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REACTIONS OF 1,3,5-TRIAZINYLNITRO-FORMALDOXIMES. 2*. THE REACTION OF 1,3,5-TRIAZINYLNITROFORMALDOXIMES WITH MONOSUBSTITUTED ACETYLENES

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1,3,5-Triazinylnitrile oxides were prepared in situ from 2-R-4-R'-1,3,5-triazin-6-ylnitroformaldoximes and were treated with substituted acetylenes to give 3,5-disubstituted isoxazoles. The X-ray data obtained for 5-hydroxymethyl-3-(4'-dimethylamino-2'-methoxy-1,3,5-triazin-6'-yl)isoxazole is discussed.

Keywords: 3,5-disubstituted isoxazoles, acetylene derivatives, 1,3,5-triazinylnitrile oxides, 1,3,5-triazinylnitroformaldoximes.

We have previously shown that deprotonation of 1,3,5-triazinylnitroformaldoximes occurs in the presence of base but the anion formed is unstable and loses nitrite ion to form a 1,3,5-triazinylnitrile oxide. The latter reacts with the enolates of dicarbonyl compounds to give 5-methyl-4-R-3-(1,3,5-triazinyl)isoxazoles [1]. Continuing study of the chemistry of 1,3,5-triazinylnitroformaldoximes we have investigated a thermal method of generating 1,3,5-triazinylnitrile oxides with their subsequent involvement in a [3+2] dipolar cycloaddition. The monosubstituted acetylenes phenylacetylene and propargyl alcohol were used as the dipolarophiles.

Heating a suspension of 2-R-4-R'-1,3,5-triazin-6-ylnitroformaldoximes **1a-e** with phenylacetylene or propargyl alcohol at 80-100ºC resulted in the formation of, respectively, the 3-(2-R-4-R'-1,3,5-triazin-6-yl)-5-phenylisoxazoles **2a-e** and 5-hydroxymethyl-3-(2-R-4-R'-1,3,5-triazin-6-yl)isoxazoles **3a-e**.

Carrying out the thermolysis of compounds **1a-e** in the dipolarophile medium (i.e. without dilution with an inert solvent) fully suppressed the dimerization of the intermediately formed 1,3,5-triazinylnitrile oxides to 3,4-di(2-R-4-R'-1,3,5-triazin-6-yl)furoxans.

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* For Communication 1 see [1].

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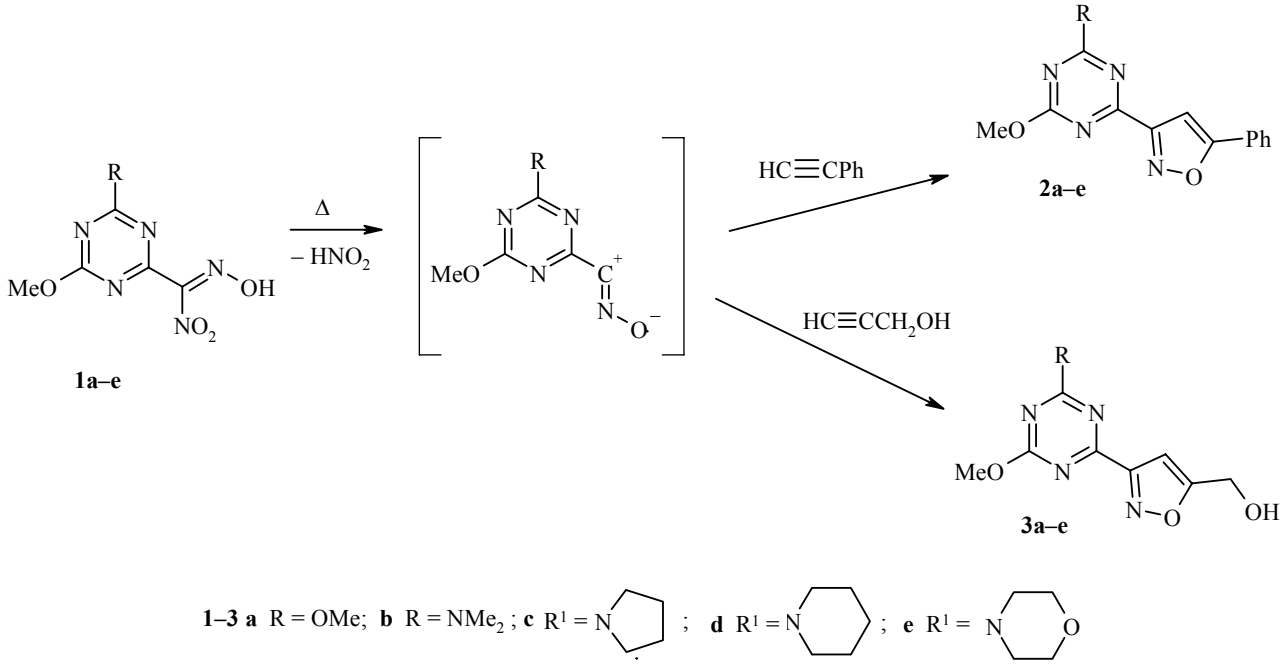
According to their ^{1}H NMR data the reaction products are exclusively the 3,5-disubstituted isoxazoles with total absence of 3,4-disubstituted isoxazoles. This conclusion was based on a comparison of the ^{1}H NMR spectra of the synthesized compounds **2a-e** and **3a-e** and 3-, 3,4-, and 3,5-substituted isoxazoles [2-5]. The formation of only 3,5-disubstituted isoxazoles points to a stereoselective addition of the monosubstituted acetylenes to the 1,3,5-triazinylnitrile oxides. In this way we were able to carry out a thermal method of generating 1,3,5-triazinylnitrile oxides from 2-R-4-R'-1,3,5-triazin-6-ylnitroformaldoximes, treatment of which with monosubstituted acetylenes gave high yields of the 3,5-disubstituted isoxazoles containing a 1,3,5-triazine ring in the 3 position.



