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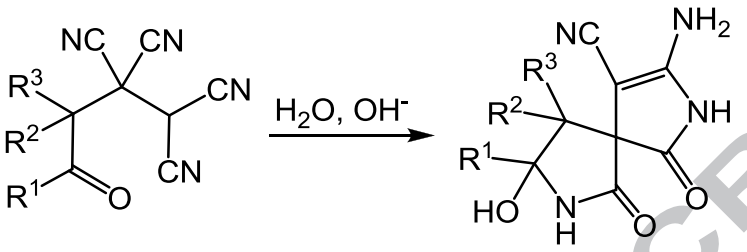

Domino synthesis of 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles

Sergey V. Fedoseev [a], Oleg V. Ershov [a], Mikhail Yu. Belikov [a], Konstantin V. Lipin [a], Ivan N. Bardasov [a]*, Oleg E. Nasakin [a], Viktor A. Tafeenko [b]

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Abstract — The domino reactions of 4-oxoalkane-1,1,2,2-tetracarbonitriles with water afford 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles in good yields.

Keywords: Heterocyclic compounds; Cyano compounds; Tetracyanoalkanones; Water; Domino synthesis; Pyrrolidine; Iminolactone; Spiro compounds.
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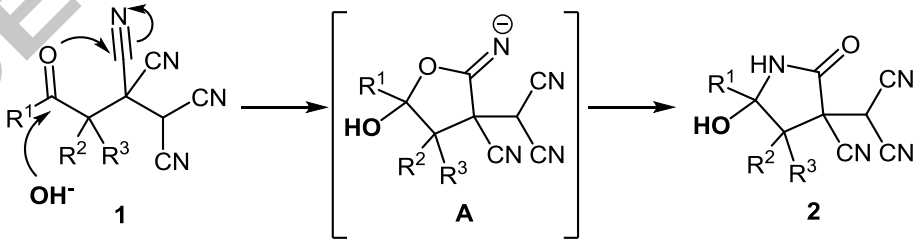
Five-membered azaheterocycles are among natural substances that have important biological significance. The 5-hydroxypyrrolidine-2-one (5-hydroxylactam) fragment is known to be a part of many biologically active compounds,[1] examples include: integrase inhibitors of HIV-1,[1a-c] tyrosine kinase,[1d] telomerase;[1e] inhibitors or agonists of the 5-hydroxytryptamine (serotonin) receptor;[1f,g] inhibitors of the Mdm2 protein with cellular tumor antigen p53;[1h] NMDA-receptor agonists;[1i] antagonists of CC chemokine receptor type 2,[1j] endothelin receptor (oteromycin);[1k] epolactaene derivatives providing apoptosis-inducing effect on BALL-1 cells;[1l] hypnotics from the cyclopyrroline group;[1m] quinolactacin C;[1n] as well as agents for the treatment of disorders of nervous or intellectual activity, memory and mental fatigue.[1o] They have also been used as synthetic intermediates in organic synthesis.[1p-u]

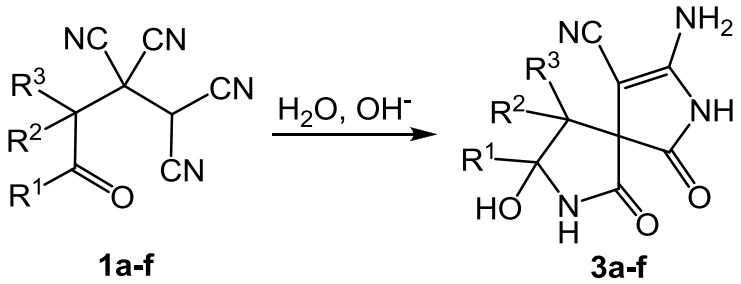
The formation of 5-hydroxylactams is often accomplished by transformation of polyelectrophilic 4-oxoalkane-1,1,2,2-tetracarbonitriles with nucleophiles.[2] Apparently, this is due to the fact that during "push-pull" tandem nucleophilic addition to the carbonyl group of the 4-oxoalkane-1,1,2,2-tetracarbonitriles, an intermediate **A** is formed, which can easily undergo rearrangement into lactam **2**,[2b] containing the 5-hydroxypyrrolidin-2-one fragment (Scheme 1).



