Synthesis and conversions of 6-nitro derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidines

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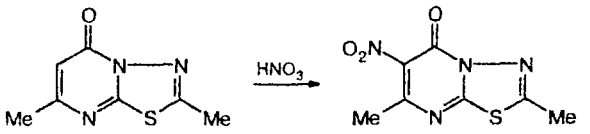
Convenient procedures were developed for the preparation of new 2-*R*-thio and 2-amino derivatives of 7-methyl-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines and products of their condensation with aldehydes.

Key words: 1,3,4-thiadiazolo[3,2-*a*]pyrimidines, 7-methyl-6-nitro-5-oxo-2-*R*-thio-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines, 2-amino derivatives of 7-methyl-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine.

The introduction of a substituent at position 6 of the 1,3,4-thiadiazolo[3,2-*a*]pyrimidine system efficiently enhances the physiological activity of the molecule.[1–3] This replacement occurs in the reactions of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine derivatives with electrophiles.[4,5]

In the present work, we studied the possibilities of the synthesis of various derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine containing the nitro group at position 6. First, we studied nitration of 2,7-dimethyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (**1**) with fuming nitric acid under different conditions. The reaction of **1** with fuming nitric acid in acetic acid did not give the desired result. Nitration of compound **1** with fuming nitric acid in low-percentage oleum afforded 2,7-dimethyl-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (**2**) in 25% yield (Scheme 1).

Scheme 1



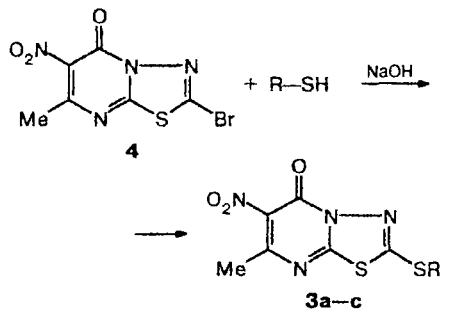
1 **2**

The nitration of 7-methyl-2-*R*-thio-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine with concentrated nitric acid in glacial acetic acid is documented.[6] It is also known that 6-nitro derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine are used in the synthesis of 2-*R*-6,7-diamino-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines.[6]

Our next aim was to study the possibility of the synthesis of 7-methyl-6-nitro-5-oxo-2-*R*-thio-5*H*-1,3,4-thiadiazolo-[3,2-*a*]pyrimidines (**3**) based on the reactions of 2-bromo-7-methyl-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (**4**) with thiols in the presence of bases. It should be noted that procedures for the synthesis of 6-nitro derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine containing labile groups have not been reported.

We demonstrated that the reactions of compound **4** with thiols proceed smoothly in aqueous ethanol in the presence of an equimolar amount of NaOH at room temperature to form the corresponding sulfides **3** (Scheme 2).

Scheme 2

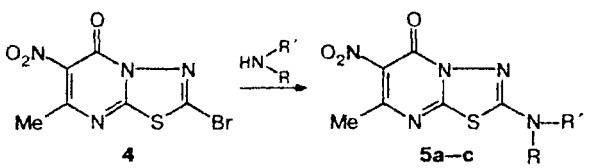


4 **3a–c**

R = Ph (**a**); 2-amino-1,3,4-thiadiazol-5-yl (**b**); 5-methyl-1,2,4-triazol-3-yl (**c**)

The reactions of bromide **4** with amines were also studied. The reactions of compound **4** with secondary amines in ethanol resulted in the replacement of the bromine atom to yield amines **5** (Scheme 3).

Scheme 3



4 **5a–c**

R = R′ = Et (**a**)
R + R′ = (—CH_2—)$_5$ (**b**), (—CH_2—$CH_2$$OCH_2$—$CH_2$—) (**c**)

† Deceased.

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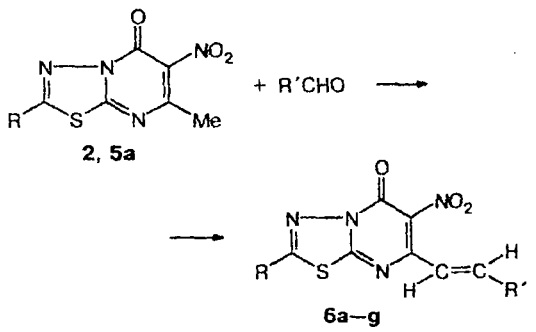
Thereupon, we studied the reactions of compounds **2** and **5a** with aromatic aldehydes. 7-Arylidene derivatives of 1,3,4-thiadiazolo[3,2-*a*]pyrimidine (**6a—g**) were synthesized in the presence of Et_3N.

