4-R-7-Nitrobenzofurazans in [3+2] cycloaddition reactions with *N*-methylazomethine ylide

S. Yu. Pechenkin,[a] A. M. Starosotnikov,[a] ★ *M. A. Bastrakov,[a] I. V. Glukhov,[b] and S. A. Shevelev[a]*

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5328. E-mail: alexey41@list.ru*
[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 499) 135 6549. E-mail: ivglukh@ineos.ac.ru*

A number of new tetrahydroisoindole derivatives fused with the furazan ring were synthesized based on the 1,3-dipolar cycloaddition of *N*-methylazomethine ylide with substituted 4-nitrobenzofurazans. Substituents in the benzene ring were found to affect the cycloaddition process.

Key words: 1,3-dipolar cycloaddition, azomethine ylides, benzofurazans, nitro compounds, polycyclic systems.

1,3-Dipolar cycloaddition reactions play an important role in organic synthesis. They are one of the simplest and available methods for the preparation of a wide range of five-membered heterocycles.[1]

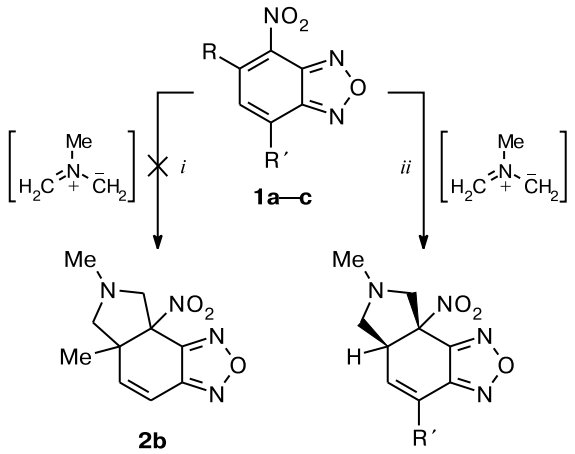
Recently,[2,3] we have reported on the [3+2] cycloaddition reactions of *N*-methylazomethine ylide with mono- and dinitrobenzazoles (indazoles, benzothiadiazoles, benzofurazans, *etc.*). All these cases included cycloaddition at the carbon—carbon double bonds, activated with the nitro groups of the nitrobenzazole benzene ring, to form pyrrolidine or pyrroline ring. In particular, 4-nitrobenzofurazan (**1a**) was shown[3] to readily react with *N*-methylazomethine ylide with the formation of tetrahydroisoindole derivative **2a** (Scheme 1). In the present work, we studied how the nature and placement of substituents in the molecule of 4-nitrobenzofurazan affect direction and characteristics of [3+2] cycloaddition processes.

N-Methylazomethine ylide was obtained *in situ* by reflux of *N*-methylglycine and paraformaldehyde in toluene.[3] It was found that 5-methyl-4-nitrobenzofurazan[4] (**1b**), in contrast to the unsubstituted at position 5 analog **1a**, does not formed cycloaddition adduct **2b** (see Scheme 1).

At the same time, isomeric 7-methyl-4-nitrobenzofurazan[4] (**1c**), similarly to compound **1a**, reacts with *N*-methylazomethine ylide to give tetrahydroisoindole derivative **2c** in high yield (see Scheme 1).

In order to study effect of the nature of substituent at position 7 of benzofurazan system on the course of [3+2] cycloaddition, we involved commercially available 7-chloro-4-nitrobenzofurazan **3** into preparation of a number of

Scheme 1



2a (75%), **2c** (81%)

R = H (**1a, 1c**), Me (**1b**)
R′ = H (**1a**, **1b**, **2a**), Me (**1c**, **2c**)

Reagents and conditions: *i*. $PhCH_3$, 110 °C; *ii*. $PhCH_3$, 110 °C, 15—30 min.

7-X-4-nitrobenzofurazans **4a—g** (Scheme 2). The chlorine atom in the starting benzofurazan **3** is known[4—6] to be readily replaced upon the action of a wide range of nucleophiles.