Scheme 1. "Push-pull" tandem nucleophilic addition and transformation of tetracyanoalkanones.

Such processes are favorable as a result of the short distance between the carbonyl oxygen and the cyanocarbon in the salts of 4-oxoalkane-1,1,2,2-tetracarbonitriles, which is 2.62-2.72 Å according to the X-ray diffraction analysis,[2b,3] being less than the sum of their Van der Waals radii. Therefore it can be assumed that a n,π *-interaction occurs, which leads to the formation of a σ-bond.

Using the above approach to obtain new derivatives of 5-hydroxypyrrolidin-2-ones, we investigated the reaction of 4-oxoalkane-1,1,2,2-tetracarbonitriles **1** with water under base catalysis. This reaction led to the formation of alkyl or aryl 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles **3a-f** in 70-91% yields (Scheme 2 and Table 1).[4]



Scheme 2. Synthesis of 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles **3a-f**.

Table 1. Synthesis of 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles **3a-f**.

Substrate	R^1	R^2	R^3	Product	Yield (%)[a]
1a	CH_3	CH_3	H	**3a**	85
1b	CH_3	C_2H_5	H	**3b**	91
1c	CH_3	CH_3	CH_3	**3c**	82
1d	$CH_2CH_2CH(t\text{-Bu})CH_2$		H	**3d**	75
1e	$(CH_2)_4$		CH_3	**3e**	78
1f	Ph	CH_3	H	**3f**	70

[a] Yield of isolated product.

The structures of compounds **3a-f** were confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, HMBC and by mass spectrometry.[5] The infrared spectra exhibited absorption bands due to the conjugated cyano group at 2185-2188 cm^{-1}, the carbonyl groups at 1611-1723 cm^{-1} and the hydroxy and amino groups at 3188-3361 cm^{-1}. The ^{1}H NMR spectra of products **3a-f** exhibited signals at 7.20-7.38 ppm for the amino group, at 10.62-10.89 ppm for the dihydropyrrole NH-group, at 8.79-9.53 ppm for the tetrahydropyrrole NH-group and other resonances as expected for the alkyl groups. A feature of the ^{1}H NMR spectra was the wide range in the position of the proton signals due to the OH group (4.79-6.26 ppm). The ^{13}C NMR spectra of the products displayed resonances in agreement with the structure. The mass spectra of compounds **3a-f** displayed peaks due to $[M - 18]^+$ fragments, that can be explained by the propensity for easy elimination of water. The HMBC spectrum of compound **3a** contained correlations expected for the proposed structure, except for a correlation with the proton of the dihydropyrrole NH-group (Figure 1).

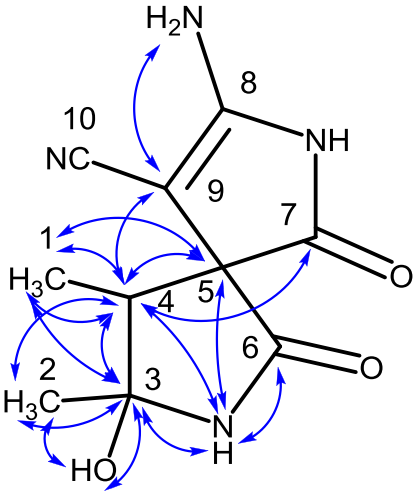


Figure 1. HMBC cross peaks in compound **3a**.

An unambiguous determination of the position of the of substituents was achieved by X-ray diffraction analysis using a single crystal of compound **3e** (Figure 2).[6] In addition, the X-ray diffraction data indicated the presence of intramolecular hydrogen bonds between the hydrogen and oxygen of the 4-OH group, which explains the wide range in the chemical shift of the proton signals of the OH groups of compounds **3** in the ^{1}H NMR spectra.

