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5,7-Substituted thiazolo[2,3-*a*]pyrimidines: Synthesis, stereochemistry and crystal structure

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Abstract

Reaction of 2-aminothiazoline (**1**) with α,β-unsaturated carbonyl compounds **2** under mild conditions (acetone, room temperature) gives two diastereomers 5-R-7-hydroxy-5*H*-tetrahydrothiazolo[2,3-*a*]pyrimidines **3**. According to ^{1}H NMR, major isomers of **3** have axial OH-groups whereas minor isomers have equatorial OH-groups. The X-ray investigation of compound **3i** reveals only **A** type diastereomer in the crystal phase. The asymmetric unit contains two forms (A1 and A2) with slightly different geometrical parameters. Each of them consists of a pair of enantiomers E1 and E2. As a result, the asymmetric unit contains the centrosymmetric dimers (A1E1...A1E2 and A2E2...A2E1), due to the intermolecular hydrogen bonds. 5,7-Diaryl-5*H*-2,3-dihydrothiazolo[2,3-*a*]pyrimidines **4** were obtained *via* reaction of **1** with **2** under stronger conditions (DMF or chloroform, heating). Structure of product **4p** was confirmed by X-ray structural analysis.

Keywords: 2-Aminothiazoline; Thiazolo[2,3-*a*]pyrimidines; NMR spectroscopy; X-ray structural analysis

1. Introduction

Reactions of α,β-unsaturated ketones with aminoazoles is the most favourable way to the series of natural-like partially hydrogenated azolopyrimidines [1]. These transformations usually proceed under mild reaction conditions with high regio- and stereoselectivity. This can be explained not only by the difference in the electrophilicity of carbonyl and β-carbon center of the ketone but also by significant differences in the nucleophilicity of amino group and adjacent endo-reaction center of azole. The distribution of the electron density and electrophilicity of carbon centers in the molecules of α,β-unsaturated ketones are relatively constant. On the other hand, the nucleophilicity of different centers of azole molecule can vary. Thus, the direction of the heterocyclization of aminoazoles is mainly governed by the nature of nucleophile.

The reaction of 2-aminothiazoline (**1**) with α,β-unsaturated carbonyl compounds **2a**–**r**, **6**–**9** has been carefully examined. This paper presents the results including synthetic details, stereochemistry and X-ray analysis of the reaction products.

2-Aminothiazolines is the well known class of chemicals exhibiting various types of biological activity. Several derivatives of 2-aminothiazoline (**1**) were characterized as nitric oxide synthetase inhibitors [2], spermagenesis modulators [3], potential cancer chemopreventive agents [4] and specific monovalent ligands for the cholera toxin [5]. Thiazolo[2,3-*a*]pyrimidines that can be obtained *via* the cyclization of 2-aminothiazoline (**1**) with α,β-unsaturated

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ketones were reported as potent antagonists of specific chemokine (CXCR2) receptors [6] and prospective anticancer agents [7].

Even though 2-aminothiazoline (**1**) and its derivatives have been investigating for many years, surprisingly limited information is available on the heterocyclization of **1** with α,β-unsaturated carbonyl compounds. We know paper [8] and patent [9], but the synthetic information described in them lack important structural details. Authors of [8] inform about the possibility to oxidize the 7-hydroxy group to keto group in the reaction of MnO_2 with 5-R-7-hydroxy-5*H*-2,3,6,7-tetrahydrothiazolo[2,3-*a*]pyrimidines which has no second substituent in position 7. Surprisingly, nothing is mentioned about both the formation of diastereomers and the dehydratation. According to our experience, these processes are very difficult to avoid.

2. Experimental

2.1. Synthesis

The general procedure for the preparation of 5-R-7-hydroxy-7-R′-5*H*-2,3,6,7-tetrahydrothiazolo[2,3-*a*]pyrimidines **3a**–**j**, 5,7-diaryl-5*H*-2,3-dihydrothiazolo[2,3-*a*]pyrimidines **4k**, **m**,**o** and 5,5′-bis-5-(4-fluorophenyl)-7-phenyl-2,3-dihydrothiazolo[2,3-*a*]pyrimidine **5r**. Amine **1** (0.80 g, 8.0 mmol) was added to the acetone solution of a corresponding aldehyde or ketone **2**. The mixture was stirred until complete dissolution of **1** and kept at room temperature in dark (time of the reaction is 1 day for **3c**, 2 days for **3a**,**f**, 4 days for **3b**,**d**, 5 days for **3g**, 13 days for **3i**, 17 days for **3e**, 20 days for **3h**, 30 days for **3j** and **5r**). The precipitate formed was filtered off, washed with acetone and dried.

Compound **5r**. ^{1}H NMR (DMSO-d_6) δ: 3.30 (m, 4H, C2-H), 4.0 (m, 4H, C3-H), 7.10–7.70 (m, 10H, $CH_{arom.}$), 7.97–8.20 (m, 8H, $CH_{arom.}$).

