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SHORT COMMUNICATIONS

Halocyclization of 2-Allyl(propargyl)sulfanyl-6-aminopyrimidin-4(3*H*)-ones

D. G. Kim,* K. Yu. Osheko, and T. V. Frolova

South Ural State University, pr. imeni Lenina 76, Chelyabinsk, 454080 Russia
**e-mail: kim_dg48@mail.ru*

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Abstract—The alkylation of 6-amino-2-thiouracil with allyl, methallyl, and propargyl halides in the presence of bases gave 2-[allyl(methallyl, propargyl)sulfanyl]-6-aminopyrimidin-4(3*H*)-ones which reacted with iodine and bromine to form fused [1,3]thiazolo[3,2-*a*]pyrimidinium systems. Their nitrosation with sodium nitrite in acid medium afforded 2-[allyl(propargyl)sulfanyl]-6-amino-5-nitrosopyrimidin-4(3*H*)-ones.

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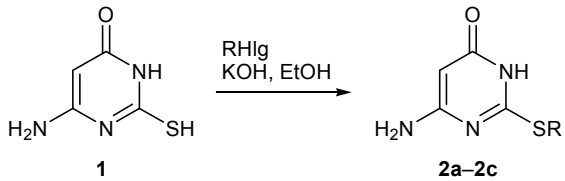
It is known that [1,3]thiazolo[3,2-*a*]pyrimidine derivatives obtained from 6-amino-2-thiouracil **1** exhibit antibacterial, antimycotic, and antiviral activities [1–3]. Thiazolo[3,2-*a*]pyrimidines can be synthesized by heterocyclization of *S*-alkenyl derivatives of 2-thiouracils by the action of electrophilic reagents [4–6]. There are contradictory published data [4, 5, 7] both on the synthesis of 2-(allylsulfanyl)-6-aminopyrimidin-4(3*H*)-one (**2a**) and 2-(methallylsulfanyl)-6-aminopyrimidin-4(3*H*)-one (**2b**) and on the reaction on allyl sulfide **2a** with halogens. Therefore, the goal of the present work was to study in more detail the synthesis of allyl sulfides **2a** and **2b** and 6-amino-2-(propargylsulfanyl)pyrimidin-4(3*H*)-one (**2c**) and their reactions with electrophiles.

The reactions of thiouracil **1** with allyl bromide and methallyl chloride were carried out in aqueous ethanol in the presence of alkali. In both cases, we isolated crystalline allyl sulfides **2a** and **2b** which were poorly soluble in water. Slivka et al. [5] obtained compounds **2a** and **2b** as dark yellow oily substances readily soluble in water. The structure of allyl sulfides **2a** and **2b** was confirmed by ^{1}H NMR spectra (no ^{1}H NMR data was given in [5]). The ^{1}H NMR spectra of **2a** and **2b** contained signals from protons of the allyl groups and 5-H at δ 5.00 and 4.86 ppm, respectively. By reaction of thiouracil **1** with propargyl bromide in aqueous–alcoholic alkali we synthesized for the first time propargyl sulfide **2c** (Scheme 1) which showed in the ^{1}H NMR spectrum signals at δ 3.16 ppm due to terminal acetylenic proton and at δ 5.04 ppm due to 5-H of the pyrimidine ring.

Allyl sulfide **2a** reacted with iodine in acetic acid to give 5-amino-3-(iodomethyl)-7-oxo-2,3,7,8-tetrahydro[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium iodide (**3a**) (Scheme 2). The melting point of **3a** coincided with the melting point reported in [5] for the product obtained by reaction of **2a** with iodine in alcohol. The positions of most signals in the ^{1}H NMR spectra of these compounds were also similar, except for the 6-H proton. The latter resonated at δ 5.72 ppm rather than at δ 6.99 ppm as given in [5], which is fairly surprising. In order to elucidate the observed inconsistency, we studied analogous reaction of sulfide **2b** with iodine. We thus isolated 5-amino-3-(iodomethyl)-3-methyl-7-oxo-2,3,7,8-tetrahydro[1,3]thiazolo[3,2-*a*]-pyrimidin-4-ium iodide (**3b**) which displayed a signal at δ 5.83 ppm (6-H) in the ^{1}H NMR spectrum (cf. δ 6.16 ppm in [5]). Probably, the value δ 6.99 ppm given in [5] was a misprint, and the correct value should be δ 5.99 ppm. Iodide **3a** was also synthesized by us by reaction of **2a** with iodine generated *in situ*. In this case, allyl sulfide **2a** was dissolved in hydriodic acid, and hydrogen peroxide was added to the solution (oxidative iodocyclization).

