Chemistry of Heterocyclic Compounds, Vol. 48, No. 6, September, 2012 (Russian Original Vol. 48, No. 6, June, 2012)

REACTIONS OF 1,3,5-TRIAZINYLNITROFORMALDOXIMES 5*. SYNTHESIS OF 5-R-3-(1,3,5-TRIAZINYL)-4,5-DIHYDRO-ISOXAZOLES

V. V. Bakharev[1], A. A. Gidaspov[1], E. V. Selezneva[1], and O. S. El'tsov[2]**

1,3,5-Triazinylnitrile oxides, formed by heating (2-methoxy-4-R-1,3,5-triazin-6-yl)nitroformaldoximes, react with monosubstituted and 1,1-disubstituted ethylenes with the formation of 3-(1,3,5-triazinyl)-5-monosubstituted and 3-(1,3,5-triazinyl)-5,5-disubstituted 2-isoxazolines. The cycloaddition occurs with high regioselectivity to give exclusively 2-isoxazolines substituted at the positions 3 and 5.

Keywords: 3-(1,3,5-triazinyl)-4,5-dihydroisoxazoles, 1,3,5-triazinylnitrile oxides, 1,3,5-triazinylnitroformaldoximes, cycloaddition.

2-Isoxazolines are widely used in organic synthesis as starting materials for preparation of β-hydroxy ketones [2-6], γ-amino alcohols [6, 7], α,β-unsaturated ketones [8], β-hydroxynitriles and β-hydroxycarboxylic acids [2, 9, 10], α- and β-amino acids [11-13], and a series of natural biologically active compounds [14, 15]. Derivatives of these heterocycles possess various types of biological activity: antimicrobial [16], antiviral [17], antidepressive [18], antidiabetic [19], antiasthmatic [20], anti-inflammatory [20, 21]. A series of derivatives of 2-isoxazoline are used as herbicides and for plant protection [22-24].

One of the basic methods for the preparation of 3,5-disubstituted 4,5-dihydroisoxazoles is the regioselective cycloaddition of nitrile oxides to alkenes [25-28]. We have previously synthesized 3,5-disubstituted isoxazoles by 1,3-dipolar cycloaddition of 1,3,5-triazinylnitrile oxides, generated by thermolysis of the corresponding 2,4-disubstituted 1,3,5-triazinylnitroformaldoximes, to monosubstituted acetylenes [29].

With the objective of synthesizing 5-mono- and 5,5-disubstituted 3-(1,3,5-triazinyl)-4,5-dihydroisoxazoles we have studied the thermolysis of (4-methoxy-6-R-1,3,5-triazin-2-yl)nitroformaldoximes **1** in the presence of monosubstituted and 1,1-disubstituted ethylenes. Heating a suspension of (4-methoxy-6-R-1,3,5-triazin-2-yl)-nitroformaldoximes **1a-c** with a 5-fold excess of acrylonitrile in toluene at 80-120°C resulted in the formation of 3-(4-methoxy-6-R-1,3,5-triazin-2-yl)-4,5-dihydroisoxazole-5-carbonitriles **2a-c** (39-45% yield) and 3,4-di(2-methoxy-4-R-1,3,5-triazin-6-yl)furoxanes **3a-c** (30-36% yield).

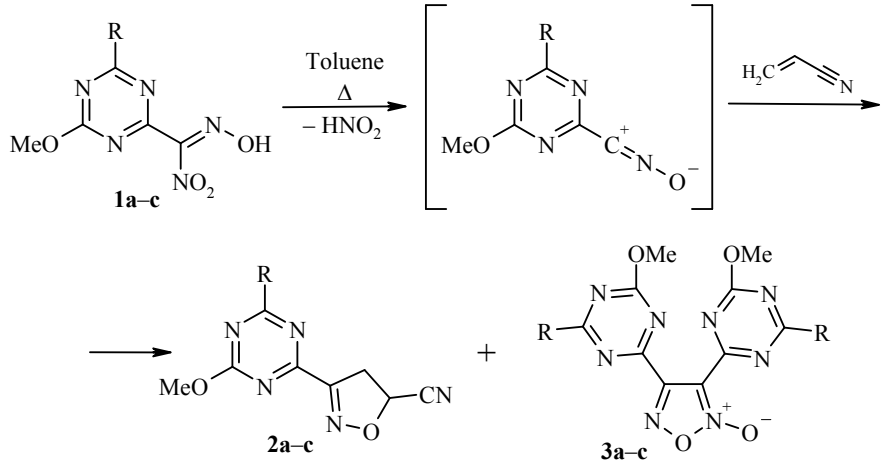
*For Communication 4, see [1].

