Chemistry of Heterocyclic Compounds, Vol. 47, No. 10, January, 2012 (Russian Original Vol. 47, No. 10, October, 2011)

SYNTHESIS OF 8-R-7-AMINO-3-*tert*-BUTYLPYRAZOLO-[5,1-*c*][1,2,4]TRIAZIN-4(6*H*)-ONES DERIVATIVES

L. M. Mironovich[1] and M. V. Kostina[1]**

8-R-7-Amino-3-tert-butylpyrazolo[5,1-c][1,2,4]triazin-4(6H)-ones derivatives were isolated by boiling them with ketones, anhydrides, benzoyl chloride, and hydrazine. The structures of the compounds were established from data of elemental analysis, IR, ^{1}H NMR, and mass spectrometry.

Keywords: pyrazolo[5,1-*c*][1,2,4]triazin-4-ones, acylation, condensation, nucleophilic substitution.

1,2,4-Triazines derivatives are applied as pesticides and medicinal preparations. In particular, pyrazolo-[5,1-*c*][1,2,4]triazin-4-ones derivatives exhibit antimicrobial activity [1, 2]. The synthesis of pyrazolo[5,1-*c*]-[1,2,4]triazin-4-ones by the action of CH acids such as 3-oxopropanethioamides [3], arylsulfonylacetonitriles [4], and 1,3-dicarbonyl compounds [5] on 6-R-4-amino-3-methylsulfanyl-4,5-dihydro-1,2,4-triazin-5-ones has been described.

The aim of the present work was the study of the reactivity of 8-R-7-amino-3-*tert*-butylpyrazolo[5,1-*c*]-[1,2,4]triazin-4(6*H*)-ones **2, 3**, which were obtained by condensation of the 4-amino-6-*tert*-butyl-3-methylsulfanyl-1,2,4-triazin-5(4*H*)-one (**1**) with activated methylene compounds (cyanoacetic ester, malonodinitrile) in a pyridine medium. Substitution of the methylsulfanyl group with carbon did not occur if there was no amino group at position 4 of the triazine ring. On boiling malonodinitrile or cyanoacetic ester in pyridine with 6-R-3-methylsulfanyl-1,2,4-triazin-5(4*H*)-one the starting compounds were isolated as reaction products, according to the elemental analysis results and spectral characteristics. Compounds **2** and **3** are insoluble in the majority of organic solvents and water, which complicate functionalization at the amino group. Acetylation of compound **2** with acetic anhydride in pyridine led to isolation of ethyl 7-(acetamido)-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*]-[1,2,4]triazine-8-carboxylate (**4**).

Acylation with benzoyl chloride in pyridine was hindered by resin formation, therefore the reaction was carried out in ethyl acetate combined with catalytic quantities of 70% perchloric acid. *N*-(3-*tert*-Butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazin-7-yl)benzamides **5, 6** were isolated in good yields.

Boiling the compound **3** in alcoholic medium with ketones led to isolation of 7-(R^1,R^2-methylidene-amino)-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carbonitriles **7, 8**. In the case of compound **2** the corresponding methylideneamino derivatives were not isolated under the experimental conditions.

The singlet of protons at 6.25 ppm present in the spectra of compounds **2, 3** was disappeared from the ^{1}H NMR spectra of compounds **4-8**. Signals of the protons of substituents at the amino group of pyrazolo[5,1-*c*]-[1,2,4]triazines appeared. Signals of the amide proton of compounds **4-6** were shifted towards low field

*Dedicated to the bright memory of Academician M. O. Lozinskii.

