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Synthesis of N-Substituted 7-Aryl-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamides

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Abstract—Three-component reaction of *N*-methyl- or *N*,*N*-diethyl-3-oxobutanamide with aromatic aldehydes and tetrazol-5-amine monohydrate gave the corresponding N-substituted 7-aryl-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxamides.

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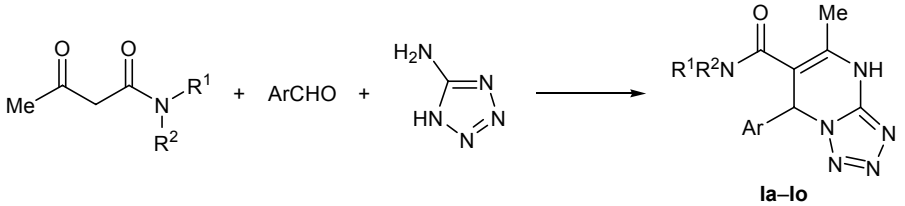
Extension of synthetic potential of known reactions via the use of new functional reagents is one of the most important lines in the development of organic chemistry. An example of such reactions leading to the formation of pyrimidine derivatives is the three-component Biginelli reaction. It was originally proposed for the synthesis of pyrimidinones from aromatic aldehydes, urea, and ethyl acetoacetate [1, 2]; at present, this reaction is successfully used for the preparation of various fused pyrimidines, in particular azolopyrimidines [3–5].

We previously reported on the three-component Biginelli reaction of *N*,*N*-dimethyl(diethyl)-3-oxobutanamide with formation of a fused heterocyclic system, namely tetrazolopyrimidines containing a dialkylcarbamoyl group [6]. While continuing studies in this field we made an attempt to synthesize new fused heterocyclic systems by extending the series of aromatic aldehydes reacting with *N*,*N*-dialkyl-3-oxobutanamides and tetrazol-5-amine. Following the procedure proposed in [6] we synthesized previously unknown compounds **Ia**–**Il** (Scheme 1). Their yield depended on the substituent nature in the initial aldehyde. Aromatic aldehydes having an electron-withdrawing group in the *para*-position reacted more readily. The reactions of *N*-methyl-3-oxobuanamide with aromatic aldehydes and tetrazole-5-amine (120–150°C, 5–10 min) gave 7-aryl-*N*,5-dimethyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamides **Im**–**Io**. The three-component condensation with *N*-methyl-3-oxobutanamide ensured higher yield of tetrazolopyrimidines as compared to *N*,*N*-dimethyl(or diethyl)-3-oxobutanamide. Presumably, the presence of two donor alkyl groups on the nitrogen atom in the initial β-carbonyl compound reduces its reactivity as CH acid.

Compounds **Ia**–**Io** were isolated as colorless crystalline substances which were soluble in chloroform, DMF, and DMSO and insoluble in water. Their IR

Scheme 1.