**To whom correspondence should be addressed, e-mail: knil@sstu.smr.ru.

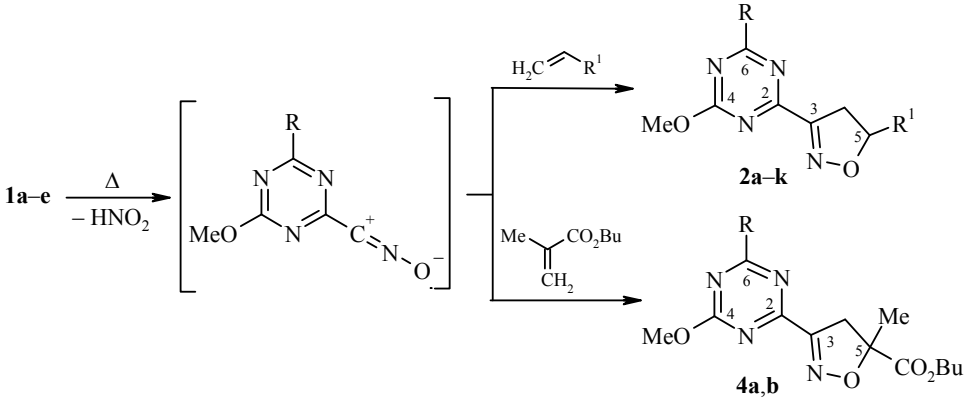
[1]Samara State Technical University, 244 Molodogvardeiskaya St., Samara 443100, Russia.
[2]Ural Federal University named after the First President of Russia B. N. Eltsin, 19 Mira St., Yekaterinburg 620002, Russia; e-mail: oleg-eltsov@yandex.ru.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, 982-988, June, 2012. Original article submitted March 11, 2011.

So, despite the use of a large excess of the dipolarophile, dimerization of the intermediate 1,3,5-triazinylnitrile oxides occurred to give the furoxanes **3a-c**. Carrying out the reaction directly in the dipolarophile without dilution with an inert solvent allowed to completely suppress this side reaction. Heating compounds **1a-e** in monosubstituted ethylenes (acrylonitrile, allyl alcohol, methyl acrylate, styrene) and 1,1-disubstituted ethylenes (butyl methacrylate) at 80-120°C gave 5-R^1-3-(4-methoxy-6-R-1,3,5-triazin-2-yl)-4,5-dihydroisoxazoles **2a-k** with 65-80% yield and butyl 3-(4-methoxy-6-R-1,3,5-triazin-2-yl)-5-methyl-4,5-dihydroisoxazol-5-carboxylates **4a-b** in 68-70% yields.



a R = OMe, **b** R = NMe_2, **c** R = $N(CH_2CH_2)_2O$



1d, 4a R = $N(CH_2)_4$; **1e, 4b** R = $N(CH_2)_5$; **2 d** R = OMe, R^1 = CH_2OH; **e** R = NMe_2, R^1 = CH_2OH;
f R = NMe_2, R^1 = C_5H_{11}; **g** R = NMe_2, R^1 = C_6H_{13}; **h** R = OMe, R^1 = CO_2Me;
i R = NMe_2, R^1 = CO_2Me; **j** R = $N(CH_2CH_2)_2O$, R^1 = CO_2Me; **k** R = $N(CH_2)_5$, R^1 = Ph

The formation of the 4,5-dihydroisoxazoles **2a-k** and **4a,b** was confirmed by the presence in their ^{13}C NMR spectra of signals in the regions of 35-44, 67-87, and 156-158 ppm (Table 1), which are characteristic of the carbon atoms C-4, C-5, and C-3, respectively, in the 4,5-dihydroisoxazole ring [9, 27, 29-32].

