[Chem. Pharm. Bull.]
[34(1) 380-384 (1986)]

The Reaction of 1,3-Disubstituted Thioureas with α,ω -Dibromoacyl Chlorides and the Formation of Spiro Compounds

TADASHI OKAWARA, KENTARO NAKAYAMA, TETSUO YAMASAKI,
and MITSURU FURUKAWA*

*Faculty of Pharmaceutical Sciences, Kumamoto University,
Oe-honmachi, Kumamoto 862, Japan*

(Received April 1, 1985)

5-Bromoalkyl-2-iminothiazolidin-4-ones (**3**) were readily synthesized from 1,3-disubstituted thioureas (**1**) and α,ω -dibromoacyl chlorides (**2**) in 5% NaOH-CH₂Cl₂. Compounds **3** were converted to the corresponding spiro compounds **9** under phase-transfer conditions or with sodium ethoxide.

Keywords—1,3-disubstituted thiourea; α,ω -dibromoacyl chloride; 5-bromoalkyl-2-iminothiazolidin-4-one; 2-iminothiazolidine-5-spirocycloalkan-4-one; dicyclopropyl disulfide; cyclization; phase-transfer catalyst

Although syntheses of heterocyclic compounds by reactions of thioureas with a variety of carboxylic acids, carboxylic esters, and aliphatic halides have been widely investigated,¹⁾ no study on the reaction with haloacyl halides has been reported. We recently found that α -haloacyl halides and dichloroacetyl chloride readily reacted with 1,3-disubstituted thioureas under basic conditions to give 2-iminothiazolidin-5-ones²⁾ and their dimers,³⁾ respectively, and that the reaction of β -haloacyl halides with 1,3-disubstituted and monosubstituted thioureas gave tetrahydrothioxopyrimidines or thiazines⁴⁾ and *N*-thioamindo- β -lactams,⁵⁾ respectively.

We report here the syntheses of 5-bromoalkyl-2-iminothiazolidin-4-ones (**3**) and 2-iminothiazolidine-5-spirocycloalkan-4-ones (**9**) by the reaction of 1,3-disubstituted thioureas (**1**) with α,ω -dibromoacyl chlorides (**2**) in 5% NaOH-CH₂Cl₂. The reaction was suc-

Chart 1

TABLE I. 5-Bromoalkyl-2-iminothiazolidin-4-ones (3)

3	n	R ¹	R ²	mp (°C)	Yield (%)
a	2	Ph	PhCH ₂	81—82	68
b	2	Ph	CH ₃	131—132	79
c	2	Ph	Ph	102—103	95
d ^{a)}	2	PhCH ₂	CH ₃	73—74	43
e	3	Ph	PhCH ₂	73	71
f	3	Ph	CH ₃	104—105	75
g	3	Ph	Ph	123	82
h ^{a)}	3	PhCH ₂	CH ₃	74—75	38
i	4	Ph	PhCH ₂	96—97	70
j	4	Ph	CH ₃	71—72	65
k	4	Ph	Ph	89—90	94
l ^{a)}	4	PhCH ₂	CH ₃	52—53	31

a) Purified by silica-gel column chromatography (CHCl₃).

cessfully carried out by slowly adding **2** to a stirred solution of **1** in 5% NaOH-CH₂Cl₂, followed by stirring for 8 h at room temperature to afford **3** in 29—95% yields. The results are summarized in Table I. Similar results were also obtained by using sat. NaHCO₃-CH₂Cl₂ instead of 5% NaOH-CH₂Cl₂.

In this reaction, there is a possibility that not only thiazolidin-4-ones (**3**) but also thiazolidin-5-ones (**4**) might be formed. The infrared (IR) spectra of the products showed carbonyl and imino absorptions at 1720—1730 and 1625—1650 cm⁻¹, respectively. In order to discriminate between **3** and **4**, the product **3** (R¹=R²=Ph, n=3) obtained from 1,3-diphenylthiourea (**1**) (R¹=R²=Ph) and α,δ-dibromopentyl chloride (**2**, n=3) was hydrolyzed under reflux in 15% NaOH-EtOH. As a result, 1,3-diphenylurea (**6**) and 2-thiacyclohexanecarboxylic acid (**8**), which was formed *via* 5-bromo-2-mercaptopentanoic acid (**7**) under alkaline conditions, were obtained. This result supports the structural assignment of the product as **3**.

