Synthesis of *N*-(2-hydroxyalkyl)-4-thiazolidinones from oxazolidines

B. F. Kukharev, V. K. Stankevich, and G. R. Klimenko*

Irkutsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 ul. Favorskogo, 664033 Irkutsk, Russian Federation. Fax: 007 (395 2) 35 6046

The reaction of oxazolidines with mercaptoacetic acid affords *N*-(2-hydroxyalkyl)-4-thiazolidinones in 58—87% yield regardless of the position of the oxazolidine—iminoalcohol tautomeric equilibrium. The structures of the resulting compounds were confirmed by IR and ^{1}H NMR spectroscopy.

Key words: oxazolidines, mercaptoacetic acid, *N*-(2-hydroxyalkyl)-4-thiazolidinones.

The reaction of Schiff's bases with mercaptoacetic acid is one of the methods for the preparation of 4-thiazolidinones.[1,2]

It is known that *N*-unsubstituted oxazolidines exist in the tautomeric equilibrium with iminoalcohols.[3—7] This fact suggests that 4-thiazolidinones can be also obtained by the reaction of oxazolidines with mercaptoacetic acid.

We have studied the reaction of mercaptoacetic acid with a number of oxazolidines that contain different amounts of the tautomeric iminoalcohol form (Scheme 1).

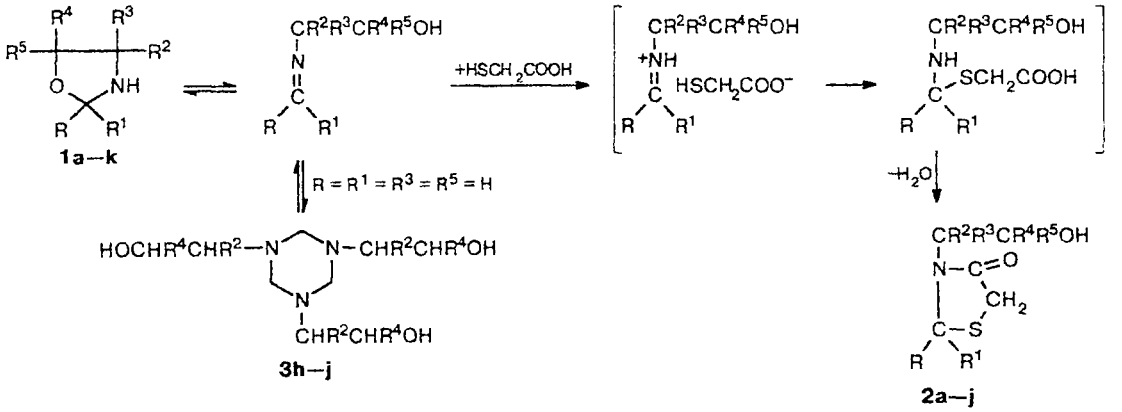
The reaction was carried out by boiling an equimolar mixture of the reagents in benzene with azeotropic distillation of water. Elimination of the calculated amount of water and homogenization of the reaction mixture served as the criteria of completion of the reaction.

In the case of 2,2-, 2,2,4-, and 2,2,5-substituted oxazolidines, which contain only alkyl substituents, the equilibrium constant K = [oxazolidine]/[iminoalcohol] (in nonpolar aprotic solvents) varies (according to the published data[4—6]) from 2 to 30. Judging from the intensity of the absorption band at 1630—1650 cm^{-1} in the IR spectra, the concentration of the imino form in oxazolidines (**1a—e**) used did not exceed 5—10%. These oxazolidines reacted with mercaptoacetic acid to form thiazolidinones (**2a—e**) in yields of 56—69%.

The reaction of mercaptoacetic acid with compound **1f**, which (according to the literature data[7]) contains no less than 90% of the acyclic form, gave thiazolidinone **2f** in 60% yield.

The reaction of mercaptoacetic acid with 4,4-dimethyloxazolidine (**1k**) yielded a salt. Further heating of the reaction mixture resulted in substantial