Compounds **4a—g** were further involved into the reaction with *N*-methylazomethine ylide under standard conditions (see Scheme 2). In the case of derivatives **4a—d**,

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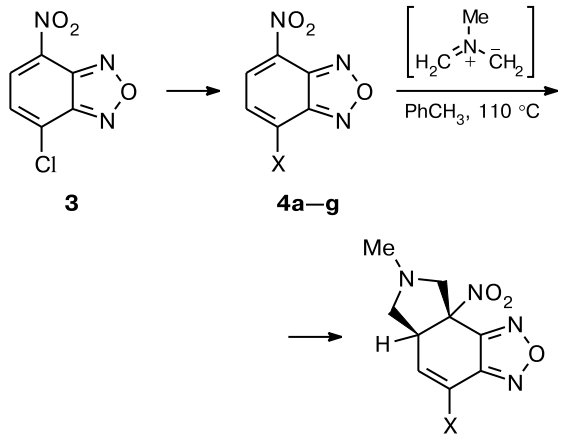
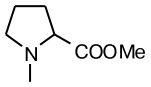
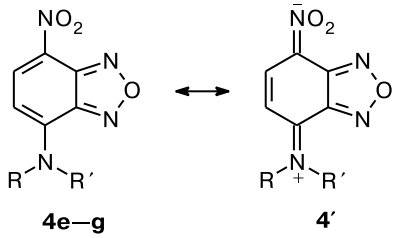
Scheme 2



Nitro compound	X	Product	Reaction time/min	Yield (%)
4a (see Ref. 5)	—SPh	**5a**	10	68
4b (see Ref. 5)	—OMe	**5b**	40	87
4c (see Ref. 4)	—SCH_2Ph	**5c**	15	96
4d (see Ref. 6)	—OPh	**5d**	15	90
4e (see Ref. 5)	$N(CH_2)_5$	—	—	—
4f (see Ref. 4)	C_6H_4NH—	—	—	—
4g (see Ref. 7)		—	—	—

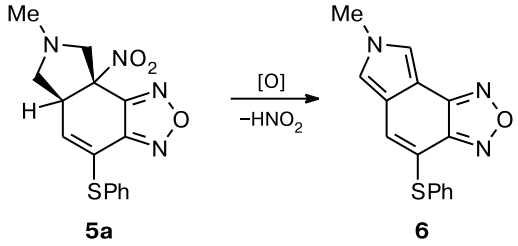
a rapid formation of cycloaddition adducts **5a—d** was observed, which were isolated in high yields. However, compounds **4e—g** bearing a dialkyl- or an arylamino group at position 7 (see Scheme 2) did not react with *N*-methylazomethine ylide even upon prolonged reflux of the reaction mixture. Such a difference in the reactivity depending on the character of the substituent can be accounted for by the fact that in the case of 7-amino derivatives **4e—g** their true structure is a hybrid of the covalent **4e—g** and betaine **4′** forms with significant contribution of the latter (Scheme 3).

Scheme 3



The cycloaddition products **2** and **5** in most cases are stable compounds, which can be stored for a long time at room temperature in air. At the same time, compound **5a** was found to gradually undergo oxidation with elimination of nitrous acid and to be quantitatively converted to isoindole **6** even on storage at −20 °C (Scheme 4).

Scheme 4



The structures of all the synthesized compounds were inferred from the NMR spectroscopic and elemental analysis data, the structure of derivative **5b** was established by X-ray diffraction studies (Fig. 1).

In the molecule of **5b**, the central benzofurazan fragment is planar, an average deviation of atoms from the central plane does not exceed 0.035(3) Å. The nitro group, in turn, is virtually perpendicular to the fragment indicated (the angle between the fragment and the plane of the nitro group is 87°). The five-membered saturated pyrrolidine fragment adopts the envelope conformation. On average, the atoms C(6), C(5A), C(8A), and C(8) come out of the plane by 0.063(3) Å, while the atom N(7) by 0.622(3) Å. The weak contacts C—H...N

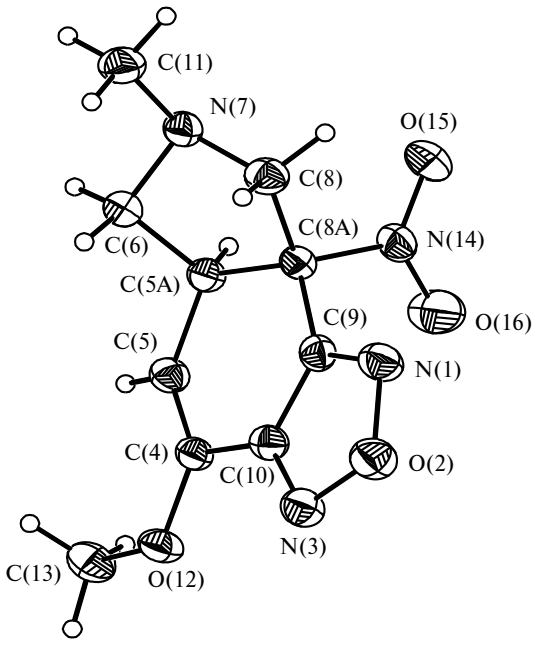


Fig. 1. Molecular structure of **5b**. Thermal ellipsoids are given for 50% probability. Selected bond distances (Å): N(1)—C(9) 1.305(3), N(1)—O(2) 1.393(2), O(2)—N(3) 1.398(2), N(3)—C(10) 1.300(3), C(8A)—N(14) 1.539(3).

and C—H...O are the major structuring interactions in the crystal.