7-Hydroxy-7-methyl-5-phenyl-5*H*-2,3,6,7-tetrahydrothiazolo[2,3-*a*]pyrimidine (**3d**). The mixture of amine **1** (15 mmol, 1.50 g) and benzalacetone (**2d**) (15 mmol, 1.50 g) in DMF (3 ml) was heated on water-bath for 4 h. Then the reaction mixture cooled down and poured into the 100 ml of ice water. Resulting precipitate was recrystallized from acetone.

7-(4-Methoxyphenyl)-5-phenyl-5*H*-2,3-dihydrothiazolo[2,3-*a*]pyrimidine (**4l**). The mixture of amine **1** (15 mmol, 1.50 g) and chalcone **2l** (10 mmol, 2.40 g) in DMF (5 ml) was refluxed for 0.5 h. The resulting solution cooled down, diluted with acetone (40 ml) and kept in cold for 24 h. The precipitate formed was filtered off, washed with acetone and dried.

7-(4-Methoxyphenyl)-5-(4-nitrophenyl)-5*H*-2,3-dihydrothiazolo[2,3-*a*]pyrimidine **4p** and 5,5′-bis-5-(4-nitrophenyl)-7-(4-methoxyphenyl)-2,3- dihydrothiazolo[2,3-*a*]pyrimidine **5p**. The mixture of amine **1** (15 mmol, 1.50 g) and chalcone **2p** (10 mmol, 2.40 g) in chloroform (50 ml) was refluxed for 18 h. Then the reaction mixture was evaporated down to volume of 10 ml and the resulting solution was kept in cold for 24 h. The precipitate of **5p** was filtered and washed with chloroform. The filtrate was diluted with acetone and kept in cold for 24 h. The precipitated solid of **4p** was filtered off, washed with acetone and dried.

Compound **5p**. ^{1}H NMR (DMSO-d_6) δ: 3.30 (m, 4H, C2-H), 3.70 (m, 4H, C3-H), 3.86 (s, 6H, OCH_3), 7.12–8.30 (m, 12H, $CH_{arom.}$), 8.37–8.40 (m, 4H, $CH_{arom.}$).

2.2. Instruments

^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-300 spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent at 25 °C and TMS as the internal standard. Mass spectra were recorded on FINNIGAN MAT. INCOS 50 instrument at 70 eV. Microanalyses were carried out on LECO CHNS-900 elemental analyzer.

2.3. X-ray diffraction study

Crystals of compounds **3i** and **4p** for X-ray diffraction experiments were grown in acetone at 20 °C.

Crystals of **3i** are triclinic. At 293 K $\boldsymbol{a} = 10.001(2)$, $\boldsymbol{b} = 11.247(2)$, $\boldsymbol{c} = 13.904(3)$ Å, $\alpha = 90.42(2)°$, $\beta = 109.94(2)°$, $\gamma = 104.39(2)°$, $V = 1426(2)$ Å^3, $M_r = 262.37$, $Z = 4$, the space group is $P\bar{1}$, $d_{calc} = 1.218$ g/cm^3, $\mu(MoK\alpha) = 0.218$ mm^{-1}, $F(000) = 560$. Intensity of 8003 reflections (4774 independent, $R_{int} = 0.047$) were measured on the ≪Xcalibur-3≫ diffractometer (graphite monochromated MoKα radiation, CCD detector, ω-scaning, $2\Theta_{max} = 50°$). The structure was solved by the direct method using SHELXTL package [10]. Positions of hydrogen atoms were calculated geometrically and refined using the ''riding'' model with $U_{iso} = nU_{eq}$ of a non-hydrogen atom bonded with the given hydrogen atom ($n = 1.5$ for methyl and hydroxyl groups and $n = 1.2$ for other hydrogen atoms). The full-matrix least-squares refinement against F^2 in the anisotropic approximation using 4533 reflections was converged to $R_1 = 0.056$ (for 1686 reflections with $F > 4\sigma(F)$), $wR_2 = 0.088$, $S = 0.746$. Atomic coordinates and crystallographic parameters have been deposited to the Cambridge Crystallographic Data Centre (CCDC 636587).