Scheme 4



	R	R'		R	R'
6a	Me	Ph	**6e**	Et_2N	4-FC_6H_4
6b	Me	4-FC_6H_4	**6f**	Et_2N	4-$MeOC_6H_4$
6c	Me	2-furil	**6g**	Et_2N	2-furyl
6d	Et_2N	Ph			

Table 1. Properties of 2-*R*-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	Molecular formula
2	25	138—140	37.01 37.16	2.52 2.67	$C_7H_6N_4O_3S$
3a	90	114—116	44.60 44.99	2.30 2.51	$C_{12}H_8N_4O_3S_2$
3b	85	234—236	22.70 22.98	1.19 1.46	$C_8H_5N_7O_3S_3$
3c	71	248—250	32.90 33.22	2.01 2.16	$C_9H_7N_7O_3S_2$
5a	86	140—142	42.47 42.57	4.43 4.50	$C_{10}H_{13}N_5O_3S$
5b	80	223—225	44.51 44.73	4.39 4.43	$C_{11}H_{13}N_5O_3S$
5c	83	316—318	40.11 40.39	3.58 3.73	$C_{10}H_{11}N_5O_4S$
6a	76	252—254	53.20 53.49	2.67 3.20	$C_{14}H_{10}N_4O_3S$
6b	84	274—276	51.0 50.59	2.85 2.73	$C_{14}H_9FN_4O_3S$
6c	89	232—234	47.51 47.36	2.79 2.65	$C_{12}H_8N_4O_4S$
6d	85	164—166	54.59 54.97	4.39 4.61	$C_{17}H_{17}N_5O_3S$
6e	87	278—280	51.70 52.43	3.91 4.14	$C_{17}H_{16}FN_5O_3S$
6f	84	198—200	53.11 53.85	4.40 4.77	$C_{18}H_{19}N_5O_4S$
6g	91	138—140	49.39 49.85	4.03 4.18	$C_{15}H_{15}N_5O_4S$

Table 2. Spectral characteristics of 2-*R*-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines

Compound	IR, ν/cm^{-1}	^1H NMR, δ (*J*/Hz)
2	1735 (C=O); 1585 (C=N); 1550 (NO_2); 1385 (NO_2)	2.64 (s, 3 H, Me); 2.32 (s, 3 H, Me)
3a	1729 (C=O); 1580 (C=N); 1545 (C=C); 1540 (NO_2); 1370 (NO_2)	7.74—7.58 (m, 5 H, Ph); 2.28 (s, 3 H, Me)
3b	3400 (NH_2); 1725 (C=O); 1660 (C=N); 1580 (C=N); 1535 (C=C); 1530 (NO_2); 1350 (NO_2)	7.72 (br.s, 2 H, NH_2); 2.30 (s, 3 H, Me)
3c	3072 (C=C); 1712 (C=O); 1662 (C=C); 1610 (C=N); 1555 (NO_2); 1349 (NO_2)	2.38 (s, 3 H, Me); 2.34 (s, 3 H, Me)
5a	3070 (C=C); 1712 (C=O); 1662 (C=C); 1610 (C=N); 1555 (NO_2); 1300 (NO_2)	3.40 (q, 4 H, 2 CH_2); 2.24 (s, 3 H, Me); 1.08 (t, 6 H, 2 Me)
5b	1730 (C=O); 1580 (C=N); 1550 (NO_2); 1380 (NO_2)	3.52 (m, 4 H, 2 CH_2); 2.26 (s, 3 H, Me); 1.52 (m, 6 H, 3 CH_2)
5c	1725 (C=O); 1577 (C=N); 1545 (NO_2); 1350 (NO_2)	3.64 (t, 4 H, 2 CH_2); 3.46 (t, 4 H, 2 CH_2); 2.42 (s, 3 H, Me)
6a	1710 (C=O); 1668 (C=C); 1656 (C=N); 1572 (NO_2); 1364 (NO_2)	7.90, 6.14 (both d, 2 H, 2 CH, J_{AB} = 16); 7.64—7.34 (m, 5 H, Ph); 2.62 (s, 3 H, Me)
6b	3108 (C=C); 1704 (C=O); 1662 (C=C); 1656 (C=N); 1588 (NO_2); 1348 (NO_2)	7.90, 6.17 (both d, 2 H, 2 CH, J_{AB} = 16); 7.80 (d, 2 H, Ph); 7.29 (d, 2 H, Ph); 2.56 (s, 3 H, Me)
6c	3000 (C=C); 1732 (C=O); 1650 (C=C); 1610 (C=N); 1570 (C=N); 1550 (NO_2); 1330 (NO_2)	7.78, 6.72 (both d, 2 H, 2 CH, J_{AB} = 16); 7.76 (d, H, CH); 6.92 (d, H, CH); 6.56 (t, H, CH); 2.60 (s, 3 H, Me)
6d	3080 (C=C); 1735 (C=O); 1655 (C=C); 1610 (C=N); 1570 (NO_2); 1370 (NO_2)	7.94, 6.94 (both d, 2 H, 2 CH, J_{AB} = 16); 7.64—7.34 (m, 5 H, Ph); 3.38 (q, 4 H, 2 CH_2); 1.14 (t, 6 H, 2 Me)
6e	2995 (C=C); 1730 (C=O); 1645 (C=C); 1605 (C=N); 1560 (NO_2); 1320 (NO_2)	7.84, 6.94 (both d, 2 H, 2 CH, J_{AB} = 16); 7.76 (d, 2 H, H arom.); 7.26 (d, 2 H, H arom.); 3.60 (q, 4 H, 2 CH_2); 1.10 (t, 6 H, 2 Me)
6f	3079 (C=C); 1737 (C=O); 1640 (C=C); 1615 (C=N); 1555 (NO_2); 1350 (NO_2)	7.84, 6.80 (both d, 2 H, 2 CH, J_{AB} = 16); 7.60 (d, 2 H, H arom.); 6.94 (d, 2 H, H arom.); 3.60 (q, 4 H, 2 CH_2); 3.46 (s, 3 H, Me); 1.10 (t, 6 H, 2 Me)
6g	2995 (C=C); 1735 (C=O); 1645 (C=C); 1610 (C=N); 1550 (NO_2); 1330 (NO_2)	7.76, 6.68 (both d, 2 H, 2 CH, J_{AB} = 16); 7.66 (d, H, CH); 6.88 (d, H, CH); 6.56 (t, H, CH); 3.78 (q, 4 H, 2 CH_2); 1.10 (t, 6 H, 2 Me)