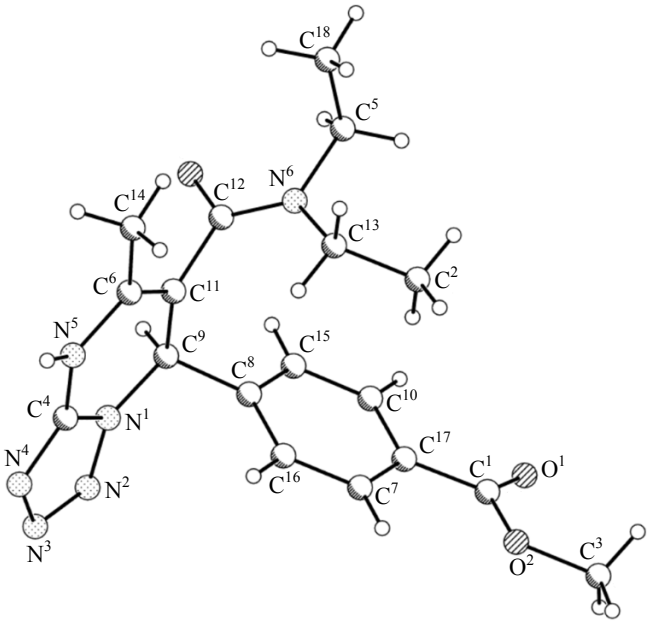


I, $R^1 = R^2 =$ Et (**a**–**l**); $R^1 =$ Me, $R^2 =$ H (**m**–**o**); Ar = 4-EtC_6H_4 (**a**), 4-$MeOC(O)C_6H_4$ (**b**), 4-MeC_6H_4 (**c**), 4-FC_6H_4 (**d**), 3-$MeOC_6H_4$ (**e**), pyridin-3-yl (**f**), 4-$MeOC_6H_4$ (**g**), 4-$O_2NC_6H_4$ (**h**), 4-BrC_6H_4 (i), 3-$O_2NC_6H_4$ (**j**), 2-$MeOC_6H_4$ (**k**, **o**), 2-$O_2NC_6H_4$ (**l**), Ph (**m**), 4-HOC_6H_4 (**n**).

spectra contained absorption bands belonging to stretching vibrations of the amide carbonyl group (1660–1680 cm^{-1}), NH groups (3150–3200 and 3420–3440 cm^{-1}), and C=C bonds (1600–1620 cm^{-1}). Compounds **Ia**–**Io** displayed in the ^1H NMR spectra signals from protons in the aromatic ring and substituent attached thereto, as well as singlets from methyl group (δ 1.75–1.92 ppm), 7-H (δ 6.26–6.66 ppm), and N^4H (10.30–10.68 ppm). In the spectra of *N*,*N*-diethyl derivatives, signals from ethyl groups on the nitrogen atom were observed at δ 0.75–0.91 (CH_3) and 3.03–3.15 ppm (CH_2), and *N*-methyl amides **Im**–**Io** were characterized by singlets from the NH and NCH_3 protons at δ 9.40–9.50 and 3.40–3.50 ppm, respectively.

In the mass spectrum of compound **Ij** we detected $[M - CO]^+$ ion peak with *m*/*z* 329) and the following fragment ion peaks: *m*/*z* 257 $[M - Et_2NCO]^+$, 77 $[Ph]^+$, and 72 $[Et_2N]^+$. The mass spectrum of **Io** contained the molecular ion peak $[M]^+$ with *m*/*z* 300 and fragment ion peaks with *m*/*z* 242 $[M - CH_3NHCO]^+$, 107 $[CH_3OC_6H_4]^+$, and 58 $[CH_3NHCO]^+$. These data were consistent with the assumed structures.

The structure of compound **Ib** was unambiguously determined by X-ray analysis (see figure). Single crystals of **Ib** were obtained by slow crystallization from ethanol. Despite the presence of an asymmetric center (C^7), compound **Ib** crystallized in centrosymmetric space group belonging to rhombic crystal system.



Structure of the molecule of methyl 4-(6-diethylcarbamoyl-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidin-7-yl)benzoate (**Ib**) according to the X-ray diffraction data.

Molecule **Ib** is planar, and the bond lengths and bond angles therein do not differ from the corresponding standard values. The NH proton in the pyrimidine ring is involved in intermolecular hydrogen bond with the carbonyl oxygen atom in the neighboring molecule [N^5–H^5 0.89(2), $H^5\cdots O^3$ 1.93(2), $N^5\cdots O^3$ 2.806(3) Å, $\angle N^5H^5O^3$ 171(2)°], symmetry transformation [$x - 1/2$, y, $-z + 3/2$].