**To whom correspondence should be addressed, e-mail: myronovych@ua.fm.

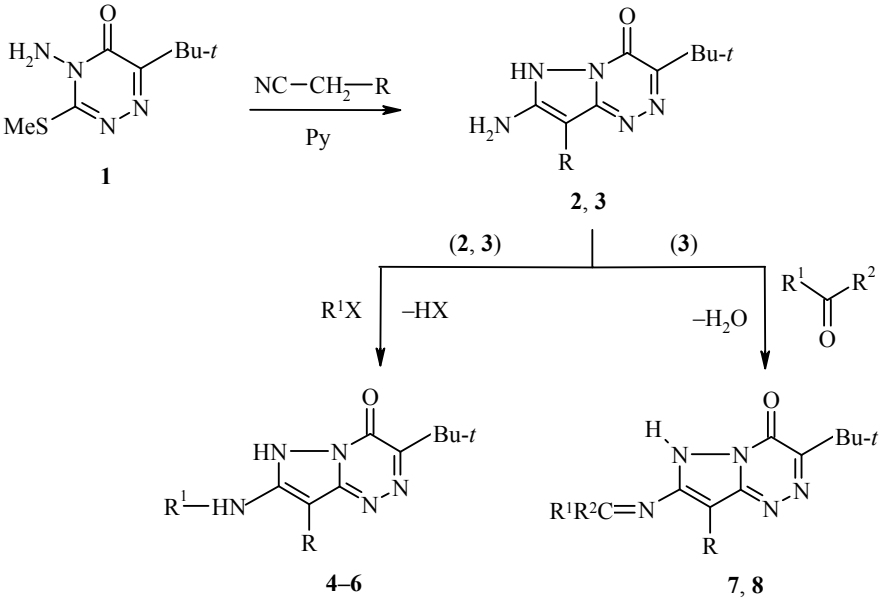
[1]Sumy State University, 2 Rimskogo-Korsakova St., Sumy 40007, Ukraine.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1555-1559, October, 2011. Original article submitted May 14, 2011.

 0009-3122/12/4710-1286

(9.78-10.56 ppm). In the IR spectra of compounds **4-6** a new absorption band appeared at 1720-1725 cm^{-1}, assigned to the stretching vibration of the C=O group in substituents and the characteristic absorption band of the amino group at 3330 cm^{-1} disappeared.

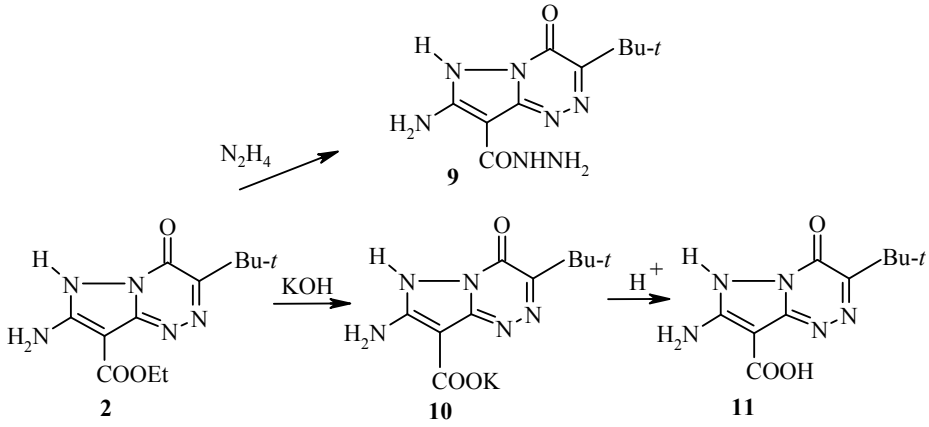
Scheme 1



2, **4**, **5** R = COOEt; **3**, **6**–**8** R = CN; **4** R^1 = Ac, X = OAc; **5**, **6** R^1 = Bz, X = Cl;
7, 8 R^1 = Me; **7** R^2 = Ph; **8** R^2 = 4-ClC_6H_4

Substitution of the ethoxy group by a hydrazine group in compound **2** occurs on boiling in 2-propanol with a 100% excess of hydrazine, with isolation of the hydrazide of 7-amino-3-*tert*-butyl-4-oxo-4,6-dihydro-pyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylic acid (**9**) (Scheme 2).

Scheme 2



Boiling the compound **2** in alcoholic alkali leads to potassium salt **10**, acidification of which with HCl to pH 5-6 leads to the corresponding carboxylic acid (**11**).

