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SYNTHESIS OF 2-ARYL AND 2-HETARYL DERIVATIVES OF 2'-AMINOSPIRO[(1,3-DIOXANE)-5,5'-THIAZOLIN]-4'-ONE AND SPIRO[(1,3-DIOXANE)-5,5'-THIAZOLIDINE]-2',4'-DIONE

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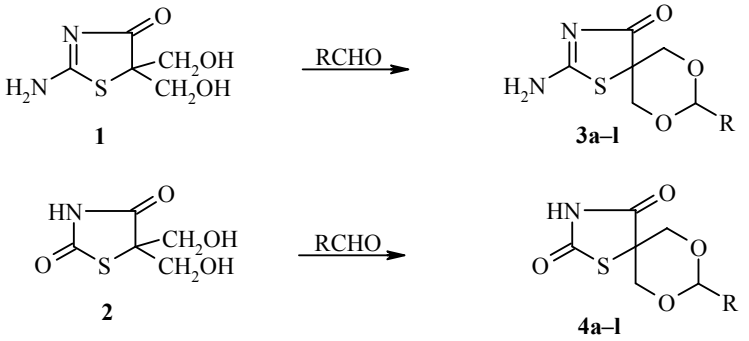
2-(Het)aryl derivatives of 2'-aminospiro[(1,3-dioxane)-5,5'-thiazolin]-4'-one or spiro[(1,3-dioxane)-5,5'-thiazolidine]-2',4'-dione are formed by the acid catalyzed interaction of 2-amino-5,5-bis(hydroxymethyl)-4-thiazolinone or its oxo analog 5,5-bis(hydroxymethyl)thiazolidine-2,4-dione with (hetero)aromatic aldehydes.

Keywords: 2-amino-5,5-bis(hydroxymethyl)-4-thiazolinone, 2-(het)aryl derivatives of 2'-aminospiro-[(1,3-dioxane)-5,5'-thiazolin]-4'-one and spiro[(1,3-dioxane)-5,5'-thiazolidine]-2',4'-dione, reactions with aldehydes.

It is known that polyatomic alcohols are able to react with aldehydes and ketones under the influence of acid catalysts to form cyclic acetals and ketals [1]. In particular derivatives of 1,3-dioxane are formed from 1,3-diols [2]. It seemed of interest to discover whether the compounds 2-amino-5,5-bis(hydroxymethyl)-4-thiazolinone (**1**) and its oxo analog 5,5-bis(hydroxymethyl)-2,4-thiazolidinone (**2**), which we synthesized previously [3], would undergo similar reactions. It seemed that they did not differ in their structures from other 1,3-diols and formed with aromatic and heteroaromatic aldehydes in the presence of acid 2-(het)aryl-2'-aminospiro[(1,3-dioxane)-5,5'-thiazolin]-4'-ones **3a-l** or 2-(het)aryl-2'-aminospiro[(1,3-dioxane)-5,5'-thiazolidine]-2',4'-diones **4a-l** respectively (Table 1).



3,**4** **a** R = Ph; **b** R = *o*-C_6H_4Cl; **c** R = *m*-C_6H_4Br; **d** R = *p*-$C_6H_4NO_2$; **e** R = *m*-$C_6H_4NO_2$; **f** R = 3-Py; **g** R = 4-Py; **h** R = *p*-$C_6H_4NMe_2$; **i** R = *p*-$C_6H_4NEt_2$; **j** R = *p*-C_6H_4OMe; **k** R = *m*,*p*-$C_6H_3(OMe)_2$; **l** R = *p*-C_6H_4Me

