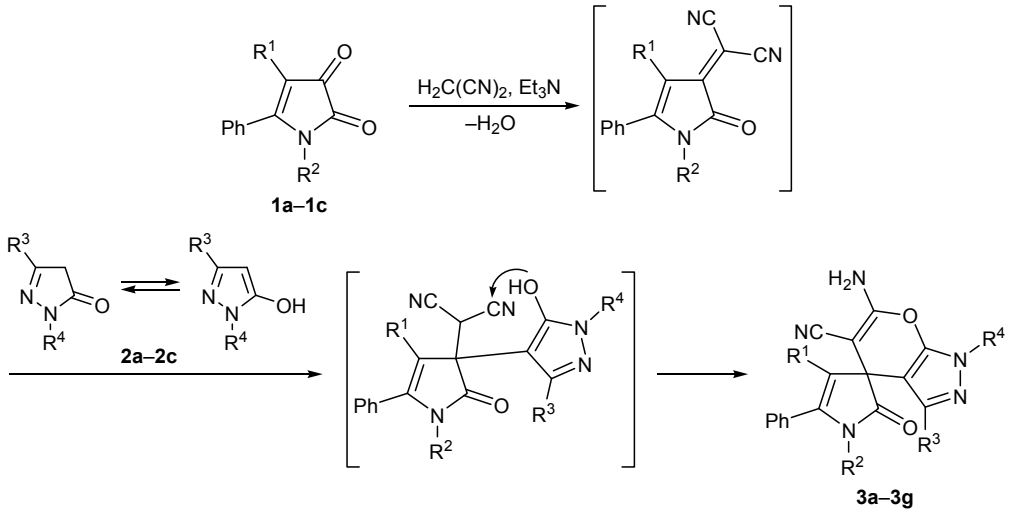
The reactions of ethyl 4,5-dioxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylates **1a** and **1b** and 4,5-diphenyl-1*H*-pyrrole-2,3-dione (**1c**) with malononitrile and 1*H*-pyrazole-5(4*H*)-ones **2a**–**2c** were carried out with equimolar amounts of the reactants in boiling anhydrous toluene in the presence of triethylamine. According to the TLC and HPLC/MS data, the reactions were complete in 20–40 min, and the products were substituted 6-amino-5-cyano-2′-oxo-5′-phenyl-1′,2′-dihydro-1*H*-spiro[pyrano[2,3-*c*]pyrazole-4,3′-pyrroles] **3a**–**3g** [10] (Scheme 1) whose structure was confirmed by the X-ray diffraction data for compound **3b**.

Compounds **3a**–**3g** were isolated as colorless crystalline substances which melted with decomposition at a high temperature and were readily soluble in DMSO, DMF, ethyl acetate, and acetone, sparingly soluble in aromatic hydrocarbons and alcohols, and insoluble in alkanes and water.

The IR spectra of **3a**–**3f** contained absorption bands due to stretching vibrations of the NH_2 and NH (3132–3413 cm^{-1}), cyano (2193–2203 cm^{-1}), and ester (**3a**–**3f**) and lactam carbonyl groups; the latter appeared as one or two broadened peaks (1701–1742 cm^{-1}). Compounds **3a**–**3g** displayed in the ^{1}H NMR spectra signals from protons of the substituents in positions *1*, *1′*, and *3* of the pyrazole and pyrrole rings and aromatic protons, broadened singlets due to protons of the NH_2 (δ 6.73–7.65 ppm) and NH groups (δ 10.44–10.52 ppm) (**3e**–**3g**), and signals corresponding to the ester ethyl group [**3a**–**3d**, δ 0.66–0.74 (t) and 3.66–3.75 ppm (q or m)]. In the ^{13}C NMR spectra of **3b**–**3d**, the lactam and ester carbonyl carbon atoms resonated at δ_C 177.9–178.5 and 160.9–161.5 ppm, respectively, and the spiro carbon signal was observed at δ_C 48.9–49.0 ppm.

