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Synthesis of *N*,7-Diaryl-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]-pyrimidine-6-carboxamides

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Abstract—Reaction of *N*-arylamides of acetoacetic acid with aromatic aldehyde and 3-amino-1,2,4-triazole derivatives has resulted in *N*,7-diaryl-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides.

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Various modifications of the Biginelli reaction [1] are promising for synthesis of carbonyl-containing heterocyclic systems [1]. Using the aminoheterocycles as heterocyclic analogues of urea, the annulated pyrimidines, in particular, azolopyrimidines, can be prepared [2–4].

The three-component reaction of benzoylpiruvic acid methyl esters with 3-amino-1,2,4-triazole hydrochloride and an aromatic aldehyde has given 4-aryl-3-benzoyl-2-methoxycarbonyl-1,4-dihydropyrimido[1,2-*b*]triazoles [5]. The three-component condensation of 3-amino-5-alkylthio-1,2,4-triazoles with aromatic aldehydes and acetoacetamides has been known as well [6].

Previously, we studied the reaction of *N*-arylamides of acetoacetic acid with aromatic aldehyde and 5-aminotetrazole monohydrate resulting in *N*,7-diaryl-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamides [7].

In this work we obtained *N*,7-diaryl-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamides **I–XIII** via the three-component reaction of *N*-arylamides of acetoacetic acid with aromatic aldehyde and 3-amino-1,2,4-triazole (see Scheme 1).

The syntheses were performed in the absence of solvent and without any catalyst, at 120–150°C during 5 min using equimolar amounts of acetoacetanilide, aromatic aldehyde, and 3-amino-1,2,4-triazole.

The presence of two nonequivalent nitrogen atoms (N^2 and N^4) in the 3-amino-1,2,4-triazole molecule suggested possible formation of two reaction products. However, compounds **I–XIII** were formed predominantly, seemingly, due to higher basicity and nucleophilicity of the N^2 atom.

Carboxamides **I–XIII** were colorless crystalline solids, soluble in DMF, DMSO, acetic acid, and ethanol and insoluble in water.

IR spectra of **I–XIII** contained the absorption bands assigned to stretching vibrations of the amide groups (1660–1680 cm^{-1}), the N–H bond (3150–3200 cm^{-1}), and the C=C bond (1600–1620 cm^{-1}).

Along with the signals of aromatic ring protons and of the corresponding substituents, the singlets of methyl (1.66–2.21 ppm), methine (6.36–7.51 ppm), and NH (8.83–9.69 and 9.78–10.30 ppm) protons were observed in ^1H NMR spectra of the prepared compounds.

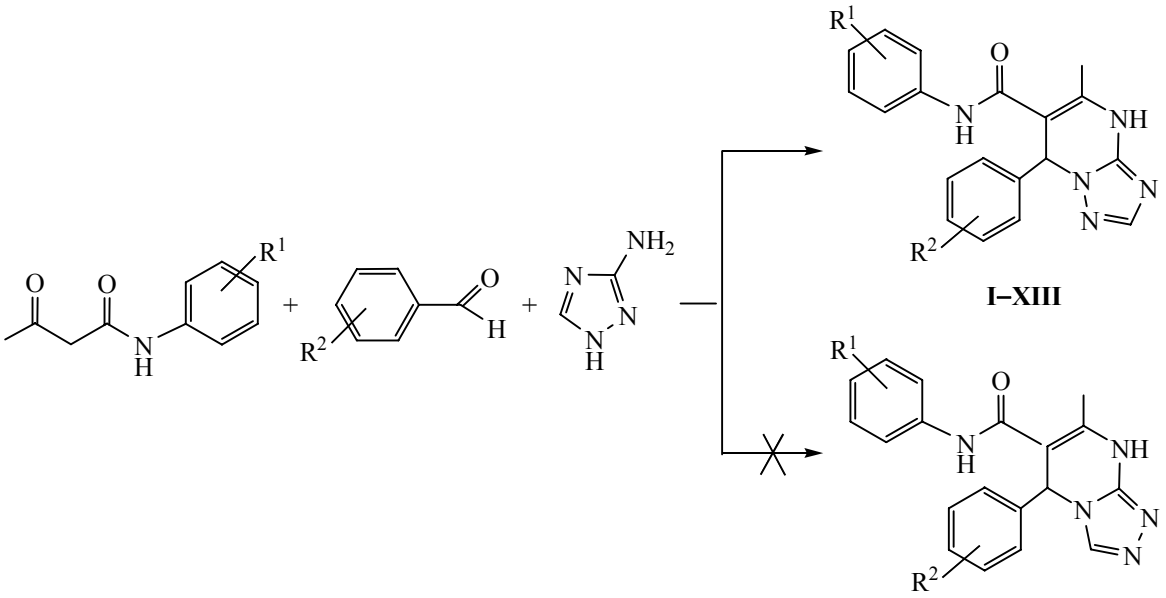
The mass spectrum of **IX** contained the peaks of $[M - (CH_3)_2C_6H_3NHCO]^+$ (*m*/*z* 256), $[M - (CH_3)_2C_6H_3NHCO - C_2H_5OC_6H_4]^+$ (*m*/*z* 135), and $[(CH_3)_2C_6H_3NH]^+$ (*m*/*z* 121), $[Ph]^+$ (*m*/*z* 77). The structure of **VIII** was confirmed by the presence of the $[M - (CH_3)_2C_6H_3NHCO]^+$ (*m*/*z* 268), $[M - (CH_3)_2C_6H_3NHCO - (CH_3)_3CC_6H_4]^+$ (*m*/*z* 135), and $[Ph]^+$ (*m*/*z* 77) fragments.

