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REACTION OF SUBSTITUTED 2-ALLYLTHIOPYRIMIDIN-4(3H)-ONES WITH SULFENYL CHLORIDES

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Reaction of substituted 2-allyl-thiopyrimidin-4(3H)-ones with p-nitrobenzosulfenyl chloride gives the products of addition at the allyl moiety, while the reaction with 2-benzothiazolyl sulfenyl chloride yields thiazolidinopyrimidines with an angular structure.

Keywords: allylthiopyrimidines, 2-benzothiazolyl sulfenyl chloride, *p*-nitrobenzosulfenyl chloride, thiazolidinopyrimidine, thiazolidinothienopyrimidines, thiazolidinoquinazolone.

Among the wide range of reactions of sulfenyl halides [1], their reaction with unsaturated compounds [2, 3] is special because these reactions occur mostly under mild conditions and lead to formation of products which often have practical application [4]. Furthermore, they are convenient models for a detailed study of the mechanism of these conversions [5].

In a series of research projects, we plan to determine: 1) the effect of the nature of the sulfenating reagents on the rate and direction of the reaction with unsaturated bifunctional compounds; 2) the effect of the structure of the unsaturated compounds on the direction of the reaction; 3) the synthetic possibilities for these reactions, with the aim of using them further for obtaining various classes of heterocyclic compounds having physiological activity.

As the object of the investigations, we selected 2-allylthiothieno[2,3-*d*]pyrimidin-4(3H)-ones **1a-c**, 2-allylthioquinazolin-4(3H)-one (**1d**), and 2-allylthio-6-methyl-4(3H)-pyrimidinone (**1e**), since their derivatives have a broad spectrum of physiological activity [6].

We showed earlier that cyclization of 2-allylthiothieno[2,3-*d*]pyrimidin-4(3H)-ones when treated with iodine or bromine leads to formation of dihydrothiazolothienopyrimidines with angular structure [7].

In this work, we studied the reaction of compounds **1a-e** with *p*-nitrobenzosulfenyl chloride (**2**) and with 2-benzothiazolylsulfenyl chloride (**3**), and we established that in the case of sulfenyl chloride **2**, the products of addition at the double bond of the allyl moiety of compounds **4a-e** are formed. Using sulfenyl chloride **3** leads to formation of cyclic derivatives **5a-e** with participation of the $N_{(1)}$ atom of the pyrimidine system.

When compounds **5** are treated with sodium acetate in DMSO, the bases **6** are formed (Scheme 1).

From the yields of compounds **5**, we can hypothesize that the nature of the substituents on the pyrimidine ring affects the cyclization of compounds **1** with 2-benzothiazolylsulfenyl chloride: acceptor substituents promote cyclization, donor substituents hinder the occurrence of the reaction.

The effect of the substituents on the pyrimidine ring seems to be weak in the case of reaction of compounds **1** with *p*-nitrobenzosulfenyl chloride.