Figure shows the structure of compound **3b** according to the X-ray diffraction data. Crystals of **3b** belong to the monoclinic system (centrosymmetric space group). The pyrrole ring and pyranopyrazole ring system are planar within 0.04 and 0.07 Å, respectively. The bond length distribution over the pyrazole ring is

Scheme 1.



1, R^1 = COOEt, R^2 = Bzl (**a**), Cy (**b**); R^1 = Ph, R^2 = H (**c**); **2**, R^3 = Me, R^4 = Ph (**a**), Bzl (**b**); R^3 = R^4 = Ph (**c**); **3**, R^1 = COOEt: R^2 = Bzl, R^3 = Me, R^4 = Ph (**a**); R^2 = R^4 = Bzl, R^3 = Me (**b**); R^2 = Bzl, R^3 = R^4 = Ph (**c**); R^2 = Cy, R^3 = Me, R^4 = Bzl (**d**); R^1 = R^4 = Ph, R^2 = H, R^3 = Me (**e**), R^1 = Ph, R^2 = H, R^3 = Me, R^4 = Bzl (**f**); R^1 = R^3 = R^4 = Ph, R^2 = H (**g**).

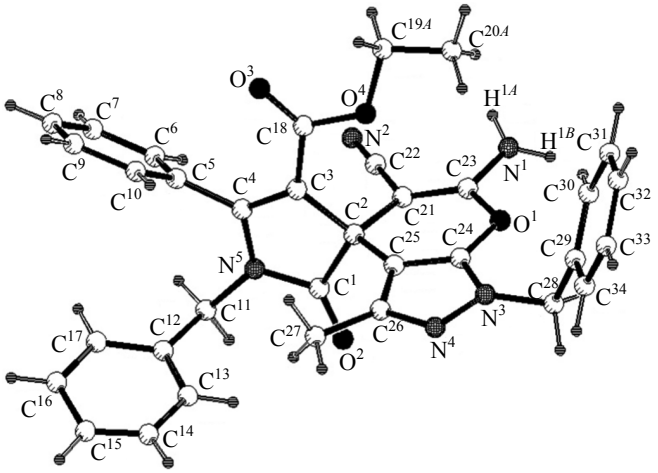
typical of heteroaromatic systems, and the other double bonds are localized. The ethyl group is disordered by two positions with equal populations. Molecules **3b** in crystal are linked to form centrosymmetric dimers through intermolecular hydrogen bonds N^1–$H^{1A}\cdots N^2$ [–*x*, 1 – *y*, –*z*]; $N^1\cdots N^2$ 3.017(3), $H^{1A}\cdots N^2$ 2.09(3), $H^{1A}\cdots N^1$ 0.96(3) Å. The dimers are linked to each other through intermolecular hydrogen bonds N^1–$H^{1B}\cdots N^4$ [1/2 – *x*, 1/2 + *y*, 1/2 – *z*]; $N^1\cdots N^4$ 2.981(2), $H^{1B}\cdots N^4$ 2.12(2), $H^{1B}\cdots N^1$ 0.89(2) Å; as a result, a two-dimensional network parallel to the [–1 0 1] plane is formed.

Presumably, compounds **3a**–**3g** are formed via initial condensation of malononitrile with pyrroledione **1a**–**1c** involving the C^3=O group of the latter, nucleophilic addition of C^4 of pyrazole **2a**–**2c** to C^3 of the condensation product, and intramolecular cyclization of the adduct via nucleophilic attack by the enolic hydroxy group on the cyano group.

The described reaction may be regarded as the first example of three-component spiro heterocyclization of substituted 1*H*-pyrrole-2,3-diones with malononitrile and five-membered heterocyclic enol, which leads to the formation of previously inaccessible spiro[pyrano-[2,3-*c*]pyrazole-4,3′-pyrrole] ring system.

