Synthesis of (*E*)-5-Arylvinyl-7-methyltetrazolo[1,5-*a*]pyrimidines

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Abstract—A three-component reaction of 5-aminotetrazole with aromatic aldehydes and acetylacetone under solvent- and catalyst-free conditions at a temperature of 150–160°C proceeds with the formation of (*E*)-5-arylvinyl-7-methyltetrazolo[1,5-*a*]pyrimidines. 5,7-Dimethyltetrazolo[1,5-*a*]pyrimidine is formed as a side-product of the reaction.

Keywords: multicomponent reactions, 5-aminotetrazole, acetylacetone, tetrazolo[1,5-*a*]pyrimidine

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Multicomponent reactions are widely used for the synthesis of various organic compounds [1–5]. Tetrazolo[1,5-*a*]pyrimidine derivatives are promising and poorly studied heterocyclic compounds obtained by multicomponent reactions [6, 7]. Compounds of this series have antimicrobial [8], antitumor [9], hypoglycemic [10], antiviral activities [11].

Earlier, various 7-aryl-substituted 4,7-dihydro-tetrazolo[1,5-*a*]pyrimidine-6(5)-carboxylates were obtained using the three-component reaction of tetrazol-5-amine with aromatic aldehydes and 1,3-dicarbonyl compound, namely aroyl(hetaryl)pyruvic or acetoacetic acid esters [12, 13]. The reaction was carried out by heating a mixture of starting reagents to 160°C in the absence of a solvent and a catalyst. Under these conditions, the reaction proceeded regioselectively to form the title compounds with high yields.

In continuation of the research, we performed the reaction using acetylacetone as a 1,3-dicarbonyl component. A mixture of (*E*)-5-arylvinyl-7-methyltetrazolo[1,5-*a*]pyrimidines **2a–2e** and 5,7-dimethyltetrazolo[1,5-*a*]pyrimidine **3** was formed in a 6:1 ratio (according to ¹H NMR data) instead of the expected 7-aryl-6-acetyl-5-methyl-4,7-dihydro-tetrazolo[1,5-*a*]pyrimidines **1**, when reacting equimolar amounts of acetylacetone, aromatic aldehyde and tetrazol-5-amine in solvent- and catalyst-free conditions at 150–160°C, (Scheme 1).

Compounds **2a–2e** are yellow crystalline substances, poorly soluble in ethanol, dioxane, acetonitrile, readily soluble in acetic acid when heated, and insoluble in water and hexane.

The IR spectra of compounds **2a–2e** and **3** contain absorption bands of medium intensity in the range of 1616–1624 cm^{–1}, which are characteristic of stretching vibrations of the C=C and C=N bonds. The ¹H NMR spectra of compounds **2a–2e** exhibit characteristic signals of the protons of the methyl group as a singlet at 2.91–2.94 ppm, the proton of the methine group of the heterocycle as a singlet at 7.69–7.75 ppm, and two olefinic protons as doublets at 7.30–7.57 and 8.02–8.28 ppm (*J* = 16.0 Hz), as well as protons of the aromatic ring and related groups.

The mass spectra of compounds **2c** and **2d** contain characteristic peaks of molecular ions with *m/z* 304 [*M* – H][–] and 266 [*M* – H][–], respectively.

Compound **3** is a white crystalline substance, readily soluble in acetic acid, chloroform, acetone, poorly soluble in ethanol and insoluble in water. The ¹H NMR spectrum contains singlet signals of the protons of two methyl groups at 2.68 and 2.87 ppm, as well as multiplet signal of the methine proton at 7.36 ppm.

To confirm the proposed structure and establish the spatial structure of compounds **2a–2e**, attempts were made to obtain a single crystal by slow crystallization,

Scheme 1.

R = 2-Cl (**a**), 4-Cl (**b**), 2,4-Cl₂ (**c**), 4-MeO (**d**), 3,4-(MeO)₂ (**e**).