The signals of the C-4 and C-5 carbons of the 4,5-dihydroisoxazole ring are very sensitive to the type of substituent at the position 5, which is also confirmed and in excellent agreement with known data [10, 28, 30-33]. In the IR spectra of compounds **2a-c**, there is a weak stretching band of the cyano group in the 2246-2250 cm^{-1} range. In the IR spectra of compounds **2d,e**, hydroxyl stretching band was noted (quite sharp at 3448 cm^{-1} for compound **2d** and broader at 3392 cm^{-1} for compound **2e**). In the IR spectra of

TABLE 1. ^{13}C NMR Spectra of Dihydroisoxazoles **2a-k** and Butyl Esters **4a,b**

Compound	Chemical shifts, δ, ppm						
	1,3,5-Triazine			4,5-Dihydroisoxazole			4-OCH_3, R, R^1
	C-2	C-4	C-6	C-3	C-4	C-5	
2a	172.7	172.7	167.2	156.6	40.1	68.2	116.4 (CN); 55.9 (OCH_3)
2b	166.1	170.8	164.9	157.4	40.6	67.6	116.7 (CN); 54.6 (OCH_3); 36.6 ($N(CH_3)_2$)
2c	165.6	171.2	165.3	157.2	40.5	67.7	116.5 (CN); 66.6 ($2OCH_2$); 54.9 (OCH_3); 44.2, 43.8 ($2NCH_2$)
2d	172.6	172.6	168.5	157.1	35.0	84.0	63.4 (CH_2OH); 55.1 (OCH_3)
2e	166.1	170.7	166.0	157.8	35.6	83.3	63.3 (CH_2OH); 54.4 (OCH_3); 36.5 ($N(CH_3)_2$)
2f	166.4	170.8	166.2	157.3	39.0	83.3	54.4 (OCH_3); 36.4 ($N(CH_3)_2$); 35.3, 24.6 (CH_2); 13.9 (CH_3)
2g	166.5	170.8	166.2	157.3	39.0	83.3	54.4 (OCH_3); 36.6, 36.3 ($N(CH_3)_2$); 35.2, 31.6, 29.0, 25.1, 22.5 (CH_2); 14.0 (CH_3)
2h	171.3	172.7	168.0	156.4	37.8	79.4	175.0 (C=O); 55.7 (OCH_3); 51.8 ($CO_2\underline{C}H_3$)
2i	166.2	170.8	165.5	157.1	38.3	79.2	174.9 (C=O); 54.5 (OCH_3); 52.8 ($CO_2\underline{C}H_3$); 36.5 ($N(CH_3)_2$)
2j	165.9	171.8	165.5	157.0	38.2	79.1	172.3 (C=O); 66.6 ($2OCH_2$); 54.8 (OCH_3); 52.9 ($CO_2\underline{C}H_3$); 44.3 ($2NCH_2$)
2k	166.5	171.2	165.3	157.3	42.3	84.2	140.5, 128.7, 128.0, 127.6, 126.05 (C Ph); 54.6 (OCH_3); 44.6 ($2NCH_2$); 25.8, 25.7 ($2CH_2$); 24.4 ($2CH_2$)
4a	165.7	170.7	164.0	156.9	44.1	87.8	177.3 (C=O); 64.6 ($CO_2\underline{C}H_2$); 54.4 (OCH_3); 46.5 ($2NCH_2$); 30.1 (CH_2); 25.0 (CH_2 pyrrolidine); 23.5 (CH_3); 19.2 (CH_2); 13.7 (CH_3)
4b	166.1	171.3	165.1	156.9	44.1	87.6	177.4 (C=O); 64.7 ($CO_2\underline{C}H_2$); 54.4 (OCH_3); 45.0, 44.4 ($2NCH_2$); 30.3 (CH_2); 25.7 (CH_2 piperidine); 24.4 (CH_2 piperidine); 23.5 (CH_3); 19.1 (CH_2); 13.6 (CH_3)

compounds **2h-j** and **4a,b**, a weak stretching band of the carbonyl group in the 1727-1745 cm^{-1} range was observed. In the ^1H NMR spectra of the compounds synthesized, proton signals of the substituents in the 1,3,5-triazine and 4,5-dihydroisoxazole rings are observed, and also signals of the protons H-4 (doublet or multiplet in the 3.6-3.9 ppm region) and H-5 (triplet in the 4.7-5.5 ppm region, except for compounds **4a,b**).

So we have developed a method for regioselective synthesis of 2-isoxazolines, substituted in the positions 3 and 5, based on the 1,3-dipolar cycloaddition of 1,3,5-triazinylnitrile oxides to mono- and disubstituted alkenes.

EXPERIMENTAL

IR spectra were recorded on an Avatar 360ESP spectrophotometer. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions with TMS as internal standard were recorded on a Bruker Avance II spectrometer (400 and 100 MHz, respectively). Elemental analyses were determined with a Eurovector EA 3000 apparatus. Melting points of the compounds synthesized were determined with a Gallenkamp melting block. The course of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates. For the isolation and purification of the synthesized compounds by column chromatography, silica gel MN Kieselgel 60 (0.063-0.200 μm) was used.