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TABLE 1. 2-Aryl(hetaryl)-2'-aminospiro[(1,3-dioxane)-5,5'-thiazolin]-4'-ones **3a-l** and 2-aryl(hetaryl)[spiro(1,3-dioxane)-5,5'-thiazolidine]-2',4'-diones **4a-l**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{12}H_{12}N_2O_3S$	54.40 / 54.53	4.49 / 4.58	10.70 / 10.60	273-275	50
3b	$C_{12}H_{11}ClN_2O_3S$	48.31 / 48.24	3.64 / 3.71	9.43 / 9.38	257-259	52
3c	$C_{12}H_{11}BrN_2O_3S$	41.88 / 42.00	3.21 / 3.23	8.28 / 8.16	269-270	46
3d	$C_{12}H_{11}N_3O_5S$	46.64 / 46.60	3.67 / 3.58	13.58 / 13.59	350-353	57
3e	$C_{12}H_{11}N_3O_5S$	46.74 / 46.60	3.64 / 3.58	13.65 / 13.59	295-298 (dec.)	78
3f	$C_{11}H_{11}N_3O_3S$	49.86 / 49.80	3.95 / 4.18	15.86 / 15.84	295-300 (dec.)	81
3g	$C_{11}H_{11}N_3O_3S$	49.89 / 49.80	4.14 / 4.18	15.89 / 15.84	302-305 (dec.)	81
3h	$C_{14}H_{17}N_3O_3S$	54.79 / 54.71	5.66 / 5.57	13.67 / 13.67	238-240 (dec.)	70
3i	$C_{16}H_{21}N_3O_3S$	57.27 / 57.29	6.30 / 6.31	12.48 / 12.53	232-234 (dec.)	35
3j	$C_{13}H_{14}N_2O_4S$	53.18 / 53.05	4.71 / 4.79	9.59 / 9.52	260-262	72
3k	$C_{14}H_{16}N_2O_5S$	51.85 / 51.84	5.01 / 4.97	8.59 / 8.64	258-260	38
3l	$C_{13}H_{14}N_2O_3S$	56.05 / 56.10	5.11 / 5.07	10.01 / 10.06	263-265 (dec.)	61
4a	$C_{12}H_{11}NO_4S$	54.39 / 54.33	4.14 / 4.18	5.36 / 5.28	203-205	60
4b	$C_{12}H_{10}ClNO_4S$	48.11 / 48.09	3.30 / 3.36	4.59 / 4.67	214-216	51
4c	$C_{12}H_{10}BrNO_4S$	42.00 / 41.88	2.82 / 2.93	4.08 / 4.07	173-175	71
4d	$C_{12}H_{10}N_2O_6S$	46.53 / 46.45	3.17 / 3.25	9.05 / 9.03	263-265 (dec.)	90
4e	$C_{12}H_{10}N_2O_6S$	46.45 / 46.45	3.21 / 3.25	9.15 / 9.03	235-238 (dec.)	82
4f	$C_{11}H_{10}N_2O_4S$	49.60 / 49.62	3.90 / 3.79	10.50 / 10.52	254-258 (dec.)	83
4g	$C_{11}H_{10}N_2O_4S$	49.43 / 49.62	3.58 / 3.79	10.47 / 10.52	272-275 (dec.)	80
4h	$C_{14}H_{16}N_2O_4S$	54.68 / 54.53	5.22 / 5.23	9.20 / 9.08	200-203 (dec.)	30
4i	$C_{16}H_{20}N_2O_4S$	57.17 / 57.12	5.92 / 5.99	8.29 / 8.33	206-208 (dec.)	82
4j	$C_{13}H_{13}NO_5S$	52.81 / 52.87	4.35 / 4.44	4.73 / 4.74	198-201	60
4k	$C_{14}H_{15}NO_6S$	51.65 / 51.68	4.60 / 4.65	4.35 / 4.31	239-241 (dec.)	47
4l	$C_{13}H_{13}NO_4S$	55.97 / 55.90	4.73 / 4.69	4.97 / 5.01	212-215	68

All reactions were carried out in sulfuric acid or boron trifluoride etherate, i.e., the acid and etherate were used as both catalysts and as reaction media. In the case of the basic aldehydes (R = *p*-$C_6H_4NMe_2$, *p*-$C_6H_4NEt_2$, 3-Py, 4-Py) this facilitated the appearance of the catalytic effect by neutralization of their basicity.

The syntheses were carried out at room temperature by simple mixing of the reagents in the following order: the aldehyde was added to a mixture of compound **1** or **2** in sulfuric acid or boron trifluoride etherate. When the reaction mixture was heterogeneous it was subjected to intense stirring. As a rule a precipitate of the

product appeared after 4h to 10 d, it was filtered off and was treated with $NaHCO_3$ solution. If a precipitate did not occur after prolonged standing or appeared in only small amounts, it was either precipitated with diglyme or absolute ether or it was isolated after neutralization with excess $NaHCO_3$.

In sulfuric acid the reaction proceeded sufficiently for isolation of the reaction products only with pyridinealdehydes, nitro- and amino-substituted benzaldehydes, i.e. in those cases in which the aryl substituent in the aldehyde itself possessed strong acceptor properties (*p*-$C_6H_4NO_2$, *m*-$C_6H_4NO_2$), or acquired them by protonation of the substituent (*p*-$C_6H_4NMe_2$, *m*-$C_6H_4NEt_2$), or of the hetaryl ring (3-Py, 4-Py). With the remaining benzaldehydes the electrophilicity of carbonyl carbon with respect to the protonic acid is evidently insufficient for condensation with the alcohol, however when a Lewis acid was used – boron trifluoride etherate – the reaction proceeded with acceptable yields.