Moreover, the formation of another isomeric compound **5** along with **3** is also possible. When the combination of R¹ and R² groups was CH₃ and PhCH₂, the proton nuclear magnetic resonance (¹H-NMR) spectra of the crude products in the reaction with **2** (n=2,4) showed methyl signals of **3** and **5** at 3.29—3.39 and 3.17—3.19 ppm, and of the benzyl methylene groups of **3** and **5** at 4.48—4.56 and 4.83—4.94 ppm, respectively, in the ratio of 54—56:46—44. The combinations of other substituents did not show ¹H-NMR signals corresponding to the isomer **5**. These results suggest that the reaction proceeds *via* the initial attack of acyl halide on the electron-rich nitrogen, followed by cyclization at the enolic sulfur.⁴⁾

Next, cyclization of **3** to the spiro compounds **9** was carried out under phase-transfer conditions. In the case of n=2, the corresponding spirocyclopropane compounds **9** were obtained in 51—92% yields. However, in the cases of n=3 and 4, similar ring closure did not occur under these conditions. The treatment of compound **3** (n=3) with NaOEt-EtOH or NaH-dioxane also did not give the spiro compound, but the treatment of **3** (n=4) with NaOEt-EtOH under reflux gave the corresponding spirocyclopentane compounds **9** (n=4) in 54—69% yields. The results are summarized in Table II.

The one-pot reaction of **1** with **2** (n=2) under phase-transfer conditions in 5% NaOH-CH₂Cl₂ in the presence of benzyltriethyl-ammonium chloride readily provided the spiro compounds **9** (n=2) in fairly good yields.

The ¹H-NMR spectrum of **9** (n=2) showed typical cyclopropane signals at 1.33—

Chart 2

TABLE II. 2-Iminothiazolidine-5-spirocycloalkan-4-ones (9)

9	R ¹	R ²	n	Condition	mp (°C)	Yield (%) ^{c)}
a	C ₆ H ₅	C ₆ H ₅ CH ₂	2	5% NaOH-CH ₂ Cl ₂ , BTEAC ^{b)}	131—132	51
b	C ₆ H ₅	CH ₃	2	5% NaOH-CH ₂ Cl ₂ , BTEAC	115—117	57
c	C ₆ H ₅	C ₆ H ₅	2	5% NaOH-CH ₂ Cl ₂ , BTEAC	154—155	92
d ^{a)}	C ₆ H ₅	C ₆ H ₅	4	NaOEt-EtOH	105—106	54
e ^{a)}	C ₆ H ₅	C ₆ H ₅ CH ₂	4	NaOEt-EtOH	83—84	69

a) Sodium ethoxide as a base was used in the formation of the spiro compound. b) BTEAC: benzyltriethylammonium chloride. c) The yields were calculated on the basis of the 5-bromoalkyl compounds (3).

1.77 ppm. All the spiro compounds **9** ($n=2$) gave satisfactory data in the ¹H-NMR, mass (MS), and IR spectra and elemental analyses.

Further applications to the synthesis of other heterocyclic compounds are being investigated.

Experimental

All the melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded with a JASCO IRA-1 grating infrared spectrometer. ¹H-NMR spectra were determined with a JEOL 60 MHz high-resolution NMR instrument. MS were measured with a JEOL 01 SG mass spectrometer.

1,3-Disubstituted Thioureas (1)—These compounds were prepared from isothiocyanates and amines in fairly good yields.^{4,6)}

Dibromoacyl Chlorides (2)—Dibromocarboxylic acids were prepared from the corresponding lactones and bromine according to Phillips and Cromwell's method.⁷⁾ The resulting acids were converted to **2** by refluxing with SOCl₂.⁸⁾

General Procedure for 5-(ω-Bromoalkyl)thiazolidin-4-ones (3)—Dibromoacyl chloride **2** (5 mmol) was added dropwise to a vigorously stirred solution of 1,3-disubstituted thiourea **1** (5 mmol) in 5% NaOH (12 ml)-CH₂Cl₂ (20 ml) under cooling with ice-water. After the addition was over, the reaction mixture was stirred for 12 h at room temperature. The CH₂Cl₂ layer was separated, washed with H₂O (10 ml × 2), dried over anhydrous MgSO₄ and evaporated to dryness. The residue was purified by recrystallization from EtOH or by silica-gel column chromatography (CHCl₃). The IR, ¹H-NMR and MS spectral data, and elemental analyses are listed in Table III.