1–3 a R = OMe; **b** R = NMe_2 ; **c** R^1 = N ; **d** R^1 = N ; **e** R^1 = N O

The structure of isoxazole **3b** was confirmed from X-ray analysis. The asymmetric part of the unit cell of compound **3b** contains one molecule of 3-(4-dimethylamino)-5-hydroxymethyl-2-methoxy-1,3,5-triazin-6-yl)isoxazole (Fig. 1).

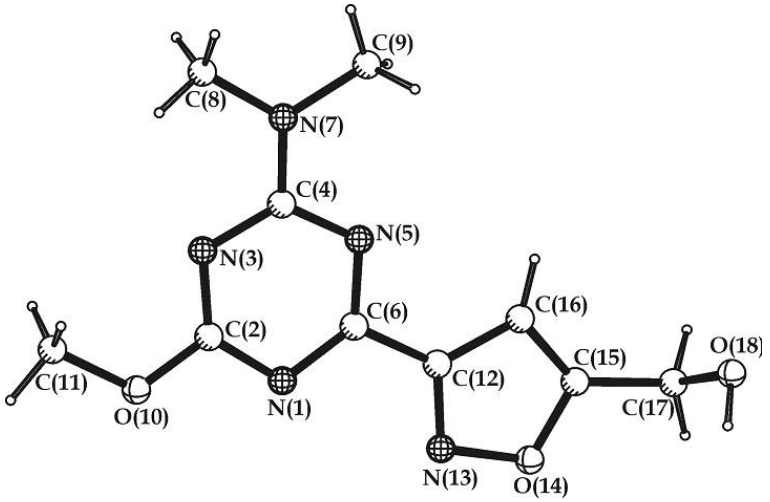


Fig. 1. Molecular geometry of the compound **3b** molecule crystal.

The triazine and isoxazole rings in the molecule are planar within the limits 0.021(2) and 0.007(2) Å respectively. The dihedral angle between the ring planes is 2.7(1)º. The dimethylamino group (which has a planar conformation, the angle of rotation relative to the triazine ring being 4.2(2)º) and the methoxy group lie in the triazine ring plane hence it can be regarded overall as a seventeen atom framework molecular plane. According to calculations made using the PLATON program this fragment is planar within the limits 0.072(3) Å. Only atom O(18) of the hydroxymethyl group deviates from this plane by 1.274(1) Å.