The acid-base properties of the heterocyclic fragment of the diol (for compound **1** pK_a of the conjugate acid is probably close to the pK_a of 2-amino-2-thiazolinone, ~2.1[4]; the estimated value of the pK_a of the acid ionization for compound **2**, based on potentiometric titration with aqueous base, is ~6.0) probably do not affect the reaction under the reaction conditions, and the other diols can condense with aromatic and heteroaromatic aldehydes in any case.

Because of the high acidity of compound **2** the amino-substituted benzaldehydes form salts with it which are difficult to dissolve and make it difficult to separate the reaction products. We observed a similar difficulty for these aldehydes in carrying out the reaction with boron trifluoride etherate, evidently because of formation of poorly soluble complexes with the etherate. In all these cases sulfolan was added to homogenize the reaction mixture. A similar method was used to obtain derivatives of veratraldehyde (3,4-dimethoxybenzaldehyde) which apparently also forms a poorly soluble complex with boron trifluoride etherate.

Compounds **3a-l** and **4a-l** are high melting crystalline compounds, which im most cases decompose on melting (Table 1), the composition and structure of which were determined *via* spectroscopic data (Table 2).

The characteristic signals in the ^{1}H NMR spectra of compounds **3a-l** and **4a-l** are found in narrow ranges of chemical shifts. Thus the proton signals for the NH_2 groups in compounds **3** fall in the range 9.1-8.9, while those for the NH groups in compounds **4** fall in the range 12.4-12.1 ppm. The signals for proton H-2 of the 1,3-dioxane rings are found in the range 6.0-5.5, and those of H-4 and H-6 in the range 4.5-4.2 ppm for all of the compounds **3** and **4**. As a rule the signals of the protons H-4 and H-6 are split into a geminal AB quartet, but in the spectra of compounds **4b,d,** and **l** these signal are singlets.

In the ^{1}H NMR spectra of compounds **3g** and **4g** two sets of proton signals were observed. On the basis of the pattern of the spectrum, the integrated intensities of the observed signals, and the elemental analyses, it can be concluded that these are individual compounds, nut which exist under the conditions of recording the spectra as a mixture of two geometric isomers in the ratios of 2.9:1 and 9:1 respectively, which probably differ in the conformation of the dioxane rings.

EXPERIMENTAL

IR spectra of KBr disks were recorded on UR-20 spectrometer. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS internal standard were recorded on Bruker AC-200 (200 MHz) (compound **4b**), Bruker AM-300 (300 MHz) (compounds **3a,c-h,j-l, 4a,c-g,k,l**), and Bruker AM-500 (500 MHz) (**3b,i, 4h-j**) instruments. TLC was carried out on Silufol UV-254 strips with 5:1 benzene–2-propanol as eluent.

2-Amino-5,5-bis(hydroxymethyl)-4-thiazolinone (1) and **5,5-bis(hydroxymethyl)thiazolidine-2,4-dione (2)** were prepared by a previousl described method [3].

TABLE 2. Spectroscopic Characteristics of Compounds **3a-l** and **4a-l**

Com-pound	IR spectrum, ν, cm^{-1}		^1H NMR spectrum, δ, ppm					
	C=O	C=N	NH	Ph(Py), m	C(2)H, s	$C(4(6))H_A$*	$C(4(6))H_B$*	R
1	2	3	4	5	6	7	8	9
3a	1680	1650	9.2, 9.0	7.4*[2]	5.8	4.4	4.2	—
3b	1675	1640	9.2, 9.0	7.8-7.2	6.0	4.4	4.2	—
3c	1675	1650	9.0	8.1-7.0	5.8	4.4	4.2	—
3d	1690	1650	9.1, 9.0	8.3, 7.7	6.0	4.5	4.2	—
3e	1700	1670	9.2, 8.9	8.3-7.6	5.9	4.5	4.2	—
3f	1690	1650	9.2, 8.9	8.6, 7.8, 7.4	5.9	4.5	4.2	—
3g*[3]	1660	1620	9.2 (1+2), 8.9 (1), 8.8 (2)	8.64 (2), 8.57 (1), 7.43 (2), 7.39 (1)	5.9 (2), 5.8 (1)	4.5 (1), 4.2 (2)	4.2 (1), 4.0 (2)	—
3h	1700	1650	9.1, 8.9	7.2, 6.6	5.6	4.4	4.1	2.9, s
3i	1700	1625	9.0, 8.8	7.2, 6.6	5.5	4.4	4.1	3.4, q*[4]; 1.2, t*[5]
3j	1665	1620	9.1, 8.9	7.3, 6.9	5.7	4.4	4.2	3.8, s
3k	1670	1640	9.1, 8.9	7.0-6.8	5.6	4.4	4.1	3.8, s
3l	1690	1650	9.1, 8.9	7.3, 7.2	5.7	4.4	4.1	2.3, s
4a	1770, 1690	1640	12.2	7.4*[2]	5.7	4.5	4.4	—