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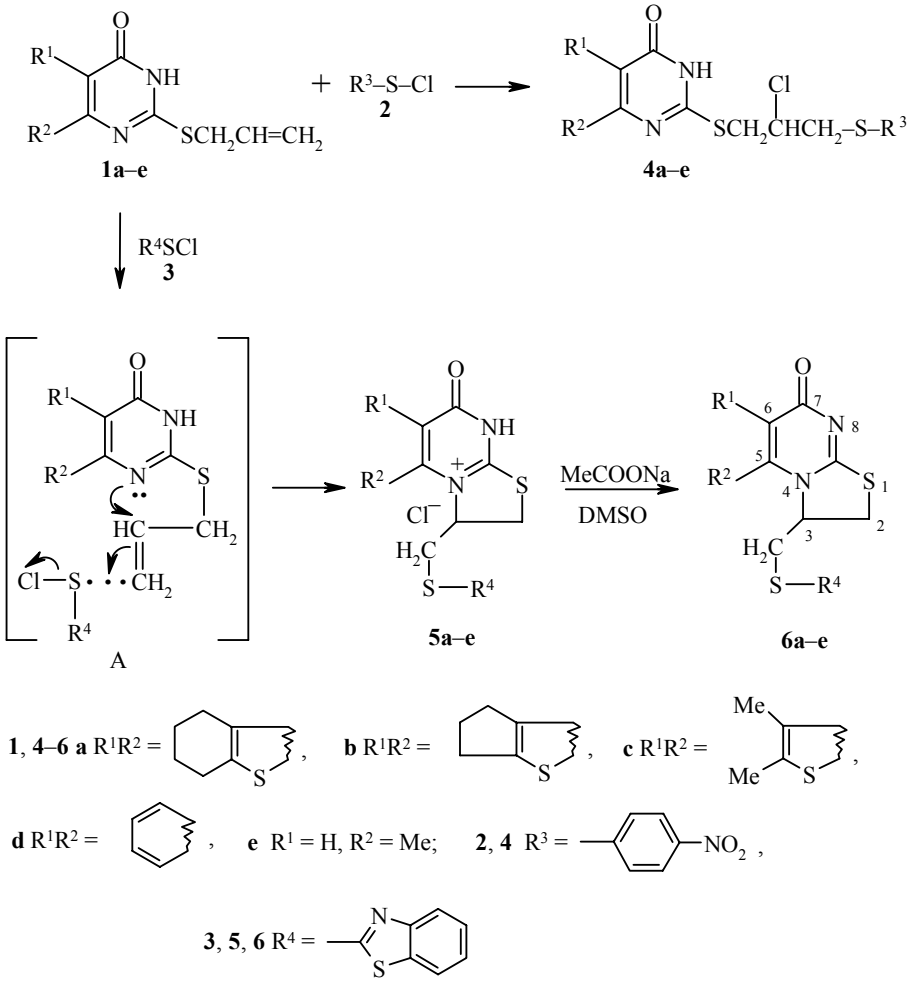
Scheme 1



In the ^{1}H NMR spectra of compounds **4**, we observe signals from the protons of Het–S–CH_2–CHCl–CH_2–S–Ar in the region 3.39-3.81 ppm (CH_2), 4.01-4.21 ppm (CH_2), and a multiplet from the methine moiety CHCl at 4.22-4.42 ppm. We cannot clearly establish the regiochemistry of addition of sulfenyl chloride **2** to the allyl moiety of compounds **1** based on these data. However, we may hypothesize that the addition occurs according to Markovnikov's rule.

The ^{1}H NMR spectroscopy data for compounds **5, 6** support formation of the thiazolidine ring. Thus signals from the protons in the methylene group of the thiazolidine ring and protons in the $\underline{CH_2}$–S–Het moiety appear in the spectra as characteristic signals for an ABX system in the 3.50-4.15 ppm region. The methine proton of the thiazolidine ring gives a multiplet in the 5.40-6.02 region (compound **5**) and the 5.26-5.72 ppm region (compound **6**). Furthermore, we see signals from the benzothiazole ring: two triplets and doublets each in the 7.36-8.04 ppm region.

The difference between the chemical shifts for the proton of the CHCl moiety in the addition products **4** (4.22-4.42 ppm) and the methine proton of the thiazolidine ring of the cyclic compounds **5, 6** (5.26-6.02 ppm) allows us to establish the structure of the products for the studied reactions.

In the IR spectra of compounds **4**, there are absorption bands for the carbonyl group in the 1675-1670 cm^{-1} region, while for compounds **5** we see these bands at 1720-1710 cm^{-1}. For compounds **6**, the absorption region for the carbonyl group was 1640-1635 cm^{-1}, which proves formation of cyclic products with participation of the $N_{(1)}$ atom of the pyrimidine ring [7, 8].