Crystals of **4p** are orthorhombic. At 293 K $\boldsymbol{a} = 8.637(2)$, $\boldsymbol{b} = 10.878(2)$, $\boldsymbol{c} = 18.003(4)$ Å, $V = 1691.4(6)$ Å^3, $M_r = 367.42$, $Z = 4$, the space group is $P2_12_12_1$, $d_{calc} = 1.443$ g/cm^3, $\mu(MoK\alpha) = 0.217$ mm^{-1}, $F(000) = 768$. Intensity of 1734 reflections were measured on an automatic four circles Siemens P3/PC diffractometer (graphite monochromated MoKα radiation, $\Theta/2\Theta$ scaning, $2\Theta_{max} = 50°$). The structure was solved by the direct method using SHELXTL package [10]. Positions of hydrogen atoms were calculated geometrically and refined using the ''riding'' model with $U_{iso} = nU_{eq}$ of a non-hydrogen atom bonded with the given hydrogen atom ($n = 1.5$ for methyl group and $n = 1.2$ for other hydrogen atoms). The full-matrix least-squares refinement against F^2 in the anisotropic approximation using 1697 reflections was converged to $R_1 = 0.066$ (for 1122

reflections with $F > 4\sigma(F)$), $wR_2 = 0.138$, $S = 1.113$. Atomic coordinates and crystallographic parameters have been deposit to the Cambridge Crystallographic Data Centre (CCDC 636586).

2.4. Quantum-chemical calculations

The molecular structure of the isomers **A** and **B** for compound **3i** was optimized using Density Functional Theory with B3LYP functional [11–14]. The standard cc-pvdz basis set [15] was used. All calculations were performed using the PC GAMESS program [16].

3. Results and discussion

3.1. Synthesis

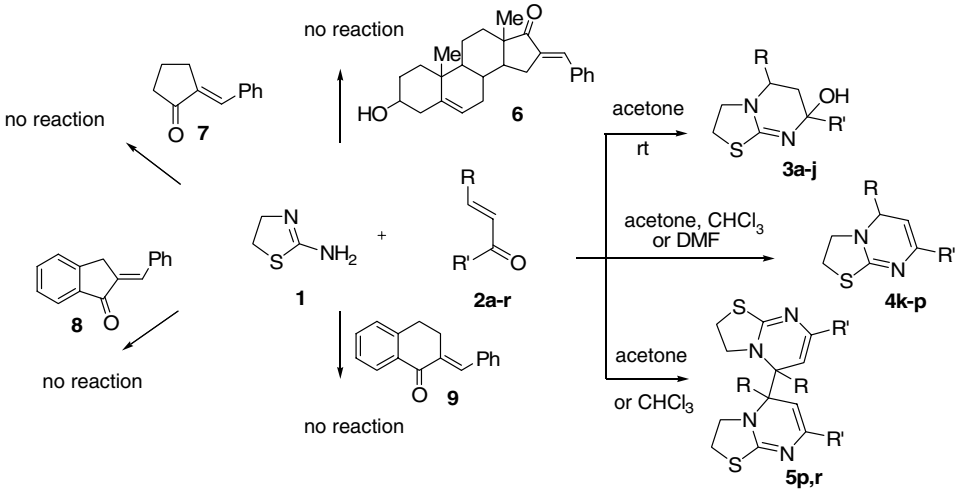
Several solvents were proposed for the heterocyclization of α,β-unsaturated ketones or aldehydes with 2-aminothiazoline (**1**), e.g. acetone, methanol, xelene and their corresponding mixtures [9]. We expanded the range of solvent and also explored various reaction conditions. The solvent (acetone, alcohols, chloroform, DMF, DMSO), temperature (ambient temperature or reflux in the appropriate solvent) and reaction time were varied in our experiments. The best protocol for the synthesis of tetrahydrothiazolopurimidines **3** (Scheme 1) was found to include the treatment of 2-aminothiazoline (**1**) with unsaturated aldehydes **2a**–**c** or arylidenacetones **2d**–**i** in acetone at room temperature. The reaction proceeds very slowly, from 1 to 17 days, and 7-hydroxy-5*H*-2,3,6,7-tetrahydrothiazolo[2,3-*a*]pyrimidines **3a**–**j** crystallized directly from the mixture as large well shaped crystals (Table 1).

Majority of chalcones **2j**–**p** failed to react in these conditions to form tetrahydrothiazolopyrimidines except **2j** that reacts with **1** very slowly to afford the target tetrahydrothiazolopyrimidine **3j** with 12% yield. Compounds **2k,m,o** produced dihydroderivatives **4k**,**m**,**o** with the low yield even at room temperature in acetone. In general, dihydrothiazolopyrimidines **4k**–**p** were obtained from corresponding chalcones with the better yield under stronger conditions, e.g. reflux in corresponding solvent (Table 2). For example, dihydrothiazolopyrimidines **4l**, **p** were obtained after reflux either in DMF or chloroform, respectively. But all our attempts to obtain thiazolopyrimidine derivatives from corresponding 4-nitrochalcone, 4-fluorochalcone, and benzalpinacoline failed.

Ketones with rigid s-*cis*-configuration of α,β-unsaturated fragment, e.g. 16-benzylidene-3β-hydroxyandrost-5-en-17-one **6**, 2-benzylidene derivatives of cyclopentanone **7**, indanone **8**, and tetralone **9**, were inert in the reaction with **1**, as expected. In all cases starting ketones were recovered.