Hydrolysis of 5-(3-Bromopropyl)-3-phenyl-2-phenyliminothiazolidin-4-one (3) (R¹ = R² = Ph, $n=3$)—A solution of **3g** (0.98 g, 2.43 mmol) in 15% NaOH (5 ml) and EtOH (20 ml) was refluxed for 6 h. After removal of EtOH, the separated diphenylurea was filtered off and the filtrate was extracted with Et₂O (15 ml × 2). The extracts were evaporated to yield diphenylurea (**6**). The alkaline filtrate was acidified with 6N HCl and extracted with Et₂O (10 ml × 3). The ethereal extract was dried over anhydrous MgSO₄ and evaporated to dryness to afford the oily 2-thiacyclohexanecarboxylic acid (**8**). Yield 0.16 g (44%). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1710 (C=O). MS (m/z): 146 (M⁺). ¹H-NMR (δ) (CDCl₃): 1.00—2.32 (6H, m, -(CH₂)₃-), 2.32—3.17 (2H, m, CH₂-CHCOOH), 3.40—3.73 (1H, m, CH), 10.3 (1H, s, COOH).

3-Substituted 2-Iminothiazolidine-5-spirocyclopropan-4-ones (9, $n=2$)—A solution of 5-(β-bromoethyl)-thiazolidin-4-one (**3**, $n=2$) (2 mmol) in 5% NaOH (5 ml), CH₂Cl₂ (10 ml), and benzyltriethylammonium chloride (20 mg) was stirred for 10 h. The CH₂Cl₂ layer was separated, washed with H₂O (10 ml × 2), dried over

TABLE III. 5-Bromoalkyl-2-iminothiazolidin-4-ones (3)

