Brief Communications

Intramolecular cyclization of 1-allyl- and 1-methallyl-6-amino-2-thiouracils

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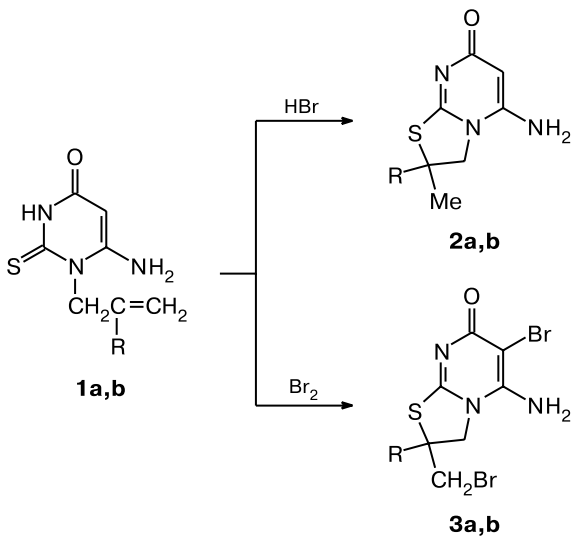
Intramolecular cyclization of 1-allyl- and 1-methallyl-6-amino-2-thiouracils afforded 5-amino-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-4-ones, whose structures were proved by chemical transformations.

Key words: allylthioureas, acylimines, hexafluoroacetone, methyl trifluoropyruvate, 6-amino-2-thiouracils, 5-amino-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-4-ones, cyclization, cyclocondensation, bromination.

Combination of two and more pharmacophoric moieties in one molecule is an approach of chemical design of biologically active substances. In this report, we consider the data on introduction of a thiazoline moiety, which is a component of various biologically active substances,[1,2] into a molecule of 6-amino-2-thiouracils by intramolecular cyclization of 1-allyl- and 1-methallyl-6-amino-2-thiouracils **1a,b**. This study is based on the known data on cyclization of *N*-allylthioureas to 2-aminothiazolines by the action of inorganic acids, halogens, and halophilic reagents.[3—6] The presence of an *N*-allylthiourea moiety in molecules **1a,b** allows one to suggest similar reactions. In fact, when heating compounds **1a,b** in 48% HBr at 120 °C for 2 h, 5-aminothiazolopyrimidinones **2a,b** were formed in 69 and 73% yields, respectively. The bromination of alcohol solutions of **1a,b** gave unambiguous results when two equivalents of molecular bromine were used, because bromination to position 5 of the pyrimidine ring occurs in parallel with the formation of the bromomethylthiazoline fragment: 5-amino-6-bromothiazolo-

Scheme 1



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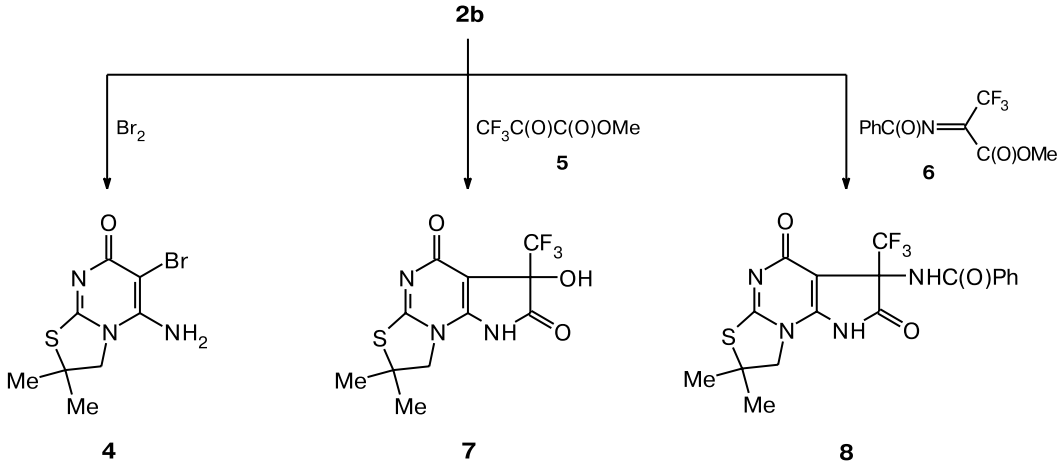
Scheme 2

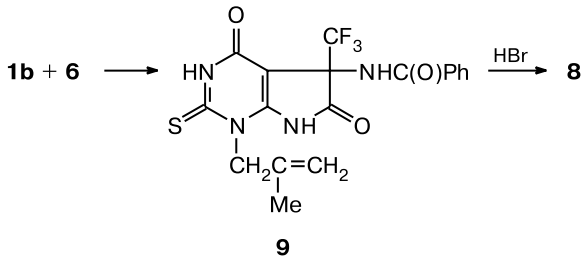


pyrimidinones **3a,b** are formed in 70 and 59% yields, respectively (Scheme 1).