Scheme 2.

but crystals suitable for X-ray diffraction analysis were not obtained. Crystallization from acetic acid yielded a single crystal of compound **3** (Fig. 1).

Compound **3** crystallizes in the centrosymmetric space group of the monoclinic system. The bicyclic system of tetrazolopyrimidine is flat within 0.02 Å. The bond

lengths and bond angles in the molecule have the typical values, with the exception of the slightly distorted C³C²C⁶ angle, 127.9(2)°. A similar deviation of the bond angle from 120°, leading to a shift of the methyl group C⁶H₃ towards the tetrazole ring, is also typical for other alkyl-substituted tetrazolopyrimidines [14, 15].

Only 5,6-dimethyltetrazolo[1,5-*a*]pyrimidine **3** was obtained, when carrying out a three-component reaction under milder conditions in the presence of sodium hydrogen sulfate in methanol according to the previously described method [16]. Tetrazolo[1,5-*a*]pyrimidine **3** was also formed by direct fusion of 5-aminotetrazole with acetylacetone (Scheme 2).

Probably, in the reaction between acetylacetone, aromatic aldehyde, and tetrazole-5-amine, at the first stage, the addition of tetrazol-5-amine to acetylacetone occurs, followed by cyclization and the formation of intermediate **3** (Scheme 3). Compound **3** has a reactive methyl group, and when it reacts with an aromatic

Fig. 1. General view of the molecule of compound **3** in the crystal.

Scheme 3.

aldehyde, condensation occurs with the formation of (*E*)-5-(2-arylethenyl)-7-methyltetrazolo[1,5-*a*]pyrimidines **2a–2e**. The reaction stereoselectivity is due to the greater stability of the *E*-isomers in comparison with the *Z*-isomers. The low yield (5–22%) of compounds **2** is probably associated with the occurrence of side reactions under these conditions.

In conclusion, the use of acetylacetone in a three-component reaction with a mixture of an aromatic aldehyde and tetrazol-5-amine leads to the formation of (*E*)-5-(2-arylethenyl)-7-methyltetrazolo[1,5-*a*]pyrimidines and 5,7-dimethyltetrazolo[1,5-*a*]pyrimidine.

EXPERIMENTAL

IR spectra were recorded on a FSM 1202 FT-IR spectrometer from mineral oil. ^1H NMR spectra were recorded on a Bruker AVANCE III HD 400 spectrometer from DMSO- d_6 solutions relative to internal TMS. Mass spectra were recorded on a Waters ACQUITY UPLC I-Class instrument by ultra-HPLC-MS method (Acquity UPLC BEH C18 1.7 μm column, acetonitrile–water mobile phases, flow rate 0.6 mL/min, Xevo TQD mass detector). Elemental analysis was performed on a PerkinElmer 2400 apparatus. Melting points were measured on a Melting Point M-565 instrument.

Single crystal X-ray diffraction analysis of compound **3** was performed on a Xcalibur Ruby diffractometer equipped with a CCD detector according to the standard method [MoK_α -radiation, 295(2) K, ω -scanning with a step of 1°]. Absorption was taken into account empirically using the SCALE3 ABSPACK algorithm [17]. The crystal system ($\text{C}_6\text{H}_7\text{N}_5$, M 149.17) is monoclinic, space group $P21/c$, $a = 8.064(3)$, $b = 12.456(6)$, $c = 7.074(3)$ Å; $\beta = 91.03(4)^\circ$, $V = 710.4(5)$ Å 3 , $Z = 4$, $d_{\text{calc}} = 1.395$ g/cm 3 ; $\mu = 0.096$ mm $^{-1}$. The structure was solved using the SHELXS program [18] and refined by full-matrix least squares in F^2 in the anisotropic approximation for all non-hydrogen atoms using the SHELXL program [19] with the OLEX2 graphical interface [20]. When refining hydrogen atoms, the *riding* model was used. Final refinement parameters: $R_1 = 0.0550$ [for 1052 reflections with $I > 2\sigma(I)$], $wR_2 =$