EXPERIMENTAL

The IR spectra were recorded on a Perkin Elmer Spectrum Two spectrometer from samples dispersed in mineral oil. The ^{1}H and ^{13}C NMR spectra were measured on Bruker AM-400 and Bruker Avance III HD 400 spectrometers at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The elemental compositions were determined on a Perkin Elmer 2400 Series II analyzer. While optimizing reactions conditions, the reaction mixtures were analyzed by HPLC/MS (Acquity UPLC BEH C18 column, grain size 1.7 μm; eluent acetonitrile–water, flow rate 0.3–0.6 mL/min; ESI MS Xevo TQD detector). The purity of the isolated compounds was checked by TLC on Silufol plates using benzene–



Ball-and-rod representation of the molecular structure of ethyl 6-amino-1,1′-dibenzyl-5-cyano-3-methyl-2′-oxo-5′-phenyl-1′,2′-dihydro-1*H*-spiro[pyrano[2,3-*c*]pyrazole-4,3′-pyrrole]-4′-carboxylate (**3b**) according to the X-ray diffraction data. Only one position of the disordered ethyl group is shown for the sake of simplicity.

ethylacetat (5:1) and ethyl acetate as eluents; spots were developed by treatment with iodine vapor.

Ethyl 6-amino-1′-benzyl-5-cyano-3-methyl-2′-oxo-1,5′-diphenyl-1′,2′-dihydro-1*H*-spiro[pyrano-[2,3-*c*]pyrazole-4,3′-pyrrole]-4′-carboxylate (3a). Pyrroledione **1a**, 1.0 mmol, was dissolved in 10 mL of anhydrous toluene, 1.0 mmol of malononitrile and 0.5 mmol of triethylamine were added, and the mixture was heated for 5 min under reflux. Pyrazolone **2a**, 1.0 mmol, was then added, the mixture was heated for 15 min under reflux and cooled, and the precipitate was filtered off. Yield 76%, mp 217–218°C (decomp., from toluene). IR spectrum, ν, cm^{-1}: 3409, 3320, 3198 (NH_2), 2203 (CN), 1742, 1676 ($C^{2'}$=O, 4′-C=O). ^{1}H NMR spectrum, δ, ppm: 0.74 t (3H, C**H**$_3$CH$_2$, J = 7.0 Hz), 1.94 s (3H, Me), 3.75 q (2H, OCH$_2$, J = 7.0 Hz), 4.50 d and 4.70 d (2H, C**H**$_2$Ph, J = 16.2 Hz), 6.93–7.80 m (15H, H$_{arom}$), 7.65 br.s (2H, NH_2). Found, %: C 70.98; H 4.82; N 12.63. $C_{33}H_{27}N_5O_4$. Calculated, %: C 71.08; H 4.88; N 12.56.

Compounds **3b**–**3g** were synthesized in a similar way.

Ethyl 6-amino-1,1′-dibenzyl-5-cyano-3-methyl-2′-oxo-5′-phenyl-1′,2′-dihydro-1*H*-spiro[pyrano-[2,3-*c*]pyrazole-4,3′-pyrrole]-4′-carboxylate (3b). Yield 70%, mp 220–223°C (decomp., from EtOAc–CH_2Cl_2, 1:3). IR spectrum, ν, cm^{-1}: 3361, 3286, 3132 (NH_2), 2193 (CN), 1731, 1704 ($C^{2'}$=O, 4′-C=O). ^{1}H NMR spectrum, δ, ppm: 0.68 t (3H, C**H**$_3$CH$_2$, J = 7.1 Hz), 1.83 s (3H, Me), 3.70 m (2H, OCH$_2$), 4.47 d and 4.65 d (2H, 1′-CH$_2$, J = 15.9 Hz), 5.16 s (2H, 1-CH$_2$), 6.91–7.50 m (17H, H$_{arom}$, NH_2). ^{13}C NMR spectrum, δ$_C$, ppm: 12.2 (3-CH$_3$), 13.3 (**C**H$_3$CH$_2$), 44.0 (1-CH$_2$), 49.0 (C^4), 50.2 (1′-CH$_2$), 55.1 (C^5), 58.9 (OCH$_2$), 92.7 (C^{3a}), 111.4 and 118.1 (CN, $C^{4'}$); 127.0, 127.3, 127.4, 127.7, 128.1, 128.2, 128.6, 129.1, 129.7, 136.1, 136.4 (C$_{arom}$); 141.7 (C^3), 145.4 (C^{7a}), 154.7 ($C^{5'}$), 161.1 and 161.5 (4-C=O, C^6), 178.0 ($C^{2'}$). Mass spectrum: m/z 572.09 $[M + H]^+$. Found, %: C 71.61; H 4.98; N 12.18. $C_{34}H_{29}N_5O_4$. Calculated, %: C 71.44; H 5.11; N 12.25. M + H 572.23.