The X-ray diffraction data for compound **Ib** were obtained from a 0.25×0.12×0.07-mm colorless needle-shaped crystal on an Xcalibur-3 diffractometer with a CCD detector [λ(MoK_α) 0.71073 Å, graphite monochromator, ω-scanning, scan step 1°, temperature 295(2) K]. The structure was solved by the direct method and was refined using SHELXTL-97 software package [7]. No correction for absorption was introduced. The positions and temperature parameters of non-hydrogen atoms were refined first in isotropic and then in anisotropic approximation by the full-matrix least-squares procedure (by F^2). The positions of C–H hydrogen atoms were determined from the electron density maxima and were refined according to the riding model; the N–H protons were localized by the direct method and were refined independently. Principal crystallographic parameters: rhombic crystals, space group *Pbca*; unit cell parameters: a = 7.9755(5), b = 16.128(2), c = 30.846(2) Å; V = 3967.8(6) $Å^3$; Z = 8; μ = 0.088 mm^{-1}. Total of 16052 reflection intensities were measured in the range 2.85 < θ < 26.38°; 4039 reflections were independent (R_{int} 0.0556), and 1611 of them were characterized by $I > 2\sigma(I)$; completeness 99.7% for θ = 26.38°. The final divergence factors were R_1 = 0.0465, wR_2 = 0.0984 [reflections with $I > 2\sigma(I)$] and R_1 = 0.1284, wR_2 = 0.1059 (all reflections); goodness of fit S = 1.006. The maximal and minimal residual spatial electron densities were 0.299 and –0.220 $\bar{e}/Å^3$. The set of crystallographic data for compound **Ib** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 865252) and is available at *http://www.ccdc.cam.ac.uk/data_request/cif* upon request.

EXPERIMENTAL

The IR spectra were measured on a Specord M-80 spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were recorded on a Bruker 500 instrument at 500.13 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan MAT INCOS-50 spectrometer.

***N*,*N*-Diethyl-7-(4-ethylphenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Ia).** A mixture of 0.01 mol of *N*,*N*-diethyl-3-oxobutanamide, 0.01 mol of 4-ethylbenzaldehyde, and 0.01 mol of tetrazol-5-amine monohydrate was heated for 20–60 min at 120–150°C until gaseous products no longer evolved and the mixture solidified. The mixture was cooled and treated with ethanol, and the precipitate was filtered off and recrystallized from ethanol. Yield 2.1 g (62%), mp 236–238°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 1680 (C=O), 1612 (C=C). ^1H NMR spectrum, δ, ppm: 1.84 s (3H, 5-CH_3), 0.80 m (6H, C**H**$_3$CH$_2$N), 1.11 t (3H, $C_6H_4CH_2C$**H**$_3$), 3.04 m (4H, CH_3C**H**$_2$N), 4.02 q (2H, CH_3C**H**$_2C_6H_4$), 6.31 s (1H, 7-H), 7.13 m (4H, C_6H_4), 10.31 s (1H, NH). Found, %: C 63.43, 63.64; H 7.06, 7.22; N 24.57, 24.77. $C_{18}H_{24}N_6O$. Calculated, %: C 63.51; H 7.11; N 24.69.

Compounds **Ib**–**Io** were synthesized in a similar way.

Methyl 4-(6-diethylcarbamoyl-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidin-7-yl)benzoate (Ib). Yield 2.66 g (72%), mp 234–236°C. IR spectrum, ν, cm^{-1}: 3180 (NH), 1680 (C=O, amide), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 0.83 m (6H, C**H**$_3$CH$_2$), 1.85 s (3H, 5-CH_3), 3.09 m (4H, CH_3C**H**$_2$), 3.79 s (3H, OCH_3), 6.46 s (1H, 7-H), 7.79 m (4H, C_6H_4), 10.43 s (1H, NH). Found, %: C 58.27, 58.41; H 5.88, 6.08; N 22.61, 22.74. $C_{18}H_{22}N_6O_3$. Calculated, %: C 58.37; H 5.99; N 22.69.

***N*,*N*-Diethyl-5-methyl-7-(4-methylphenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Ic).** Yield 1.89 g (58%), mp 218–220°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 0.91 m (6H, C**H**$_3$CH$_2$), 1.86 s (3H, 5-CH_3), 2.19 s (3H, C**H**$_3C_6H_4$), 3.07 m (4H, CH_3C**H**$_2$), 6.26 s (1H, 7-H), 7.23 m (4H, C_6H_4), 10.34 s (1H, NH). Found, %: C 62.50, 62.69; H 6.74, 6.90; N 25.63, 25.83. $C_{17}H_{22}N_6O$. Calculated, %: C 62.56; H 6.79; N 25.75.