It is significant that the dihedral angles between the 1,3,5-triazine and isoxazole rings for the two independent molecules of 4-ethoxycarbonyl-3-(2-methoxy-4-pyrrolidinyl-1,3,5-triazin-6-yl)-5-methylisoxazole are 84.0(2)º and 64.1(2)º [1]. This is evidently due to the presence of the substituent in position 4 of the isoxazole ring which leads to repulsion of the unshared electron pairs of the 1,3,5-triazine ring nitrogen atom and the oxygen atom of the ethoxycarbonyl group. With the absence of a 4 substituent in the 3-(4-dimethylamino-2-methoxy-1,3,5-triazin-6-yl)-5-hydroxymethylisoxazole (**3b**) the rings virtually lie in a single plane. Moreover, an insignificant (0.02 Å) decrease was seen in the inter ring C–C bond when compared with 4-ethoxycarbonyl-3-(2-methoxy-4-pyrrolidinyl-1,3,5-triazin-6-yl)-5-methylisoxazole [1].

The crystal packing of compound **3b** is primarily determined by intermolecular hydrogen bonds of the type OH···N. Due to these bonds the compound **3b** molecules form centrosymmetric hydrogen bonded dimers (as in Fig. 2). The hydrogen bond parameters are: O(18)–H(18)···(N(1)' bond (1-*x*, 1-*y*, 2-*z*), *d* O(18)–H(18) = 0.91(2), *d* H(18)···N(1)' = 2.04(2), *d* O(18)···N(1)' = 2.926(2) Å, ω O(18)H(18)N(1)' = 164(2)º.

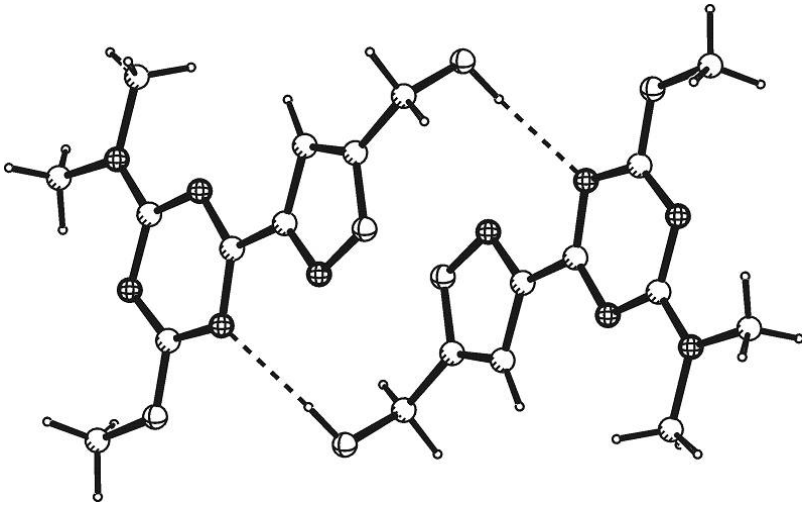


Fig. 2. H-Dimers in the molecule of compound **3b** formed *via* O(18)–H(18)···N(1)' hydrogen bonding in the crystal.

TABLE 1. Bond Lengths (*d*) in the Compound **3b** Molecule

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
N(1)–C(6)	1.340(3)	C(4)–N(7)	1.333(2)	C(15)–C(17)	1.492(3)
N(1)–C(2)	1.341(2)	C(6)–C(12)	1.474(2)	C(11)–O(10)	1.446(3)
N(3)–C(2)	1.317(2)	C(12)–N(13)	1.311(2)	N(7)–C(8)	1.450(3)
N(3)–C(4)	1.357(3)	C(12)–C(16)	1.410(3)	N(7)–C(9)	1.464(4)
N(5)–C(6)	1.322(2)	N(13)–O(14)	1.401(2)	O(18)–C(17)	1.408(2)
N(5)–C(4)	1.352(2)	O(14)–C(15)	1.346(2)		
C(2)–O(10)	1.333(3)	C(16)–C(15)	1.341(2)		

TABLE 2. Valence Angles (ω) in the Compound **3b** Molecule

Angle	ω, deg	Angle	ω,deg
C(6)–N(1)–C(2)	112.46(15)	N(13)–C(12)–N(6)	121.28(16)
C(2)–N(3)–C(4)	113.94(16)	C(12)–C(16)–C(6)	126.97(15)
C(6)–N(5)–C(4)	114.52(15)	C(12)–N(13)–O(14)	104.87(14)
N(3)–C(2)–O(10)	119.70(16)	C(15)–O(14)–N(13)	109.16(13)
N(3)–C(2)–N(1)	127.71(16)	C(15)–C(16)–C(12)	104.74(15)
O(10)–C(2)–N(1)	112.59(15)	C(16)–C(15)–O(14)	109.47(15)
N(7)–C(4)–N(5)	117.60(16)	C(16)–C(15)–C(17)	133.70(16)
N(7)–C(4)–N(3)	118.15(16)	O(14)–C(15)–C(17)	116.71(16)
N(5)–C(4)–N(3)	124.24(16)	C(4)–N(7)–C(8)	121.83(18)
N(5)–C(6)–N(1)	126.96(16)	C(4)–N(7)–C(9)	120.54(17)
N(5)–C(6)–C(12)	114.68(15)	C(8)–N(7)–C(9)	117.59(20)
N(1)–C(6)–C(12)	118.35(15)	O(18)–C(17)–C(15)	112.32(15)
N(13)–C(12)–C(16)	111.75(16)	C(2)–O(10)–C(11)	117.67(16)