In conclusion, a number of new tetrahydroisoindole derivatives fused to the furazan ring were synthesized based on the 1,3-dipolar cycloaddition reaction of *N*-methylazomethine ylide with substituted 4-nitrobenzofurazans. The cycloaddition process was found to be affected by substituents in the benzene ring.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75 MHz; solvent $CDCl_3$). Chemical shifts are given relative to Me_4Si. Mass spectra were obtained on a MS-30 Kratos instrument (EI, 70 eV). Reaction progress and purity of compounds were monitored by TLC on Silufol UV-254 plates. Compounds **1b**,**c** and **4a**—**f** were synthesized according to the procedures published earlier (see in the text), compound **4g** was obtained similarly to **4e**, its physicochemical characteristics agree with those reported in the literature.[7]

Preparation of compounds 2c and 5a—d (general procedure). A mixture of compound **1** or **4a**—**d** (1 mmol), paraformaldehyde (0.18 g, 6 mmol), and sarcosine (0.44 g, 5 mmol) in toluene (15 mL) was refluxed during the time indicated in Scheme 2 until the starting nitro compound disappeared (TLC), then the mixture was cooled, and an insoluble precipitate was filtered off. The filtrate was concentrated, the residue, if necessary, was purified by column chromatography (SiO_2, eluent $CHCl_3$).

4,7-Dimethyl-8a-nitro-6,7,8,8a-tetrahydro-5a*H*-[1,2,5]-oxadiazolo[3,4-*e*]isoindole (2c). Brown oil, the yield was 0.17 g (81%). Found (%): C, 51.16; H, 5.01; N, 23.47. $C_{10}H_{12}N_4O_3$. Calculated (%): C, 50.84; H, 5.12; N, 23.72. ^{1}H NMR, δ: 2.18 (t, 1 H, J = 9.2 Hz); 2.24 (s, 3 H); 2.37 (s, 3 H); 2.96 (d, 1 H, J = 12.0 Hz); 3.37 (t, 1 H, J = 8.6 Hz); 3.97 (m, 1 H); 4.22 (d, 1 H, J = 11.5 Hz); 6.08 (d, 1 H, J = 3.3 Hz). ^{13}C NMR, δ: 17.4, 40.9, 47.9, 62.3, 66.0, 87.7, 122.3, 131.5, 148.8, 150.0. MS, m/z: 236 $[M]^+$.

7-Methyl-8a-nitro-4-phenylthio-6,7,8,8a-tetrahydro-5a*H*-[1,2,5]oxadiazolo[3,4-*e*]isoindole (5a). Yellowish brown oil, the yield was 0.23 g (68%). Found (%): C, 54.27; H, 4.45; N, 17.21. $C_{15}H_{14}N_4O_3S$. Calculated (%): C, 54.53; H, 4.27; N, 16.96. ^{1}H NMR, δ: 2.18 (t, 1 H, J = 9.0 Hz); 2.37 (s, 3 H); 2.96 (d, 1 H, J = 11.4 Hz); 3.31 (t, 1 H, J = 8.6 Hz); 4.02 (m, 1 H); 4.20 (d, 1 H, J = 11.5 Hz); 5.99 (d, 1 H, J = 5.0 Hz); 7.41—7.62 (m, 5 H). ^{13}C NMR, δ: 40.7, 48.9, 61.8, 65.6, 87.2, 122.8, 129.1, 129.3, 129.6, 131.7, 133.5, 148.0, 148.4.

4-Methoxy-7-methyl-8a-nitro-6,7,8,8a-tetrahydro-5a*H*-[1,2,5]oxadiazolo[3,4-*e*]isoindole (5b). Brown crystals, the yield was 0.22 g (87%), m.p. 92—94 °C. Found (%): C, 47.95; H, 4.61; N, 22.03. $C_{10}H_{12}N_4O_4$. Calculated (%): C, 47.62; H, 4.80; N, 22.21. ^{1}H NMR, δ: 2.2 (t, 1 H, J = 9.05 Hz); 2.39 (s, 3 H); 2.93 (d, 1 H, J = 11.5 Hz); 3.39 (t, 1 H, J = 8.5 Hz); 3.84 (s, 3 H); 4.08 (m, 1 H); 4.24 (d, 1 H, J = 4.9 Hz); 5.32 (d, 1 H, J = 5.1 Hz).