5-Aminothiazolopyrimidinones **2a,b** and **3a,b** are solid crystalline substances, whose compositions and structures were proved by the data of elemental analysis, NMR spectroscopy, and chemical transformations. For instance, pyrimidinone **2b** undergoes reactions characteristic of enamines (Scheme 2), namely, it is brominated to position 5 to form pyrimidinone **4** and interacts with 1,2-bis-electrophilic reagents: indacenedione **7** and indacenylbenzamide **8** are formed as a result of cyclocondensation of **2b** with methyl trifluoropyruvate **5** and methyl trifluoropyruvate *N*-benzoylimine (**6**).

Pyrimidinone **4** and pyrrolothiazolopyrimidines **7** and **8** are crystalline solids, whose compositions and structures were proved by the data of elemental analysis and NMR spectroscopy. Pyrrolothiazolopyrimidine **8** was prepared by an unambiguous synthesis. Thus, thiouracil **1b** on heating in DMF undergoes the earlier described[7] cyclocondensation with imine **6** to form pyrrolo[2,3-*d*]pyrimidinedione **9**, which is transformed into compound **8** being heated in 48% HBr at 120 °C for 2 h (Scheme 3).

Scheme 3



1-Allyl- and 1-methallyl-6-amino-2-thiouracils were synthesized by a procedure known for synthesis of aminouracils[8] using refluxing of methyl cyanoacetate with allyl- and methallylthioureas in a methanolic solution of sodium methoxide.

Thus, 1-allyl- and 1-methallyl-6-amino-2-thiouracils undergo cyclization to 5-aminotriazolopyrimidinones under the action of HBr and bromine, similarly to other compounds containing the *N*-allylthioamide moiety. A similar reaction can be extended to the products of transformations of 1-allyl- and 1-methallyl-6-amino-2-thiouracils.

Experimental

^{1}H and ^{19}F NMR spectra were recorded on a Bruker DXP 200 spectrometer. Melting points were determined in a glass capillary. Methyl trifluoropyruvate *N*-benzoylimine (**6**) was synthesized according to a previously published procedure.[9] Allylthiourea, methallylthiourea, methyl cyanoacetate, and methyl trifluoropyruvate (Aldrich) were used as received.

1-Allyl-6-amino-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (1a). Sodium (6.9 g, 0.3 mol) was dissolved in MeOH (100 mL), and allylthiourea (11.6 g, 0.1 mol) and methyl cyanoacetate (9.9 g, 0.1 mol) were added. The reaction mixture was refluxed for 6 h, cooled, diluted with H_2O (300 mL), and neutralized with AcOH. A precipitate formed was filtered off and recrystallized from EtOH to obtain thiouracil **1a** (13.2 g, 72%), m.p. 218—220 °C. Found (%): C, 45.41; H, 4.78; N, 22.81. $C_7H_9N_3OS$. Calculated (%): C, 45.59; H, 4.95; N, 22.93. ^{1}H NMR (DMSO-d_6), δ: 4.87 (s, 1 H, —CH=); 5.09—5.21 (m, 4 H, $—CH_2N + CH_2=$); 5.78—5.96 (m, 1 H, —CH=); 6.97 (s, 2 H, NH_2); 11.7 (s, 1 H, NH).

6-Amino-1-(2-methylallyl)-2-thioxo-2,3-dihydro-1*H*-pyrimidin-4-one (1b) was synthesized similarly to **1a** from methallylthiourea (13.0 g, 0.1 mol) and methyl cyanoacetate (9.9 g, 0.1 mol). The yield was 13.5 g (69%). M.p. 231—233 °C. Found (%): C, 48.52; H, 5.77; N, 21.12. $C_8H_{11}N_3OS$. Calculated (%): C, 48.71; H, 5.62; N, 21.30. ^{1}H NMR (DMSO-d_6), δ: 1.79 (s, 3 H, Me); 4.55 (s, 2 H, $CH_2=$); 4.86 (s, 1 H, —CH=); 5.01 (s, 2 H, NH_2); 6.97 (s, 2 H, CH_2N); 11.65 (s, 1 H, NH).

