Aminoazoles in the three-component synthesis of 7-substituted 6-ethoxycarbonyl-5-methyl-4,7-dihydroazolo[1,5-*a*]pyrimidines

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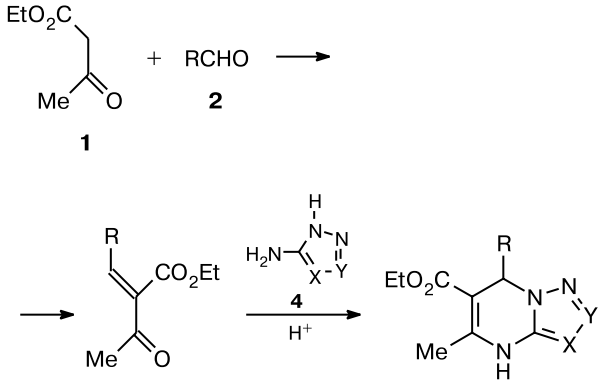
The three-component synthesis of 7-substituted 6-ethoxycarbonyl-5-methyl-4,7-dihydroazolo[1,5-*a*]pyrimidines was carried out for the first time by the reactions of aminoazoles (3-aminopyrazole, 3-amino-1,2,4-triazole, or 5-aminotetrazole) with acetoacetic ester and aliphatic, aromatic, or heteroaromatic aldehyde.

Key words: three-component synthesis, aminoazoles, 7-substituted 6-ethoxycarbonyl-5-methyl-4,7-dihydroazolo[1,5-*a*]pyrimidines.

In recent years, growing attention has been paid to analogs of purines and nucleosides, including azolopyrimidines containing the bridgehead nitrogen atom and their dihydro derivatives, among which promising biologically active compounds were found.[1—3] The main method for the synthesis of azolodihydropyrimidines involves cyclocondensation of aminoazoles with α,β-unsaturated carbonyl compounds of the chalcone[4] or enone[5] types. For example, 7-substituted 6-alkoxycarbonyl-5-methyl-4,7-dihydroazolo[1,5-*a*]pyrimidines were prepared in two steps. First, the reaction of acetoacetic ester **1** with aldehyde **2** afforded CH-active compound **3** (R = H, Ar, Alk, Het) followed by its condensation with aminoazole **4** to give the target products **5**—**7**.[6—8] In particular, compound **6b** was prepared in 45% yield from 3-amino-1,2,4-triazole **4b** and ethyl α-acetylcrotonate **3** (R = Me)[8].



R = Ph (**2a**), Me (**2b**), H (**2c**), 4-Py (**2d**)

	R	X	Y
4a	—	CH	CH
4b	—	N	CH
4c	—	N	N
5	Ph	CH	CH

	R	X	Y
6a	Ph	N	CH
6b	Me	N	CH
6c	H	N	CH
6d	4-Py	N	CH
7	4-Py	N	N

We developed a one-pot synthesis of 7-substituted 6-ethoxycarbonyl-5-methyl-4,7-dihydroazolo[1,5-*a*]pyrimidines **5**—**7** by three-component condensation of aminoazoles **4**, acetoacetic ester **1**, and aldehydes **2**. Apparently, α,β-unsaturated carbonyl compound **3** is formed *in situ* in the course of the reaction.

This method is applicable to a broad spectrum of aromatic, aliphatic, and heteroaromatic aldehydes and allows one to prepare 5,6,7-substituted pyrazolo-, 1,2,4-triazolo-, and tetrazolodihydropyrimidines in 50—67% yields.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker DRX-400 instrument (400 MHz) in DMSO-d_6 or $CDCl_3$. The chemical shifts are given in the δ scale with respect to Me_4Si (internal standard). The IR spectra were measured on a IR-75 spectrophotometer in Nujol mulls. The course of the reactions and the purities of the compounds were monitored by TLC on Sorbfil plates (chloroform—ethanol, 9 : 1, as the eluent).

6-Ethoxycarbonyl-5-methyl-4,7-dihydroazolo[1,5-*a*]pyrimidines (5—7) (general procedure). One—two drops of concentrated HCl were added to a suspension of acetoacetic ester (10 mmol), the corresponding aminoazole (10 mmol), and the corresponding aldehyde (10 mmol) in ethanol (10 mL). The reaction mixture was refluxed for 5—7 h and then kept at ~20 °C until the reaction was completed (8—10 h). The precipitate that formed was filtered off and purified by recrystallization from ethanol or a 1 : 2 methanol—water mixture.

6-Ethoxycarbonyl-5-methyl-7-phenyl-4,7-dihydropyrazolo[1,5-*a*]pyrimidine (5). The yield was 55.5%, m.p. 189—190 °C.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1677—1678, August, 2003.