Scheme 1



a: R + R^1 = (CH$_2$)$_5$, R^2 = R^3 = R^4 = R^5 = H; **b:** R + R^1 = (CH$_2$)$_5$, R^2 = R^3 = R^4 = H, R^5 = Me; **c:** R + R^1 = (CH$_2$)$_6$, R^2 = R^3 = R^4 = R^5 = H; **d:** R = Me, R^1 = Bu, R^2 = R^3 = R^4 = R^5 = H; **e:** R = R^2 = R^3 = R^5 = H, R^1 = Pr^i, R^4 = CH$_2$OMe; **f:** R = R^2 = R^3 = R^4 = R^5 = H, R^1 = Ph; **g:** R = R^1 = R^2 = R^3 = H, R^4 = R^5 = Me; **h:** R = R^1 = R^2 = R^3 = R^4 = R^5 = H; **i:** R = R^1 = R^2 = R^3 = R^5 = H, R^4 = Me; **j:** R = R^1 = R^3 = R^4 = R^5 = H, R^2 = Et; **k:** R = R^1 = R^3 = R^5 = H, R^2 = R^3 = Me

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Table 1. Yields and characteristics of 4-thiazolidinones **2a—j**

Compound	Yield (%)	B.p./°C (*p*/Torr)	M.p. /°C	n_D^{20}	d_4^{20}	Found / Calculated (%) C	H	N	S	Molecular formula
2a	62	209—211 (3)	87—88			55.34 55.78	8.03 7.96	6.78 6.50	14.95 14.89	$C_{10}H_{17}NO_2S$
2b	66	191—196 (3)	48—50			57.77 57.65	8.14 8.35	6.09 6.12	13.57 13.98	$C_{11}H_{19}NO_2S$
2c	58	211—215 (3)		1.5422	1.1631	57.34 57.65	8.18 8.35	6.21 6.12	14.12 13.98	$C_{11}H_{19}NO_2S$
2d	56	190—191 (4)		1.5280	1.1218	55.62 55.27	8.78 8.81	6.31 6.44	14.77 14.75	$C_{10}H_{19}NO_2S$
2e	69	182—185 (10)	43—44	1.5122[a]	1.1579[a]	51.23 51.48	8.33 8.21	5.89 6.00	13.91 13.74	$C_{10}H_{19}NO_3S$
2f	60	201—203 (4)		1.6005	1.2662	59.22 59.17	5.41 5.87	6.15 6.27	14.72 14.36	$C_{11}H_{13}NO_2S$
2g	84	145—147 (3)	89—90			48.12 47.98	7.30 7.48	7.71 7.99	18.23 18.30	$C_7H_{13}NO_2S$
2h	63	182—185 (4)	63—64			41.03 40.80	6.38 6.16	9.20 9.52	21.59 21.78	$C_5H_9NO_2S$
2i	85	163—165 (5)		1.5392	1.2552	44.41 44.70	6.69 6.88	8.97 8.69	19.52 19.89	$C_6H_{11}NO_2S$
2j	87	174—176 (5)		1.5330	1.2258	47.67 47.98	7.56 7.48	7.80 7.99	18.55 18.30	$C_7H_{13}NO_2S$

[a] Determined for a supercooled liquid.

