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Spiro Heterocyclization of 4-Aryl-4-oxobutane-1,1,2,2-tetracarbonitriles to 3*H*-Pyrrole Derivatives, 2-Oxa-7-azaspiro[4.4]nona-3,6,8-trienes

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Abstract—4-Aryl-3-methyl-4-oxobutane-1,1,2,2-tetracarbonitriles reacted with morpholine to give 8-amino-3-aryl-1-imino-4-methyl-6-(morpholin-4-yl)-2-oxa-7-azaspiro[4.4]nona-3,6,8-triene-9-carbonitriles.

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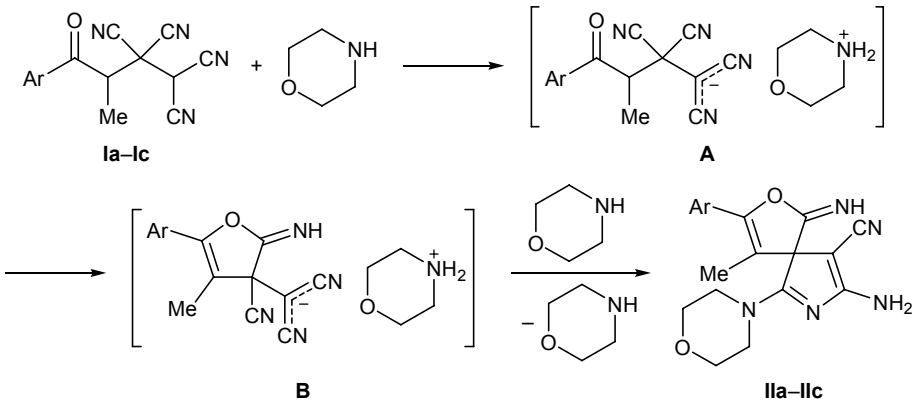
4-Oxoalkane-1,1,2,2-tetracarbonitriles are extensively studied representatives of the series of polynitrile compounds. Derivatives of 4-oxoalkane-1,1,2,2-tetracarbonitriles are known as potential antitumor agents [1] and coordination polymers with interesting topology [2].

We now perform extensive studies on the transformations of 4-oxoalkane-1,1,2,2-tetracarbonitriles by the action of nitrogen-centered nucleophiles [3]. 4-Oxoalkane-1,1,2,2-tetracarbonitriles were reported to react with ammonia and amines to form 3-amino-7-oxo-4,6-diazabicyclo[3.2.1]oct-2-ene-1,2-dicarbonitriles [4], 3-amidinio-2-aminopyridine-4-carboxylates [5], diethylammonium 3,4-dicyano-5,6,7,8-tetrahydroquinolin-2-olates [6], and ammonium 4-aryl-4-oxo-1,1,2-tricyanobut-2-en-1-ides [7]. We recently showed that the reaction of 4-oxoalkane-1,1,2,2-tetracarbonitriles with morpholine leads to 5-amino-2-(morpholin-4-yl)-3*H*-pyrrole-3,4-dicarbonitriles [8, 9] and found that nitrogen-centered nucleophiles preferably add to the β-cyano groups of polyelectrophilic tetranitriles. The resulting compounds are representatives of a poorly explored class of aza heterocycles, 3*H*-pyrroles, which may be regarded as nitrogen-containing cyclopentadiene analogs. Despite limited published data, some 3*H*-pyrroles were found to exhibit antimicrobial and antitumor activity [10–12].

With a view to synthesize new functionally substituted 3*H*-pyrrole derivatives, we extended the series of 4-oxoalkane-1,1,2,2-tetracarbonitrile substrates and examined their reaction with morpholine in more detail. The reactions of 4-aryl-3-methyl-4-oxobutane-1,1,2,2-

Scheme 1.



Ar = Ph (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**).

tetracarbonitriles **Ia**–**Ic** with morpholine gave no analogs of 5-amino-2-(morpholin-4-yl)-3*H*-pyrrole-3,4-dicarbonitriles described in [8, 9]. In this case, the process involved more profound transformation with participation of the carbonyl and β-cyano group, and the products were previously unknown 8-amino-3-aryl-1-imino-4-methyl-6-(morpholin-4-yl)-2-oxa-7-azaspiro[4.4]nona-3,6,8-triene-9-carbonitriles **IIa**–**IIc** (yield 65–71%, Scheme 1) as representatives of rare spiro fused 3*H*-pyrroles.