0.1766 (for all 1670 independent reflections), $S = 1.026$. X-Ray crystallographic parameters were deposited at the Cambridge Crystallographic Data Center (CCDC 2058640) and can be requested at www.ccdc.cam.ac.uk/data_request/cif

(*E*)-5-[(2-Chlorophenyl)vinyl]-7-methyltetrazolo[1,5-*a*]pyrimidine (2a). A mixture of 0.01 mol (1 mL) of acetylacetone, 0.01 mol (1.1 mL) of 2-chlorobenzaldehyde, 0.01 mol (1.03 g) of tetrazol-5-amine monohydrate was kept at 150–160°C until gas evolution ceased. The resulting mixture was cooled to room temperature, treated with ethanol. The precipitated crystals were filtered off and recrystallized from acetic acid. Yield 0.33 g (12%), mp 192–194°C (AcOH). IR spectrum, ν , cm $^{-1}$: 2954 ($\text{C}_{\text{Alk}}\text{--H}$), 1616 ($\text{C}=\text{C}$), 1462 (Ar). ^1H NMR spectrum, δ , ppm: 2.92 s (3H, CH_3), 7.45–8.02 m (4H $_{\text{Ar}}$), 7.52 d (1H, $\text{CH}_A=\text{CH}_B$, $J = 16.0$ Hz), 7.72 s (1H, C^6H), 8.28 d (1H, $\text{CH}_A=\text{CH}_B$, $J = 16.0$ Hz). Found, %: C 57.44; H 3.66; N 25.68. $\text{C}_{13}\text{H}_{10}\text{ClN}_5$. Calculated, %: C 57.42; H 3.68; N 25.76. M 256.04.

Compounds **2b–2e** were prepared similarly.

(*E*)-5-[(4-Chlorophenyl)vinyl]-7-methyltetrazolo[1,5-*a*]pyrimidine (2b). Yield 0.42 g (15%), mp 216–218°C (AcOH). IR spectrum, ν , cm $^{-1}$: 2932 ($\text{C}_{\text{Alk}}\text{--H}$), 1624 ($\text{C}=\text{C}$), 1462 (Ar). ^1H NMR spectrum, δ , ppm: 2.93 s (3H, CH_3), 7.48 d (1H, $\text{CH}_A=\text{CH}_B$, $J = 16.0$ Hz), 7.55 s (2H $_{\text{Ar}}$), 7.84 d (2H $_{\text{Ar}}$), 8.07 s (1H, $\text{CH}_A=\text{CH}_B$, $J = 16.0$ Hz). Found, %: C 57.51; H 3.62; N 25.74. $\text{C}_{13}\text{H}_{10}\text{ClN}_5$. Calculated, %: C 57.42; H 3.68; N 25.76. M 256.04

(*E*)-5-[(2,4-Dichlorophenyl)vinyl]-7-methyltetrazolo[1,5-*a*]pyrimidine (2c). Yield 0.67 g (22%), mp 200–202°C (AcOH). IR spectrum, ν , cm $^{-1}$: 2924 ($\text{C}_{\text{Alk}}\text{--H}$), 1620 ($\text{C}=\text{C}$), 1462 (Ar). ^1H NMR spectrum, δ , ppm: 2.94 s (3H, CH_3), 7.57 d (1H, $\text{CH}_A=\text{CH}_B$, $J = 16.0$ Hz), 7.58 d (1H $_{\text{Ar}}$, $J = 2.2$ Hz), 7.77 d (1H $_{\text{Ar}}$, $J = 2.2$ Hz), 8.07 d (1H $_{\text{Ar}}$, $J = 8.4$ Hz), 8.24 d (1H, $\text{CH}_A=\text{CH}_B$, $J = 16.0$ Hz). Mass spectrum, m/z (I_{rel} , %): 304 (100) [$M - \text{H}$] $^-$. Found, %: C 50.98; H 2.87; N 22.84. $\text{C}_{13}\text{H}_9\text{Cl}_2\text{N}_5$. Calculated, %: C 50.96; H 2.94; N 22.86. M 305.02.

