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SYNTHESIS OF 4,5-DIHYDRO-1,3,4-THIADIAZOLE-2-CARBOXAMIDE AND 2-CARBAMOYL-4,5-DIHYDRO-1,3,4-THIADIAZOLE 1-OXIDE DERIVATIVES BASED ON HYDRAZONES OF OXAMIC ACID THIOHYDRAZIDES

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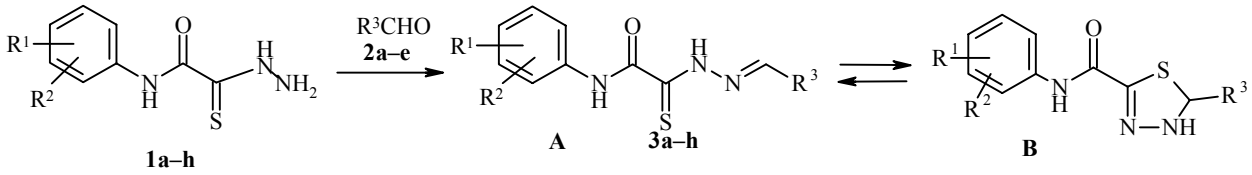
We have developed a method for obtaining derivatives of 4,5-dihydro-1,3,4-thiadiazole-2-carboxamide by acylation of hydrazones of oxamic acid thiohydrazides. Oxidation of the dihydrothiadiazole ring of the indicated products by hydrogen peroxide leads to formation of 2-carbamoyl-4,5-dihydro-1,3,4-thiadiazole 1-oxides.

Keywords: hydrazones, 1,3,4-dihydrothiadiazole, dihydro-1,3,4-thiadiazole 1-oxide, 1,3,4-thiadiazole, oxamic acid thiohydrazides, thiophene.

We have developed previously a convenient general method for obtaining monothiooxamides by reaction of accessible chloroacetamides with a pre-prepared solution of elemental sulfur in amine [1] and showed that modification of the thioamide group in these monothiooxamides under treatment with N-nucleophiles allows us to obtain a variety of hetarene carboxamides [2-4], while in the reaction with hydrazines oxamic acid thiohydrazides of type **1** are formed (see Scheme 1) [5]. For the latter, we studied the possibility of conversion to 1,3,4-dihydrothiadiazole derivatives, which are of interest for obtaining biologically active compounds [6, 7].

Scheme 1



2 a R^3 = Ph, **b** R^3 = 2-thienyl, **c** R^3 = 4-$O_2NC_6H_4$, **d** R^3 = 2-$O_2NC_6H_4$, **e** R^3 = 5-methyl-2-thienyl; **1**, **3** R^1, R^2, and R^3 are given in Table 1.

* Dedicated to J. P. Stradins on his 70th birthday.

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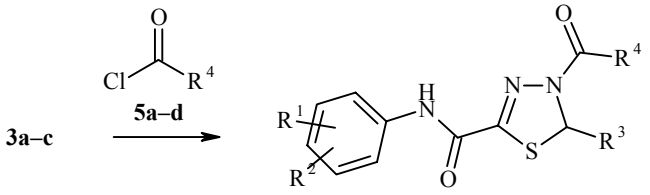
In this work, from oxamic acid thiohydrazides **1a-h** and aldehydes **2a-e**, we have synthesized for the first time the corresponding hydrazones **3a-h** (Scheme 1), based on which we obtained the previously undescribed 4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **4a-g** (Scheme 2) and 2-carbamoyl-4,5-dihydro-1,3,4-thiadiazole 1-oxides **5a-c** (Scheme 3).

Scheme 2



4a–g

4 a $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = Me$; **b** $R^1 = 3\text{-Cl}$, $R^2 = 4\text{-Cl}$, $R^3 = Ph$, $R^4 = Me$; **c** $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = Et$; **d** $R^1 = 3\text{-Cl}$, $R^2 = 4\text{-Cl}$, $R^3 = Ph$, $R^4 = Et$; **e** $R^1 = R^2 = H$, $R^3 = R^4 = Ph$; **f** $R^1 = R^2 = H$, $R^3 = R^4 = 2\text{-thienyl}$; **g** $R^1 = R^2 = H$, $R^3 = 2\text{-thienyl}$, $R^4 = Ph$; **5 a** $R^4 = Me$; **b** $R^4 = Et$; **c** $R^4 = Ph$; **d** $R^4 = 2\text{-thienyl}$

Hydrazones **3a-h** were obtained in 60% to 80% yields. According to the ^1H NMR spectra for these compounds, they are found in solution as two tautomeric forms: linear form **A** and cyclic form **B**.