***N*,*N*-Diethyl-7-(4-fluorophenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Id).** Yield 2.38 g (72%), mp 207–209°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 0.81 m (6H, C**H**$_3$CH$_2$), 1.86 s (3H, 5-CH_3), 3.14 m (4H, CH_3C**H**$_2$), 6.39 s (1H, 7-H), 7.15 m (4H, C_6H_4), 10.37 s (1H, NH). Found, %: C 58.07, 58.21; H 5.73, 5.83; N 25.33, 25.56. $C_{16}H_{19}FN_6O$. Calculated, %: C 58.17; H 5.80; N 25.44.

***N*,*N*-Diethyl-7-(3-methoxyphenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Ie).** Yield 2.01 g (59%), mp 179–181°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 0.80 m (6H, C**H**$_3$CH$_2$), 1.79 s (3H, 5-CH_3), 3.12 m (4H, CH_3C**H**$_2$), 3.61 s (3H, CH_3O), 6.27 s (1H, 7-H), 7.13 m (4H, C_6H_4), 10.30 s (1H, NH). Found, %: C 59.57, 59.76; H 6.37, 6.57; N 24.49, 24.56. $C_{17}H_{22}N_6O_2$. Calculated, %: C 59.63; H 6.48; N 24.54.

***N*,*N*-Diethyl-5-methyl-7-(pyridin-3-yl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (If).** Yield 1.97 g (63%), mp 215–217°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 0.81 m (6H, C**H**$_3$CH$_2$), 1.80 s (3H, 5-CH_3), 3.14 m (4H, CH_3C**H**$_2$), 6.39 s (1H, 7-H), 7.15 m (4H, pyridine), 10.62 s (1H, NH). Found, %: C 57.42, 57.60; H 6.07, 6.19; N 31.21, 31.41. $C_{15}H_{19}N_7O$. Calculated, %: C 57.49; H 6.11; N 31.29.

***N*,*N*-Diethyl-7-(4-methoxyphenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Ig).** Yield 2.39 g (70%), mp 246–248°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 0.80 m (6H, C**H**$_3$CH$_2$), 1.75 s (3H, 5-CH_3), 3.12 m (4H, CH_3C**H**$_2$), 3.58 s (3H, CH_3O), 6.55 s (1H, 7-H), 7.27 m (4H, C_6H_4), 10.56 s (1H, NH). Found, %: C 59.57, 59.76; H 6.37, 6.57; N 24.49, 24.56. $C_{17}H_{22}N_6O_2$. Calculated, %: C 59.63; H 6.48; N 24.54.

***N*,*N*-Diethyl-5-methyl-7-(4-nitrophenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Ih).** Yield 2.43 g (68%), mp 244–246°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 0.90 m (6H, C**H**$_3$CH$_2$), 1.89 s (3H, 5-CH_3), 3.09 m (4H, CH_3C**H**$_2$), 6.66 s (1H, 7-H), 8.21 m (4H, C_6H_4), 10.67 s (1H, NH). Found, %: C 53.69, 53.91; H 5.29, 5.39; N 27.36, 27.46. $C_{16}H_{19}N_7O_3$. Calculated, %: C 53.78; N 5.36; N 27.44.

7-(4-Bromophenyl)-*N*,*N*-diethyl-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Ii). Yield 2.78 g (71%), mp 246–247°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C). ^1H NMR spectrum, δ, ppm: 0.90 m (6H, C**H**$_3$CH$_2$), 1.87 s (3H, 5-CH_3), 3.08 m (4H, CH_3C**H**$_2$), 6.46 s (1H, 7-H), 7.55 m (4H, C_6H_4), 10.56 s (1H, NH). Found, %: C 49.06, 49.24; H 4.81, 4.98; N 21.37, 21.50. $C_{16}H_{19}BrN_6O$. Calculated, %: C 49.12; H 4.89; N 21.48.

***N*,*N*-Diethyl-5-methyl-7-(3-nitrophenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Ij).** Yield 2.28 g (64%), mp 236–238°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C).