5-Amino-2-methyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-7(7*H*)-one (2a). A suspension of thiouracyl **1a** (9.15 g, 0.05 mol) in 48% HBr (50 mL) was heated for 2 h at 120 °C. Then the reaction mixture was cooled, diluted with H_2O (200 mL), and neutralized with 10% NaOH. A precipitate formed was filtered off and recrystallized from EtOH to obtain pyrimidinone **2a** (6.3 g, 69%). M.p. 271—273 °C. Found (%): C, 45.47; H, 4.81; N, 22.78. $C_7H_9N_3OS$. Calculated (%): C, 45.59; H, 4.95; N, 22.93. ^{1}H NMR (DMSO-d_6), δ: 1.55 (d, 3 H, Me, J = 6.3 Hz); 4.34 (m, 2 H, CH_2N + CHS); 4.63 (m, 1 H, CH_2N); 6.02 (s, 1 H, —CH=); 8.87 (s, 2 H, NH_2).

5-Amino-2,2-dimethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-7(7*H*)-one (2b) was synthesized similarly to **2a** from **1b** (9.85 g). The yield was 7.2 g (73%). M.p. 284—286 °C. Found (%): C, 48.53; H, 5.79; N, 21.19. $C_8H_{11}N_3OS$. Calculated (%): C, 48.71; H, 5.62; N, 21.30. ^{1}H NMR (DMSO-d_6), δ: 1.62 (s, 6 H, Me); 4.11 (s, 2 H, CH_2); 4.85 (s, 1 H, —CH=); 6.57 (s, 2 H, NH_2).

5-Amino-6-bromo-2-bromomethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-7(7*H*)-one (3a). Molecular bromine (3.2 g, 0.02 mol) was added to a suspension of thiouracil **1a** (1.83 g, 0.01 mol) in EtOH (20 mL) at 20 °C. The reaction mixture was stirred for 1 h, diluted with H_2O (100 mL), and neutralized with 10% NaOH. A precipitate formed was filtered off and recrystallized from EtOH to obtain pyrimidinone **3a** (2.4 g, 70%). M.p. 227—229 °C. Found (%): C, 24.49; H, 1.91; N, 12.18. $C_7H_7Br_2N_3OS$. Calculated (%): C, 24.65; H, 2.07; N, 12.32. ^{1}H NMR (DMSO-d_6), δ: 3.95 (d, 2 H, CH_2Br, J = 5.8 Hz); 4.33—4.48 (m, 3 H, —CH= + CH_2); 7.04 (s, 2 H, NH_2).

5-Amino-6-bromo-2-bromomethyl-2-methyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-7(7*H*)-one (3b) was synthesized similarly to **3a** from **1b** (1.97 g). The yield was 2.1 g (59%). M.p. 238—240 °C. Found (%): C, 27.21; H, 2.73; N, 11.72. $C_8H_9Br_2N_3OS$. Calculated (%): C, 27.06; H, 2.55; N, 11.87. ^{1}H NMR (DMSO-d_6), δ: 1.75 (s, 3 H, Me); 3.96 (d, 1 H, CH_2Br, J = 10.5 Hz); 4.01 (d, 1 H, CH_2Br, J = 10.5 Hz); 4.14, 4.55 (both d, 1 H each, CH_2N, J = 11.9 Hz); 6.89 (s, 2 H, NH_2).

5-Amino-6-bromo-2,2-dimethyl-2,3-dihydrothiazolo[3,2-*a*]pyrimidin-7(7*H*)-one (4). Molecular bromine (3.2 g, 0.02 mol) was added to a suspension of pyrimidinone **2b** (1.97 g, 0.01 mol) in EtOH (20 mL) at 20 °C. The reaction mixture was stirred for 1 h, diluted with H_2O (100 mL), and neutralized with 10% NaOH. A precipitate formed was filtered off and recrystallized from EtOH to obtain pyrimidinone **4** (1.8 g, 69%). M.p. 240—242 °C. Found (%): C, 34.62; H, 3.52; N, 15.41. $C_8H_{10}BrN_3OS$. Calculated (%): C, 34.79; H, 3.65; N, 15.22. ^{1}H NMR (DMSO-d_6), δ: 1.59 (s, 6 H, Me); 4.24 (s, 2 H, NH_2); 6.91 (s, 1 H, NH).