Unexpected product with high melting point was isolated from the reaction of 2-aminothiazoline (**1**) with chalcones **2p** and **2r**. The only difference in the NMR spectra of the isolated compound in comparison with corresponding spectra of dihydrothiazolopyrimidines **4** was the absence of C-5 and C-6 protons. The mass-spectra of these compounds showed molecular ion $[(2M\text{-}2)+1]^+$, where M is the molecular weight of corresponding dihydroderivative. Based on these data we assigned 5,5′-bis-5,7-diaryl-2,3-dihydrothiazolo[2,3-*a*]pyrimidine structures **5p**, **r** to the isolated compounds. For the present we have not confirmed the mechanistic hypothesis about the formation of dimers **5**.

In comparison to dihydroderivatives **4** all 7-hydroxytetrahydropyrimidines **3** were unstable at elevated temperatures. All attempts to recrystallize compounds **3** from hot acetone or alcohols led to the complex mixture of products where starting amine and unsaturated component were detected by HPLC and NMR. The same results were obtained after dissolution of tetrahydroderivatives in DMSO. These results clearly confirmed the instability of



Scheme 1. Reaction of 2-aminothiazoline (**1**) with α,β-unsaturated carbonyl compounds.

the tetrahydroderivatives **3** and reversible nature of the reaction. Based on these results we related the observed instability of compounds **3** not to the electronic properties of compounds **2** but to the stereochemistry of formed tetrahydrothiazolopyrimidines.

All compounds **3** and **4** were characterized by NMR (^{1}H, ^{13}C) spectroscopy (Tables 3–5). The structures of compounds **3i** and **4p** were confirmed by single crystal X-ray analysis (Figs. 1 and 2).

3.2. Stereochemistry

Especial attention was paid to the stereochemistry of the reaction 2-aminothiazoline (**1**) with α,β-unsaturated carbonyl compounds. During the cyclization of **1** into **3** two new chiral centers are formed. Depending on the outcome of the reaction we can expect the formation of two or one diastereomeric pairs. The detailed analysis of ^{1}H NMR spectra of synthesized compounds clarifies this point.

The common features of NMR spectra of compounds **3** were complex multiplets of thiazoline ring protons at 2.90–3.50 ppm, multiplet (**3a–c**) or two doublets of doublets (**3d–j**) for C-6 proton at 1.70–2.20 ppm and doublet of doublets for C-5 proton at 3.70–4.60 ppm (Table 3). The spectra of compounds **3a–c** also contained doublet of doublets for C-7 protons at 7.19–7.40 ppm. The OH proton appeared at 3.90–4.30 ppm as a broad signal. It should be noted that spectra of all compounds contained the double set of pyrimidine ring protons which was the clear indication of the diastereomers formation. The signals from both sets were well resolved and the ratio of diastereomers can be extracted from the integral intensities of corresponding signals (Table 3). The analysis of the coupling constant was used to assign the stereochemistry of the isomers. The coupling constants

Table 1
Characterization data of compounds **3a–j**

Compound	R	R′	M.p. (°C)	Yield (%)	Elemental analysis (%)
3a	Me	H	145–146 (138–140)[a]	53	Found: C, 48.83; H, 6.99; N, 16.27; S, 18.60. Calcd. for $C_7H_{12}N_2OS$ (172.25): C, 48.81; H, 7.02; N, 16.26; S, 18.62
3b	Ph	H	153–154 (160–161)[a]	52	Found: C, 61.50; H, 6.00; N, 11.98; S, 13.67. Calcd. for $C_{12}H_{14}N_2OS$ (235.32): C, 61.51; H, 6.02; N, 11.96; S, 13.68
3c	4-$NO_2C_6H_4$	H	145–147	42	Found: C, 51.63; H, 4.68; N, 15.04; S, 11.49. Calcd. for $C_{12}H_{13}N_3O_3S$ (279.31): C, 51.60; H, 4.69; N, 15.04; S, 11.48
3d	Ph	Me	135–138 (129–134)[a]	61	Found: C, 62.84; H, 6.53; N, 11.25; S, 12.93. Calcd. for $C_{13}H_{16}N_2OS$ (248.34): C, 62.87; H, 6.49; N, 11.28; S, 12.91
3e	4-$MeOC_6H_4$	Me	143–145	60	Found: C, 60.39; H, 6.51; N, 10.07; S, 11.50. Calcd. for $C_{14}H_{18}N_2O_2S$ (278.37): C, 60.41; H, 6.52; N, 10.06; S, 11.52
3f	4-ClC_6H_4	Me	138–139	43	Found: C, 55.19; H, 5.34; N, 9.87; S, 11.35. Calcd. for $C_{13}H_{15}ClN_2OS$ (282.79): C, 55.21; H, 5.35; N, 9.91; S, 11.34
3g	4-FC_6H_4	Me	137–138	69	Found: C, 58.66; H, 5.72; N, 10.48; S, 12.01. Calcd. for $C_{13}H_{15}FN_2OS$ (266.33): C, 58.63; H, 5.68; N, 10.52; S, 12.04
3h	4-$Me_2NC_6H_4$	Me	119–121	41	Found: C, 61.79; H, 7.28; N, 14.40; S, 11.03. Calcd. for $C_{15}H_{21}N_3OS$ (291.41): C, 61.82; H, 7.26; N, 14.42; S, 11.00
3i	Ph	Et	133–135	40	Found: C, 64.11; H, 6.94; N, 10.69; S, 12.22. Calcd. for $C_{14}H_{18}N_2OS$ (262.37): C, 64.09; H, 6.91; N, 10.68; S, 12.22
3j	Ph	Ph	117–119 (111–115)[a]	12	Found: C, 69.62; H, 5.83; N, 9.04; S, 10.31. Calcd. for $C_{18}H_{18}N_2OS$ (310.41): C, 69.65; H, 5.84; N, 9.02; S, 10.33