Compounds **1a-e** were synthesized by a known method [34].

Reactions of (4-Methoxy-6-R-1,3,5-triazin-2-yl)nitroformaldoximes 1a-c with Acrylonitrile in Toluene (General Method). A suspension of nitroformaldoxime **1a-c** (0.5 mmol) and acrylonitrile (1.64 ml, 2.5 mmol) in toluene (20 ml) was heated for 4 h at 80-100°C. The toluene and excess acrylonitrile were evaporated in vacuum, the residue was dissolved in AcOEt and separated on a column with a 4:1 dichloroethane–AcOEt eluent. Yields of 4,5-dihydroisoxazoles **2a** 45%, **2b** 42%, **2c** 39%, of furoxanes **3a** 30%, **3b** 35%, **3c** 36%. The analytical data for 3-(4-methoxy-6-R-1,3,5-triazin-2-yl)-4,5-dihydroisoxazole-5-carbonitriles **2a-c** are given below, while for the furoxanes **3a-c** correspond fully to the literature data [34].

3-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4,5-dihydroxazole-5-carbonitrile (2a). A suspension of nitroformaldoxime **1a** (2.29 g, 1 mmol) in acrylonitrile (15 ml) was heated to 85-95°C and maintained at this temperature for 8 h. The excess of acrylonitrile was removed in vacuum, the residue was dissolved in AcOEt and passed through a layer of silica gel, the AcOEt was removed in vacuum, and the residue was treated with water (20 ml). The insoluble residue was filtered off, washed with water (5 ml), and dried in air. Yield 1.79 g (76%); mp 123-125°C. IR spectrum (KBr), ν, cm^{-1}: 3025, 3002, 2977, 2950, 2877, 2246, 1604, 1560, 1504, 1467, 1421, 1398, 1373, 1297, 1240, 1205, 1147, 1108, 1031, 1000, 935, 923, 881, 835, 819. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.80 (2H, d, *J* = 6.8, 4-CH_2); 4.05 (6H, s, 2OCH_3); 5.52 (1H, t, *J* = 6.8, 5-CH). Found, %: C 45.83; H 3.82; N 29.92. $C_9H_9N_5O_3$. Calculated, %: C 45.96; H 3.86; N 29.78.

3-(6-Dimethylamino-4-methoxy-1,3,5-triazin-2-yl)-4,5-dihydroisoxazole-5-carbonitrile (2b) was prepared analogously to compound **2a** from nitroformaldoxime **1b** (2.42 g, 1 mmol). Yield 1.98 g (80%); mp 130-132°C. IR spectrum (KBr), ν, cm^{-1}: 2993, 2956, 2939, 2857, 2804, 2248, 1598, 1567, 1517, 1471, 1413, 1365, 1294, 1224, 1141, 1070, 1024, 910, 891, 813. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.18 (3H, s) and 3.21 (3H, s, $N(CH_3)_2$); 3.77-3.81 (2H, m, 4-CH_2); 3.95 (3H, s, OCH_3); 5.43 (1H, t, *J* = 7.6, 5-CH). Found, %: C 48.50; H 4.98; N 33.72. $C_{10}H_{12}N_6O_2$. Calculated, %: C 48.38; H 4.87; N 33.85.

3-(4-Methoxy-6-morpholino-1,3,5-triazin-2-yl)-4,5-dihydroisoxazole-5-carbonitrile (2c) was obtained analogously to compound **2a** from nitroformaldoxime **1c** (2.84 g, 1 mmol). Yield 1.98 g (72%); mp 150-153°C. IR spectrum (KBr) ν, cm^{-1}: 2998, 2966, 2929, 2894, 2856, 2250, 1612, 1565, 1513, 1473, 1450, 1373, 1299, 1268, 1234, 1112, 1068, 1043, 999, 910, 885, 865, 811. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.74-3.81 (10H, m, $N(CH_2CH_2)_2O$, 4-CH_2); 4.01 (3H, s, OCH_3); 5.44 (1H, t, *J* = 9.2, 5-CH). Found, %: C 49.53; H 4.94; N 28.79. $C_{12}H_{14}N_6O_3$. Calculated, %: C 49.65; H 4.86; N 28.95.