4-Benzylthio-7-methyl-8a-nitro-6,7,8,8a-tetrahydro-5a*H*-[1,2,5]oxadiazolo[3,4-*e*]isoindole (5c). Yellow oil, the yield was 0.18 g (96%). Found (%): C, 55.94; H, 4.39; N, 16.08. $C_{16}H_{16}N_4O_4S$. Calculated (%): C, 55.80; H, 4.68; N, 16.27. ^{1}H NMR, δ: 1.98 (t, 1 H, J = 9.0 Hz); 2.33 (s, 3 H); 2.86 (d, 1 H, J = 11.4 Hz); 3.25 (t, 1 H, J = 8.6 Hz); 3.95 (m, 1 H); 4.17 (m, 3 H); 6.18 (d, 1 H, J = 4.9 Hz); 7.20—7.40 (m, 5 H). ^{13}C NMR, δ: 36.7, 40.8, 48.9, 61.8, 65.9, 87.3, 120.6, 127.6, 128.7, 129.0, 136.1, 136.3, 148.5, 148.8. MS, m/z: 344 $[M]^+$.

7-Methyl-8a-nitro-4-phenoxy-6,7,8,8a-tetrahydro-5a*H*-[1,2,5]oxadiazolo[3,4-*e*]isoindole (5d). Brown oil, the yield was 0.17 g (90%). Found (%): C, 57.58; H, 4.33; N, 18.02. $C_{15}H_{14}N_4O_4$. Calculated (%): C, 57.32; H, 4.49; N, 17.83. ^{1}H NMR, δ: 2.22 (t, 1 H, J = 9.1 Hz); 2.40 (s, 3 H); 2.98 (d, 1 H, J = 11.5 Hz); 3.33 (t, 1 H, J = 8.3 Hz); 4.02 (m, 1 H); 4.25 (d, 1 H, J = 11.5 Hz); 5.45 (d, 1 H, J = 5.0 Hz); 7.12—7.47 (m, 5 H). ^{13}C NMR, δ: 40.7, 47.7, 62.6, 65.4, 87.2, 111.5, 119.9, 125.2, 129.9, 142.1, 145.9, 150.2, 153.7.

7-Methyl-4-phenylthio-7*H*-[1,2,5]oxadiazolo[3,4-*e*]isoindole (6). Needle-like brown crystals, m.p. 123—125 °C. Found (%): C, 63.79; H, 4.08; N, 14.72. $C_{15}H_{11}N_3OS$. Calculated (%): C, 64.04; H, 3.94; N, 14.94. ^{1}H NMR, δ: 3.92 (s, 3 H); 7.01 (s, 1 H); 7.24—7.50 (m, 7 H). ^{13}C NMR, δ: 37.3, 106.7, 114.3, 119.0, 119.1, 122.2, 127.1, 129.0, 130.4, 131.8, 135.4, 144.8, 149.8. MS, m/z: 281 $[M]^+$.

X-ray diffraction studies of compound 5b. Crystals of compound **5b** ($C_{10}H_{12}N_4O_4$, M = 252.24) are monoclinic, space group $P2(1)/c$, at T = 120 K a = 8.3955(16) Å, b = 14.535(3) Å, c = 10.2904(19) Å, β = 113.063(4)°, V = 1155.4(4) Å^3, Z = 4, $F(000)$ = 528, d_{calc} = 1.450 g cm^{-3}, μ = 0.012 mm^{-1}. Parameters of a unit cell and intensities of 2526 reflections were measured on a Bruker SMART 1K automatic diffractometer (T = 120 K, λ(Mo-Kα) irradiation, graphite monochromator, ω- and ω-scan technique, θ_{max} = 27°). To obtain the data, absorption of the X-ray irradiation was applied using the SADABS program.[8] The structure was solved by direct method and refined by full-matrix least squares method in anisotropic approximation for non-hydrogen atoms. Positions of hydrogen atoms were calculated geometrically and refined in isotropic approximation with the fixed positional (the riding model) and thermal parameters. The final R-factors are as follows: R_1 = 0.0478 for 1487 independent reflections with $I > 2\sigma(I)$ and wR_2 = 0.0915 for all the 2526 independent reflections. Number of refined parameters was 164. All the calculations were performed using the SHELXTL PLUS (Version 5.10) program package.[9] Tables of atomic coordinates, bond distances, bond angles, and anisotropic temperature parameters for compound **5b** were deposited with the Cambridge Structural Database.

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