[a] Literature melting point [9].

Table 2
Characterization data of compounds **4k–p** and **5p**, **r**

Compound	R	R′	M.p. (°C)	Yield(%)	Elemental analysis (%)
4k	Ph	4-MeC_6H_4	197–198	32	Found: C, 74.46; H, 5.95; N, 9.16; S, 10.44. Calcd. for $C_{19}H_{18}N_2S$ (306.42): C, 74.47; H, 5.92; N, 9.14; S, 10.46
4l	Ph	4-$MeOC_6H_4$	150–151	17	Found: C, 70.80; H, 5.60; N, 8.72; S, 9.95. Calcd. for $C_{19}H_{18}N_2OS$ (322.42): C, 70.78; H, 5.63; N, 8.69; S, 9.94
4m	4-MeC_6H_4	Ph	137–139	30	Found: C, 74.49; H, 5.95; N, 9.13; S, 10.44. Calcd. for $C_{19}H_{18}N_2S$ (306.42): C, 74.47; H, 5.92; N, 9.14; S, 10.46
4o	4-ClC_6H_4	Ph	130–132	40	Found: C, 66.18; H, 4.67; N, 8.53; S, 9.80. Calcd. for $C_{18}H_{15}ClN_2S$ (326.84): C, 66.15; H, 4.63;N, 8.57; S, 9.81
4p	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	190–191	34	Found: C, 62.12; H, 4.64; N, 11.47; S, 8.70. Calcd. for $C_{19}H_{17}N_3O_3S$ (367.42): C, 62.11; H, 4.66;N, 11.44; S, 8.73
5p	4-$NO_2C_6H_4$	4-$MeOC_6H_4$	299–301	7	Found: C, 62.25; H, 4.44; N, 11.50; S, 8.73. Calcd. for $C_{38}H_{32}N_6O_6S_2$ (732.83): C, 62.28; H, 4.40;N, 11.47; S, 8.75
5r	4-FC_6H_4	Ph	227–229	7	Found: C, 69.90; H, 4.52; N, 9.02;S, 10.37. Calcd. for $C_{36}H_{28}F_2N_4S_2$ (618.76): C, 69.86; H, 4.56; N, 9.05; S, 10.36

Table 3
^{1}H NMR spectral characteristics of the synthesized compounds **3a**–**j**[a] ($CDCl_3$, δ, ppm)