[3-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4,5-dihydroisoxazol-5-yl]methanol (2d). A suspension of nitroformaldoxime **1a** (2.29 g, 1 mmol) in allyl alcohol (15 ml) was heated to 85-95°C and maintained at that temperature for 5 h. The excess allyl alcohol was evaporated in vacuum. The residue was treated analogously to the compound **2a**. Yield 1.63 g (68%); mp 117-119°C (decomp.). IR spectrum (KBr), ν, cm^{-1}: 3448, 3012, 2954, 2904, 2858, 1600, 1544, 1508, 1465, 1450, 1390, 1363, 1290, 1238, 1193, 1108, 1070, 1039, 937, 846, 823, 790. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.84 (1H, br. s, OH); 3.29-3.46 (2H, m C$\underline{H_2}$OH); 3.69 (1H, dd, J_{gem} = 8.0, $J_{4,5}$ = 4.5) and 3.87 (1H, dd, J_{gem} = 8.0, $J_{4,5}$ = 3.0, 4-CH_2); 4.06 (6H, s, 2OCH_3); 4.95 (1H, m, 5-CH). Found, %: C 45.09, H 5.11, N 23.25. $C_9H_{12}N_4O_4$. Calculated, %: C 45.00; H 5.04; N 23.32.

[3-(6-Dimethylamino-4-methoxy-1,3,5-triazin-2-yl)-4,5-dihydroisoxazol-5-yl]methanol (2e) was prepared analogously to compound **2d** from nitroformaldoxime **1b** (2.42 g, 1 mmol). Yield 1.77 g (70%); mp 136-138°C (decomp.). IR spectrum (KBr), ν, cm^{-1}: 3392, 3008, 2939, 2871, 1610, 1591, 1556, 1511, 1475, 1413, 1369, 1292, 1220, 1081, 1022, 989, 935, 898, 817, 784. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.10 (3H, s) and 3.15 (3H, s, $N(CH_3)_2$); 3.25-3.35 (3H, m, CH_2OH); 3.64 (1H, dd, J_{gem} = 8.0, $J_{4,5}$ = 4.8) and 3.76 (1H, dd, J_{gem} = 8.0, $J_{4,5}$ = 3.3, 4-CH_2), 3.89 (3H, s, OCH_3); 4.82-4.86 (1H, m, CH). Found, %: C 47.53, H 5.78, N 27.72. $C_{10}H_{15}N_5O_3$. Calculated, %: C 47.43, H 5.97, N 27.65.

[4-Methoxy-6-(5-pentyl-4,5-dihydroisoxazol-3-yl)-1,3,5-triazin-2-yl]dimethylamine (2f). A suspension of nitroformaldoxime **1b** (2.42 g, 1 mmol) in 1-heptene (15 ml) was heated to 90-95°C and maintained at this temperature for 4 h. The excess of 1-heptene was evaporated in vacuum. The residue was dissolved in AcOEt and passed through a layer of silica gel. The AcOEt was evaporated in vacuum, and the residue was dried in vacuum. Yield 1.96 g (67%). Light-yellow viscous liquid. IR spectrum (thin film), ν, cm^{-1}: 2954, 2931, 2860,

1587, 1560, 1519, 1469, 1411, 1365, 1292, 1261, 1222, 1093, 1022, 929, 902, 815, 790. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.81 (3H, t, *J* = 7.2, CH_3); 1.24-1.78 (8H, m, $(CH_2)_4$); 3.12 (3H, s) and 3.18 (3H, s, $N(CH_3)_2$); 2.93-2.98 (1H, m) and 3.26-3.36 (1H, m, 4-CH_2); 3.91 (3H, s, OCH_3); 4.72 (1H, m, 5-CH). Found, %: C 57.43; H 7.99; N 23.72. $C_{14}H_{23}N_5O_2$. Calculated, %: C 57.32; H 7.90; N 23.87.

[6-(5-Hexyl-4,5-dihydroisoxazol-3-yl)-1,3,5-triazin-2-yl]-4-methoxydimethylamine (2g) was obtained analogously to the compound **2f** from nitroformaldoxime **1b** (2.42 g, 1 mmol) and 1-octene (15 ml) at 115-120°C. Yield 2.24 g (73%). Light-yellow viscous liquid. IR spectrum (thin film), ν, cm^{-1}: 2952, 2927, 2856, 1587, 1560, 1517, 1457, 1411, 1365, 1292, 1261, 1222, 1091, 1022, 929, 904, 815. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 (3H, t, *J* = 6.8, CH_3); 1.23-1.72 (10H, m, $(CH_2)_5$); 3.14 (3H, s) and 3.20 (3H, s, $N(CH_3)_2$); 2.94-2.99 (1H, m) and 3.29-3.39 (1H, m, 4-CH_2); 3.92 (3H, s, OCH_3); 4.72-4.76 (1H, m, 5-CH). Found, %: C 58.76, H 8.24, N 22.63. $C_{15}H_{25}N_5O_2$. Calculated, %: C 58.61; H 8.20; N 22.78.