The X-ray diffraction data for compound **3b** were acquired from a 0.50×0.40×0.05 mm colorless scaly single crystal on an Xcalibur R diffractometer with a CCD-detector according to a standard procedure [MoK_α radiation, 293(2) K, ω-scanning, scan step 1°] [11]. A correction for absorption was applied empirically using SCALE3 ABSPACK algorithm [11]. Monoclinic crystal system, space group $P2_1/n$; unit cell parameters: a = 12.965(2), b = 14.374(3), c = 16.735(2) Å; β = 100.994(15)°; V = 3061.5(9) Å^3; Z = 4. Total of 16138 reflections were collected in the range 2.83° < θ < 29.38°, including 7216 independent reflections and 4469 reflections with $I > 2\sigma(I)$; completeness 99.8% for θ < 26.00°. The structure was solved by the direct method and was refined against F^2 by the full-matrix mean-squares procedure in anisotropic approximation for all non-hydrogen atoms. The positions of the NH_2 hydrogen atoms were determined by the difference synthesis and were refined in isotropic approximation. The positions of the other hydrogen atoms were refined according to the riding model in isotropic approximation with dependent thermal parameters. All calculations were performed using SHELX97 software package [12]. Final divergence factors R_1 = 0.0622, wR_2 = 0.1610 for reflections with $I > 2\sigma(I)$ and R_1 = 0.1038, wR_2 = 0.1866 for all reflections; goodness of fit 1.066; Δρ = 0.270/–0.246 $\bar{e}$Å^{-3}. The set of crystallographic data for compound **3b** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 1401800).

Ethyl 6-amino-1′-benzyl-5-cyano-2′-oxo-1,3,5′-triphenyl-1′,2′-dihydro-1*H*-spiro[pyrano[2,3-*c*]pyrazole-4,3′-pyrrole]-4′-carboxylate (3c). Yield 63%, mp 208–210°C (decomp., from EtOAc). IR spectrum, ν, cm^{-1}: 3411, 3374, 3321, 3198, 3320, 3198 (NH_2), 2203 (CN), 1738 ($C^{2'}$=O, 4′-C=O). ^{1}H NMR spectrum, δ, ppm: 0.70 t (3H, C**H**$_3$CH$_2$, J = 7.1 Hz), 3.70 m (2H, OCH$_2$), 4.18 d and 4.61 d (2H, C**H**$_2$Ph, J = 16.1 Hz), 6.73 br.s (2H, NH_2), 6.87–7.91 m (20H, H$_{arom}$). ^{13}C NMR spectrum, δ$_C$, ppm: 13.4 (**C**H$_3$CH$_2$), 44.2 (**C**H$_2$Ph), 48.9 (C^4), 55.5 (C^5), 58.8 (OCH$_2$), 94.7 (C^{3a}), 111.9 and 117.7 (CN, $C^{4'}$); 120.6, 126.9, 127.1, 127.2, 127.8, 127.9, 128.1, 128.2, 128.4, 128.8, 128.9, 129.6, 129.7, 132.4, 135.8, 137.1 (C$_{arom}$); 145.5 and 147.7 (C^3, C^{7a}), 154.8 ($C^{5'}$), 160.9 and 161.0 (4′-C=O, C^6), 178.5 ($C^{2'}$). Found, %: C 73.61; H 4.78; N 11.27. $C_{38}H_{29}N_5O_4$. Calculated, %: C 73.65; H 4.72; N 11.30.