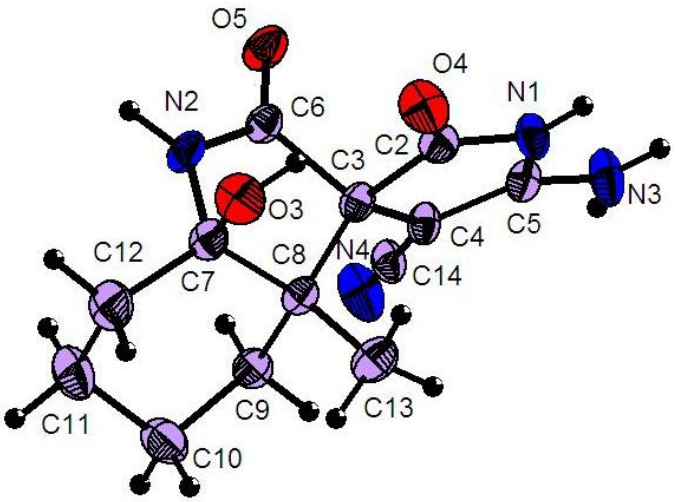
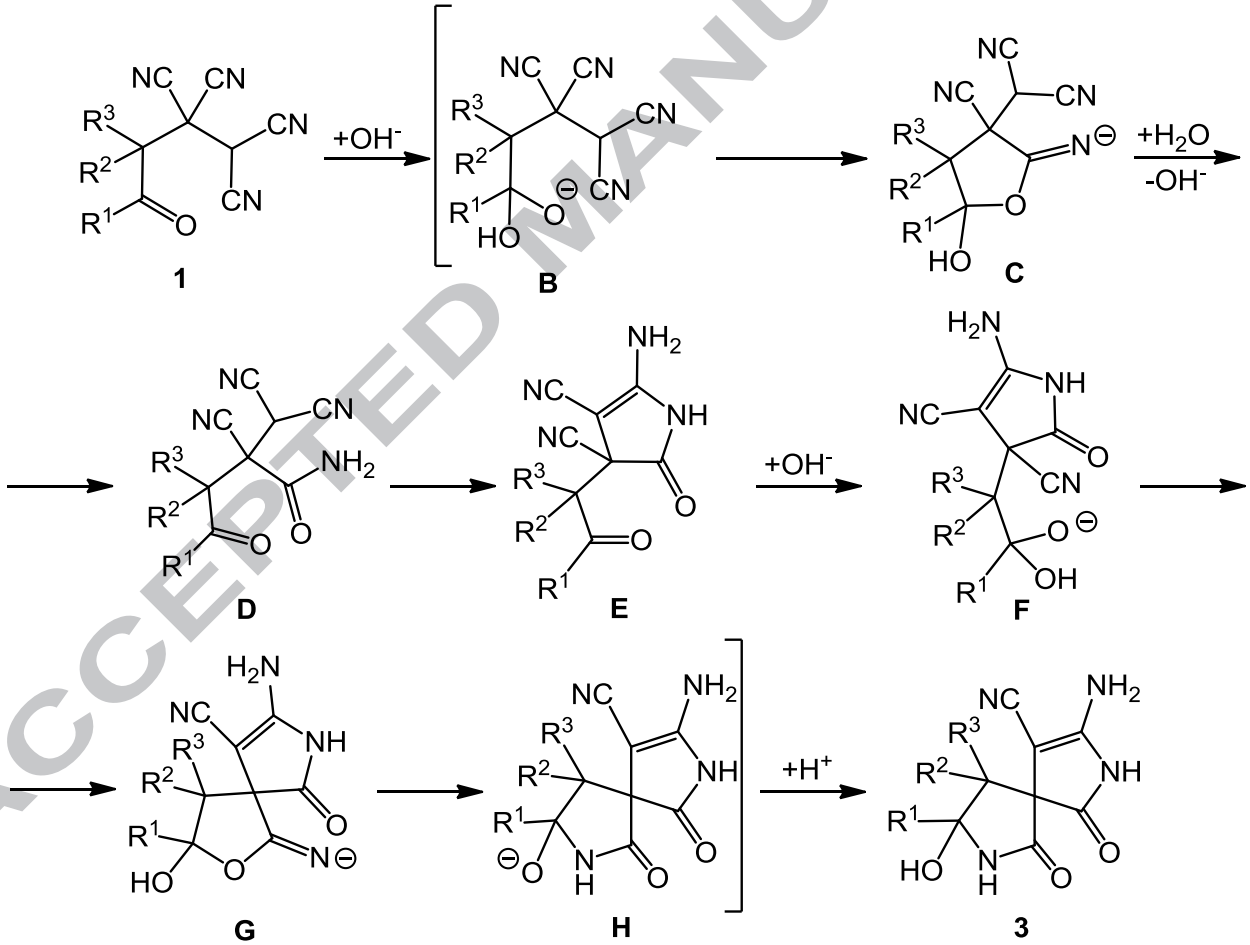