Methyl 3-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4,5-dihydroisoxazole-5-carboxylate (2h). A suspension of nitroformaldoxime **1a** (2.29 g, 1 mmol) in methyl acrylate (15 ml) was heated to 80-85°C and maintained at this temperature for 5 h. The excess methyl acrylate was evaporated in vacuum, the residue was dissolved in AcOEt and passed through a layer of silica gel. The AcOEt was evaporated in vacuum and the residue was dried in vacuum. Yield 1.98 g (74%). Colorless transparent viscous liquid. IR spectrum (thin film), ν, cm^{-1}: 3002, 2954, 2929, 2850, 1733, 1596, 1556, 1508, 1436, 1392, 1357, 1199, 1164, 1124, 1108, 1037, 825. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.70 (2H, d, *J* = 4.0, 4-CH_2); 3.80 (3H, s, CO_2CH_3); 4.08 (6H, s, $2OCH_3$); 5.28-5.32 (1H, m, 5-CH). Found, %: C 44.92; H 4.47; N 20.95. $C_{10}H_{12}N_4O_5$. Calculated, %: C 44.78; H 4.51; N 20.89.

Methyl 3-(6-dimethylamino-4-methoxy-1,3,5-triazin-2-yl)-4,5-dihydroisoxazole-5-carboxylate (2i) was prepared analogously to compound **2h** from nitroformaldoxime **1b** (2.42 g, 1 mmol). Yield 2.22 g (79%). Colorless transparent viscous liquid. IR spectrum (thin film), ν, cm^{-1}: 2989, 2956, 2914, 2875, 1753, 1735, 1608, 1564, 1513, 1473, 1436, 1371, 1294, 1224, 1162, 1081, 1068, 1020, 921, 894, 815, 676. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.14 (3H, s) and 3.18 (3H, s, $N(CH_3)_2$); 3.61 (2H, d, *J* = 4.2, 4-CH_2); 3.74 (3H, s, CO_2CH_3); 3.93 (3H, s, OCH_3); 5.18 (1H, t, *J* = 8.2, 5-CH). Found, %: 47.05, H 5.27; N 24.99. $C_{11}H_{15}N_5O_4$. Calculated, %: C 46.97; H 5.38; N 24.90.

Methyl 3-(4-methoxy-6-morpholino-1,3,5-triazin-2-yl)-4,5-dihydroisoxazole-5-carboxylate (2j) was obtained analogously to compound **2h** from nitroformaldoxime **1b** (2.42 g, 1 mmol). Yield 2.42 g (75%). Colorless transparent viscous liquid. IR spectrum (thin film) ν, cm^{-1}: 2996, 2958, 2923, 2858, 1745, 1565, 1517, 1467, 1448, 1371, 1282, 1230, 1114, 1043, 1002, 892, 815. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.66-3.88 (10H, m, $N(CH_2CH_2)_2O$, 4-CH_2); 3.81 (3H, s, CO_2CH_3); 3.98 (3H, s, OCH_3); 5.24 (1H, t, *J* = 8.0, 5-CH). Found, %: C 48.43; H 5.44; N 21.76. $C_{13}H_{17}N_5O_5$. Calculated, %: C 48.30; H 5.30; N 21.66.

4-Methoxy-2-(5-phenyl-4,5-dihydroisoxazol-3-yl)-6-(piperidin-1-yl)-1,3,5-triazine (2k). A suspension of nitroformaldoxime **1e** (2.82 g, 1 mmol) in styrene (10 ml) was heated to 115-120°C and maintained at this temperature until the starting compound **1e** disappeared (4 h, according to TLC data). The excess styrene was evaporated in vacuum. The residue was treated analogously to compound **2h.** Yield 2.20 g (65%). Colorless transparent viscous liquid. IR spectrum (thin film), ν, cm^{-1}: 3060, 3010, 2933, 2917, 2848, 1600, 1550, 1508, 1457, 1367, 1288, 1232, 1124, 1099, 1024, 981, 914, 887, 817, 761, 702, 669. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49-1.68 (6H, m, $3CH_2$); 3.40-3.48 (2H, m, 4-CH_2); 3.78-3.84 (4H, m, $N(CH_2)_2$); 3.97 (3H, s, OCH_3); 5.79 (1H, t, *J* = 8.0, 5-CH); 7.28-7.36 (5H, m, H Ph). Found, %: C 63.79; H 6.11; N 20.55. $C_{18}H_{21}N_5O_2$. Calculated, %: C 63.70; H 6.24; N 20.63.