EXPERIMENTAL

IR spectra were recorded on an Avatar 360ESP spectrophotometer for KBr tablets and ^{1}H NMR spectra on a Bruker AM-300 (300 MHz) spectrometer using DMSO-d_6 (compounds **2a-e**) or $CDCl_3$ (compounds **3a-e**) with TMS as internal standard.

Compounds **1a-e** were prepared as in method [6].

X-ray Structural Analysis of the Crystals of Compound 3b was carried out at 20ºC on a Bruker Smart APEX II CCD diffractometer (λMoKα radiation [λ = 0.71073 Å], graphite monochromator, ω-scanning). The SAINT Plus program [7] was used in the treatment of the starting group of experimental intensities. The structure was solved by a direct method and refined by F^2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms. All of the calculations were performed using the SHELXTL PLUS5 program package [8]. Hydrogen atoms were revealed in difference Fourier synthesis and refined isotropically. All of the figures and analysis of the intermolecular interactions were carried out using the PLATON program [9].

Crystals of compound **3b** were prepared from a mixture of dichloroethane and methanol (1:1) as colorless, transparent, triclinic prisms. $C_{10}H_{13}N_5O_3$. M = 251.25, a = 8.1898(8), b = 8.6088(8), c = 9.5926(9) Å; α = 67.721(1), β = 88.074(1), γ = 70.766(1)º; V = 587.7(1) Å^3, d_{calc} = 1.42 g/cm^3, Z = 2, space group P-1. Scanning angle 2.3º ≤ θ ≤ 26.0º. 2209 Independent reflections were measured, 1444 of which had I > 2σ. Calculation of absorbance was not included due to its insignificance (μ(Mo) = 1.1 cm^{-1}). The final divergence factor values were R_{ob} = 0.037 and R_{wob} = 0.096. The study of the single crystal study was carried out in the Department of X-ray Structure Investigation of the Shared Use Center at Laboratory of Research by Diffraction Methods of the A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Science Center of the Russian Academy of Sciences. The atomic coordinates and structural parameters have been placed in the Cambridge crystallographic database (CCDC 704356).

3-(2,4-Dimethoxy-1,3,5-triazin-6-yl)-5-phenylisoxazole (2a). A suspension of compound **1a** (2.46 g, 1 mmol) in phenylacetylene (15 ml) was heated to 90-100ºC and held at this temperature with stirring until the starting **1a** had disappeared (TLC, 1-1.5 h). After this time the excess phenylacetylene was removed under reduced pressure and the residue was treated with cold ethyl acetate (2×5 ml). The crystalline product was filtered off and washed on the filter with cold ethyl acetate (5 ml). Yield 2.33 g (82%); mp 168-170ºC. IR spectrum, ν, cm^{-1}: 3151, 3045, 3006, 2952, 2877, 1610, 1544, 1521, 1467, 1448, 1430, 1396, 1350, 1228, 1199,

1105, 1052, 995, 933, 850, 831, 808, 771, 692. ^{1}H NMR spectrum, δ, ppm: 3.99 (6H, s, OCH_3); 7.55 (4H, m, CH isoxazole and 3H Ph) and 7.94 (2H, m, Ph). Found, %: C 59.35; H 4.32; N 19.60. $C_{14}H_{12}N_4O_3$. Calculated, %: C 59.15; H 4.25, N 19.71.