EXPERIMENTAL

The IR spectra were recorded on a UR-10 instrument in KBr pellets. The ^{1}H NMR spectra were recorded on a Varian Mercury VX-200 instrument (at 200 MHz) in DMSO-d_6, with HMDS as internal standard (0 ppm). The mass spectra (EI, 70 eV) were obtained on a MC-1302 mass spectrometer. The purity of products was checked by TLC on Silufol UV-254 plates in the system chloroform–methanol, 9:1.

Compound **1** was obtained by the procedure of [6] (mp 126-127°C).

8-R-7-Amino-3-*tert*-butylpyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-ones (2, 3) (General Method). Cyanoacetic ester or malonodinitrile (7 mmol) was added to a suspension of sulfide **1** (1.07 g, 5 mmol) in pyridine (15 ml) with stirring. The mixture was boiled for 3.5-4 h, cooled, the solid was filtered off, and air-dried.

Ethyl 7-Amino-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate (2). Crystallized from dioxane. Yield 0.94 g (68%), white crystals; mp 242-244°C (decomp). IR spectrum, ν, cm^{-1}: 3300 (NH_2), 1715 (C=O), 1680 (C=O), 1615, 1570, 1530, 1470. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 1.35 (9H, s, $C(CH_3)_3$); 4.27 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 6.25 (2H, s, NH_2); 13.2 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 279 (100) $[M]^+$, 264 (20), 206 (25), 205 (69), 155 (49), 149 (27), 110 (15), 67 (26), 57 (22), 52 (14). Found, %: C 51.62; H 6.11; N 25.11. $C_{12}H_{17}N_5O_3$. Calculated, %: C 51.61; H 6.13; N 25.08.

7-Amino-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carbonitrile (3). Crystallized from pyridine. Yield 0.98 g (84%), white crystals; mp >305°C (decomp.). IR spectrum, ν, cm^{-1}: 3300 (NH_2), 2270 (C≡N), 1690 (C=O), 1610, 1525, 1470, 1310, 1095, 995. ^{1}H NMR spectrum, δ, ppm: 1.34 (9H, s, $C(CH_3)_3$); 6.25 (2H, s, NH_2); 14.2 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 232 (19) $[M]^+$, 217 (16), 189 (9), 123 (18), 122 (21), 109 (12), 92 (18), 79 (47), 68 (17), 67 (40), 66 (100), 57 (46), 53 (10), 52 (36), 51 (19), 50 (10), 41 (26). Found, %: C 51.73; H 5.20; N 36.15. $C_{10}H_{12}N_6O$. Calculated, %: C 51.72; H 5.21; N 36.18.

Ethyl 7-Acetamido-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate (4). A mixture of compound **2** (0.28 g, 1 mmol) and acetic anhydride (0.2 g, 2 mmol) in pyridine (10 ml) was boiled for 6 h, cooled, methanol (10 ml) was added, the solid was filtered off and air-dried. The product was crystallized from methanol. Yield 0.23 g (71%), white crystals; mp 221-222°C. IR spectrum, ν, cm^{-1}: 1720 (C=O), 1715 (C=O), 1685 (C=O), 1620, 1570, 1520, 1470. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 1.37 (9H, s, *t*-Bu); 2.15 (3H, s, CH_3); 4.28 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 9.78 (1H, s, NH); 13.3 (1H, br. s, NH). Found, %: C 52.31; H 6.03; N 21.80. $C_{14}H_{19}N_5O_4$. Calculated, %: C 52.33; H 5.96; N 21.79.

Ethyl 7-Benzamido-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylate (5). A mixture of compound **2** (0.28 g, 1 mmol) and benzoyl chloride (0.35 ml, 3 mmol) in ethyl acetate (10 ml) with a drop of 70% perchloric acid was boiled for 12 h, cooled, the solid was filtered off, and chromatographically pure compound **5** was obtained. Yield 0.3 g (80%), white crystals; mp 233-234°C. IR spectrum, ν, cm^{-1}: 1725 (C=O), 1710 (C=O), 1680 (C=O), 1615, 1580, 1530, 1475. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.4 (9H, s, $C(CH_3)_3$); 1.22 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 4.28 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.52-7.67 (3H, m, H *m*- and *p*-Ph); 7.97 (2H, d, *J* = 7.6, H *o*-Ph); 10.56 (1H, s, NH); 13.6 (1H, s, NH). Found, %: C 59.55; H 5.51; N 18.30. $C_{19}H_{21}N_5O_4$. Calculated, %: C 9.52; H 5.52; N 18.27.