1066-5285/03/5208-1768 $25.00

Found (%): C, 67.66; H, 5.98; N, 15.00. $C_{16}H_{17}O_2N_3$. Calculated (%): C, 67.85; H, 6.00; N, 14.84. IR, ν/cm^{-1}: 3280 (NH); 1720 (C=O). ^{1}H NMR (DMSO-d_6), δ: 0.955 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 6.8 Hz); 2.35 (s, 3 H, Me); 3.84 (t, 2 H, CH$_3$C$\underline{H}_2$, J = 6.8 Hz); 5.10 (s, 1 H, C(7)H); 7.06 (s, 1 H, C(2)H); 7.14 (m, 5 H, Ph); 9.42 (s, 1 H, C(3)H); 11.94 (s, 1 H, NH).

6-Ethoxycarbonyl-5-methyl-7-phenyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (6a). The yield was 56.2%, m.p. 190—192 °C. Found (%): C, 63.36; H, 5.52; N, 19.69. $C_{15}H_{16}O_2N_4$. Calculated (%): C, 63.38; H, 5.63; N, 19.72. IR, ν/cm^{-1}: 3288 (NH); 1710 (C=O). ^{1}H NMR (DMSO-d_6), δ: 1.04 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 7.2 Hz); 2.42 (s, 3 H, Me); 3.94 (q, 2 H, CH$_3$C$\underline{H}_2$, J = 7.2 Hz); 6.27 (s, 1 H, C(7)H); 7.26 (m, 5 H, Ph); 7.64 (s, 1 H, C(2)H); 10.77 (s, 1 H, NH).

6-Ethoxycarbonyl-5,7-dimethyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (6b). The yield was 51.9%, m.p. 150—152 °C (*cf.* lit. data[8]). Found (%): C, 54.16; H, 6.00; N, 25.32. $C_{10}H_{13}O_2N_4$. Calculated (%): C, 54.30; H, 5.88; N, 25.33. IR, ν/cm^{-1}: 3285 (NH); 1705 (C=O). ^{1}H NMR (DMSO-d_6), δ: 1.23 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 4.0 Hz); 1.37 (d, 3 H, Me, J = 6.0 Hz); 2.31 (s, 3 H, Me), 4.13 (q, 2 H, CH$_3$C$\underline{H}_2$, J = 4.0 Hz); 5.31 (q, 1 H, C(7)H, J = 6.0 Hz); 7.71 (s, 1 H, C(2)H); 10.50 (s, 1 H, NH).

6-Ethoxycarbonyl-5-methyl-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (6c). The yield was 65.5%, m.p. 196—198 °C. Found (%): C, 51.83; H, 5.75; N, 26.80. $C_9H_{12}O_2N_4$. Calculated (%): C, 51.92; H, 5.77; N, 26.92. IR, ν/cm^{-1}: 3280 (NH); 1700 (C=O). ^{1}H NMR (DMSO-d_6), δ: 1.22 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 4.0 Hz); 2.32 (s, 3 H, Me); 4.12 (q, 2 H, CH$_3$C$\underline{H}_2$, J = 4.0 Hz); 4.82 (s, 2 H, CH$_2$); 7.71 (s, 1 H, C(2)H); 10.40 (s, 1 H, NH).

6-Ethoxycarbonyl-5-methyl-7-(4-pyridyl)-4,7-dihydro-1,2,4-triazolo[1,5-*a*]pyrimidine (6d). The yield was 67.2%, m.p. 138—140 °C. Found (%): C, 54.50; H, 4.77; N, 29.09. $C_{13}H_{14}O_2N_6$. Calculated (%):C, 54.54; H, 4.89; N, 29.37. IR, ν/cm^{-1}: 3260 (NH); 1775 (C=O). ^{1}H NMR ($CDCl_3$), δ: 1.15 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 7.2 Hz); 2.60 (s, 3 H, Me); 4.09 (q, 2 H, CH$_3$C$\underline{H}_2$, J = 7.2 Hz); 6.42 (s, 1 H, C(7)H); 7.24 (dd, 2 H, Py, J = 1.6 Hz); 8.58 (dd, 2 H, Py, J = 1.6 Hz); 7.64 (s, 1 H, C(2)H); 11.28 (s, 1 H, NH).

6-Ethoxycarbonyl-5-methyl-7-phenyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine (7). The yield was 60.9%, m.p. 205—206 °C. Found (%): C, 59.09; H, 5.28; N, 24.51. $C_{15}H_{16}O_2N_4$. Calculated (%): C, 58.95; H, 5.26; N, 24.56. IR, ν/cm^{-1}: 3300 (NH); 1715 (C=O). ^{1}H NMR (DMSO-d_6), δ: 1.02 (t, 3 H, C$\underline{H}_3$CH$_2$, J = 6.4 Hz); 2.46 (s, 3 H, Me); 3.94 (q, 2 H, CH$_3$C$\underline{H}_2$, J = 6.4 Hz); 6.58 (s, 1 H, C(7)H); 7.30 (m, 5 H, Ph); 11.28 (s, 1 H, NH).

This study was financially supported by the Russian Foundation for Basic Research (Project No. 02-03-32332-a).

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Received November 27, 2002;
in revised form April 14, 2003