EXPERIMENTAL

IR spectra were registered with Specord M-80 spectrophotometer in mineral oil. ^1H NMR spectra

[†] Deceased.

Scheme 1.



R^1 = H, R^2 = 3-NO_2 (**I**); R^1 = H, R^2 = 2-OMe (**II**); R^1 = 2-Me, R^2 = 4-OH (**III**); R^1 = 2-Me, R^2 = 3-NO_2 (**IV**); R^1 = 2,4-$(Me)_2$, R^2 = 2-OMe (**V**); R^1 = 2,4-$(Me)_2$, R^2 = 4-NO_2 (**VI**); R^1 = 2,4-$(Me)_2$, R^2 = 3-NO_2 (**VII**); R^1 = 2,4-$(Me)_2$, R_2 = 4-*t*-Bu (**VIII**); R^1 = 2,4-$(Me)_2$, R^2 = 4-OEt (**IX**); R^1 = 2,4-$(Me)_2$, R^2 = 4-OH (**X**); R^1 = 4-Cl, R^2 = 2-OMe (**XI**); R^1 = 4-Cl, R^2 = 3-NO_2 (**XII**); R^1 = 4-Cl, R^2 = H (**XIII**).

were recorded with Bruker 500 (500.13 MHz) instrument using DMSO-d_6 as solvent and TMS as internal reference. Mass spectra were recorded with Finnigan MAT INCOS-50 spectrometer (70 eV). Melting points were determined with M-565 instrument.

5-Methyl-7-(3-nitrophenyl)-*N*-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (I). A mixture of 0.01 mol of acetoacetanilide, 0.01 mol of 3-nitrobenzaldehyde, and 0.01 mol of 3-amino-1,2,4-triazole was incubated in the absence of solvent at 120–150°C during 5 min until gas evolving ceased. After cooling, the residue was treated with ethanol, filtered off, and recrystallized from ethanol. Yield 2.25 g (68%), mp 267–269°C. IR spectrum, ν, cm^{-1}: 1600 (C=C), 1680 (CON), 3160 (NH). ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, CH_3), 6.62 s (1H, CH), 6.91–8.07 m (9H, C_6H_5, $NO_2C_6H_4$), 9.66 s (1H, NH), 10.23 s (1H, N^4H). Found, %: C 60.55, 60.76; H 4.23, 4.39; N 22.21, 22.41. $C_{19}H_{16}N_6O_3$. Calculated, %: C 60.63; H 4.28; N 22.33.

Compounds **II**–**XIII** were obtained similarly.

5-Methyl-7-(2-methoxyphenyl)-*N*-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (II). Yield 2.41 g (66%), mp 226–228°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3180 (NH). ^{1}H NMR spectrum, δ, ppm: 2.09 s (3H, CH_3), 3.58 s (3H, CH_3O), 6.67 s (1H, CH), 6.76–7.49 m (9H, C_6H_5, $CH_3OC_6H_4$), 9.61 s (1H, NH), 9.96 s (1H, N^4H). Found, %: C 66.37, 66.52; H 5.19, 5.39; N 19.30, 19.43. $C_{20}H_{19}N_5O_2$. Calculated, %: C 66.47; H 5.30; N 19.38.

7-(4-Hydroxyphenyl)-5-methyl-*N*-(2-methylphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (III). Yield 2.26 g (62%), mp 260–262°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^{1}H NMR spectrum, δ, ppm: 1.83 s (3H, CH_3), 2.19 s (3H, $CH_3C_6H_4$), 6.32 s (1H, CH), 6.58–7.52 m (8H, $CH_3C_6H_4$, HOC_6H_4), 9.03 s (1H, NH), 9.94 s (1H, HO), 9.97 s (1H, N^4H). Found, %: C 66.38, 66.54; H 5.24, 5.37; N 19.27, 19.47. $C_{20}H_{19}N_5O_2$. Calculated, %: C 66.47; H 5.30; N 19.38.