So in the indicated spectra, we see a signal from the proton in the 5 position of the heterocycle of form **B** in the 6.5-7.1 ppm region, and also a signal from the proton of the N=CH–R^3 moiety of linear form **A** in the 8.7-9.1 ppm region. We determined the ratio of the tautomers **3A** and **3B** from the intensity ratio for the indicated signals (see Table 1), and we established that the ratio is affected by the substituents both in the "aldehyde" (R^3) and the "thiohydrazide" (R^1, R^2) moieties of the molecule (Table 1).

So introducing an electron-acceptor substituent R^3 shifts the equilibrium toward formation of the cyclic product **B** (compounds **3a,d**), while electron-acceptor substituents R^1, R^2 may have an opposite effect (compound **3d,e**).

Hydrazones **3a-h** react smoothly with aliphatic, aromatic, and heteroaromatic acid chlorides, in this case forming the corresponding 2-carbamoyl-4,5-dihydro-1,3,4-thiadiazoles **4a-g**. During the reaction with acid chlorides, probably the cyclic form **B** of hydrazone reacts.

The reaction can be conducted in a single flask by adding aldehyde **2** and acid chloride **5** sequentially to the solution of thiohydrazide **1** in DMF.

TABLE 1. Substituent Dependence of the Ratio of Tautomeric Forms of Hydrazones in Solutions, in DMSO-d_6 at T = 297 K

Compound*	R^1	R^2	R^3	Ratio, %	
				A	**B**
3a	H	H	Ph	10	90
3b	3-Cl	4-Cl	Ph	0	100
3c	H	H	2-thienyl	30	70
3d	H	H	$4\text{-}O_2NC_6H_4$	0	100
3e	3-Cl	4-Cl	$4\text{-}O_2NC_6H_4$	20	80
3f	3-Cl	4-Cl	$2\text{-}O_2NC_6H_4$	0	100
3g	2-Me	3-Me	5-methyl-2-thienyl	40	60
3h	H	3-Me	5-methyl-2-thienyl	50	50

* R^1, R^2, R^3 are given for compounds **1** and **3**.