Compound	H-2, H-3	H-5	H-6	R	R′	Ratio of isomers
3a	2.90–3.50 (m, 4H)	3.73 (m, 1H) [3.73 (m, 1H)]	1.50–1.80(m, 1H) [1.80–2.10 (m, 1H)]	1.19 (d, 3H) [1.22 (d, 3H)]	5.00 (t, 1H) [5.10(dd, 1H)]	3:1
3b	2.90–3.50 (m, 4H)	4.45 (dd, 1H) [4.34 (dd, 1H)]	1.90–2.20 (m, 1H)	7.20–7.40 (m, 5H)	5.04 (dd, 1H) [5.25(dd, 1H)]	4:1
3c	3.00–3.50 (m, 4H)	4.55 (dd, 1H) [4.45 (dd, 1H)]	1.90–2.20 (m, 1H)	7.48 (d, 2H), 8.25 (d, 2H)	5.03 (t, 1H) [5.27(dd, 1H)]	4:1
3d	2.90-3.50 (m, 4H)	4.47 (dd, 1H) [4.25 (dd, 1H)]	1.77 (t, 1H) [2.19 (dd, 1H)	7.10–7.30 (m, 5H)	1.41 (s, 3H)	5:1
3e	2.90–3.50 (m, 4H)	4.40 (dd, 1H) [4.21 (dd, 1H)]	1.76 (dd, 1H) [2.15 dd, 1H)]	3.83 (s, 3H), 6.91 (d, 2H), 7.25 (d, 2H)	1.50 (s, 3H)	5:1
3f	2.90–3.50 (m, 4H)	4.44 (dd, 1H) [4.23 (dd, 1H)]	1.75 (t, 1H) [2.15 (dd, 1H)]	7.27 (d, 2H), 7.36 (d, 2H)	1.50 (s, 3H)	5:1
3g	2.90–3.50 (m, 4H)	4.47 (dd, 1H) [4.25 (dd, 1H)]	1.74 (t, 1H) [2.16, dd, 1H)]	7.06 (d, 2H), 7.30 (d, 2H)	1.51 (s, 3H)	5:1
3h	2.90–3.50 (m, 4H)	4.40 (dd, 1H) [4.25 (dd, 1H)]	1.76 (t, 1H) [2.14 (dd, 1H)]	6.71 (d, 2H),7.17 (d, 2H)	1.50 (s, 3H)	5:1
3i	2.90–3.40 (m, 4H)	4.47 (dd, 1H) [4.22 (dd, 1H)]	1.70 (t, 1H) [2.11 (dd, 1H)]	7.30–7.50 (m, 5H)	0.96 (t, 3H), 1.85 (m, 2H) [1.05 (t, 3H), 1.85 (m, 2H)]	5:1
3j	2.90–3.50 (m, 4H)	4.58 (dd, 1H) [3.80 (dd, 1H)]	1.81 (dd, 1H) [2.33 (dd, 1H)]	7.20–7.60 (m, 10H)		3:1

[a] In square brackets gave signals of minor diastereomers.

Table 4
^{13}C NMR spectral data of the synthesized compounds **3b**–**h** and **4k**, **p** ($CDCl_3$, δ, ppm)

Compound	C-2	C-3	C-5	C-6	C-7	C-8_a
3b	36.3	51.9	56.2	25.9	75.7	162.6
3c	36.4	52.0	60.5	25.0	75.5	164.5
3d	42.4	51.4	57.0	25.6	80.2	160.2
3g	42.2	51.5	56.4	25.6	80.4	164.8
3h	42.2	51.5	56.4	25.7	80.6	164.3
4k	25.4	51.6	61.7	100.8	142.5	–
4o	25.5	51.6	61.1	101.1	142.7	163.1

of H-7 to H-6a and H-6e in the spectrum of compound **3a** were 3.9 and 4.6 Hz, respectively. This is characteristic to $^3J_{aa}$ and $^3J_{ae}$ type of constants. This was the clear indication of the equatorial configuration of the proton at C-7 center in the major isomer. Based on this analysis we can assign structure **A** to the major isomer formed in the reaction of 2-aminothiazoline (**1**) with crotonic aldehyde. Another isomer was assigned with structure **B**. The ratio of the isomers in the case of compound **3a** was 3:1. The same result was obtained for **3b** and **3c**. The signal of C-5 proton exhibited the same multiplicity, coupling constant and chemical shift throughout the series. This proved the assumption that the stereochemistry of the major isomer is represented by structure **A** (Fig. 3). The intramolecular hydrogen bond is likely to play a key role in the stabilization of the isomer **A** in comparison with structure **B** where no hydrogen bonding was possible.

According to experimental data the ratio of isomers **A** and **B** varied from 3:1 to 5:1 throughout the series (Table 3). The results of the quantum-chemical calculations (B3LYP/cc-pvdz) revealed that isomer **A** is more stable than isomer **B** (energy difference is 1.06 kcal/mol).

The major isomer **A** for compound **3i** was isolated by crystallization from acetone and the structure was confirmed by single crystal X-ray analysis.

3.3. X-ray structural analysis

The X-ray investigation of the crystals of compound **3i** demonstrated that in the crystal phase only **A** type diastereomer is present. The asymmetric unit contains two forms (A1 and A2) with slightly different geometrical parameters. Each of them consists of a pair of enantiomers E1 and E2. As a result, the asymmetric unit contains four molecules; they will be donated A1E1, A1E2, A2E1 and A2E2.