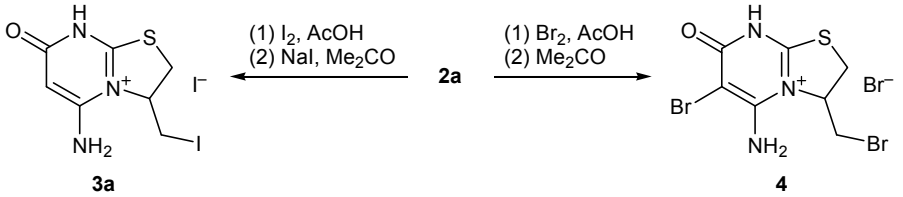
Scheme 1.



1 **2a–2c**

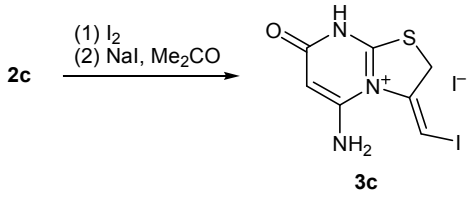
R = CH_2=$CHCH_2$ (**a**), CH_2=$C(Me)CH_2$ (**b**), CH≡CCH_2 (**c**).

Scheme 2.



The reaction of propargyl sulfide **2c** with iodine afforded previously unknown 5-amino-3-(iodomethylidene)-7-oxo-2,3,7,8-tetrahydro[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium iodide (**3c**) (Scheme 3). The 6-H proton in **3c** resonated in the ^{1}H NMR spectrum at δ 5.70 ppm, which is in agreement with the results obtained for iodide **3a**. We believe that the exocyclic double bond in iodide **3c** has *E* configuration, as in the iodocyclization product of 6-methyl-2-(propargylsulfanyl)pyrimidin-4(3*H*)-one, whose structure was proved by ^{13}C NMR [8].

Scheme 3.

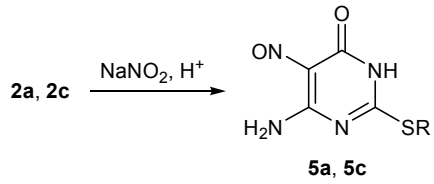


According to the data of [5], the reaction of **2a** with 2 equiv of bromine produced 5-amino-3-(bromomethyl)-7-oxo-2,3,7,8-dihydro[1,3]thiazolo[3,2-*a*]pyrimidinium bromide which showed a signal of 6-H at δ 6.97 ppm in the ^{1}H NMR spectrum; this value seems doubtful.

We have found that the cyclization of **2a** in the reaction with bromine at the same reactant ratio is accompanied by replacement of hydrogen in the pyrimidine ring by bromine with formation of 5-amino-6-bromo-3-(bromomethyl)-7-oxo-2,3,7,8-tetrahydro[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium bromide (**4**) (Scheme 2). In keeping with published data, analogous cyclization and substitution were also observed in the bromination of 2-(allylsulfanyl)-6-methylpyrimidin-4(3*H*)-one [9] and 1-allyl-6-amino-2-thiouracil [10].

The ease of hydrogen substitution in the pyrimidine ring was confirmed by the fact that the reactions of sulfides **2a** and **2c** with a soft electrophile, nitrous acid generated *in situ* from sodium nitrite in acid medium, resulted in nitrosation at the 5-position with formation of 2-[allyl(propargyl)sulfanyl]-6-amino-5-nitroso-pyrimidin-4(3*H*)-ones **5a** and **5c**, respectively (Scheme 4). The nitrosation of 6-amino-2-[methyl (ethyl, benzyl)sulfanyl]pyrimidin-4(3*H*)-ones was reported previously [11, 12].

Scheme 4.



The ^{1}H NMR spectra of **5a** and **5c** contained signals typical of allyl and propargyl substituents, but no signal assignable to 5-H was present. The IR spectra of these compounds displayed absorption bands at 1559 and 1256–1253 cm^{-1} due to vibrations of the N=O group. Compounds **5a** and **5c** are colored blue, which is characteristic of nitrosoarenes [13].