Figure 2. ORTEP diagram of (3*S**,3a*R**,7a*S**)-5'-amino-7a-hydroxy-3a-methyl-2,2'-dioxo-1,1',2,2',3a,4,5,6,7,7a-decahydrospiro[indole-3,3'-pyrrole]-4'-carbonitrile (**3e**).



Scheme 3. Proposed mechanism for the synthesis of 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles **3a-f**.

Tetracyanoalkanones are known to be moderately strong C-H acids, however we suggest that the first stage involves nucleophilic addition of the hydroxide to the carbonyl group of **1** to give **B** (Scheme 3). Next, a push-pull tandem nucleophilic addition occurs, resulting in iminofuran anion **C**. Ring-opening leads to carboxamide **D** and subsequent cyclization involving the carboxamide and cyano groups forms the pyrrole **E**. Similar transformations of tetracyanoalkanones (**C** → **E**) are described in the literature.[2] Next addition of the hydroxide anion forms **F**, which is followed by intramolecular cyclization to give spirane **G**. Iminolactone-

lactam rearrangement then leads to diazaspirane **H**.[2a] The final product **3** would be formed after acidification of the reaction mixture.

The structures of spiranes **3a-f** contain three asymmetric centers. In our case, according to ^{1}H NMR and ^{13}C NMR spectroscopy of **3a**, only one diastereomer was formed. Hence, the reaction proceeds stereoselectively with 100% diastereomeric purity.

In conclusion, 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles **3a-f** have been obtained for the first time as a result of a domino process in one synthetic operation. The structures of the products contain an important biologically active 5-hydroxypyrrolidin-2-one fragment.

