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Synthesis and Structure of Thiazolopyrimidine Derivatives

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Abstract—Three-component condensations of ethyl acetoacetate with 1,3-thiazol-2-amine and aromatic aldehydes in isopropyl alcohol at 20°C under ultrasonic activation lead to the formation of ethyl 5-aryl-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylates, ethyl 5-aryl-7-hydroxy-7-methyl-6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylates, or ethyl 2-hydroxy-2-methyl-2*H*-chromene-3-carboxylate, depending on the position and nature of substituents in the aldehyde component. The structure of the isolated compounds was determined by one- and two-dimensional NMR and IR spectroscopy, and a plausible mechanism of their formation was proposed.

Keywords: three-component condensation, ultrasonic activation, thiazolopyrimidines, ethyl acetoacetate, aromatic aldehydes, 1,3-thiazol-2-amine, NMR, IR spectra

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Thiazolopyrimidines are heterocyclic analogs of purine bases, and they exhibit a broad spectrum of pharmacological activity [1–6], which stimulates studies of the synthesis of new compounds of this series, including potentially biologically active ones. A modern synthetic approach to thiazolopyrimidine derivatives is based on multicomponent sonochemical reactions in accordance with the "green chemistry" principles such as environmental safety, atom economy, and efficiency. Three-component syntheses of aryl-substituted thiazolopyrimidinecarboxylates, including those carried out under ultrasonic irradiation, have been reported in [7–9]. However, the effect of substituents in the aromatic ring of the aldehyde component on the reaction course was not studied.

Herein, we describe three-component condensations of aromatic aldehydes with ethyl acetoacetate and 1,3-thiazol-2-amine. The series of aldehyde components included unsubstituted benzaldehyde, 2-methyl-, 2-nitro-, 2-hydroxy-, 2-chloro-, 4-chloro-, 4-bromo-, and 3-methoxy-4-hydroxybenzaldehydes, and 2-hydroxynaphthalene-1-carbaldehyde. The reactions were carried out with equimolar amounts of the reactants in isopropyl alcohol at 20°C under ultrasonic irradiation.

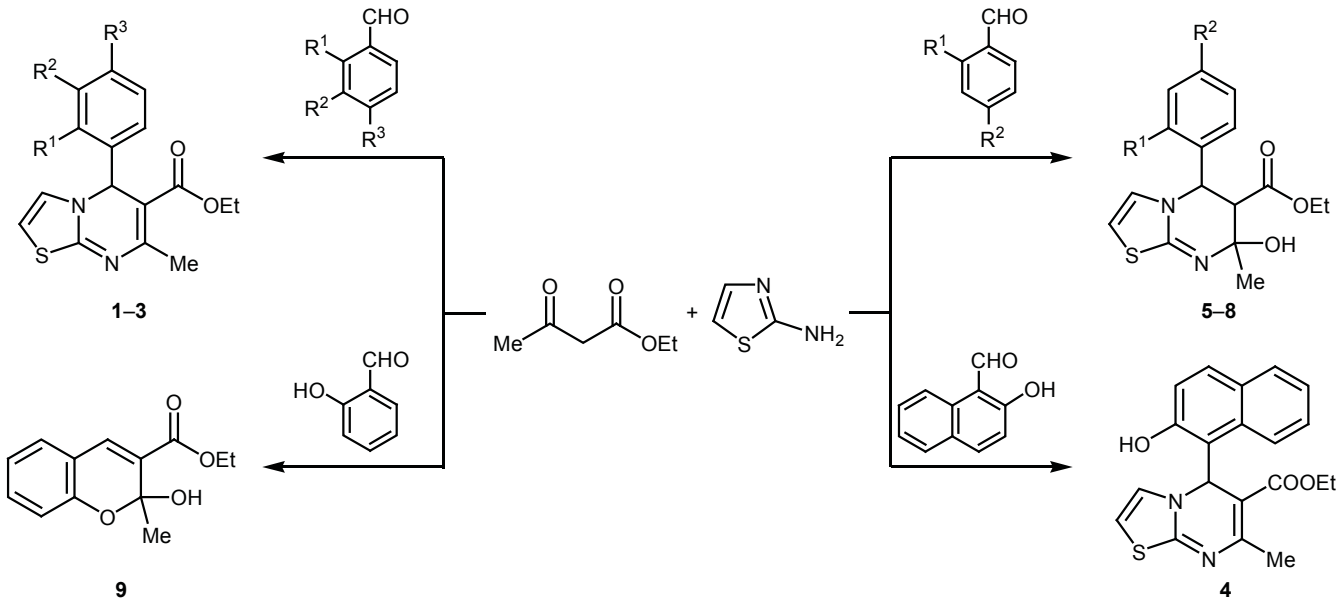
The position of substituents in the initial aldehyde was the crucial factor determining the reaction direction. The reactions with benzaldehyde, 2-chloro- and 4-hydroxy-3-methoxybenzaldehydes, and 2-hydroxynaphthalene-1-carbaldehyde afforded ethyl 5-aryl-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylates **1**–**4**, 5-aryl-7-hydroxy-7-methyl-6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylates **5**–**8** were obtained from 2-nitro-, 2-methyl-, 4-chloro-, and 4-bromobenzaldehydes, and ethyl 2-hydroxy-2-methyl-2*H*-chromene-3-carboxylate (**9**) was isolated in the condensation with salicylaldehyde (Scheme 1).