TABLE 1. Physicochemical Characteristics of Compounds **4-6**

Compound	Empirical formula	Found, % / Calculated, %					mp, °C*	Yield, %
		C	H	Cl	N	S		
4a	$C_{19}H_{18}ClN_3O_3S_3$	48.64 / 48.76	3.76 / 3.88	7.64 / 7.58	8.71 / 8.98	20.47 / 20.55	215-217	61
4b	$C_{18}H_{16}ClN_3O_3S_3$	47.54 / 47.62	3.47 / 3.55	7.85 / 7.81	9.16 / 9.26	21.04 / 21.19	204-207	63
4c	$C_{17}H_{16}ClN_3O_3S_3$	46.14 / 46.20	3.58 / 3.65	8.07 / 8.02	9.46 / 9.51	21.61 / 21.77	200-202	69
4d	$C_{17}H_{14}ClN_3O_3S_2$	49.84 / 50.06	3.39 / 3.46	8.65 / 8.69	10.17 / 10.30	15.64 / 15.72	196-197	68
4e	$C_{14}H_{14}ClN_3O_3S_2$	45.14 / 45.22	3.68 / 3.79	9.47 / 9.53	11.28 / 11.30	17.17 / 17.25	161-164	43
5a	$C_{20}H_{18}ClN_3OS_4$	49.84 / 50.04	3.71 / 3.78	7.26 / 7.38	8.63 / 8.75	26.68 / 26.72	136-139	48
5b	$C_{19}H_{16}ClN_3OS_4$	48.79 / 48.96	3.43 / 3.46	7.57 / 7.61	8.96 / 9.02	27.49 / 27.52	148-151	42
5c	$C_{18}H_{16}ClN_3OS_4$	47.53 / 47.61	3.44 / 3.55	7.67 / 7.81	9.13 / 9.25	28.06 / 28.25	138-140	45
5d	$C_{18}H_{14}ClN_3OS_3$	51.37 / 51.48	3.28 / 3.36	8.37 / 8.44	9.96 / 10.01	22.84 / 22.91	136-138	62
5e	$C_{15}H_{14}ClN_3OS_3$	46.78 / 46.92	3.57 / 3.68	9.14 / 9.23	10.89 / 10.94	25.01 / 25.05	194-196	8
6a	$C_{20}H_{17}N_3OS_4$	54.03 / 54.15	3.79 / 3.86	—	9.42 / 9.47	28.83 / 28.91	248-250	80
6b	$C_{19}H_{15}N_3OS_4$	53.02 / 53.12	3.43 / 3.52	—	9.74 / 9.78	29.73 / 29.86	238-239	87
6c	$C_{18}H_{15}N_3OS_4$	51.65 / 51.77	3.54 / 3.62	—	9.97 / 10.06	30.82 / 30.71	211-213	98
6d	$C_{18}H_{13}N_3OS_3$	56.28 / 56.37	3.37 / 3.42	—	10.79 / 10.96	25.03 / 25.08	222-223	69
6e	$C_{15}H_{13}N_3OS_3$	51.77 / 51.85	3.65 / 3.77	—	12.04 / 12.09	27.59 / 27.68	220-222	53

***** Compounds **4a-e, 6a-e** were recrystallized from an alcohol–DMSO mixture.

TABLE 2. ^{1}H NMR and IR Spectra of Compounds **4-6**

Compound	IR spectrum, ν(C=O), cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
1	2	3
4a	1665	1.77 (4H, m, $2CH_2$); 2.71-2.81 (4H, m, $2CH_2$); 3.47-3.74 (2H, m, CH_2); 4.02-4.18 (2H, m, CH_2); 4.27-4.36 (1H, m, CH); 7.72, 8.17 (4H, 2d, J_1 = 9.0, J_2 = 8.7, C_6H_4); 12.66 (1H, br. s, NH)
4b	1670	2.30-2.43 (2H, m, CH_2); 2.87-2.89 (4H, m, $2CH_2$); 3.48-3.77 (2H, m, CH_2); 4.02-4.21 (2H, m, CH_2); 4.29-4.39 (1H, m, CH); 7.73, 8.17 (4H, 2d, J_1 = 8.8, J_2 = 8.7, C_6H_4); 12.75 (1H, br. s, NH)
4c	1670	2.30 (6H, s, $2CH_3$); 3.39-3.73 (2H, m, CH_2); 4.00-4.19 (2H, m, CH_2); 4.22-4.36 (1H, m, CH); 7.70, 8.15 (4H, 2d, J_1 = 9.0, J_2 = 8.8, C_6H_4); 12.62 (1H, br. s, NH)
4d	1680	3.63-3.81 (2H, m, CH_2); 4.04-4.18 (2H, m, CH_2); 4.34-4.42 (1H, m, CH); 7.37-8.17 (8H, m, $2C_6H_4$); 12.67 (1H, br. s, NH)