Table 5
^{1}H NMR spectral data of the synthesized compounds **4k**–**p** ($CDCl_3$, δ, ppm)

Compound	H-2	H-3	H-5	H-6	R	R′
4k	3.10 (m, 2H)	3.40 (m, 2H)	5.26 (d, 1H)	5.32 (d, 1H)	7.40 (m, 5H)	2.34 (s, 3H), 7.12 (d, 2H), 7.62 (d, 2H)
4l	3.10 (m, 2H)	3.20 (m, 2H)	5.28 (d, 1H)	5.32 (d, 1H)	7.35 (m, 5H)	3.71 (s, 3H), 6.84 (d, 2H), 7.58 (d, 2H)
4m[a]	3.43 (m, 2H)	3.51 (m, 2H)	5.29 (d, 1H)	5.48 (d, 1H)	2.28 (s, 3H), 7.20–7.29 (m, 7H), 7.68 (d, 2H)	
4o	3.10 (m, 2H)	3.30 (m, 2H)	5.15 (d, 1H)	5.25 (d, 1H)	7.25 (d, 2H), 7.63 (d, 2H)	7.20–7.23 (m, 5H)
4p	3.20 (m, 2H)	3.50 (m, 2H)	5.41 (d, 1H)	5.53 (d, 1H)	7.64 (d, 2H), 8.28 (d, 2H)	3.73 (s, 3H), 6.86 (d, 2H), 7.62 (d, 2H)

[a] The spectrum was recorded in DMSO-d_6.

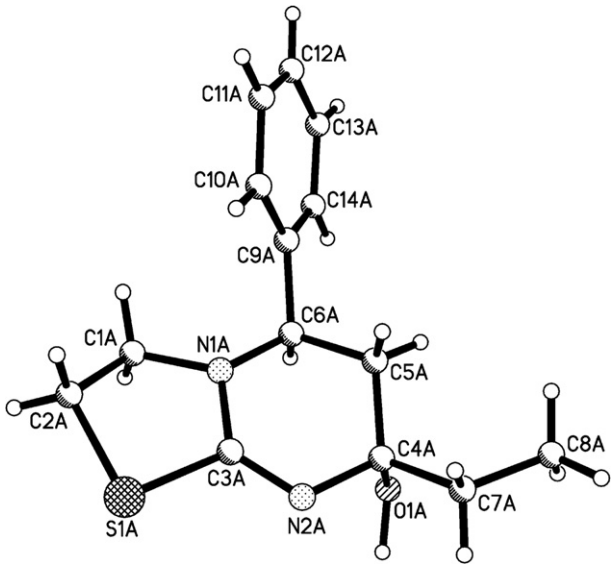


Fig. 1. Molecular structure of tetrahydrothiazolo[2,3-*a*]pyrimidine **3i**.

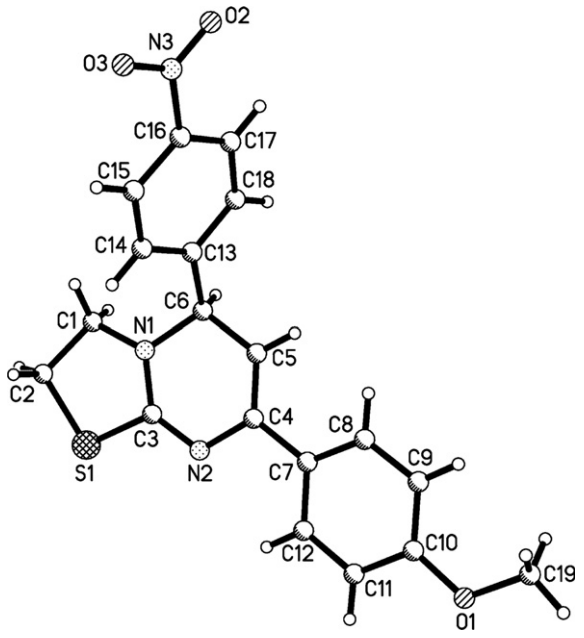


Fig. 2. Molecular structure of dihydrothiazolo[2,3-*a*]pyrimidine **4p**.

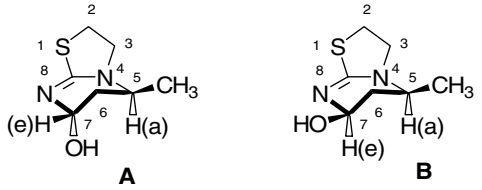


Fig. 3. Diastereomeric pair of 7-hydroxytetrahydropyrimidine **3a**.

The thiazoline ring adopts the envelope conformation in both enantiomers. Deviation of the C(1) atom from the mean plane of remaining atoms of the ring is 0.52 Å for both molecules A1 and A2. The tetrahydropyrimidine ring adopts a conformation which is intermediate between the sofa and half-chair (the puckering parameters [17] are $S = 0.71$, $\Theta = 30.5°$, $\Psi = 13.2°$ for molecule A1 and $S = 0.71$, $\Theta = 28.5°$, $\Psi = 11.3°$ for A2). Deviation of the C(5) and C(6) atoms from the mean plane of remaining atoms of the ring are −0.48 and 0.17 Å for A1 and −0.48 and 0.15 Å for A2, respectively. The phenyl substituent has a pseudoequatorial orientation (the C(3)–N(1)–C(6)–C(9) torsion angle is −157.4(3)° for molecule A1 and 156.0(3)° for molecule A2 and is turned relatively to the N(1)–C(6) bond (the N(1)–C(6)–C(9)–C(10) torsion angle is 38.1(5)° for A1 and −39.5(5)° for A2). The ethyl substituent has a pseudoequatorial orientation (the C(3)–N(2)–C(4)–C(7) torsion angle is 147.2(3)° for A1 and −147.7(3)° for A2). The C(7)–C(8) bond has antiperiplanar orientation with respect to the N(2)–C(4) bond (the N(2)–C(4)–C(7)–C(8) torsion angle is −178.4(3)° for A1 and −179.4(3)° for A2). The hydroxy group has a pseudoaxial orientation (the C(3)–N(2)–C(4)–O(1) torsion angle is −93.7(3)° for A1 and 92.9(3)° for A2).