3	IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}	$^1\text{H-NMR}$ (δ) in CDCl_3	m/z (M^+)	Formula	Analysis (%)		
					Calcd	Found	
					C	H	N
a	1730 (C=O)	2.66 (2H, m, CH_2 , $J=6.0$ Hz)	388	$\text{C}_{18}\text{H}_{17}\text{BrN}_2\text{OS}$	55.54	4.40	7.20
	1630 (C=N)	3.63 (2H, m, CH_2 , $J=6.0$ Hz), 4.50 (1H, m, CH, $J=5.0$ Hz), 4.53 (2H, s, PhCH_2), 7.25 (5H, s, PhCH_2), 7.17—7.54 (5H, m, Ph)	400		(55.79)	4.37	(7.07)
b	1730 (C=O)	2.47 (2H, m, CH_2 , $J=6.0$ Hz)	312	$\text{C}_{12}\text{H}_{13}\text{BrN}_2\text{OS}$	46.01	4.18	8.94
	1650 (C=N)	3.12 (3H, s, CH_3), 3.52 (2H, s, CH_2), 4.27 (1H, q, CH, $J=5.0$ Hz), 7.07—7.50 (5H, m, Ph)	314		(46.55)	4.09	(8.76)
c	1725 (C=O)	2.60 (2H, m, CH_2)	374	$\text{C}_{17}\text{H}_{15}\text{BrN}_2\text{OS}$	54.41	4.03	7.46
	1630 (C=N)	3.57 (2H, m, CH_2 , $J=6.0$ Hz), 4.44 (1H, q, CH, $J=6.0$ Hz), 6.83—7.54 (10H, m, $\text{Ph} \times 2$)	376		(54.41)	3.88	(7.26)
d	1730 (C=O)	2.60 (2H, m, CH_2)	326	$\text{C}_{13}\text{H}_{15}\text{BrN}_2\text{OS}$	47.72	4.62	8.56
	1640 (C=N)	3.11 (3H, s, CH_3), 3.63 (2H, m, CH_2), 4.43 (1H, q, CH, $J=5.0$ Hz), 4.85 (2H, s, PhCH_2), 7.32 (5H, s, Ph)	328		(47.72)	4.45	(8.62)
e	1730 (C=O)	1.77—2.47 (4H, m, $\text{CH}_2 \times 2$)	402	$\text{C}_{19}\text{H}_{19}\text{BrN}_2\text{OS}$	56.58	4.75	6.95
	1640 (C=N)	3.08 (2H, m, CH_2), 4.23 (1H, m, CH), 4.50 (2H, s, PhCH_2), 7.23 (5H, s, PhCH_2), 7.20—7.49 (5H, m, Ph)	404		(56.85)	4.57	(7.26)
f	1730 (C=O)	1.80—2.43 (4H, m, $\text{CH}_2 \times 2$)	326	$\text{C}_{18}\text{H}_{15}\text{BrN}_2\text{OS}$	47.71	4.62	8.56
	1640 (C=N)	3.12 (3H, s, CH_3), 3.43 (2H, m, CH_2), 4.26 (1H, m, CH), 7.10—7.56 (5H, m, Ph)	328		(47.72)	4.64	(8.88)
g	1730 (C=O)	1.75—2.37 (4H, m, $\text{CH}_2 \times 2$)	388	$\text{C}_{18}\text{H}_{17}\text{BrN}_2\text{OS}$	55.53	4.40	7.20
	1630 (C=N)	3.42 (2H, m, CH_2), 4.27 (1H, m, CH), 6.85—7.57 (10H, m, $\text{Ph} \times 2$)	390		(55.55)	4.37	(7.21)
h	1710 (C=O)	1.77—2.30 (4H, m, $\text{CH}_2 \times 2$)	340	$\text{C}_{14}\text{H}_{17}\text{BrN}_2\text{OS}$	49.27	5.02	8.21
	1650 (C=N)	3.22 (3H, s, CH_3), 3.40 (2H, m, CH_2), 4.12 (1H, m, CH), 4.50 (2H, s, PhCH_2), 7.33 (5H, s, Ph)	342		(48.98)	4.92	(8.18)
i	1730 (C=O)	1.66—2.27 (6H, m, $\text{CH}_2 \times 3$)	416	$\text{C}_{20}\text{H}_{21}\text{BrN}_2\text{OS}$	57.56	5.07	6.71
	1650 (C=N)	3.42 (2H, t, CH_2 , $J=6.0$ Hz), 4.23 (1H, m, CH), 4.53 (2H, s, PhCH_2), 7.24 (5H, s, PhCH_2), 7.20—7.48 (5H, m, Ph)	418		(57.46)	5.10	(6.71)
j	1730 (C=O)	1.63—2.33 (6H, m, $\text{CH}_2 \times 3$)	340	$\text{C}_{14}\text{H}_{17}\text{BrN}_2\text{OS}$	49.27	5.02	8.21
	1650 (C=N)	3.10 (3H, s, CH_3), 3.43 (2H, t, CH_2 , $J=6.0$ Hz), 4.23 (1H, m, CH), 7.13—7.51 (5H, m, Ph)	342		(49.29)	5.01	(8.40)
k	1720 (C=O)	1.66—2.32 (6H, m, $\text{CH}_2 \times 3$)	402	$\text{C}_{19}\text{H}_{19}\text{BrN}_2\text{OS}$	56.58	4.75	6.95
	1630 (C=N)	3.40 (2H, t, CH_2 , $J=6.0$ Hz), 4.23 (1H, m, CH), 6.83—7.50 (10H, m, $\text{Ph} \times 2$)	404		(57.02)	4.80	(6.89)
l	1705 (C=O)	1.43—2.13 (6H, m, $\text{CH}_2 \times 3$)	354	$\text{C}_{15}\text{H}_{19}\text{BrN}_2\text{OS}$	50.71	5.39	7.89
	1650 (C=N)	3.15 (3H, s, CH_3), 3.37 (2H, t, CH_2 , $J=6.0$ Hz), 4.10 (1H, m, CH), 4.87 (2H, s, PhCH_2), 7.30 (5H, s, Ph)	356		(50.91)	5.45	(7.63)

TABLE IV. Spectral Data for 2-Iminothiazolidine-5-spirocycloalkan-4-ones (9)