3-(4-Dimethylamino-2-methoxy-1,3,5-triazin-6-yl)-5-phenylisoxazole (2b) was prepared similarly to compound **2a** from compound **1b** (2.42 g, 1 mmol). Yield 2.38 g (80%); mp 163-165ºC. IR spectrum, ν, cm^{-1}: 3153, 3062, 3012, 2927, 2869, 1591, 1567, 1525, 1467, 1446, 1429, 1367, 1315, 1259, 1214, 1070, 1047, 938, 946, 817, 802, 771, 698. ^{1}H NMR spectrum, δ, ppm: 3.18 and 3.24 (6H, two s, Δν = 18 Hz, NCH_3); 3.98 (3H, s, OCH_3); 7.53 (4H, m, CH isoxazole and 3H Ph) and 7.90 (2H, m, Ph). Found, %: C 60.52; H 5.21; N 23.67. $C_{15}H_{15}N_5O_2$. Calculated, %: C 60.60; H 5.09; N 23.55.

3-(2-Methoxy-4-pyrrolidinyl-1,3,5-triazin-6-yl)-5-phenylisoxazole (2c) was prepared similarly to compound **2a** from compound **1c** (2.68 g, 1 mmol). Yield 2.39 g (74%); mp 205-207ºC. IR spectrum, ν, cm^{-1}: 3147, 3068, 3056, 2971, 2954, 2883, 1587, 1560, 1523, 1479, 1461, 1432, 1359, 1338, 1311, 1226, 1062, 985, 946, 804, 769, 692. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.00 (4H, m, CH_2); 3.62 and 3.74 (4H, two t, *J* = 6.8, NCH_2); 4.02 (3H, s, OCH_3); 7.51 (4H, m, CH isoxazole and 3H Ph); 7.84 (2H, m, Ph). Found, %: C 63.04; H 5.46; N 21.50. $C_{17}H_{17}N_5O_2$. Calculated, %: C 63.15; H 5.30; N 21.66.

3-(2-Methoxy-4-piperidino-1,3,5-triazin-6-yl)-5-phenylisoxazole (2d) was prepared similarly to compound **2a** from compound **1d** (2.82 g, 1 mmol). Yield 2.60 g (77%); mp 152-153ºC. IR spectrum, ν, cm^{-1}: 3141, 3039, 3000, 2941, 2921, 2858, 1577, 1525, 1465, 1448, 1429, 1369, 1286, 1228, 1095, 1054, 1002, 977, 948, 923, 889, 815, 773, 696. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60 (6H, m, CH_2); 3.82 and 3.92 (4H, two t, *J* = 7.0, NCH_2); 3.99 (3H, s, OCH_3); 7.55 (4H, m, CH isoxazole and 3H Ph), and 7.98 (2H, m, Ph). Found, %: C 64.15; H 5.74; N 20.78. $C_{18}H_{19}N_5O_2$. Calculated, %: C 64.08; H 5.68; N 20.76.

3-(2-Methoxy-4-morpholino-1,3,5-triazin-6-yl)-5-phenylisoxazole (2e) was prepared similarly to compound **2a** from compound **1e** (2.84 g, 1 mmol). Yield 2.75 g (81%); mp 184-186ºC. IR spectrum, ν, cm^{-1}: 3142, 3054, 3037, 2958, 2929, 2869, 1610, 1569, 1525, 1471, 1446, 1363, 1278, 1226, 1116, 1064, 1014, 981, 948, 887, 802, 769, 696. ^{1}H NMR spectrum, δ, ppm: 3.70, 3.82 and 3.91 (8H, three m, NCH_2CH_2O); 3.99 (3H, s, OCH_3); 7.56 (4H, m, CH isoxazole and 3H Ph), and 7.92 (2H, m, Ph). Found, %: C 60.28; H 5.00; N 20.52. $C_{17}H_{17}N_5O_3$. Calculated, %: C 60.17; H 5.05; N 20.64.

3-(2,4-Dimethoxy-1,3,5-triazin-6-yl)-5-hydroxymethylisoxazole (3a). A suspension of compound **1a** (2.46 g, 1 mmol) in propargyl alcohol (10 ml) was heated to 85-95ºC and held at this temperature with stirring until the starting compound **1a** had disappeared (TLC, 1-1.5 h). Excess propargyl alcohol was then removed at reduced pressure and the residue was treated with cold ethyl acetate (2×5 ml). The crystalline product was filtered off and washed on the filter with cold ethyl acetate (5 ml). Yield 2.07 g (86%); mp 130-132ºC (decomp.). IR spectrum, ν, cm^{-1}: 3423, 3158, 3008, 2962, 2917, 1608, 1560, 1529, 1490, 1477, 1457, 1430, 1394, 1359, 1199, 1110, 1079, 1045, 983, 945, 825, 800. ^{1}H NMR spectrum, δ, ppm; 4.01 (6H, s, OCH_3); 3.80 (1H, br. s, OH); 4.81 (2H, s, CH_2); 6.86 (1H, s, CH). Found, %: C 45.47; H 4.15; N 23.46. $C_9H_{10}N_4O_4$. Calculated, %: C 45.38; H 4.23; N 23.52.