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9
4b	1760, 1715	1610	12.4	7.4-7.6	6.0	4.5*[2]		—
4c	1760, 1710	1615	12.2	7.3-7.7	5.7	4.4	4.3	—
4d	1750, 1700	1620	12.2	8.2, 7.7	6.0	4.5*[2]		—
4e	1750, 1700	1630	12.2	8.2, 7.8, 7.7	5.9	4.6	4.4	—
4f	1790, 1710	1610	12.2 (1+2)	8.8-7.3	5.8	4.5	4.4	—
4g*[3]	1750, 1710	1620	12.2 (1), 12.0 (2)	8.59 (1+2), 7.44 (2), 7.37 (1)	5.8 (1), 5.7 (2)	4.5 (1), 4.4 (2)	4.4 (1), 4.2 (2)	—
4h	1750, 1710	1625	12.2	7.2, 6.6	5.5	4.4	4.4	3.0, s
4i	1760, 1700	1630	12.1	7.2, 6.6	5.5	4.4	4.3	3.4, q*[4]; 1.1, t*[5]
4j	1775, 1700	1630	12.3	7.3, 6.9	5.7	4.5	4.4	3.8, s
4k	1755, 1710	1615	12.2	7.0-6.8	5.6	4.5	4.4	3.8, s
4l	1750, 1700	1620	12.2	7.3, 7.2	5.7	4.4*[2]		2.3, s

* Protons H-4, H-6 absorb as a geminal AB quartet. From the chemical shifts of H_A and H_B, J^{gem}_{AB} = 11 Hz.

*[2] Singlet signal.

*[3] In the ^{1}H NMR spectra there are two sets of signals, corresponding to two conformers, a major (1) and a minor (2).

*[4] Signal of methylene protons.

*[5] Signal of methyl protons.

2'-Amino-2-phenylspiro[(1,3-dioxane)-5,5'-thiazolin]-4'-one (3a). Benzaldehyde (0.69 g, 0.66 ml, 6.5 mmol) was added with stirring to a mixture of the monohydrate of compound **1** (1.0 g, 5.1 mmol) and boron trifluoride etherate (2 ml). The initial compound **1** dissolved partially and then a new precipitate appeared and the reaction mixture thickened by degrees. After dilution with an equal volume of absolute ether, stirring was continued for 10 h, the solid was then filtered off, washed with absolute ether, treated with 10% aqueous $NaHCO_3$, and washed with water.

Compounds 3b, c, j, and l were obtained analogously from compound **1** and *o*-chlorobenzaldehyde, *m*-bromobenzaldehyde, *p*-methoxybenzaldehyde, and *p*-methylbenzaldehyde respectively.

2'-Amino-2-(3-nitrophenyl)spiro[(1,3-dioxane)-5,5'-thiazolin]-4'-one (3e). *m*-Nitrobenzaldehyde (3.2 g, 21.2 mmol) was added to a solution of compound **1** (4.0 g, 20.6 mmol) in sulfuric acid (12 ml). The reaction mixture was diluted over 2 d with 1.5 volumes of absolute ether and then kept in a refrigerator for a week. The precipitate was filtered off, washed with diglyme, treated with 10% aqueous $NaHCO_3$, and washed with water.

Compound 3d was obtained analogously from compound **1** and *p*-nitrobenzaldehyde.

2'-Amino-2-(3-pyridyl)spiro[(1,3-dioxane)-5,5'-thiazolin]-4'-one (3f). 3-Pyridinecarbaldehyde (3.7 g, 3.3 ml, 34.5 mmol) was added to a mixture of compound **1** (6.8 g, 35.0 mmol) and sulfuric acid (12 ml). After 4 d the reaction mixture was poured into 10% aqueous $NaHCO_3$ (350 ml). After evolution of CO_2 had ceased, the precipitate which formed was filtered off and washed with water.

Compounds 3g (from compound **1** and the hydrate of 4-pyridinecarbaldehyde), **4f** (from compound **2** and 3-pyridinealdehyde), and **4g** (from compound **2** and the hydrate of 4-pyridinecarbaldehyde) were prepared analogously.