Thus, the reaction of 6-amino-2-thiouracil with propargyl bromide gives 6-amino-2-(propargylsulfanyl)pyrimidin-4(3*H*)-one whose reaction with iodine leads to fusion of 1,3-thiazole ring. The cyclization of 2-(allylsulfanyl)-6-aminopyrimidin-4(3*H*)-one to thiazolopyrimidine system by the action of bromine is accompanied by substitution of hydrogen in the pyrimidine ring by bromine. 2-Allyl(propargyl)sulfanyl-6-aminopyrimidin-4(3*H*)-ones undergo nitrosation at the 5-position of the pyrimidine ring.

Reactions of 6-amino-2-thiouracil 1 with allyl bromide, methallyl chloride, and propargyl bromide (*general procedure***).** 6-Amino-2-thiouracil **1**, 1.61 g (10 mmol), was added to a solution of 0.56 g (10 mmol) of potassium hydroxide in 15 mL of water, a solution of 15 mmol of the corresponding halogen derivative in 1 mL of ethanol was then added, and the mixture was stirred for 1 h. The precipitate was filtered off, washed with water, dried, and recrystallized from propan-2-ol.

6-Amino-2-(prop-2-en-1-ylsulfanyl)pyrimidin-4(3*H*)-one (2a). Yield 1.592 g (87%), white powder, mp 188–190°C. IR spectrum, ν, cm^{-1}: 3474 v.s (NH_2),

3287, 3198, 3091 (=CH_2), 2712, 2364, 1656 s (C=O), 1620, 1571, 1543, 1454, 1373 (=CH), 1296, 1252, 1227, 981, 977, 924 (=CH), 814, 609, 532. ^{1}H NMR spectrum, δ, ppm: 3.75 d (2H, SCH_2, J = 6.9 Hz), 5.00 s (1H, 5-H), 5.10 d (1H, =CH_2, J = 16.9 Hz), 5.33 d (1H, =CH_2, J = 10.0 Hz), 6.00 m (1H, =CH), 6.49 s (2H, NH_2).

6-Amino-2-(2-methylprop-2-en-1-ylsulfanyl)pyrimidin-4(3*H*)-one (2b). Yield 1.576 g (80%), white powder, mp 264–266°C. ^{1}H NMR spectrum, δ, ppm: 1.76 s (3H, CH_3), 3.78 s (2H, SCH_2), 4.84 s (1H, =CH_2), 4.92 s (1H, =CH_2), 5.04 s (1H, 5-H), 6.47 s (2H, NH_2).

6-Amino-2-(prop-2-yn-1-ylsulfanyl)pyrimidin-4(3*H*)-one (2c). Yield 1.574 g (87%), white powder, mp 206–208°C. IR spectrum, ν, cm^{-1}: 3456 v.s (NH_2), 3271 v.s (≡C–H), 2122 (C≡C), 1672 s (C=O), 1612, 1571, 1543, 1454, 1385, 1365 (≡CH), 1300, 1236, 1191, 981, 916, 819, 710, 686 (≡CH), 593, 536, 463, 447. ^{1}H NMR spectrum, δ, ppm: 3.16 t (1H, ≡CH, J = 2.6 Hz), 3.92 d (2H, SCH_2, J = 2.6 Hz), 5.04 s (1H, 5-H), 6.55 s (2H, NH_2). Found, %: C 46.34; H 3.94; N 23.23. $C_7H_7N_3OS$. Calculated, %: C 46.39; H 3.89; N 23.19.

5-Amino-3-(iodomethyl)-7-oxo-2,3,7,8-tetrahydro[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium iodide (3a). *a*. Allyl sulfide **2a**, 0.183 g (1 mmol), was added to a solution of 0.508 g (2 mmol) of iodine in 10 mL of acetic acid. After 24 h, the solvent was evaporated, the residue was dissolved in acetone and treated with sodium iodide, and the precipitate was filtered off. Yield 0.197 g (45%), mp 178–179°C (decomp.); published data [5]: mp 177–178°C. ^{1}H NMR spectrum, δ, ppm: 3.50–4.01 d.d (2H, SCH_2), 3.62 m (2H, CH_2I), 5.25 m (1H, NCH, J = 8.99 Hz), 5.72 s (1H, 6-H), 8.59–8.63 br.s (2H, NH_2).

b. Allyl sulfide **2a**, 0.183 g (1 mmol), was dissolved in 5 mL of hydriodic acid, and 0.2 mL of 30% hydrogen peroxide was added. After 24 h, the precipitate was filtered off and dissolved in acetone, sodium iodide was added to the solution, and the precipitate was filtered off. Yield 0.257 g (59%).