5-Methyl-*N*-(2-methylphenyl)-7-(3-nitropenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (IV). Yield 2.81 g (72%), mp 248–250°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^{1}H NMR spectrum, δ, ppm: 1.81 s (3H, CH_3), 2.25 s (3H, $CH_3C_6H_4$), 6.59 s (1H, CH), 6.80–8.24 m (8H, $CH_3C_6H_4$, $NO_2C_6H_4$), 9.24 s (1H, NH), 10.24 s (1H, N^4H). Found, %: C 61.47, 61.65; H 4.59, 4.75; N 21.42, 21.62. $C_{20}H_{18}N_6O_3$. Calculated, %: C 61.53; H 4.65; N 21.53.

5-Methyl-*N*-(2,4-dimethylphenyl)-7-(2-methoxyphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (V). Yield 3.03 g (78%), mp 228–230°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^1H NMR spectrum, δ, ppm: 1.80 s (3H, CH_3), 2.15 s and 2.19 s [6H, $(\underline{CH_3})_2C_6H_3$], 3.66 s (3H, CH_3O), 6.67 s (1H, CH), 6.81–7.36 m [7H, $(CH_3)_2\underline{C_6}\underline{H_3}$, $CH_3O\underline{C_6}\underline{H_4}$], 8.83 s (1H, NH), 9.78 s (1H, N^4H). Found, %: C 67.73, 67.97; H 5.88, 6.03; N 17.88, 18.07. $C_{22}H_{23}N_5O_2$. Calculated, %: C 67.85; H 5.95; N 17.98.

5-Methyl-*N*-(2,4-dimethylphenyl)-7-(4-nitrophenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (VI). Yield 4.14 g (76%), mp 274–276°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^1H NMR spectrum, δ, ppm: 1.79 s (3H, CH_3), 2.19 s and 2.22 s [6H, $(\underline{CH_3})_2C_6H_3$], 6.54 s (1H, CH), 6.79–8.12 m [7H, $(CH_3)_2\underline{C_6}\underline{H_3}$, $NO_2C_6H_4$], 8.99 s (1H, NH), 10.12 s (1H, N^4H). Found, %: C 62.24, 62.41; H 4.87, 5.07; N 20.69, 20.87. $C_{21}H_{20}N_6O_3$. Calculated, %: C 62.37; H 4.98; N 20.78.

5-Methyl-*N*-(2,4-dimethylphenyl)-7-(3-nitrophenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (VII). Yield 4.41 g (81%), mp 273–275°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^1H NMR spectrum, δ, ppm: 1.66 s (3H, CH_3), 2.07 s and 2.20 s [6H, $(\underline{CH_3})_2C_6H_3$], 6.57 s (1H, CH), 6.65–8.04 m [7H, $(CH_3)_2\underline{C_6}\underline{H_3}$, $NO_2\underline{C_6}\underline{H_4}$], 9.13 s (1H, NH), 10.16 s (1H, N^4H). Found, %: C 62.13, 62.39; H 4.90, 5.05; N 20.65, 20.89. $C_{21}H_{20}N_6O_3$. Calculated, %: C 62.37; H 4.98.; N 20.78.

***N*-(2,4-Dimethylphenyl)-7-(4-*tert*-butylphenyl)-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (VIII).** Yield 2.78 g (67%), mp 220–222°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^1H NMR spectrum, δ, ppm: 1.23 s (9H, $(\underline{CH_3})_3CC_6H_4$), 1.68 s (3H, CH_3), 2.18 s and 2.36 s [6H, $(\underline{CH_3})_2C_6H_3$], 6.35 s (1H, CH), 6.81–7.51 m [7H, $(CH_3)_2\underline{C_6}\underline{H_3}$, $(CH_3)_3C\underline{C_6}\underline{H_4}$], 8.99 s (1H, NH), 9.99 c (1H, N^4H). Found, %: C 72.19, 72.38; H 6.98, 7.13; N 16.73, 16.92. $C_{25}H_{29}N_5O$. Calculated, %: C 72.26; H 7.03; N 16.85.

***N*-(2,4-Dimethylphenyl)-5-methyl-7-(4-ethoxyphenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (IX)**. Yield 2.54 g (63%), mp 229–231°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^1H NMR spectrum, δ, ppm: 1.34 t (3H, $\underline{CH_3}CH_2O$, *J* 7.0 Hz), 1.78 s (3H, CH_3), 2.18 s and 2.20 s [6H, $(\underline{CH_3})_2C_6H_3$], 3.97 q (2H, $CH_3\underline{CH_2}O$, *J* 7.0 Hz), 6.36 s (1H, CH), 6.73–7.50 m [7H, $(CH_3)_2\underline{C_6}\underline{H_3}$, $CH_3CH_2O\underline{C_6}\underline{H_4}$], 8.99 s (1H, NH), 9.97 s (1H, N^4H). Found, %: C 68.35, 68.55; H 6.17, 6.32; N 17.27, 17.46. $C_{23}H_{25}N_5O_2$. Calculated, %: C 68.47; H 6.25; N 17.36.