2'-Amino-2-(4-dimethylaminophenyl)spiro[(1,3-dioxane)-5,5'-thiazolin]-4'-one (3h). *p*-Dimethylaminobenzaldehyde (1.4 g, 9.4 mmol) was added to a solution of compound **1** (2.0 g, 10.3 mmol) in sulfuric acid (3 ml). After 4-5 d a precipitate formed an additional amount of which was formed by diluting the reaction mixture with diglyme. After standing for 4 d in the refrigerator, the precipitate was filtered off, washed with diglyme, treated with 10% aqueous $NaHCO_3$ until evolution of CO_2 ceased, filtered again, boiled with a mixture of 10% aqueous $NaHCO_3$ (10 ml) and *i*-PrOH (10 ml) for 30 min, filtered hot and washed with water.

2'-Amino-2-(4-diethylaminophenyl)spiro[(1,3-dioxane)-5,5'-thiazolin]-4'-one (3i). *p*-Diethylaminobenzaldehyde (1.5 g, 8.5 mmol) was added to a solution of compound **1** (2.0 g, 10.3 mmol) in sulfuric acid (3 ml). After 3 days the reaction mixture was poured into 10% aqueous $NaHCO_3$ (100 ml), the precipitate was filtered off and recrystallized from ethanol.

2-Phenylspiro[(1,3-dioxane)-5,5'-thiazolidine]-2',4'-dione (4a). Benzaldehyde (0.69 g, 0.66 ml, 6.5 mmol) was added to an intensely stirred mixture of compound **2** (1.0 g, 5.6 mmol) and boron trifluoride etherate (2 ml). Along with the dissolution of compound **2**, the gradual formation of a new precipitate was observed. After 2h stirring the reaction mixture was diluted with an equal volume of absolute ether, stirring was continued for a further 10 h, the precipitate formed was filtered off, washed with absolute ether, treated with 10% aqueous $NaHCO_3$, and washed with water.

Compounds 4b,c,j, and **l** were obtained analogously to compound **4a** from compound **2** and *o*-chlorobenzaldehyde, *m*-bromobenzaldehyde, *p*-methoxybenzaldehyde, and *p*-methylbenzaldehyde respectively.

2-(4-Nitrophenyl)spiro[(1,3-dioxane)-5,5'-thiazolidine]-2',4'-dione (4d). *p*-Nitrobenzaldehyde (3.2 g, 21.2 mmol) was added to a mixture of compound **2** (4.0 g, 22.6 mmol) and sulfuric acid (12 ml). After 2 d the reaction mixture was diluted with 1.5 volumes of diglyme and kept in the refrigerator for a week. The precipitate was filtered off, washed with diglyme, treated with 10% aqueous $NHCO_3$, and washed with water.

Compound 4e was prepared analogously from compound **2** and *m*-nitrobenzaldehyde.

2-(4-Diethylaminophenyl)spiro[(1,3-dioxane)-5,5'-thiazolidine]-2',4'-dione (4i). Boron trifluoride etherate (8 ml) and compound **2** (1.7 g, 9.6 mmol) were added to a solution of *p*-dimethylaminobenzaldehyde in sulfolane (10 ml). The reaction mixture was shaken periodically and compound **2** dissolved progressively. After

10 d the reaction mixture was poured into 10% aqueous $NaHCO_3$ (100 ml), the precipitate was filtered off and washed successively with water and ethanol.

Compound 4h was obtained from compound **2** and *p*-dimethylaminobenzaldehyde analogously.

2-(3,4-Dimethoxyphenyl)spiro[(1,3-dioxane)-5,5'-thiazolidine]-2',4'-dione (4k). Boron trifluoride etherate (6 ml) and compound **2** (3.0g, 16.9 mmol) were added successively with stirring to a solution of 3,4-dimethoxybenzaldehyde (2.8 g, 16.8 mmol) in sulfolane (30 ml). Stirring was continued until compound **2** had dissolved. After 4 h the reaction mixture was poured into 10% aqueous $NaHCO_3$ (100 ml). The precipitate was filtered off and washed successively with water and ethanol.

Compound 3k was obtained analogously from compound **1** and 3,4-dimethoxybenzaldehyde.

All of the precipitated compounds were dried initially in air and then in vacuum to constant weight.

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REFERENCES

1. K. Buler and D. Pearson. *Organic Syntheses* [Russian translation], Mir, Moscow (1973), **1**, p. 582.
2. S. M. Ramsh and A. G. Ivanenko. *Khim. Geterotsikl. Soed.,* 1743 (2003).
3. S. M. Ramsh, N. A. Smorygo, and A. I. Ginak. *Khim. Geterotsikl. Soed.,* 1066 (1984).