^{1}H NMR spectrum, δ, ppm: 0.88 m (6H, C**H**$_3$CH$_2$), 1.92 s (3H, 5-CH$_3$), 3.12 m (4H, CH$_3$C**H**$_2$), 6.62 s (1H, 7-H), 7.55 m (4H, C$_6$H$_4$), 10.62 s (1H, NH). Found, %: C 53.69, 53.65; H 5.29, 5.40; N 27.32, 27.50. $C_{16}H_{19}N_7O_3$. Calculated, %: C 53.78; H 5.36; N 27.44.

***N*,*N*-Diethyl-7-(2-methoxyphenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Ik).** Yield 1.64 g (44%), mp 198–199°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.80 m (6H, C**H**$_3$CH$_2$), 1.82 s (3H, 5-CH$_3$), 3.12 m (4H, CH$_3$C**H**$_2$), 3.65 s (3H, CH$_3$O), 6.57 s (1H, 7-H), 7.67 m (4H, C$_6$H$_4$), 10.34 s (1H, NH). Found, %: C 59.57, 59.76; H 6.37, 6.57; N 24.49, 24.56. $C_{17}H_{22}N_6O_2$. Calculated, %: C 59.63; H 6.48; N 24.54.

***N*,*N*-Diethyl-5-methyl-7-(2-nitrophenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Il).** Yield 1.93 g (54%), mp 225–227°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1680 (C=O), 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.80 m (6H, C**H**$_3$CH$_2$), 1.86 s (3H, 5-CH$_3$), 3.15 m (4H, CH$_3$C**H**$_2$), 6.58 s (1H, 7-H), 7.79 m (4H, C$_6$H$_4$), 10.68 s (1H, NH). Found, %: C 53.69, 53.65; H 5.29, 5.40; N 27.32, 27.50. $C_{16}H_{19}N_7O_3$. Calculated, %: C 53.78; H 5.36; N 27.44.

***N*,5-Dimethyl-7-phenyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxamide (Im).** Yield 1.86 g (64%), mp 243–245°C. IR spectrum, ν, cm^{-1}: 1612 (C=C), 1680 (C=O), 3200 (NH), 3420 (NH, amide). ^{1}H NMR spectrum, δ, ppm: 1.89 s (3H, 5-CH$_3$), 3.40 s (3H, NCH$_3$), 6.40 s (1H, 7-H), 8.14 m (5H, C$_6$H$_5$), 9.45 s (1H, NH), 10.30 s (1H, 4-H). Found, %: C 57.68, 57.84; H 5.16, 5.31; N 31.21, 31.17. $C_{13}H_{14}N_6O$. Calculated, %: C 57.77; H 5.22; N 31.09.

7-(4-Hydroxyphenyl)-*N*,5-dimethyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (In). Yield 2.34 g (72%), mp 272–274°C. IR spectrum, ν, cm^{-1}: 3440 (NH, amide), 3200 (NH), 1675 (C=O), 1600 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.90 s (3H, 5-CH$_3$), 3.50 s (3H, NCH$_3$), 7.90 s (1H, OH), 6.64 s (1H, 7-H), 6.85 m (4H, C$_6$H$_4$), 9.40 s (1H, NH), 10.40 s (1H, 4-H). Found, %: C 54.46, 54.66; H 4.87, 5.02; N 29.23, 29.44. $C_{13}H_{14}N_6O_2$. Calculated, %: C 54.54; H 4.93; N 29.35.

7-(2-Methoxyphenyl)-*N*,5-dimethyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (Io). Yield 2.22 g (69%), mp 235–237°C. IR spectrum, ν, cm^{-1}: 3420 (NH, amide), 3150 (NH), 1680 (C=O), 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.91 s (3H, 5-CH$_3$), 3.40 s (3H, NCH$_3$), 3.70 s (3H, CH$_3$O), 6.65 s (1H, 7-H), 7.10 m (4H, C$_6$H$_4$), 9.50 s (1H, 4-H), 10.50 s (1H, NH). Found, %: C 55.91, 56.11; H 5.32, 5.46; N 27.85, 28.06. $C_{14}H_{16}N_6O_2$. Calculated, %: C 55.99; H 5.37; N 27.98.

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