Presumably, CH acids **Ia**–**Ic** initially react with morpholine to give salts **A**. Structural analogs of salts **A** containing metal or ammonium cations were reported previously [2, 7, 13]. In the next step, intramolecular cyclization of **A** yields iminofurans **B** which undergo further transformations in the presence of excess morpholine, eventually leading to formation of spiro heterocyclic compounds **IIa**–**IIc**. The possibility for formation of iminofurans from 4-oxoalkane-1,1,2,2-tetracarbonitriles under basic conditions was demonstrated in [14, 15]. It is also known that iminofurans structurally similar to intermediates **B** are converted into 3*H*-pyrroles in the presence of morpholine [8]. As we showed previously [8, 9], 3*H*-pyrroles **IIa**–**IIc** are formed via transformation of just β- rather than γ-cyano groups in the initial 4-oxoalkane-1,1,2,2-tetracarbonitriles, which is due to reduced electrophilicity of the γ-cyano groups in reactions with basic reagents.

There are only a few published data on analogs of **IIa**–**IIc** with spiro-fused 3*H*-pyrrole and furan rings [16, 17]. The structure of compounds **IIa**–**IIc** was confirmed by their IR, ^{1}H NMR, and mass spectra and elemental analyses. The mass spectra of **IIa**–**IIc** contained the molecular ion peaks with a relative intensity of 55–93%. According to the IR data, amino and imino groups (3133–3347 cm^{-1}) and a conjugated cyano group (strong bands at 2167–2173 cm^{-1}) were present in the molecules of **IIa**–**IIc**. In the ^{1}H NMR spectra we observed singlets from protons in the methyl group on the furan ring (δ 1.75–1.80 ppm) and signals from amino groups (δ 7.13–7.28 ppm), aromatic protons (δ 7.30–7.65 ppm), and =NH protons (8.91–9.23 ppm). Protons in the morpholine substituent resonated as broadened signals at δ 3.10–3.80 ppm. The ^{1}H NMR spectra of **IIa**–**IIc** in DMSO-d_6 at room temperature displayed double sets of signals, indicating formation of isomer mixtures. We believe that this pattern is related to *E* and *Z* configuration of the C=NH group where the proton on the nitrogen atom can occupy different positions.

Thus we have discovered a new path of the reaction of 4-oxoalkane-1,1,2,2-tetracarbonitriles with nitrogen-centered nucleophiles, which leads to the formation of polyfunctionalized spiro-fused 3*H*-pyrrole derivatives, 8-amino-3-aryl-1-imino-4-methyl-6-(morpholin-4-yl)-2-oxa-7-azaspiro[4.4]nona-3,6,8-triene-9-carbonitriles.

EXPERIMENTAL

The progress of reactions was monitored, and the purity of products was checked, by TLC on Silufol UV-254 plates; spots were visualized under UV light, by treatment with iodine vapor, and by thermal decomposition. The IR spectra were recorded on an FSM-1202 spectrometer with Fourier transform from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker DRX-500 spectrometer at 500.13 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The elemental compositions were determined on a Laboratorni Přistroje analyzer. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT INCOS-50 mass spectrometer.

Spiro-fused 3*H*-pyrroles IIa–IIc (*general procedure*). A solution of 0.5 mmol of 4-aryl-3-methyl-4-oxobutane-1,1,2,2-tetracarbonitrile **Ia**–**Ic** in 3 ml of anhydrous ethyl acetate was cooled to –10 to –15°C, 0.087 g (1 mmol) of morpholine was added under vigorous stirring, and the yellow–orange mixture was left to stand in a closed vessel at –10 to –15°C. After 3–4 days, the yellowish precipitate was filtered off, washed on a filter with cold ethyl acetate and diethyl ether, and dried in a vacuum desiccator.

8-Amino-1-imino-4-methyl-6-(morpholin-4-yl)-3-phenyl-2-oxa-7-azaspiro[4.4]nona-3,6,8-triene-9-carbonitrile (IIa). Yield 0.122 g (71%), mp 158–159°C (decomp.). IR spectrum, ν, cm^{-1}: 3133–3347 (NH, NH_2), 2167 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.77* s and 1.80 s (3H, CH_3); 3.10–3.80 m (8H, morpholine); 7.15 s and 7.26* s (2H, NH_2); 7.44–7.63 m (5H, H_{arom}); 8.95 s and 9.16* s (1H, NH); isomer ratio 59:41. Mass spectrum: *m*/*z* 349 (I_{rel} 93%) $[M]^+$. Found, %: C 65.39; H 5.38; N 19.96. $C_{19}H_{19}N_5O_2$. Calculated, %: C 65.32; H 5.48; N 20.04. *M* 349.39.

8-Amino-3-(4-chlorophenyl)-1-imino-4-methyl-6-(morpholin-4-yl)-2-oxa-7-azaspiro[4.4]nona-3,6,8-triene-9-carbonitrile (IIb). Yield 0.132 g (69%), mp 187–188°C (decomp.). IR spectrum, ν, cm^{-1}: 3143–3331 (NH, NH_2), 2169 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.76* s and 1.79 s (3H, CH_3); 3.10–3.75 m (8H, morpholine); 7.17 s and 7.28* s (2H,

* Hereinafter, signals belonging to the minor isomer are marked with an asterisk.