Compounds **1**, **2**, and **9** were reported previously [7–10]; the structure of the newly synthesized compounds was determined on the basis of their elemental compositions, one- and two-dimensional NMR spectra, and IR spectra.

The ^{1}H NMR spectra of thiazolopyrimidines **1**–**4** showed signals of the 5-H proton (δ 6.13–6.15 ppm, s), ester ethoxy groups (δ 3.60–4.17 and 1.11–1.30 ppm for methylene and methyl protons, respectively), and 7-methyl group (δ 1.75–2.28 ppm, s). The IR spectra of **1**–**4** displayed absorption bands due to C=C (1650–1723 cm^{-1}), C=N (1500–1646 cm^{-1}), C–H (CH_3, 2869–2951 cm^{-1}), and C=O groups (1700–1790 cm^{-1}).

In the ^{1}H NMR spectra of 7-hydroxy analogs **5**–**8**, the key signals were those of 5-H (δ 4.04–6.41 ppm, d), 6-H (δ 2.47–4.49 ppm, d), OH (δ 1.16–2.15 ppm, s), and CH_2CH_3 (δ 3.82–4.18 m and 0.90–1.13 ppm, t). In the spectra of **5** and **8**, the 5-H, 6-H, OH, and OEt signals were doubled (see Experimental) due to the presence of two diastereoisomers. Molecules **5**–**8** possess 3 asymmetric carbon atoms (C^5, C^6, C^7), so

Scheme 1.

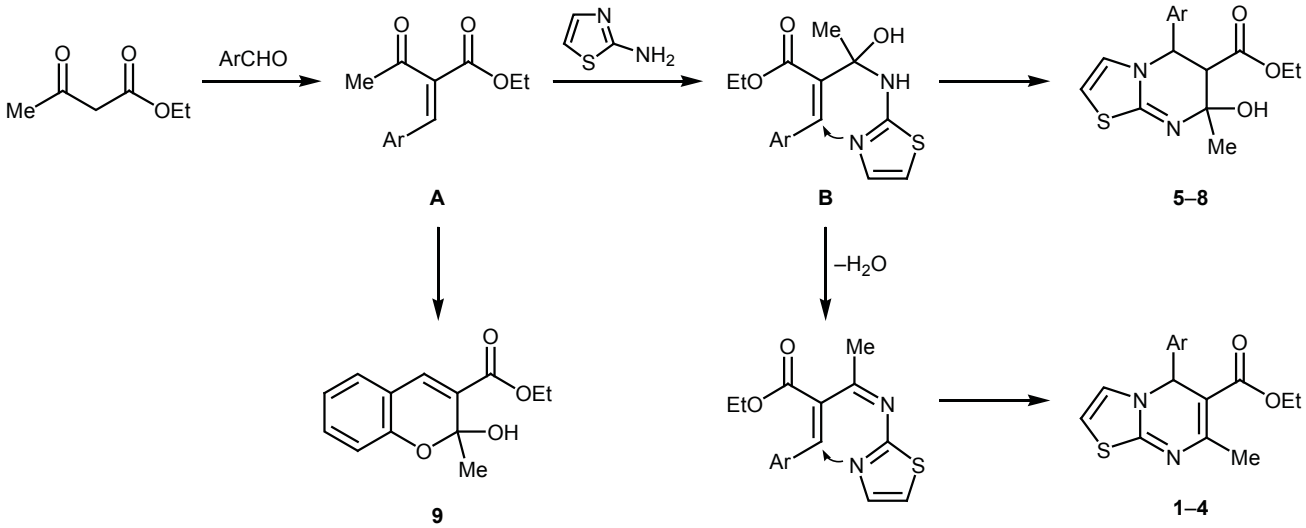


1, $R^1 = R^2 = R^3 = H$; **2**, $R^1 = Cl$, $R^2 = R^3 = H$; **3**, $R^1 = H$, $R^2 = OMe$, $R^3 = OH$; **5**, $R^1 = NO_2$, $R^2 = H$; **6**, $R^1 = Me$, $R^2 = H$; **7**, $R^1 = H$, $R^2 = Cl$; **8**, $R^1 = H$, $R^2 = Br$.