TABLE 2. Characteristics of Compounds **3, 4, 6**

Compound	Empirical formula	Found, % / Calculated, %					Mass spectrum, *m/z*	mp, °C	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	Yield, %
		C	H	N	S	Cl				
1	2	3	4	5	6	7	8	9	10	11
3a	$C_{15}H_{13}N_3OS$	63.54 / 63.58	4.67 / 4.62	14.85 / 14.83	11.30 / 11.32	—	283	153-155	6.60 (1H, s, S–CH– (**B**)); 7.00 (2H, m, C_6H_5); 7.40 (7H, m, C_6H_5); 7.90 (1H, d, *J* = 7.9, C_6H_5); 8.90 (s, N=CH (**A**)); 9.15 (s, NH(**B**)); 10.00 (s, 2 NH (**B**)); 10.10 (s, NH (**A**)); 10.30 (s, NH (**A**))	76
3b	$C_{15}H_{11}Cl_2N_3OS$	51.19 / 51.15	3.11 / 3.15	11.90 / 11.93	9.12 / 9.10	20.15 / 20.13	352	165-167	6.65 (1H, s, S–CH– (**B**)); 7.40-7.60 (4H, m, C_6H_5 (**B**)); 7.90 (1H, d, *J* = 7.92, C_6H_5 (**B**)); 8.10 (1H, s, C_6H_5 (**B**)); 9.40 (1H, s, NH (**B**)); 10.50 (1H, s, NH (**B**))	79
3c	$C_{13}H_{11}N_3OS_2$	54.00 / 53.96	3.85 / 3.83	14.50 / 14.52	22.17 / 22.16	—	289	153-156	6.60 (s, S–CH–(**B**)); 6.80-7.70 (8H, m, C_6H_5); 8.90 (s, N=CH (**A**)); 9.15 (s, NH(**B**)); 10.00 (s, 2NH (**B**)); 10.10 (s, NH (**A**)); 10.30 (s, NH (**A**))	61
3d	$C_{15}H_{12}N_4O_3S$	54.91 / 54.87	3.64 / 3.68	17.09 / 17.06	9.74 / 9.77	—	328	202-204	6.75 (1H, s, S–CH– (**B**)); 7.10 (1H, t, *J* = 7.4, C_6H_5 (**B**)); 7.30 (2H, t, *J* = 7.6, C_6H_5 (**B**)); 7.70 (4H, m, C_6H_5 (**B**)); 8.30 (2H, d, *J* = 8.9, C_6H_5 (**B**)); 9.40 (1H, s, NH (**B**)); 10.20 (1H, s, NH (**B**))	79
3e	$C_{15}H_{10}Cl_2N_4O_3S$	45.36 / 45.35	2.57 / 2.54	14.07 / 14.10	8.12 / 8.07	17.81 / 17.85	396	203-206	6.80 (s, S–CH– (**B**)); 7.50 (d, *J* = 8.7, C_6H_5); 7.70 (3H, m, C_6H_5); 8.10 (2H, m, C_6H_5); 8.30 (3H, m, C_6H_5); 8.70 (s, CH=N (**A**)); 9.50 (s, NH(**B**)); 10.50 (s, NH (**B**))	85
3f	$C_{15}H_{10}Cl_2N_4O_3S$	45.32 / 45.35	2.51 / 2.54	14.14 / 14.10	8.05 / 8.07	17.87 / 17.85	396	190-192	7.00 (1H, s, S–CH– (**B**)); 7.50-7.75 (4H, m, C_6H_5 (**B**)); 7.90 (1H, m, C_6H_5 (**B**)); 8.10 (2H, m, C_6H_5 (**B**)); 9.50 (1H, s, NH (**B**)); 10.50 (1H, s, NH (**B**))	81
3g	$C_{16}H_{17}N_3OS_2$	57.92 / 57.98	5.23 / 5.17	12.73 / 12.68	19.30 / 19.35	—	331	134-136	2.10 (m, CH_3); 2.20 (s, CH_3); 2.30 (s, CH_3); 2.40 (s, CH_3); 6.60 (s, S–CH–(**B**)); 6.80-7.70 (5H, m, C_6H_5); 8.90 (s, N=CH (**A**)); 9.15 (s, NH(**B**)); 9.60 (s, NH (**B**)); 10.10 (s, NH (**A**)); 10.35 (s, NH (**A**))	56

TABLE 2 (continued)