9	IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1}	$^1\text{H-NMR}$ (δ) in CDCl_3	m/z (M^+)	Formula	Analysis (%)		
					Calcd	Found	
					C	H	N
a	1735 (C=O)	1.37 (2H, m, CH_2)	308	$\text{C}_{18}\text{H}_{16}\text{N}_2\text{OS}$	71.10	5.23	9.08
	1640 (C=N)	1.77 (2H, m, CH_2), 4.25 (2H, s, CH_2), 7.27 (5H, s, Ph), 7.15—7.70 (5H, m, Ph)			(70.72)	5.20	8.99
b	1720 (C=O)	1.33 (2H, m, CH_2)	232	$\text{C}_{12}\text{H}_{12}\text{N}_2\text{OS}$	62.04	5.21	12.06
	1640 (C=N)	1.73 (2H, m, CH_2), 3.08 (3H, s, CH_3), 7.37 (5H, m, Ph)			(62.43)	5.25	11.83
c	1730 (C=O)	1.34 (2H, m, CH_2)	294	$\text{C}_{17}\text{H}_{14}\text{N}_2\text{OS}$	69.36	4.79	9.52
	1630 (C=N)	1.75 (2H, m, CH_2), 6.60—7.83 (10H, m, Ph $\times 2$)			(69.35)	4.81	9.35
d	1725 (C=O)	1.50—2.90 (8H, m, $\text{CH}_2 \times 4$)	322	$\text{C}_{19}\text{H}_{18}\text{N}_2\text{OS}$	70.78	5.63	8.69
	1625 (C=N)	6.55—7.83 (10H, m, Ph $\times 2$)			(71.12)	5.75	8.51
e	1725 (C=O)	1.52—2.66 (8H, m, $\text{CH}_2 \times 4$)	336	$\text{C}_{20}\text{H}_{20}\text{N}_2\text{OS}$	71.40	5.99	8.33
	1625 (C=N)	5.05 (2H, s, CH_2N), 6.85—7.67 (5H, m, Ph), 7.45 (5H, s, PhCH_2)			(71.71)	6.21	8.60

anhydrous MgSO_4 , and evaporated to dryness. The residue was recrystallized from EtOH or subjected to column chromatography on silica-gel with CHCl_3 as the eluant. The spectral data and elemental analyses are listed in Table IV.

3-Substituted 2-Phenyliminothiazolidine-5-spirocyclopentan-4-ones (9, $n=4$)—A solution of 5-(δ -bromobutyl)thiazolidin-4-one (3, $n=4$) (2 mmol) in EtONa–EtOH was refluxed for 6 h. After removal of EtOH, the residue was dissolved in CHCl_3 (70 ml), the insoluble part was filtered off, and the filtrate was washed with H_2O (10 ml $\times 2$), dried over anhydrous MgSO_4 , and evaporated to dryness. The residue was purified by column chromatography on silica-gel with CHCl_3 as the eluant. The spectral data and elemental analyses are listed in Table IV.

One-Pot Synthesis of 3-Phenyl-2-phenyliminothiazolidine-5-spirocyclopropan-4-one (9) ($\text{R}^1 = \text{R}^2 = \text{Ph}$, $n=2$)— α,γ -Dibromobutyryl chloride (2, $n=2$) (1.32 g, 5 mmol) was gradually added to a solution of diphenylthiourea (1, $\text{R}^1 = \text{R}^2 = \text{Ph}$) (1.14 g, 5 mmol) in 5% NaOH (8 ml)– CH_2Cl_2 (20 ml) under cooling with ice-water. After the addition was over, 5% NaOH (5 ml) and benzyltriethylammonium chloride (20 mg) were added to the reaction mixture, and the whole was stirred at room temperature for 12 h. The CH_2Cl_2 layer was worked up as described above. mp 154–155°C. Yield: 0.96 g (65%).

References

- 1) A. R. Katritzky and A. J. Boulton, "Advances in Heterocyclic Chemistry," Vol. 18, Academic Press, London, 1975, p. 99.
- 2) T. Okawara, K. Nakayama, and M. Furukawa, *Heterocycles*, **19**, 157 (1982).
- 3) T. Okawara, K. Nakayama, and M. Furukawa, *Synthesis*, **1982**, 1064.
- 4) T. Okawara, K. Nakayama, and M. Furukawa, *Chem. Pharm. Bull.*, **31**, 507 (1983).
- 5) T. Okawara, K. Nakayama, and M. Furukawa, *Chem. Lett.*, **1982**, 1791.
- 6) S. R. Sandler and W. Karo, "Organic Functional Group Preparation," Vol. 2, Academic Press, New York, 1971, pp. 135–165.
- 7) B. A. Phillips and N. H. Cromwell, *J. Heterocycl. Chem.*, **1973**, 795.
- 8) T. Okawara, T. Matsuda, and M. Furukawa, *Chem. Pharm. Bull.*, **30**, 1225 (1982).