Table 2. Data of IR and ^{1}H NMR spectroscopy for 4-thiazolidinones **2a—j**

Compound	IR, ν/cm^{-1}	^{1}H NMR ($CDCl_3$), δ (*J*/Hz)
2a	1630 (C=O); 3420 (OH)	1.08—1.79 (m, 10 H, $(CH_2)_5$); 3.44 (t, 2 H, NCH_2); 3.50 (s, 2 H, SCH_2CO); 3.74 (t, 2 H, OCH_2); 4.00 (br.s, 1 H, OH) (at 60 °C t)
2b	1640 (C=O); 3430 (OH)	1.20 (d, 3 H, Me); 1.20—1.77 (m, 10 H, $(CH_2)_5$); 3.16—3.46 (m, 2 H, NCH_2); 3.51 (s, 2 H, SCH_2CO); 3.96 (m, 1 H, OCH); 4.11 (br.s, 1 H, OH)
2c	1650 (C=O); 3350 (OH)	1.52—1.90 (m, 12 H, $(CH_2)_6$); 3.49 (t, 2 H, NCH_2); 3.62 (s, 2 H, SCH_2CO); 3.72 (t, 2 H, OCH_2); 4.12 (br.s, 1 H, OH)
2d	1650 (C=O); 3300 (OH)	0.90—0.98 (m, 6 H, 2 Me); 1.30—1.58 (m, 6 H, $(CH_2)_3$); 3.18 (m, 2 H, NCH_2); 3.38 (br.s, 1 H, OH); 3.55 (s, 2 H, SCH_2CO); 3.82 (m, 2 H, OCH_2)
2e	1660 (C=O); 3350 (OH)	0.84 and 0.93 (both d, 6 H, CMe_2); 2.33 (m, 1 H, $CHMe_2$); 3.36 (s, 3 H, OMe); 3.20—3.42 (m, 2 H, NCH_2); 3.49 (s, 2 H, SCH_2CO); 3.70 (m, 2 H, OCH_2); 3.92 (m, 1 H, OCH); 4.09 (br.s, 1 H, OH); 4.84 (d, 1 H, SCHN, ^3J = 2.4)
2f	1485, 1500 (Ph); 1650 (C=O); 3020, 3050 (=CH); 3380 (OH)	3.47—3.61 (m, 4 H, NCH_2CH_2O); 3.69 (s, 2 H, SCH_2CO); 4.10 (br.s, 1 H, OH); 5.83 (s, 1 H, SCHN); 7.29 (s, 5 H, Ph)
2g	1635 (C=O); 3700 (OH)	1.22 (s, 6 H, 2 Me); 3.34 (s, 2 H, NCH_2); 3.40 (br.s, 1 H, OH); 3.55 (s, 2 H, SCH_2CO); 4.61 (s, 2 H, SCH_2N)
2h	1630 (C=O); 3300 (OH)	3.49 (t, 2 H, NCH_2); 3.56 (d, 2 H, SCH_2CO, ^4J = 1.4); 3.76 (t, 2 H, OCH_2); 3.93 (br.s, 1 H, OH); 4.54 (d, 2 H, SCH_2N, ^4J = 1.4)
2i	1650 (C=O); 3380 (OH)	1.20 (d, 3 H, Me); 3.28—3.40 (m, 2 H, NCH_2); 3.57 (s, 2 H, SCH_2CO); 3.98 (br.s, 1 H, OH); 4.05 (m, 1 H, OCH); 4.55 (s, 2 H, SCH_2N)
2j	1650 (C=O); 3380 (OH)	0.91 (t, 3 H, Me); 1.58 (m, 2 H, CCH_2C); 3.48 (m, 1 H, NCH); 3.58 (s, 2 H, SCH_2CO); 3.68 (br.s, 1 H, OH); 3.92 (m, 2 H, OCH_2); 4.30 and 4.52 (both d, 2 H, SCH_2N, AB system)

resinification of this salt, which was accompanied by partial elimination of water (~30% of the calculated amount), but the expected thiazolidinone was not found among the reaction products.

This result could be attributed to the fact that because of the *gem*-dimethyl effect in oxazolidine **1k**, the concentration of the tautomeric iminoalcohol is very low (in the IR spectrum, the absorption band of the C=N bond is virtually absent). However, if this is the case, it is difficult to explain why 5,5-dimethyloxazolidine (**1g**), which also exists only in the cyclic form, reacts readily with mercaptoacetic acid to form thiazolidinone **2g** in high yield (84%). Apparently, thiazolidinone was not formed from compound **1k** because of steric hindrances caused by the ring closure.

It is known that 2- and 3-unsubstituted oxazolidines (**1h—j**) undergo trimerization to form perhydrotriazines (**3h—j**) along with tautomeric conversion into iminoalcohols, while oxazolidine **1h** occurs (under ordinary conditions) only as a trimer.[8] However, when these oxazolidines (perhydrotriazines) were used in the reaction, 4-thiazolidinones (**2h—j**) were also obtained in high yields.

Therefore, oxazolidines can be used in the preparative synthesis of *N*-(2-hydroxyalkyl)-4-thiazolidinones no matter what form (imino or trimeric) predominates.

Experimental

The ^{1}H NMR spectra were recorded on a JEOL FX-90Q instrument (90 MHz, HMDS as the internal standard) at 30 °C. The IR spectra were obtained on a Specord 75-IR spectrophotometer in a thin layer (for liquids) and as KBr pellets (for solid compounds).

The purity of the compounds was monitored by GLC on an LKhM-80 chromatograph (katharometer as the detector; helium as the carrier gas; a stainless steel 3000×3-mm column packed with 3% OV-17 on Inerton super (0.160—0.200 mm)) with heating from 90 to 260 °C at a rate of 4 K min^{-1}.

The initial oxazolidines were prepared by condensation of aminoalcohols and carbonyl compounds according to known procedures.[6,9]

General procedure for the preparation of thiazolidinones 1a—j. Mercaptoacetic acid (0.1 mol) was added to a solution of oxazolidine **1a—j** (0.1 mol) in benzene (100 mL), and the reaction mixture was boiled with a Dean—Stark trap until liberation of water ceased. Then the reaction mixture was cooled. Thiazolidinones **2a—j** were isolated by distillation *in vacuo*. The yields and characteristics of the resulting compounds are listed in Table 1. The data of IR and ^{1}H NMR spectroscopy are given in Table 2.

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