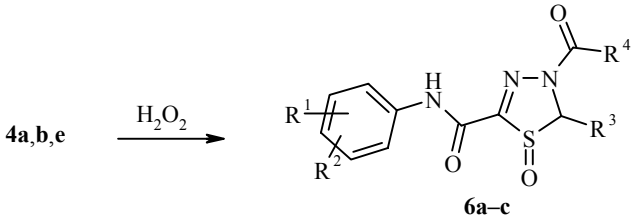
1	2	3	4	5	6	7	8	9	10	11
3h	$C_{15}H_{15}N_3OS_2$	56.79 56.76	4.74 4.76	13.21 13.24	20.24 20.20	—	317	116-118	2.20 (3H, s, CH_3); 2.55 (3H, s, CH_3); 6.60 (s, S–CH–(**B**)); 6.80-7.70 (7H, m, C_6H_5); 8.90 (s, N=CH (**A**)); 9.15 (s, NH(**B**)); 10.00 (s, 2 NH (**B**)); 10.10 (s, NH (**A**)); 10.30 (s, NH (**A**))	54
4a*	$C_{17}H_{15}N_3O_2S$	62.71 62.75	4.68 4.65	12.88 12.91	9.89 9.85	—	325	144-147	2.40 (3H, s, CH_3); 7.20 (2H, m, CH, C_6H_5); 7.40 (7H, m, C_6H_5); 7.75 (2H, d, J = 7.6, C_6H_5); 10.50 (1H, s, NH)	87
4b	$C_{17}H_{13}Cl_2N_3O_2S$	51.76 51.79	3.34 3.32	10.64 10.66	8.10 8.13	18.01 17.98	393	175-178	2.40 (3H, s, CH_3); 7.20 (1H, s, CH); 7.40 (5H, m, C_6H_5); 7.70 (2H, m, C_6H_5); 8.10 (1H, s, C_6H_5); 10.65 (1H, s, NH)	80
4c	$C_{18}H_{17}N_3O_2S$	63.66 63.70	5.02 5.05	12.41 12.38	9.42 9.45	—	339	152-161	1.00 (3H, t, CH_3); 2.85 (2H, m, J = 7, CH_2); 7.20 (2H, m, CH, C_6H_5); 7.40 (7H, m, C_6H_5); 7.75 (2H, d, J = 7.92, C_6H_5); 10.50 (1H, s, NH)	82
4d	$C_{18}H_{15}Cl_2N_3O_2S$	52.93 52.95	3.71 3.70	10.27 10.29	7.87 7.85	17.34 17.37	407	164-167	1.00 (3H, t, CH_3); 2.80 (2H, m, J = 7, CH_2); 7.20 (1H, s, CH); 7.40 (5H, m, C_6H_5); 7.70 (3H, m, C_6H_5); 8.10 (2H, s, C_6H_5); 10.65 (1H, s, NH)	82
4e	$C_{22}H_{17}N_3O_2S$	68.23 68.20	4.40 4.42	10.81 10.84	8.32 8.28	—	387	176-180	7.10 (1H, t, J = 7.4, CH, C_6H_5); 7.40-7.60 (13H, m, CH, C_6H_5); 8.00 (2H, d, J = 7.9, C_6H_5); 10.40 (1H, s, NH)	74
4f	$C_{18}H_{13}N_3O_2S_3$	54.14 54.12	3.31 3.28	10.49 10.52	24.11 24.08	—	399	179-182	7.00 (1H, m, C_6H_5); 7.20 (4H, m, Het, CH, C_6H_5); 7.40 (2H, m, C_6H_5); 7.55 (1H, m, Het); 7.75 (2H, m, Het, C_6H_5); 8.00 (1H, m, C_6H_5); 8.25 (1H, d, J = 7.9, C_6H_5); 10.55 (1H, s, NH)	70
4g	$C_{20}H_{15}N_3O_2S_2$	61.09 61.05	3.83 3.84	10.72 10.68	16.33 16.30	—	393	189-192	7.00 (1H, t, J = 7.4, C_6H_5); 7.10 (1H, t, J = 7.4, C_6H_5); 7.30-7.80 (10H, m); 8.00 (2H, d, J = 7.9, C_6H_5); 10.45 (1H, s, NH)	67
6a*[2]	$C_{17}H_{15}N_3O_3S$	59.78 59.81	4.47 4.43	12.34 12.31	9.42 9.39	—	341	208-212	2.60 (3H, s, CH_3); 7.00 (1H, s, CH); 7.20 (1H, t, J = 7.4, C_6H_5); 7.35 (7H, m, C_6H_5); 7.75 (2H, d, J = 7.9, C_6H_5); 10.75 (1H, s, NH)	71
6b	$C_{17}H_{13}Cl_2N_3O_3S$	49.80 49.77	3.17 3.19	10.22 10.24	7.85 7.82	17.31 17.28	409	237-240	2.60 (3H, s, CH_3); 7.20 (1H, s, CH); 7.40 (5H, m, C_6H_5); 7.70 (2H, m, C_6H_5); 8.10 (1H, s, C_6H_5); 10.85 (1H, s, NH)	65
6c	$C_{22}H_{17}N_3O_3S$	65.47 65.49	4.28 4.25	10.39 10.41	7.91 7.95	—	403	220-224	7.10 (1H, t, J = 7.37, C_6H_5); 7.40-7.60 (13H, m, CH, C_6H_5); 8.00 (2H, d, J = 8.38, C_6H_5); 10.70 (1H, s, NH)	46

* ^{13}C NMR spectrum, δ, ppm: 22.1, 69.6, 120.9, 124.7, 125.5, 128.6, 128.7, 128.75, 137.3, 140.9, 147.0, 156.8, 169.3.