TABLE 2 (continued)

1	2	3
4e	1675	2.18 (3H, s, CH_3); 3.45-3.72 (2H, m, CH_2); 4.01-4.17 (2H, m, CH_2); 4.29-4.36 (4H, m, $2CH_2$); 6.04 (1H, s, CH); 7.76, 8.17 (4H, 2d, $J_1 = J_2 = 8.7$, C_6H_4)
5a	1720	1.69-1.80 (4H, m, $2CH_2$); 2.63-2.79 (4H, m, $2CH_2$); 3.95-4.13 (4H, m, $2CH_2$); 5.42-5.50 (1H, m, CH); 7.38, 7.48 (2H, 2t, $J_1 = J_2 = 7.2$, 2H arom.); 7.72, 7.99 (2H, 2d, $J_1 = 7.8$, $J_2 = 7.5$, 2H arom.)
5b	1720	2.33-2.42 (2H, m, CH_2); 2.62-2.97 (4H, m, $2CH_2$); 3.76-4.13 (4H, m, $2CH_2$); 5.49-5.56 (1H, m, CH); 7.38, 7.49 (2H, 2t, $J_1 = 8.1$, $J_2 = 6.9$, 2H arom.); 7.75, 7.99 (2H, 2d, $J_1 = 7.8$, $J_2 = 8.7$, 2H arom.)
5c	1715	2.23 (3H, s, CH_3); 2.41 (3H, s, CH_3); 3.73-4.12 (4H, m, $2CH_2$); 5.40-5.50 (1H, m, CH); 7.38, 7.49 (2H, 2t, $J_1 = J_2 = 7.2$, 2H arom.); 7.75, 8.00 (2H, 2d, $J_1 = J_2 = 8.0$, 2H arom.)
5d	1720	3.76-4.15 (4H, m, $2CH_2$); 5.93-6.02 (1H, m, CH); 7.39-8.42 (8H, m, 8H arom.)
5e	1720	2.68 (3H, s, CH_3); 3.61-4.14 (4H, m, $2CH_2$); 5.47-5.53 (1H, m, CH); 6.15 (1H, s, CH), 7.40, 7.51 (2H, 2t, $J_1 = J_2 = 7.5$, 2H arom.); 7.80, 8.04 (2H, 2d, $J_1 = J_2 = 7.5$, 2H arom.)
6a	1640	1.69-1.79 (4H, m, $2CH_2$); 2.71-2.73 (4H, m, $2CH_2$); 3.59-4.01 (4H, m, $2CH_2$); 5.27-5.33 (1H, m, CH); 7.36, 7.47 (2H, 2t, $J_1 = 7.8$, $J_2 = 8.1$, 2H arom.); 7.76, 7.96 (2H, 2d, $J_1 = 7.5$, $J_2 = 8.1$, 2H arom.)
6b	1635	2.32-2.41 (2H, m, CH_2); 2.65-2.93 (4H, m, $2CH_2$); 3.61-4.03 (4H, m, $2CH_2$); 5.31-5.38 (1H, m, CH); 7.37, 7.48 (2H, 2t, $J_1 = 7.8$, $J_2 = 8.0$, 2H arom.); 7.79, 7.98 (2H, 2d, $J_1 = 8.1$, $J_2 = 7.8$, 2H arom.)
6c	1640	2.24 (3H, s, CH_3); 2.37 (3H, s, CH_3); 3.60-4.01 (4H, m, $2CH_2$); 5.28-5.33 (1H, m, CH); 7.38, 7.49 (2H, 2t, $J_1 = 6.9$, $J_2 = 6.6$, 2H arom.); 7.79, 7.99 (2H, 2d, $J_1 = J_2 = 7.8$, 2H arom.)
6d	1650	3.62-3.97 (4H, m, $2CH_2$); 5.65-5.72 (1H, m, CH); 7.39-8.24 (8H, m, 8CH)
6e	1645	2.55 (3H, s, CH_3); 3.50-3.91 (4H, m, $2CH_2$); 5.26-5.31 (1H, m, CH); 5.75 (1H, s, CH), 7.39, 7.50 (2H, 2t, $J_1 = 7.8$, $J_2 = 8.0$, 2H arom.); 7.81, 8.04 (2H, 2d, $J_1 = J_2 = 7.8$, 2H arom.)