Butyl 3-[4-Methoxy-6-(pyrrolidin-1-yl)-1,3,5-triazin-2-yl]-5-methyl-4,5-dihydroisoxazole-5-carboxylate (4a). A suspension of nitroformaldoxime **1d** (2.68 g, 1 mmol) in butyl methacrylate (10 ml) was heated to 105-110°C and maintained at this temperature for 3 h. The excess of butyl methacrylate was removed in vacuum, and the residue was treated analogously to compound **2h**. Yield 2.54 g (70%). Light-yellow viscous liquid. IR spectrum (thin film), ν, cm^{-1}: 2960, 2935, 2873, 1729, 1577, 1564, 1513, 1459, 1369, 1342, 1272, 1241, 1180, 1155, 1064, 1020, 966, 945, 819, 750. ^{1}H NMR spectrum, δ, ppm (*J* , Hz): 0.86 (3H, t, *J* = 7.6, CH_3); 1.26-1.34 (2H, m, CH_2); 1.55-1.58 (2H, m, CH_2); 1.60 (3H, s, 5-CH_3); 1.91 (4H, d, *J* = 9.6, $2CH_2$);

3.48-3.54 (4H, m, $N(CH_2)_2$); 3.83 (2H, s, 4-CH_2); 3.89 (3H, s, OCH_3); 4.09 (2H, t, J = 6.4, CO_2CH_2). Found, %: C 56.30; H 7.11; N 19.15. $C_{17}H_{25}N_5O_4$. Calculated, %: C 56.19; H 6.93; N 19.27.

Butyl 3-[4-methoxy-6-(piperidin-1-yl)-1,3,5-triazin-2-yl]-5-methyl-4,5-dihydroisoxazole-5-carboxylate (4b) was prepared analogously to compound **4a** from nitroformaldoxime **1e** (2.82 g, 1 mmol). Yield 2.56 g (68%). Light-yellow viscous liquid. IR spectrum (thin film), ν, cm^{-1}: 2958, 2935, 2873, 1727, 1558, 1515, 1465, 1371, 1290, 1272, 1241, 1176, 1155, 1064, 1022, 966, 945, 819, 750. ^{1}H NMR spectrum, δ, ppm (J, Hz): 0.86 (3H, t, J = 7.6, CH_3); 1.27-1.34 (2H, m, CH_2); 1.47-1.55 (8H, m, $4CH_2$); 1.59 (3H, s, CH_3); 3.77-3.81 (4H, m, $N(CH_2)_2$); 3.81 (2H, s, 4-CH_2); 3.87 (3H, s, OCH_3); 4.09 (2H, t, J = 6.4, CO_2CH_2). Found, %: C 57.34; H 7.35; N 18.40. $C_{18}H_{27}N_5O_4$. Calculated, %: C 57.28; H 7.21; N 18.55.