The structures of the resulting compounds were confirmed by the data of elemental analysis and ^{1}H NMR and IR spectroscopy (Tables 1 and 2). The IR spectra of the resulting compounds have a characteristic stretching absorption band of the carbonyl group at 1725—1735 cm^{-1} and two intense absorption bands of the NO_2 group at 1540 and 1350 cm^{-1}.

In the ^{1}H NMR spectrum of compound **2**, the signal for the proton at position 6 is absent. The ^{1}H NMR spectra of 7-arylidene-2-*R*-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines **6** have a doublet signal for the vinylic protons at δ 6.92 and 7.86 with a spin-spin coupling constant of 16—17 Hz, which allows the assignment of the *trans* configuration to the vinyl substituent in compounds **6a—g**.

Experimental

The ^{1}H NMR (in DMSO-d_6) spectra were recorded on a Tesla BS-58773 C spectrometer operating at 100 MHz with HMDS as the internal standard (δ). The IR spectra were obtained on a UR-20 spectrometer in KBr pellets. The melting points were determined on a Boetius heating microtable. 2-Bromo-7-methyl-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (**4**) was prepared according to a known procedure.[4]

2,7-Dimethyl-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (2). Compound **1** (18.1 g, 0.1 mol) was dissolved in a 1 : 1 mixture of 10% oleum and 98% H_2SO_4 (20 mL). The reaction mixture was cooled to 0 °C and HNO_3 (d = 1.5, 0.12 mol) was added with stirring. The mixture was stirred for 5 h, then ice (200 g) was added, and the mixture was left for 3 h. The precipitate that formed was filtered off and washed with water. The yield was 5.69 g (25%). M.p. 138—140 °C (from propan-2-ol). IR, ν/cm^{-1}: 1735 (C=O); 1654 (C=N). ^{1}H NMR, δ: 2.64 (s, 3 H, Me); 2.32 (s, 3 H, Me).

2-Arylthio-7-methyl-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines (3a—c). A solution of NaOH (0.4 g, 0.01 mol) in water (5 mL) was added to a solution of a thiol (0.01 mol) in EtOH (10 mL) and the reaction mixture was stirred for 15 min. Then compound **4** (2.91 g, 0.01 mol) was added and the reaction mixture was stirred for 2 h. The precipitate that formed was filtered off and washed with water (15 mL).

2-Alkylamino-7-methyl-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines (5a—c). Compound **4** (2.91 g, 0.01 mol) was dissolved in dioxane (15 mL) and then an amine (0.02 mol) was added with stirring. The reaction mixture was stirred at room temperature for 2 h and then refluxed for 5 min. After cooling, the reaction mixture was poured into water (50 mL). The precipitates of compounds **5a—c** were filtered off and washed with water.

2-*R*-7-(2-Arylvinyl)-6-nitro-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidines (6a—g). An aromatic aldehyde (0.01 mol) and a catalytic amount of triethylamine were added to a solution of compound **2** or **4a** (0.01 mol) in ethanol (20 mL). The reaction mixture was refluxed for 3 h, cooled, diluted with water, and neutralized with dilute hydrochloric acid. The precipitate that formed was filtered off.

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