(*E*)-5-Amino-3-(iodomethylidene)-7-oxo-2,3,7,8-tetrahydro[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium iodide (3c). *a*. Yield 0.222 g (51%), mp 184–186°C. ^{1}H NMR spectrum, δ, ppm: 4.34 s (2H, SCH_2), 5.70 s (1H, 6-H), 7.21 s (1H, CHI), 8.51 s (2H, NH_2). Found, %: C 19.30; H 1.60; N 9.67. $C_7H_7I_2N_3OS$. Calculated, %: C 19.33; H 1.62; N 9.66.

5-Amino-6-bromo-3-(bromomethyl)-3-methyl-7-oxo-2,3,7,8-tetrahydro[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium bromide (4). Allyl sulfide **2a**, 0.183 g (1 mmol), was added to a solution of 0.13 mL (2.5 mmol) of bromine in 10 mL of acetic acid. After 24 h, the precipitate was filtered off and dissolved in acetone, and the undissolved material was filtered off and dried. Yield 0.127 g (30%), mp >310°C. ^{1}H NMR spectrum, δ, ppm: 3.60 d.d (2H, SCH_2), 4.00 m (2H, CH_2Br), 5.25 m (1H, NCH, J = 8.99 Hz), 8.57 br.s (2H, NH_2). Found, %: C 19.96; H 1.95; N 9.98. $C_7H_8Br_3N_3OS$. Calculated, %: C 19.93; H 1.91; N 9.96.

Compounds 5a and 5c (*general procedure*). Sodium nitrite, 15 mmol, was added to a solution of 1 mmol of sulfide **2a** or **2c** in acetic acid, and the mixture was stirred for 2 h. The solvent was evaporated, and the residue was washed with water.

6-Amino-5-nitroso-2-(prop-2-en-1-ylsulfanyl)pyrimidin-4(3*H*)-one (5a). Yield 0.091 g (43%), green–blue powder, mp 173°C (decomp.). IR spectrum, ν, cm^{-1}: 3303 s (NH_2), 3158, 3060, 2898, v.s 1692 (C=O), 1620, 1559 (N=O), 1506, 1462, 1389 (=CH), 1312, 1256 (N=O), 1175, 1118, 1037, 993, 965 (=CH), 860, 823, 787, 714, 678, 653, 569, 544, 492, 455. ^{1}H NMR spectrum, δ, ppm: 3.84 s (2H, SCH_2, J = 6.9 Hz), 5.13–5.39 d.d (2H, =CH_2, J = 9.8, 17.0 Hz), 5.92 m (1H, =CH), 11.17 s and 11.25 s (2H, NH_2). Found, %: C 39.65; H 3.79; N 26.44. $C_7H_8N_4O_2S$. Calculated, %: C 39.61; H 3.80; N 26.40.

6-Amino-5-nitroso-2-(prop-2-yn-1-ylsulfanyl)pyrimidin-4(3*H*)-one (5c). Yield 0.160 g (76%), blue powder, mp 181–183°C (decomp.). IR spectrum, ν, cm^{-1}: 3280 (NH_2), 3222 s (≡C–H), 3075, 2973, 2100 (C≡C), v.s 1696 (C=O), 1628, 1624, 1616, 1559 (N=O), 1506, 1495, 1465, 1456, 1437, 1420, 1384 br (≡CH), 1314, 1272, 1253 (N=O), 1181, 1125, 1026, 968, 854, 807, 785, 754, 725, 708, 693 (≡CH), 668, 665, 650, 630, 575, 547, 491, 468, 418. ^{1}H NMR spectrum, δ, ppm: 3.29 s (1H, ≡CH), 4.07 s (2H, SCH_2), 9.13 s (1H, NH), 11.24 s and 12.77 s (2H, NH_2). Found, %: C 39.97; H 2.86; N 26.69. $C_7H_6N_4O_2S$. Calculated, %: C 39.99; H 2.88; N 26.65.

The ^{1}H NMR spectra were recorded on a Bruker DRX-400 spectrometer at 400 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The IR spectra were recorded on a Bruker Tensor 27 spectrometer with Fourier transform.

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