NH_2); 7.56–7.65 m (4H, H_{arom}); 9.00 s and 9.23* s (1H, NH); isomer ratio 56:44. Mass spectrum, *m*/*z* (I_{rel}, %): 385 (15) $[^{35}Cl\text{-}M]^+$, 383 (46) $[^{37}Cl\text{-}M]^+$. Found, %: C 59.56; H 4.69; N 18.14. $C_{19}H_{18}ClN_5O_2$. Calculated, %: C 59.45; H 4.73; N 18.25. *M* 383.83.

8-Amino-1-imino-4-methyl-3-(4-methylphenyl)-6-(morpholin-4-yl)-2-oxa-7-azaspiro[4.4]nona-3,6,8-triene-9-carbonitrile (IIc). Yield 0.118 g (65%), mp 170–171°C (decomp.). IR spectrum, ν, cm^{-1}: 3156–3324 (NH, NH_2), 2173 (C≡N). ^1H NMR spectrum, δ, ppm: 1.75* s and 1.77 s (3H, 4-CH_3); 2.35 s (3H, 4′-CH_3); 3.10–3.80 m (8H, morpholine); 7.13 s and 7.24* s (2H, NH_2); 7.30–7.52 m (4H, H_{arom}); 8.91 s and 9.10* s (1H, NH); isomer ratio 57:43. Mass spectrum: *m*/*z* 363 (I_{rel} 55%) $[M]^+$. Found, %: C 66.21; H 5.73; N 19.18. $C_{20}H_{21}N_5O_2$. Calculated, %: C 66.10; H 5.82; N 19.27. *M* 363.41.

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REFERENCES

1. Nasakin, O.E., Lyshchikov, A.N., Kayukov, Ya.S., and Sheverdov, V.P., *Khim.-Farm. Zh*., 2000, vol. 34, no. 4, p. 11.
2. Carlucci, L., Ciani, G., Proserpio, D.M., and Sironi, A., *Angew. Chem., Int. Ed. Engl*., 1996, vol. 35, p. 1088.
3. Belikov, M.Yu., *Cand. Sci. (Chem.) Dissertation*, Kazan. 2011.
4. Nasakin, O.E., Sheverdov, V.P., Moiseeva, I.V., Lyshchikov, A.N., Ershov, O.V., and Nesterov, V.N., *Tetrahedron Lett*., 1997, vol. 38, p. 4455.
5. Nasakin, O.E., Sheverdov, V.P., Ershov, O.V., Moiseeva, I.V., Lyshchikov, A.N., Khrustalev, V.N., and Antipin, M.Yu., *Mendeleev Commun*., 1997, vol. 7, p. 112.
6. Belikov, M.Yu., Ershov, O.V., Eremkin, A.V., Kayukov, Ya.S., and Nasakin, O.E., *Russ. J. Org. Chem*., 2010, vol. 46, p. 615.
7. Belikov, M.Yu., Ershov, O.V., Eremkin, A.V., Kayukov, Ya.S., and Nasakin, O.E., *Russ. J. Org. Chem*., 2010, vol. 46, p. 597.
8. Belikov, M.Yu., Ershov, O.V., Eremkin, A.V., Nasakin, O.E., Tafeenko, V.A., and Nurieva, E.V., *Tetrahedron Lett*., 2011, vol. 52, p. 6407.
9. Belikov, M.Yu., Ershov, O.V., Lipovskaya, I.V., Eremkin, A.V., and Nasakin, O.E., *Russ. J. Org. Chem*., 2011, vol. 47, p. 1426.
10. Padmavathi, V., Radha, L.T., Mahesh, K., and Padmaja, A., *Chem. Pharm. Bull*., 2009, vol. 57, p. 1200.
11. Cirrincione, G., Almerico, A.M., Grimaudo, S., Diana, P., Mingoia, F., Barraja, P., and Misuraca, F., *Farmaco*, 1996, vol. 51, p. 49.
12. Cirrincione, G., Almerico, A.M., Dattolo, G., Aiello, E., Grimaudo, S., Diana, P., and Misuraca, F., *Farmaco*, 1992, vol. 47, p. 1555.
13. Nasakin, O.E., Lukin, P.M., and Nikolaev, E.G., *Zh. Org. Khim*., 1987, vol. 23, p. 659.
14. Nasakin, O.E., Sheverdov, V.P., Moiseeva, I.V., Ershov, O.V., Chernushkin, A.N., and Tafeenko, V.A., *Russ. J. Gen. Chem*., 1999, vol. 69, p. 291.
15. Ducker, J.M. and Gunter, M.J., *Aust. J. Chem*., 1973, vol. 26, p. 1551.
16. Melsa, P., Cajan, M., Havlas, Z., and Mazal, C., *J. Org. Chem*., 2008, vol. 73, p. 3032.
17. Perrin, S., Monnier, K., and Laude, B., *Bull. Soc. Chim. Belg*., 1996, vol. 105, p. 777.