7-(4-Hydroxyphenyl)-*N*-(2,4-dimethylphenyl)-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (X). Yield 2.96 g (79%), mp 253–255°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^1H NMR spectrum, δ, ppm: 1.79 s (3H, CH_3), 2.18 s and 2.20 s [6H, $(\underline{CH_3})_2C_6H_3$], 6.32 s (1H, CH), 6.58–7.49 m [7H, $(CH_3)_2\underline{C_6}\underline{H_3}$, $HO\underline{C_6}\underline{H_4}$], 9.09 s (1H, NH), 9.97 s (1H, HO), 9.94 s (1H, N^4H). Found, %: C 67.06, 67.27; H 5.57, 5.74; N 18.54, 18.75. $C_{21}H_{21}N_5O_2$. Calculated, %: C 67.18; H 5.64; N 18.65.

5-Methyl-7-(2-methoxyphenyl)-*N*-(4-chlorophenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (XI). Yield 3.40 g (86%), mp 241–243°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^1H NMR spectrum, δ, ppm: 2.21 s (3H, CH_3), 3.68 s (3H, CH_3O), 6.56 s (1H, CH), 7.09–8.21 m (8H, ClC_6H_4, $CH_3O\underline{C_6}\underline{H_4}$), 9.57 s (1H, NH), 9.76 s (1H, N^4H). Found, %: C 60.62, 60.81; H 4.47, 4.68; N 17.58, 17.76. $C_{20}H_{18}ClN_5O_2$. Calculated, %: C 60.69; H 4.58; N 17.69.

5-Methyl-7-(3-nitrophenyl)-*N*-(4-chlorophenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (XII). Yield 3.04 g (74%), mp 252–254°C. IR spectrum, ν, cm^{-1}: 1620 (C=C), 1680 (CON), 3190 (NH). ^1H NMR spectrum, δ, ppm: 2.21 s (3H, CH_3), 6.61 s (1H, CH), 7.09–8.21 m (8H, ClC_6H_4, $NO_2C_6H_4$), 9.69 s (1H, NH), 10.29 s (1H, N^4H). Found, %: C 55.46, 55.67; H 3.60, 3.76; N 20.34, 20.51. $C_{19}H_{15}ClN_6O_3$. Calculated, %: C 55.55; H 3.68; N 20.46.

5-Methyl-7-phenyl-*N*-(4-chlorophenyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine-6-carboxamide (XIII). Yield 2.53 g (69%), mp 241–243°C. IR spectrum, ν, cm^{-1}: 1612 (C=C), 1680 (CON), 3200 (NH). ^1H NMR spectrum, δ, ppm: 1.77 s (3H, CH_3), 6.57 s (1H, CH), 7.09–7.60 m (9H, ClC_6H_4, C_6H_5), 9.65 s (1H, NH), 10.30 s (1H, N^4H). Found, %: C 62.27, 62.45; H 4.34, 4.50; N 19.04, 19.23. $C_{19}H_{16}ClN_5O$. Calculated, %: C 62.38; H 4.41; N 19.14.

REFERENCES

1. Vdovina, S.V. and Mamedov, V.A., *Russ. Chem. Rev*., 2008, vol. 77, no. 12, p. 1017.
2. Gein, V.L., Gein, L.F., Tsyplyakova, E.P., and Vakhrin, M.I., *Russ J. Org. Chem*., 2007, vol. 43, no. 9, p. 1382.
3. Gein, V.L., Mishunin, V.V., Tsyplyakova, E.P., and Vakhrin, M.I., *Pharm. Chem. J.*, 2009, vol. 43, no. 12, p. 652.
4. Desenko, S.M., Gladkov, E.S., and Nenaidenko, V.G., *Chem. Heterocycl. Comp.*, 2004, no. 1, p. 65.
5. Gein, V.L., Gein, L.F., and Tsyplyakova, E.P., *Chem. Heterocycl. Comp.*, 2003, no. 6, p. 821.
6. Chebanov, V.A., Muravyova, E.A., Desenko, S.M., Musatov, V.I., Knyazeva, I.V., Shishkina, S.V., Shishkin, O.V., and Kappe, C.O., *J. Comb. Chem*., 2006, no. 8, p. 427.
7. Gein, V.L., Zamaraeva, T.M., Kurbatova, A.A., and Vakhrin, M.I., *Pharm. Chem. J.*, 2010, vol. 44, no. 7, p. 366.