Ethyl 6-amino-1-benzyl-5-cyano-1′-cyclohexyl-3-methyl-2′-oxo-5′-phenyl-1′,2′-dihydro-1*H*-spiro-[pyrano[2,3-*c*]pyrazole-4,3′-pyrrole]-4′-carboxylate (3d). Yield 56%, mp 205–207°C (decomp., from Me_2CO). IR spectrum, ν, cm^{-1}: 3347, 3293, 3178 (NH_2), 2197 (CN), 1732, 1701 ($C^{2'}$=O, 4′-C=O). ^{1}H NMR spectrum, δ, ppm: 0.66 t (3H, C**H**$_3$CH$_2$, J = 7.0 Hz), 0.86–2.08 m (10H, CH$_2$), 1.92 s (3H, Me), 3.08 m (1H, 1′-CH), 3.66 m (2H, OCH$_2$), 5.15 s (2H, C**H**$_2$Ph), 7.21–7.56 m (10H, H$_{arom}$), 7.38 br.s (2H, NH_2). ^{13}C NMR spectrum, δ$_C$, ppm: 12.2 (3-CH$_3$), 13.2 (**C**H$_3$CH$_2$); 24.5, 25.2, 25.3, 28.7, 29.1 (CH$_2$); 48.9 (C^4), 50.1 (**C**H$_2$Ph), 54.5 (1′-CH), 55.6 (C^5), 58.7

(OCH_2), 92.9 (C^{3a}), 111.2 and 117.6 (CN, $C^{4'}$); 127.4, 127.7, 128.6, 129.7, 130.0, 136.5 (C_{arom}); 141.7 (C^3), 145.6 (C^{7a}), 155.7 ($C^{5'}$), 161.1 and 161.3 (4′-C=O, C^6), 177.9 ($C^{2'}$). Found, %: C 70.41; H 5.86; N 12.49. $C_{33}H_{33}N_5O_4$. Calculated, %: C 70.32; H 5.90; N 12.43.

6-Amino-3-methyl-2′-oxo-1,4′,5′-triphenyl-1′,2′-dihydro-1*H*-spiro[pyrano[2,3-*c*]pyrazole-4,3′-pyrrole]-5-carbonitrile (3e). Yield 81%, mp 236–237°C (decomp., from EtOAc–Me_2CO, 2:1). IR spectrum, ν, cm^{-1}: 3413, 3310, 3186 (NH_2, NH), 2203 (CN), 1703 ($C^{2'}$=O). ^{1}H NMR spectrum, δ, ppm: 2.11 s (3H, Me), 6.97–7.76 m (15H, H_{arom}), 7.52 br.s (2H, NH_2), 10.52 s (1H, NH). Found, %: C 73.96; H 4.54; N 14.89. $C_{29}H_{21}N_5O_2$. Calculated, %: C 73.87; H 4.49; N 14.85.

6-Amino-1-benzyl-3-methyl-2′-oxo-4′,5′-diphenyl-1′,2′-dihydro-1*H*-spiro[pyrano[2,3-*c*]pyrazole-4,3′-pyrrole]-5-carbonitrile (3f). Yield 72%, mp 244–246°C (decomp., from EtOAc). IR spectrum, ν, cm^{-1}: 3362, 3310, 3183 (NH_2, NH), 2198 (CN), 1707 ($C^{2'}$=O). ^{1}H NMR spectrum, δ, ppm: 1.99 s (3H, Me), 5.12 s (2H, CH_2Ph), 6.89–7.34 m (17H, H_{arom}, NH_2), 10.44 s (1H, NH). Found, %: C 74.08; H 4.69; N 14.54. $C_{30}H_{23}N_5O_2$. Calculated, %: C 74.21; H 4.77; N 14.42.

6-Amino-2′-oxo-1,3,4′,5′-tetraphenyl-1′,2′-dihydro-1*H*-spiro[pyrano[2,3-*c*]pyrazole-4,3′-pyrrole]-5-carbonitrile (3g). Yield 57%, mp 235–238°C (decomp., from EtOAc). ^{1}H NMR spectrum, δ, ppm: 6.69–7.85 m (20H, H_{arom}), 7.59 br.s (2H, NH_2), 10.51 s (1H, NH). Found, %: C 76.61; H 4.40; N 13.02. $C_{34}H_{23}N_5O_2$. Calculated, %: C 76.53; H 4.34; N 13.13.

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