EXPERIMENTAL

The IR spectra were recorded on a UR-20 in KBr disks. The 1H NMR spectra were obtained on a Varian VXR-300 spectrometer (300 MHz) in DMSO-d_6, internal standard TMS.

The procedure for synthesis of 2-allylthiothieno[2,3-*d*]pyrimidin-4(3H)-ones **1a-c** and 2-allylthioquinazolin-4(3H)-one (**1d**) is described in [9]; the procedure for synthesis of 2-allylthio-6-methyl-4(3H)-hydropyrimidinone (**1e**) is described in [8]; the procedure for synthesis of *p*-nitrobenzosulfenyl chloride (**2**) is described in [10]; and the procedure for synthesis of 2-benzothiazolyl sulfenyl chloride (**3**) is described in [11].

The physicochemical and spectral characteristics of the synthesized compounds are given in Tables 1 and 2.

2-[2-Chloro-3-(*p*-nitrobenzosulfenyl)propylthio]-5,6-R^1,R^2-thieno[2,3-*d*]pyrimidin-4(3H)-ones 4a-c, 2-[2-Chloro-3-(*p*-nitrobenzosulfenyl)propylthio]quinazolin-4(3H)-one (4d), and 2-[2-Chloro-3-(*p*-nitrobenzosulfenyl)propylthio]-6-methyl-4(3H)-pyrimidinone (4e). Sulfenyl chloride **2** (0.45 g, 2.4 mmol) was added to a suspension of the corresponding compound **1** (2 mmol) in chloroform (30 ml). The mixture was stirred for 9-18 h at a temperature of 15-25°C; the precipitate of compound **4** was filtered out, washed with chloroform and then ether, and recrystallized from DMSO.

3-(2-Benzothiazolylthio)methyl-6,7-R^1,R^2-8-oxo-2,3-dihydro-9H-thiazolo[3,2-*a*]thieno[3,2-*e*]-pyrimidinium Chlorides 5a-c, 3-(2-Benzothiazolylthio)methyl-9-oxo-2,3-dihydro-10H-thiazolo[3,2-*a*]-quinazolonium Chloride (5d), and 3-(2-Benzothiazolylthio)methyl-5-methyl-7-oxo-2,3-dihydro-8H-thiazolo[3,2-*a*]pyrimidinium Chloride (5e) were synthesized as for compounds **4**, from 2-benzothiazolyl sulfenyl chloride and the corresponding compounds **1**.

3(2-Benzothiazolylthio)methyl-6,7-R^1,R^2-8-oxo-2,3-dihydrothiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidines 6a-c, 3-(2-Benzothiazolylthio)methyl-9-oxo-2,3-dihydrothiazolo[3,2-*a*]quinazolone (6d), and 3-(2-Benzothiazolylthio)methyl-5-methyl-7-oxo-2,3-dihydrothiazolo[3,2-*a*]pyrimidine (6e). A 20% aqueous solution of sodium acetate (10 ml) was added with stirring to a solution of salt **5** (2 mmol) in DMSO (10 ml). After 0.5 h, the precipitate formed was filtered out and washed with alcohol and then ether. They were recrystallized from a 1:2 alcohol–DMSO mixture.

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