that the existence of 8 optically active forms and 3 racemates is possible. Protons signals of **5** were unambiguously assigned to sp^3- and sp^2-carbon atoms on the basis of cross peaks in the ^1H–^{13}C HSQC spectrum.

Scheme 2 shows a plausible mechanism of the formation of compounds **1**–**9**. Initial condensation of aromatic aldehyde with ethyl acetoacetate gives α,β-unsaturated ketone **A** which reacts with 1,3-thiazol-2-amine to form hemiaminal **B**. Intramolecular cyclization of the latter involving the thiazole nitrogen atom leads to hydroxydihydrothiazolopyrimidine system **5**–**8**; this process is favored by the presence of electron-withdrawing groups in the aldehyde moiety and steric effect of the methyl group. The formation of compounds **1**–**4** implies that the cyclization of **B** is preceded by dehydration. In the reaction with salicylaldehyde, intermediate **A** undergoes cyclization to form pyran ring due to spatial proximity of the hydroxy

Scheme 2.



1, Ar = Ph; **2**, Ar = 2-ClC_6H_4; **3**, Ar = 4-OH-3-$MeOC_6H_3$; **4**, Ar = 2-hydroxynaphthalen-1-yl; **5**, Ar = 2-$O_2NC_6H_4$; **6**, Ar = 2-MeC_6H_4; **7**, Ar = 4-ClC_6H_4; **8**, Ar = 4-BrC_6H_4.

group in the *ortho* position of the benzene ring and carbonyl group of the acetyl fragment. Unlike salicylaldehyde, the hydroxy group in 2-hydroxynaphthalene-1-carbaldehyde is less nucleophilic because of more extended conjugation system, so that no cyclization of the corresponding intermediate **A** occurs.

In summary, we have synthesized new compounds of the thiazolo[3,2-*a*]pyrimidine series and studied the effect of the structure of the aldehyde component on the direction of their three-component condensation with ethyl acetoacetate and 1,3-thiazol-2-amine. Some of the synthesized compounds showed a pronounced cytotoxicity against HeLa cell line and are therefore promising for further studies [11].

EXPERIMENTAL

The IR spectra were recorded in KBr on an FSM 1201 spectrometer with Fourier transform (Russia). The ^{1}H and ^{1}H–^{13}C HSQC spectra were recorded on a Varian spectrometer (USA) at 400 MHz for ^{1}H using $CDCl_3$, acetone-d_6, or DMSO-d_6 as solvent and tetramethylsilane as internal standard. Elemental analysis was performed with a Vario MICRO cube automatic CHNS analyzer (Germany). The melting points were measured in open capillaries. The progress of reactions was monitored by TLC on Silufol UV-254 plates using hexane–ethyl acetate–chloroform (2:2:1) as eluent; spots were visualized under UV light or by treatment with iodine vapor. The reactions were carried out using a UZV-2.8 ultrsonic bath (Russia; ultrasound power 230 W, heating power 130 W, ultrasound frequency 35 kHz).

1,3-Thiazol-2-amine (chemically pure, ethyl acetoacetate (pure), benzaldehyde (pure), 2-methylbenzaldehyde (chemically pure), 2-nitrobenzaldehyde (chemically pure), 2-hydroxybenzaldehyde (chemically pure), 2-chlorobenzaldehyde (chemically pure), 4-chlorobenzaldehyde (chemically pure), 4-bromobenzaldehyde (chemically pure), 4-hydroxy-3-methoxybenzaldehyde (chemically pure), 2-hydroxynaphthalene-1-carbaldehyde (chemically pure), and isopropyl alcohol (pure) were commercial products.

Compounds 1–9 (*general procedure***).** Equimolar amounts of ethyl acetoacetate, aromatic aldehyde, and 1,3-thiazol-2-amine (3 mmol each) were dissolved in 3 mL of isopropyl alcohol, and the solution was subjected to ultrasonic irradiation for 120–180 min at 20°C. The solid product was filtered off, washed with isopropyl alcohol (3×20 mL), and dried in air.