In the crystal phase each enantiomer of **3i** forms the centrosymmetric dimers with an opposite enantiomer possessing the same geometrical parameters (A1E1…A1E2 and A2E2…A2E1 dimers). The intermolecular hydrogen bonds are O(1c)–H(1Oc)···N(2c)′ (1−*x*, −y, 1−z) H···N 1.82 Å O–H···N 163° and O(1d)–H(1Od)···N(2d)′ (1−*x*, 1−*y*, 2−*z*) H···N 1.78 Å O–H···N 174°.

The X-ray investigation of the crystals of compound **4p** demonstrated that the thiazoline ring adopts the twist conformation. Deviation of the C(1) and C(2) atoms from the plane of remaining atoms of the ring is −0.32 and 0.23 Å, respectively. The tetrahydropyrimidine ring adopts a conformation which is intermediate between the sofa and half-chair (the puckering parameters [17] are $S = 0.34$, $\Theta = 33.8°$, $\Psi = 17.6°$). Deviation of the C(5) and C(6) atoms from the plane of remaining atoms of the ring are −0.24 and −0.43 Å, respectively.

The length of the N(1)–C(3) bond (1.362(7) Å) indicates the conjugation between the lone pair of the nitrogen atom and π-system of the azomethyne group despite the trigonal-pyramidal configuration of the N(1) atom. The substituent at the C(6) atom has pseudoequatorial orientation (the C(4)–C(5)–C(6)–C(13) torsion angle is 137.3(6)°). This position of the substituent results in the appearance of the shortened intramolecular contact H(14)···N(1) 2.58 Å (the sum of the corresponding Van der Waals radii [18] is 2.67 Å). The nitro group is coplanar to the aromatic ring (the O(2)–N(3)–C(16)–C(17) torsion angle is 0.3(9)°). It can be assumed that this orientation of the nitro group is stabilized by the H(15)···O(3) 2.44 Å and H(17)···O(2) 2.42 Å attractive interactions.

The methoxyphenyl substituent is slightly turned relatively to the C(4)–C(5) double bond (the C(5)–C(4)–C(7)–C(8) torsion angle is 7.8(9)°) because of the repulsion between the bicyclic fragment and aromatic ring (the shortened intramolecular contacts H(5)···C(8) 2.65 Å (2.87 Å),

H(5)···H(8) 2.09 Å (2.34 Å), H(8)···C(5) 2.67 Å (2.87 Å), H(12)···N(2) 2.45 Å (2.67 Å)). The methoxy group is almost coplanar to the benzene ring (the C(19)–O(1)–C(10)–C(9) torsion angle is −3.3(9)°) in spite of the shortened intramolecular contacts H(9)···C(19) 2.51 Å (2.87 Å), H(9)···H(19b) 2.31 Å (2.34 Å), H(9)···H(19c) 2.30 Å (2.34 Å), H(19b)···C(9) 2.76 Å (2.87 Å), H(19c)···C(9) 2.71 Å (2.87 Å).

4. Conclusions

Reactions of 2-aminothiazoline (**1**) with α,β-unsaturated carbonyl compounds **2** in different reaction conditions have been investigated. We discovered that 7-hydroxytetrahydrothiazolo[2,3-*a*]pyrimidines **3** can be obtained with reasonable yields under mild conditions (acetone, room temperature). Two diastereoisomers, **A** (with axial OH-group) and **B** (with equatorial OH-group), of tetrahydrothiazolo[2,3-*a*]pyrimidine products have been identified and the structures and the ratio of the isomers were determined using NMR spectroscopy. Structure **A**, confirmed by X-ray structural analysis in the case of **3i**, has been shown to be the major isomer in all cases. The intramolecular hydrogen bond plays a key role in the stabilization of the isomer **A** in solutions compared to structure **B** where no hydrogen bonding is possible. Under stronger reaction conditions (DMF or chloroform, heating) the formation of 2,3-dihydrothiazolo[2,3-*a*]pyrimidines **4** is much more preferable. Molecular structure of **4p** was confirmed by X-ray structural analysis.

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