3-(4-Dimethylamino-2-methoxy-1,3,5-triazin-6-yl)-5-hydroxymethylisoxazole (3b) was prepared similarly to compound **3a** from compound **1b** (2.42 g, 1 mmol). Yield 2.03 g (81%); mp 140-143ºC. IR spectrum, ν, cm^{-1}: 3346; 3172, 3012, 2933, 2875, 1604, 1592, 1525, 1473, 1415, 1373, 1338, 1261, 1216, 1105, 1066, 1037, 981, 921, 900, 815, 802. ^{1}H NMR spectrum, δ, ppm: 3.19 and 3.27 (6H, two s, Δν = 24 Hz, NCH_3); 4.00 (3H, s, OCH_3); 3.85 (1H, br. s, OH); 4.82 (2H, s, CH_2); 6.83 (1H, s, CH). Found, %: C 47.68; H 5.30; N 27.81. $C_{10}H_{13}N_5O_3$. Calculated, %: C 47.81; H 5.22; N 27.87.

5-Hydroxymethyl-3-(2-methoxy-4-pyrrolidinyl-1,3,5-triazin-6-yl)isoxazole (3c) was prepared similarly to compound **3a** from compound **1c** (2.68 g, 1 mmol). Yield 2.08 g (75%); mp 184-185ºC (decomp.). IR spectrum, ν, cm^{-1}: 3347, 3155, 3025, 2973, 2925, 2877, 1587, 1565, 1521, 1473, 1434, 1369, 1336, 1236, 1184, 1164, 1110, 1056, 1039, 981, 912, 844, 819, 804. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.01 (4H, m, CH_2);

2.81 (1H, br. s, OH); 3.63 and 3.72 (4H, two t, J = 7.0, NCH_2); 4.06 (3H, s, OCH_3); 4.85 (2H, s, CH_2); 6.88 (1H, s, CH). Found, %: C 52.10; H 5.49; N 25.20. $C_{12}H_{15}N_5O_3$. Calculated, %: C 51.98; H 5.45; N 25.26.

5-Hydroxymethyl-3-(2-methoxy-4-piperidino-1,3,5-triazin-6-yl)isoxazole (3d) was prepared similarly to compound **3a** from compound **1d** (2.82 g, 1 mmol). Yield 2.27 g (78%); mp 125-127ºC (decomp.). IR spectrum, ν, cm^{-1}: 3330, 3128, 3000, 2933, 2861, 1577, 1521, 1475, 1434, 1375, 1290, 1261, 1226, 1110, 1043, 995, 979, 919, 817, 794. ^{1}H NMR spectrum, δ, ppm (J, Hz): 1.69 (6H, m, CH_2); 2.48 (1H, br. s, OH); 3.85 and 3.95 (4H, two t, J = 7.2, NCH_2); 4.06 (3H, s, OCH_3); 4.83 (2H, s, CH_2); 6.89 (1H, s, CH). Found, %: C 53.48; H 6.01; N 23.97. $C_{13}H_{17}N_5O_3$. Calculated, %: C 53.60; H 5.88; N 24.04.

5-Hydroxymethyl-3-(2-methoxy-4-morpholino-1,3,5-triazin-6-yl)isoxazole (3e) was prepared similarly to compound **3a** from compound **1e** (2.84 g, 1 mmol). Yield 2.34 g (80%); mp 163-165ºC. IR spectrum, ν, cm^{-1}: 3300, 3133, 2996, 2929, 2854, 1577, 1523, 1479, 1436, 1378, 1282, 1234, 1112, 1045, 1016, 981, 925, 892, 817, 800. ^{1}H NMR spectrum, δ, ppm: 2.62 (1H, br. s, OH); 3.74 and 3.86 (8H, m, NCH_2CH_2O); 4.04 (3H, s, OCH_3); 4.86 (2H, s, CH_2); 6.85 (1H, s, CH). Found, %: C 49.22; H 5.28; N 23.99. $C_{12}H_{15}N_5O_4$. Calculated, %: C 49.14; H 5.16; N 23.88.

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