Ethyl 7-methyl-5-phenyl-5*H*-[1,3]thiazolo[3,2-*a*]-pyrimidine-6-carboxylate (1). Yield 0.15 g (34%), off-white crystals, mp 98–100°C [7–9].

Ethyl 5-(2-chlorophenyl)-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (2). Yield 0.42 g (42%), yellow crystals, mp 105–107°C [8, 9].

Ethyl 5-(4-hydroxy-3-methoxyphenyl)-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (3). Yield 0.49 g (48%), colorless crystals, mp 177–179°C. IR spectrum, ν, cm^{-1}: 3204 (OH), 2899 (CH_3), 2820 (OCH_3), 1700 (C=O), 1654 (C=C), 1500 (C=N), 1594–1606 (C=C_{arom}). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.14 t (3H, C**H**$_3$CH$_2$, J = 12.0 Hz), 2.28 s (3H, CH_3), 2.49 s (3H, OCH_3), 3.91–4.03 m (2H, CH_3C**H**$_2$), 6.13 s (1H, 5-H), 6.59–6.70 m (3H, H_{arom}), 6.69 d (1H, 2-H, J = 4.0 Hz), 7.18 d (1H, 3-H, J = 4.0 Hz), 9.04 s (1H, OH). Found, %: C 58.90; H 5.61; N 8.39. $C_{17}H_{18}N_2O_4S$. Calculated, %: C 58.96; H 5.20; N 8.09.

Ethyl 5-(2-hydroxynaphthalen-1-yl)-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (4). Yield 0.52 g (47%), brown crystals, mp 123–126°C. IR spectrum, ν, cm^{-1}: 3210 (OH), 2899 (CH_3), 1704 (C=O), 1650 (C=C), 1501 (C=N), 1595–1610 (C=C_{arom}). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.30 t (3H, C**H**$_3$CH$_2$, J = 12.0 Hz), 1.75 s (3H, CH_3), 3.60–3.79 m (2H, C**H**$_2$CH$_3$), 6.15 s (1H, 5-H), 6.49 d (1H, 2-H, J = 4.0 Hz), 7.10 d (1H, 3-H, J = 4.0 Hz), 6.58–7.19 m (3H, H_{arom}), 8.00 s (1H, OH). Found, %: C 65.75; H 4.65; N 7.17. $C_{20}H_{18}N_2O_3S$. Calculated, %: C 65.57; H 4.92; N 7.65.

Ethyl 7-hydroxy-7-methyl-5-(2-nitrophenyl)-6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (5). Yield 0.28 g (26%), yellow crystals, mp 127–128°C. IR spectrum, ν, cm^{-1}: 3100 (OH), 2900 (CH_3), 1700 (C=O), 1600 (C=C), 1590–1608 (C=C_{arom}), 1550–1575 (NO_2, asym.), 1230–1290 (NO_2, sym.). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.03 t and 1.13 t (3H, CH_2C**H**$_3$, J = 12.0 Hz), 1.16 s and 2.15 s (1H, OH), 2.44 s (3H, CH_3), 4.02–4.08 m and 4.10–4.20 m (2H, C**H**$_2$CH$_3$), 4.26 d and 4.45 d (1H, 6-H, J = 8.0 Hz), 6.05 d and 6.33 d (1H, 5-H, J = 8.0 Hz), 6.45–8.08 m (6H, 2-H, 3-H, H_{arom}). ^{1}H/^{13}C HSQC spectrum, δ/δ_C, ppm: 1.03/13.54 and 1.13/13.56 (CH_2C**H**$_3$/CH_2**C**H$_3$), 2.44/27.94 (CH_3/CH_3), 4.01/61.58 and 4.18/62.19 (C**H**$_2$CH$_3$/**C**H$_2$CH$_3$), 4.26/62.32, 4.45/60.29 (6-H/C^6), 6.05/55.32 and 6.33/53.35 (5-H/C^5). Found, %: C 52.71; H 4.92; N 11.77. $C_{16}H_{17}N_3O_5S$. Calculated, %: C 52.89; H 4.68; N 11.57.