***N*-(3-*tert*-Butyl-8-cyano-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazin-7-yl)benzamide (6).** A mixture of compound **3** (0.23 g, 1 mmol) and benzoyl chloride (0.35 ml, 3 mmol) in ethyl acetate (10 ml) with a drop of 70% perchloric acid was boiled for 12 h. The excess solvent was removed to 1/3 volume, the mixture was cooled, 2-propanol (10 ml) was added, the solid was filtered off, and chromatographically pure compound **6** was obtained. Yield 0.26 g (79%), white crystals; mp 284-290°C (decomp.). IR spectrum, ν, cm^{-1}: 2275 (C≡N), 1720 (C=O), 1690 (C=O), 1610, 1525, 1470, 1315, 1095, 990. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (9H, s, $C(CH_3)_3$); 7.55 (3H, t, *J* = 7.3, H *m*- and *p*-Ph); 7.87 (2H, d, *J* = 8.0, H *o*-Ph); 11.6 (1H, s, NH). Found, %: C 60.70; H 4.81; N 25.02. $C_{17}H_{16}N_6O_2$. Calculated, %: C 60.71; H 4.79; N 24.99.

7-R^1,R^2-Methylideneamino-3-*tert*-butylpyrazolo[5,1-*c*][1,2,4]triazin-4(6*H*)-ones (7, 8) (General Method). A mixture of compound **3** (0.23 g, 1 mmol) and ketone (acetophenone, *p*-chloroacetophenone) (2 mmol) in methanol (10 ml) was boiled for 4 h, cooled, and the solid filtered off.

3-*tert*-Butyl-4-oxo-7-(1-phenylethylidene)amino-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carbonitrile (7). Crystallized from 2-propanol. Yield 0.22 g (65%), white crystals; mp >300°C (decomp.). IR spectrum, ν, cm^{-1}: 2270 (C≡N), 1690 (C=O), 1615, 1525, 1470, 1320, 1095, 990. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (9H, s, $C(CH_3)_3$); 2.57 (3H, s, CH_3); 7.47-7.63 (3H, m, *m*- and *p*-Ph); 7.94 (2H, d, *J* = 7.0, H *o*-Ph); 14.17 (1H, s, NH). Found, %: C 64.63; H 5.40; N 25.11. $C_{18}H_{18}N_6O$. Calculated, %: C 64.66; H 5.43; N 25.13.

3-*tert*-Butyl-7-[1-(4-chlorophenyl)ethylidene]amino-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carbonitrile (8). Crystallized from 2-propanol. Yield 0.25 g (69%), white crystals; mp 292-297°C (decomp.). IR spectrum, ν, cm^{-1}: 2275 (C≡N), 1690 (C=O), 1615, 1525, 1470, 1310, 1110, 995. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (9H, s, $C(CH_3)_3$); 2.56 (3H, s, CH_3); 7.58 (2H, d, *J* = 8.4, H *m*-Ar); 7.95 (2H, d, *J* = 8.6, H *o*-Ar); 14.15 (1H, s, NH). Found, %: C 58.62; H 4.69; N 22.83. $C_{18}H_{17}N_6OCl$. Calculated, %: C 58.62; H 4.65; N 22.79.