REFERENCES

1. V. V. Bakharev, A. A. Gidaspov, E. V. Selezneva, V. E. Parfenov, I. V. Ul'yankina, I. S. Nazarova, Yu. T. Palatova, and O. S. El'tsov, *Khim. Geterotsikl. Soedin*., 1521 (2011). [*Chem. Heterocycl. Compd*., **47**, 1258 (2011)].
2. E. V. Koroleva and F. A. Lakhvich, *Usp. Khim*., **66**, 31 (1997).
3. S. S. Ghabrial, I. Thomsen, and K. G. B. Torsell, *Acta Chem. Scand.*, **B41**, 426 (1987).
4. J. A. Kenar, *J. Am. Oil Chem. Soc.*, **79**, 351 (2002).
5. A. P. Kozikovski and M. Adamczyk, *Tetrahedron Lett.*, **23**, 3123 (1982).
6. D. Jiang and Y. Chen, *J. Org. Chem.*, **73**, 9181 (2008).
7. V. Jäger, V. Buß, and W. Schwab, *Tetrahedron Lett.*, 19, 3133 (1978).
8. H. Grund and V. Jäger, *Liebigs Ann. Chem*., 80 (1980).
9. A. P. Kozikovski and M. Adamczyk, *J. Org. Chem.*, **48**, 366 (1983).
10. S. Yang, W. Hayden, K. Faber, and H. Griengl, *Synthesis*, 365 (1992).
11. R. A. Mosey, J. S. Fisk, and J. J. Tepe, *Tetrahedron: Asymmetry*, **19**, 2755 (2008).
12. G. Cremonesi, P. D. Croce, F. Fontana, C. Fiorelli, and C. La Rosa, *Tetrahedron: Asymmetry*, **19**, 2850 (2008).
13. A. A. Fuller, B. Chen, A. R. Minter, and A. K. Mapp, *J. Am. Chem. Soc*., **127**, 5376 (2005).
14. J. Zhang and D. P. Curran, *J. Chem. Soc.*, *Perkin Trans. 1*, 2627 (1991).
15. A. P. Kozikovski, *Acc. Chem. Res*., **17**, 410 (1984).
16. I. Zadroźna, J. Kurkowska, N. Kruszewska, and I. Makuch, *Farmaco*, **55**, 499 (2000).
17. H. Kai, H. Matsumoto, N. Hattori, A. Takase, T. Fujiwara, and H. Sugimoto, *Bioorg. Med. Chem. Lett.*, **11**, 1997 (2001).
18. Y. R. Prasad, P. R. Kumar, and D. Ramesh, *Int. J. Chem. Sci.*, **5,** 542 (2007).
19. A. L. Norman and M. D. Mosher, *Tetrahedron Lett*., **49**, 4153 (2008).
20. W. Schwab, N. Anagnostopolus, R. R. Barlett, R. Schleyerbach, and K. U. Weithmann, US Pat. Appl. 5814627.
21. B. R. Dravyakar, D. P. Kavade, P. B. Khedekar, and K. P. Bhusari, *Ind. J. Chem.*, **47B**, 1559 (2008).
22. I. T. Hwang, H. R. Kim, D. J. Jeon, K. S. Hong, J. H. Song, and K. Y. Cho, *J. Agric. Food Chem*., **53**, 8639 (2005).
23. H. J. Loher, W. Schwab, K. Bauer, and H. Bieringer, US Pat. Appl. 5314863.
24. Basappa, M. P. Sadashiva, K. Mantelingu, S. Nanjunda Swamy, and K. S. Rangappa, *Bioorg. Med. Chem*., **11**, 4539 (2003).
25. S. A. Lang, Jr. and Y.-I. Lin, in: A. R. Katritzky and C. W. Rees (editors), *Comprehensive Heterocyclic Chemistry*, Vol. 6, Pergamon, Oxford (1984), pp.1-130.
26. I. Morao, B. Lecea, and F. P. Cossio, *J. Org. Chem*., **62**, 7033 (1997).
27. K. V. Gothelf and K. A. Jorgensen, *Chem. Rev*., **98**, 863 (1998).

28. G. Giacomelli, L. De Luca, and A. Porcheddu, *Tetrahedron*, **59**, 5437 (2003).
29. V. V. Bakharev, A. A. Gidaspov, E. V. Peresedova, D. B. Krivolapov, E. V. Mironova, and I. A. Litvinov, *Khim. Geterotsikl. Soedin*., 1345 (2009). [*Chem. Heterocycl. Compd.,* **45**, 1075 (2009)].
30. O. Tsuge, S. Kanemasa, H. Suga, and N. Nakagawa, *Bull. Chem. Soc. Jpn*., **60**, 2463 (1987).
31. A. T. Hamme II, J. Xu, J. Wang, J. Cook, and E. Ellis, *Heterocycles*, **65**, 2885 (2005).
32. P. Li, H.-J. Gi, L. Sun, and K. Zhao, *J. Org. Chem*., **63**, 366 (1998).
33. V. Singh, S. Madapa, G. P. Yadav, P. R. Maulik, and S. Batra, *Synthesis*, 1995 (2006).
34. V. V. Bakharev, A. A. Gidaspov, E. V. Peresedova, V. G. Granik, N. B. Grigor'ev, V. I. Levina, I. S. Severina, A. Yu. Shchegolev, D. E. Dmitriev, and A. B. Sheremetev, *Izv. AN, Ser. Khim*., 1900 (2009).