Acknowledgement

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4. *Typical procedure for the preparation of 3-amino-8-hydroxy-1,6-dioxo-2,7-diazaspiro[4.4]non-3-ene-4-carbonitriles **3a-f**.* 4-Oxoalkane-1,1,2,2-tetracarbonitrile **1** (10 mmol) was stirred in 20 ml of 5% NaOH aqueous solution of for 1.5-2 h at room temperature. After completion of the reaction (TLC), the solution was cooled to 0-5 °C and neutralized with 25% AcOH. The resulting precipitate was filtered and washed with H_2O, *i*-PrOH and EtOAc.
5. Analytical data for compounds **3a-f**. Compound **3a**. mp 201-202 °C; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 0.88 (3H, d, J = 7.1 Hz, CH_3), 1.36 (3H, s, CH_3), 2.26 (1H, q, J = 7.1 Hz, CH), 4.83 (1H, s, OH), 7.30 (2H, s, NH_2), 9.12 (1H, s, NH), 10.75 (1H, s, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 7.57, 24.50, 45.62, 53.00, 64.91, 84.74, 117.33, 157.97, 169.94, 176.48. IR (mineral oil, cm^{-1}): 3400 (OH), 3228-3290 (NH), 2186 (CN), 1652-1663 (C=O). MS (EI, 70 eV): *m/z* (%) 218 [M–18]$^+$ (7). Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.76; H, 5.13; N, 23.76. Compound **3b**. mp 205-206 ºC; ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 0.90 (3H, t, J = 7.5 Hz, CH_3), 1.29-1.35 (1H, m, CH_2), 1.40 (3H, s, CH_3), 1.56-1.62 (1H, m, CH_2), 2.12 (1H, dd, J = 6.4, 8.3 Hz, CH), 4.79 (1H, s, OH), 7.22 (2H, s, NH_2), 9.06 (1H, s, NH), 10.72 (1H, br s, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 12.08, 17.61, 25.40, 51.86, 54.75, 64.31, 84.54, 117.28, 157.33, 169.70, 176.25. IR (mineral oil, cm^{-1}): 3414 (OH), 3220-3326 (NH), 2188 (CN), 1665-1696 (C=O). MS (EI, 70 eV): *m/z* (%) 232 [M–18]$^+$ (44). Anal. Calcd for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.81; H, 5.65; N, 22.34. Compound **3c**: mp: 283-284 ºC (dec.); ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 0.90 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.22 (3H, s, CH_3), 5.66 (1H, s, OH), 7.26 (2H, s, NH_2), 8.99 (1H, s, NH), 10.85 (1H, br s, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 16.77, 21.46, 25.19, 48.76, 51.50, 68.69, 87.77, 119.10, 159.07, 169.13, 177.53. IR (mineral oil, cm^{-1}): 3408 (OH), 3273-3325 (NH), 2187 (CN), 1711-1690 (C=O). MS (EI, 70 eV): *m/z* (%) 232 [M–18]$^+$ (35). Anal. Calcd for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.83; H, 5.62; N, 22.41. Compound **3d**. mp 231-232 ºC (dec.); ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 0.83 (9H, s, $3CH_3$), 0.84-0.89 (1H, m, CH), 1.08-1.15 (2H, m, CH_2), 1.56-1.64 (2H, m, CH_2), 1.76-1.80 (1H, m, CH_2), 1.96-2.02 (1H, m, CH_2), 2.33-2-38 (1H, m, CH), 6.26 (1H, s, OH), 7.20 (2H, s, NH_2), 8.79 (1H, s, NH), 10.62 (1H, br s, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 22.34, 26.97, 27.04, 29.49, 32.16, 32.21, 34.16, 44.15, 50.18, 52.60, 65.34, 84.56, 119.19, 158.89, 170.53, 177.82. IR (mineral oil, cm^{-1}): 3396 (OH), 3229-3314 (NH), 2187 (CN), 1723-1676 (C=O). MS (EI, 70 eV): *m/z* (%) 300 [M–18]$^+$ (41). Anal. Calcd for $C_{16}H_{22}N_4O_3$: C, 60.36; H, 6.97; N, 17.60. Found: C, 60.39; H, 6.99; N, 17.56. Compound **3e**. mp 284-285 ºC (dec.); ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 0.94 (3H, s, CH_3), 1.03-1.16 (1H, m, CH_2), 1.23-1.32 (1H, m, CH_2), 1.41-1.62 (5H, m, $(CH_2)_3$), 1.82-1.88 (1H, m, CH_2), 6.12 (1H, s, OH), 7.24 (2H, s, NH_2), 8.84 (1H, s, NH), 10.87 (1H, br s, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 14.39, 21.49, 22.55, 32.11, 36.83, 49.34, 51.19, 70.85, 87.12, 119.72, 159.88, 170.73, 177.85. IR (mineral oil, cm^{-1}): 3571 (OH), 3347-3188 (NH), 2185 (CN), 1679-1611 (C=O). MS (EI, 70 eV): *m/z* (%) 258 [M–18]$^+$ (20). Anal. Calcd for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28. Found: C, 56.53; H, 5.85; N, 20.24. Compound **3f**. mp 225-226 ºC (dec.); ^{1}H NMR (500.13 MHz, DMSO-d_6): δ 0.81 (3H, d, J = 7.1 Hz, CH_3), 2.32 (1H, q, J = 7.1 Hz, CH_2), 5.51 (1H, s, OH), 7.34-7.37 (1H, m, C_6H_5), 7.38 (2H, s, NH_2), 7.40-7.44 (2H, m, C_6H_5), 7.46-7.49 (2H, m, C_6H_5), 9.53 (1H, s, NH), 10.89 (1H, br s, NH). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 7.11, 49.06, 53.23, 65.12, 87.62, 117.51, 125.97, 128.39, 128.58, 141.76, 158.27, 170.96, 176.82. IR (mineral oil, cm^{-1}): 3569 (OH), 3361-3196 (NH), 2186 (CN), 1689-1622 (C=O). MS (EI, 70 eV): *m/z* (%) 280 [M–18]$^+$ (26). Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.44; H, 4.72 N, 18.76.
6. Crystallographic data (excluding structure factors) for the structure **3e** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary

publication number CCDC 907955. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].