*[2] ^{13}C NMR spectrum, δ, ppm: 21.8, 85.1, 120.8, 124.8, 126.3, 127.0, 128.0, 128.8, 129.3, 129.4, 132.05, 137.4, 147.8, 156.5, 169.6.

Oxidation of compounds **4a,b,e**, having different substituents on the 4 and 5 positions of the heterocycle, by hydrogen peroxide in acetic acid leads to 2-carbamoyl-4,5-dihydro-1,3,4-thiadiazole 1-oxides **6a-c** in good yields.

Scheme 3



6a–c

6 a $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = Me$; **b** $R^1 = 3\text{-Cl}$, $R^2 = 4\text{-Cl}$, $R^3 = Ph$, $R^4 = Me$;
c $R^1 = R^2 = H$, $R^3 = R^4 = Ph$

Thus upon acylation of accessible hydrazones of oxamic acid thiohydrazides, 2-carbamoyl-4,5-dihydro-1,3,4-thiadiazoles are formed, the oxidation of which leads to 2-carbamoyl-4,5-dihydro-1,3,4-thiadiazole 1-oxides containing different substituents on the ring.

EXPERIMENTAL

The ^1H NMR spectra were recorded on Bruker WM-200 (200 MHz) and WM-250 (250 MHz) spectrometers in DMSO-d_6; the ^{13}C NMR spectra were recorded on a Bruker AC-200 (50 MHz) apparatus in DMSO-d_6. The mass spectra were recorded on a Varian MAT CH-6 mass-spectrometer with direct injection of the sample into the emission source, ionization energy was 70 eV, and operating voltage 1.75 kV. The IR spectra were taken on a Specord M-80 for KBr disks. The melting points were measured on a Boetius hot stage and were uncorrected. For analysis of all the reaction masses and monitoring the purity of the isolated products, we used TLC on Silufol UV-254 plates in the solvent systems ethyl acetate–hexane, 1:2 (**3a-h, 5a-g**) and 1:1 (**6a-c**).

The characteristics of compounds **3, 4**, and **6** are given in Table 2.

Oxamic Acid Thiohydrazides 1a-h were obtained by the procedure in [5].

N-Aryl-2-arylidene(hetarylidene)hydrazino-2-thiooxacetamides (Hydrazones of Oxamic Acid Thiohydrazides) (3a-h). (General Procedure). Aldehyde **2** (1.1 mmol) was added to oxamic acid thiohydrazide **1** (1 mmol) in ethyl alcohol (5 ml). The reaction mixture was boiled for 20 min, then cooled down to room temperature; the precipitate of product **3** was filtered off and washed with hot ethanol.

N-Aryl-4-acetyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamides (4a-g). (General Procedure). A. Acid chloride **5a-d** (1.5 mmol) was added to thiohydrazone **3a-c** (1 mmol) dissolved in DMF (3 ml) at room temperature. The reaction mixture was stirred for 2 h, then poured into water; the precipitate of product **4** was filtered off and recrystallized from ethanol.

B. Aldehyde **2a** (1.1 mmol) was added to oxamic acid thiohydrazide **1a,b** (1 mmol) in DMF (3 ml). The reaction mixture was held for 10 min at 50°C, then cooled down to room temperature, and then acid chloride **5a** (1.5 mmol) was added. The reaction mass was stirred for 2 h and poured into water; the precipitate of products **4a,b** was filtered off and recrystallized from ethanol. The yield of compound **4a** and **4b** was respectively 52% and 47%. The products were identical to samples obtained by procedure A (mp, ^1H NMR spectra and mass spectra).

N-Aryl-4-acetyl-2-carbamoyl-N-4,5-dihydro-1,3,4-thiadiazole 1-Oxides (6a-c). (General Procedure). 15% H_2O_2 (2 ml) was added to dihydrothiadiazole **3** (0.5 mmol) in acetic acid (8 ml). The reaction mixture was boiled for 15 min, then cooled down to room temperature and poured into water. The precipitate was filtered off, and oxides **6a-c** were isolated from the precipitate using TLC (hexane–ethyl acetate, 1:1). IR spectrum, ν, cm^{-1}: **6a** – 1040 (S=O), **6b** – 1032 (S=O), **6c** – 1028 (S=O).

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