3-Hydroxy-7,7-dimethyl-3-trifluoromethyl-1,3,7,8-tetrahydropyrrolo[3,2-e][1,3]thiazolo[3,2-*a*]pyrimidine-2,4-dione (7). Methyl trifluoropyruvate **5** (1.56 g, 0.01 mol) was added to a solution of pyrimidinone **2b** (1.97 g, 0.01 mol) in DMF (10 mL). The reaction mixture was heated for 1 h at 100 °C and diluted with H_2O (100 mL). A precipitate formed was filtered off and recrystallized from EtOH to obtain indacenedione **7** (2.6 g, 81%). M.p. 293—295 °C. Found (%): C, 41.29; H, 3.31; N, 13.22. $C_{11}H_{10}F_3N_3O_3S$. Calculated (%): C, 41.12; H, 3.14; N, 13.08. ^{1}H NMR (DMSO-d_6), δ: 1.69 (s, 6 H, Me); 4.21 (AB system, 2 H, CH_2, J = 11.6 Hz); 7.26 (br.s, 1 H, OH); 11.87 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 1.61 s.

3-Benzoylamino-7,7-dimethyl-3-trifluoromethyl-1,3,7,8-tetrahydropyrrolo[3,2-*e*][1,3]thiazolo[3.2-*a*]pyrimidine-2,4-dione (8). ***A.*** Methyl trifluoropyruvate *N*-benzoylimine (**6**) (2.59 g, 0.01 mol) was added to a solution of pyrimidinone **2b** (1.97 g, 0.01 mol) in DMF (10 mL). The reaction mixture was heated for 1 h at 100 °C and diluted with H_2O (100 mL). A precipitate formed was filtered off and recrystallized from EtOH to obtain benzamide **8** (3.1 g, 73%). M.p. 317—319 °C.

B. A suspension of benzamide **9** (2.12 g, 0.005 mol) in 48% HBr (10 mL) was heated for 2 h at 120 °C. Then the reaction mixture was cooled, diluted with H_2O (50 mL), and neutralized with 10% NaOH. A precipitate formed was filtered off and recrystallized from EtOH to obtain benzamide **8** (1.6 g, 75%). M.p. 317—319 °C. Found (%): C, 50.77; H, 3.71; N, 13.32. $C_{18}H_{15}F_3N_4O_3S$. Calculated (%): C, 50.94; H, 3.56; N, 13.20. ^{1}H NMR (DMSO-d_6), δ: 1.74 (s, 6 H, Me); 4.21, 4.35 (both d, 1 H each, CH_2, J = 11.4 Hz); 7.46 (m, 3 H, CH_{Ar}); 7.94 (m, 2 H, CH_{Ar}); 9.88 (s, 1 H, NH); 12.04 (s, 1 H, NH). ^{19}F NMR (DMSO-d_6), δ: 5.82 s.

5-Benzoylamino-1-(2-methylallyl)-2-thioxo-5-trifluoromethyl-2,3,5,7-tetrahydro-1*H*-pyrrolo[2,3-*d*]pyrimidine-4,6-dione (9). Methyl trifluoropyruvate *N*-benzoylimine (**6**) (2.59 g, 0.01 mol) was added to a solution of thiouracil **1b** (1.97 g, 0.01 mol) in DMF (10 mL). The reaction mixture was heated for 1 h at 100 °C and diluted with H_2O (100 mL). A precipitate formed was filtered off and recrystallized from EtOH to obtain benzamide **9** (3.3 g, 78%). M.p. 301—303 °C. Found (%): C, 50.78; H, 3.43; N, 13.37. $C_{18}H_{15}F_3N_4O_3S$. Calculated (%): C, 50.94; H, 3.56; N, 13.20. ^{1}H NMR (DMSO-d_6), δ: 1.86 (s, 3 H, Me); 4.63 (m, 1 H, =CH_2); 4.92 (m, 1 H, CH_2N + =CH_2); 7.47 (m, 3 H, CH_{Ar}); 7.93 (m, 2 H, CH_{Ar}); 9.91, 12.10, 12.42 (all s, 1 H each, NH). ^{19}F NMR (DMSO-d_6), δ: 4.90 s.

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