7-Amino-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carbohydrazide (9). 100% Hydrazine (0.2 g, 6 mmol) was added to a suspension of compound **2** (0.558 g, 2 mmol) in 2-propanol. The mixture was boiled for 2 h, filtered, and the solvent excess was evaporated to 2/3 volume. The mixture was cooled, the solid was filtered off and air-dried. Purification was carried out by dissolving in dioxane with subsequent precipitation with water (dioxane–water, 1:1). Yield 0.41 g (78%), white crystals; mp 285-295°C (resinified). IR spectrum, ν, cm^{-1}: 3310 (NH_2), 3215, 3100, 3010, 2905, 1720 (C=O), 1685 (C=O), 1620, 1580, 1530, 1480, 1320, 1100. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (9H, s, $C(CH_3)_3$); 4.15 (3H, m, $NHNH_2$); 6.2 (2H, s, NH_2); 13.3 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 265 (20) $[M]^+$, 218 (19), 191 (5), 190 (31), 170 (5), 162 (3), 149 (30), 139 (26), 124(20), 111 (19), 97 (27), 96 (21), 95 (10), 84 (6), 69 (18), 68 (80), 67 (100), 58 (3), 57 (37), 56 (2), 55 (7), 54 (3), 53 (5), 49 (14), 45 (10), 41 (58), 40 (27). Found, %: C 45.30; H 5.64; N 37.03. $C_{10}H_{15}N_7O_2$. Calculated, %: C 45.28; H 5.70; N 36.96.

Potassium Salt of 7-Amino-3-*tert*-butyl-4-oxo-4,5-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylic Acid (10). A mixture of compound **2** (0.279 g, 1 mmol) and KOH (0.11 g, 2 mmol) in 2-propanol (10 ml) was boiled for 2 h, the solid was filtered off, and a chromatographically pure white crystalline substance was obtained. Yield 0.21 g (73%); mp 257-265°C (decomp.). IR spectrum, ν, cm^{-1}: 3300 (NH_2), 1720 (C=O), 1690 (C=O), 1615, 1525, 1470, 1315, 1095, 995. ^{1}H NMR spectrum, δ, ppm: 1.30 (9H, s, $C(CH_3)_3$); 6.15 (2H, s, NH_2); 13.25 (1H, br. s, NH). Found, %: C 41.53; H 4.20; N 24.24. $C_{10}H_{12}N_5O_3K$. Calculated, %: C 41.51; H 4.18; N 24.21.

7-Amino-3-*tert*-butyl-4-oxo-4,6-dihydropyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylic Acid (11). Compound **10** (0.29 g, 1 mmol) was dissolved in distilled water (15 ml), HCl was added to pH 5-6, the precipitated solid was filtered off and crystallized from methanol. Yield 0.23 g (93%), a beige colored substance; mp >300°C. IR spectrum, ν, cm^{-1}: 3300 (NH_2), 3200-3400 (OH), 1720 (C=O), 1690 (C=O), 1610, 1520, 1470, 1315, 1095, 995. ^{1}H NMR spectrum, δ, ppm: 1.30 (9H, s, $C(CH_3)_3$); 6.15 (2H, s, NH_2); 12.70 (1H, s, COOH); 13.25 (1H, br. s, NH). Found, %: C 47.83; H 5.24; N 27.91. $C_{10}H_{13}N_5O_3$. Calculated, %: C 47.81; H 5.22; N 27.87.

REFERENCES

1. L. M. Mironovich and V. K. Promonenkov, *Results of Science and Technics*, *Ser. Org. Khimiya*, VINITI, Vol. 22, Moscow (1990).
2. F. El-Mariah, M. Hosny, and A. Deeb, *Phosphorus, Sulphur, Silicon Relat. Elem.*, **181**, 2505 (2006).
3. V. N. Britsun, A. N. Esipenko, and M. O. Lozinskii, *Ukr. Khim. Zh.*, **73**, No. 4, 114 (2007).
4. V. N. Britsun, I. M. Bazavova, A. N. Esipenko, and M. O. Lozinskii, *Khim. Geterotsikl. Soedin.*, 1844 (2003). [*Chem. Heterocycl. Comp.*, **39**, 1623 (2003).]
5. A. A. El-Barbary, M. A. El-Badawi, and Y. M. Loksha, *J. Heterocycl. Chem.*, **38**, 711 (2001).
6. W. Merz, US Pat. Appl. 4113767 (1978).