Ethyl 7-hydroxy-7-methyl-5-(2-methylphenyl)-6,7-dihydro-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-

carboxylate (6). Yield 0.35 g (35%), off-white crystals, mp 131–132°C. IR spectrum, ν, cm^{-1}: 3099 (OH), 2880 (CH_3), 1700 (C=O), 1606 (C=C), 1600–1615 (C=C_{arom}), 1500 (C=N). ^1H NMR spectrum (acetone-d_6), δ, ppm: 0.90 t (3H, C**H**$_3$CH$_2$, J = 12.0 Hz), 1.98 s (1H, OH), 2.25 s (3H, CH_3), 2.47 d (1H, 6-H, J = 8.0 Hz), 3.68 s (3H, C**H**$_3$C$_6$H$_4$), 4.04 d (1H, 5-H, J = 8.0 Hz), 3.82–3.88 m (2H, C**H**$_2$CH$_3$), 6.57–7.30 m (4H, H_{arom}), 6.59 d (1H, 2-H, J = 4.0 Hz), 6.96 d (1H, 3-H, J = 4.0 Hz). $^1H/^{13}C$ HSQC spectrum, δ/δ_C, ppm: 0.90/13.80 (CH$_2$C**H**$_3$/CH$_2$**C**H$_3$), 2.25/29.74 (CH_3/CH_3), 2.47/39.90 (6-H/C^6), 3.68/55.34 (C**H**$_3$C$_6$H$_4$/**C**H$_3$C$_6$H$_4$), 3.85/61.25 (C**H**$_2$CH$_3$/**C**H$_2$CH$_3$), 4.04/65.61 (5-H/C^5). Found, %: C 61.54; H 6.10; N 8.32. $C_{17}H_{20}N_2O_3S$. Calculated, %: C 61.44; H 6.02; N 8.78.

Ethyl 5-(4-chlorophenyl)-7-hydroxy-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (7). Yield 0.38 g (41%), yellow crystals, mp 117–119°C. IR spectrum, ν, cm^{-1}: 2970 (CH_3), 1700 (C=O), 1609 (C=C), 1599–1615 (C=C_{arom}), 1510 (C=N). ^1H NMR spectrum (acetone-d_6), δ, ppm: 1.12 t (3H, CH$_2$C**H**$_3$, J = 12.0 Hz), 1.64 s (1H, OH), 2.39 s (3H, CH_3), 4.01–4.13 m (2H, C**H**$_2$CH$_3$), 4.17 d (1H, 6-H, J = 4.0 Hz), 5.95 d (1H, 5-H, J = 4.0 Hz), 6.45 d (1H, 2-H, J = 4.0 Hz), 7.05 d (1H, 3-H, J = 4.0 Hz), 7.19–7.40 m (4H, H_{arom}). $^1H/^{13}C$ HSQC spectrum, δ/δ_C, ppm: 1.12/13.39 (C**H**$_3$CH$_2$/**C**H$_3$CH$_2$), 2.39/24.41 (CH_3/CH_3), 4.07/61.45 (C**H**$_2$CH$_3$/**C**H$_2$CH$_3$), 4.17/61.53 (6-H/C^6), 5.95/54.78 (5-H/C^5). Found, %: C 54.39; H 4.48; N 8.37. $C_{16}H_{17}ClN_2O_3S$. Calculated, %: C 54.47; H 4.82; N 7.94.

Ethyl 5-(4-bromophenyl)-7-hydroxy-7-methyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-6-carboxylate (8). Yield 0.37 g (43%), brown crystals, mp 125–127°C. IR spectrum, ν, cm^{-1}: 2935 (CH_3), 1712 (C=O), 1622 (C=C), 1589–1604 (C=C_{arom}), 1499 (C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.13 t (3H, CH$_2$C**H**$_3$, J = 12.0 Hz), 1.67 s and 2.30 s (1H, OH), 2.18 s (3H, CH_3), 3.94 d and 4.04 d (1H, 6-H, J = 8.0 Hz), 4.02–4.07 m and 4.09–4.14 m (2H, C**H**$_2$CH$_3$), 5.41 d and 5.56 d (1H, 5-H, J = 12.0 Hz), 6.48 d (1H, 2-H), 6.79–7.44 m (4H, H_{arom}), 7.07 d (1H, 3-H, J = 4.0 Hz). Found, %: C 48.65; H 3.95; N 7.38. $C_{16}H_{17}BrN_2O_3S$. Calculated, %: C 48.36; H 4.28; N 7.05.

Ethyl 2-hydroxy-2-methyl-2*H*-chromene-3-carboxylate (9). Yield 0.08 g (22%), colorless crystals, mp 111–113°C [10].

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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