(E)-5-[(4-Methoxyphenyl)vinyl]-7-methyl-tetrazolo[1,5-a]pyrimidine (2d). Yield 0.15 g (6%), mp 204–206°C (AcOH). IR spectrum, ν , cm^{-1} : 2916 ($\text{C}_{\text{Alk}}\text{-H}$), 1624 ($\text{C}=\text{C}$), 1462 (Ar). ^1H NMR spectrum, δ , ppm: 2.91 s (3H, CH_3), 3.81 s (3H, CH_3O), 7.05–7.76 m (4H_{Ar}), 7.30 d (1H, $\text{CH}_\text{A}=\text{CH}_\text{B}$, $J = 16.0$ Hz), 8.04 d (1H, $\text{CH}_\text{A}=\text{CH}_\text{B}$, $J = 16.0$ Hz). Mass spectrum, m/z (I_{rel} , %): 266 (95) [$M - \text{H}$] $^-$. Found, %: C 62.96; H 4.79; N 26.28. $\text{C}_{14}\text{H}_{13}\text{N}_5\text{O}$. Calculated, %: C 62.85; H 4.86; N 26.29. M 267.11

(E)-5-[(3,4-Dimethoxyphenyl)vinyl]-7-methyltetrazolo[1,5-a]pyrimidine (2e). Yield 0.13 g (5%), mp 198–200°C (AcOH). IR spectrum, ν , cm^{-1} : 2912 ($\text{C}_{\text{Alk}}\text{-H}$), 1612 ($\text{C}=\text{C}$), 1377 (Ar). ^1H NMR spectrum, δ , ppm: 2.91 s (3H, CH_3), 3.84 c (3H, CH_3O), 3.87 s (3H, CH_3O), 7.06–7.44 m (3H_{Ar}), 7.36 d (1H, $\text{CH}_\text{A}=\text{CH}_\text{B}$, $J = 16.0$ Hz), 8.02 d (1H, $\text{CH}_\text{A}=\text{CH}_\text{B}$, $J = 16.0$ Hz). Found, %: C 60.48; H 5.64; N 23.51. $\text{C}_{15}\text{H}_{15}\text{N}_5\text{O}_2$. Calculated, %: C 60.54; H 5.61; N 23.54. M 297.12

5,7-Dimethyltetrazolo[1,5-a]pyrimidine (3). a. A mixture of 0.01 mol (1 mL) of acetylacetone, 0.01 mol (1.03 g) of tetrazol-5-amine monohydrate was kept for 2 min at 150–160°C until the reaction mixture solidified. The residue was cooled to room temperature and treated with ethanol. The precipitated crystals were filtered off and recrystallized from ethanol. Yield 80%.

b. To a solution of 0.01 mol (1 mL) of acetylacetone, 0.01 mol (1.1 mL) of 2-chlorobenzaldehyde, 0.01 mol (1.03 g) of tetrazol-5-amine monohydrate in 15 mL of methanol was added 0.001 mol (0.12 g) of NaHSO_4 . The resulting mixture was boiled for 2 h. The precipitated crystals were filtered off, washed with water, dried at room temperature, and recrystallized from ethanol. Yield 77%, mp 150–152°C (EtOH). IR spectrum, ν , cm^{-1} : 1624 ($\text{C}=\text{C}$), 1531 ($\text{C}=\text{N}$), 1377 ($\text{C}-\text{CH}_3$). ^1H NMR spectrum, δ , ppm: 2.68 s and 2.87 s (6H, CH_3), 7.36 m (1H, CH). Found, %: C 48.25; H 4.71; N 46.89. $\text{C}_6\text{H}_7\text{N}_5$. Calculated, %: C 48.27; H 4.69; N 46.93. M 149.07.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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