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

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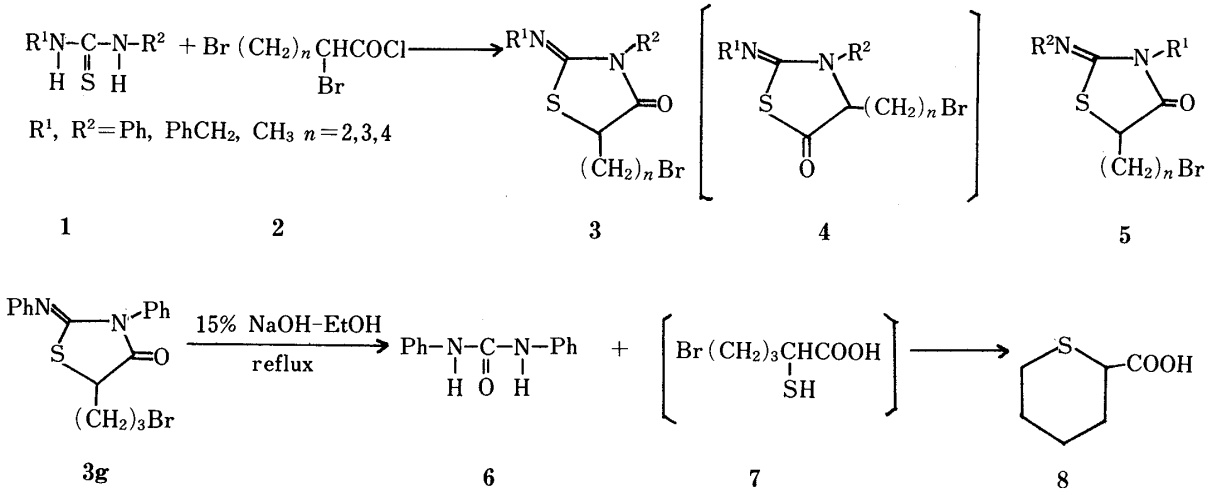
5-Bromoalkyl-2-iminothiazolidin-4-ones (**3**) were readily synthesized from 1,3-disubstituted thioureas (**1**) and α,ω-dibromoacyl chlorides (**2**) in 5% NaOH–$CH_2Cl_2$. Compounds **3** were converted to the corresponding spiro compounds **9** under phase-transfer conditions or with sodium ethoxide.

**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-ones[2] and their dimers,[3] respectively, and that the reaction of β-haloacyl halides with 1,3-disubstituted and monosubstituted thioureas gave tetrahydrothioxopyrimidines or thiazines[4] 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–$CH_2Cl_2$. The reaction was suc-




1 2 3 4 5

3g 6 7 8

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 ($CDCl_3$).

cessfully carried out by slowly adding **2** to a stirred solution of **1** in 5% NaOH–$CH_2Cl_2$ 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. $NaHCO_3$–$CH_2Cl_2$ instead of 5% NaOH–$CH_2Cl_2$.

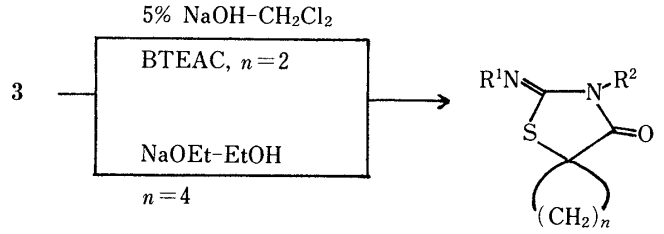
In this reaction, there is a possibility that not only thiazolidin-4-ones (**3**) but also thiazolidin-5-ones (**4**) might be formed. The infrared (IR) spectra of the products showed carbonyl and imino absorptions at 1720—1730 and 1625—1650 $cm^{-1}$, respectively. In order to discriminate between **3** and **4**, the product **3** ($R^1=R^2=Ph$, $n=3$) obtained from 1,3-diphenylthiourea (**1**) ($R^1=R^2=Ph$) and $\alpha,\delta$-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 $R^1$ and $R^2$ groups was $CH_3$ and $PhCH_2$, the proton nuclear magnetic resonance ($^1$H-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 $^1$H-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–$CH_2Cl_2$ in the presence of benzyltriethyl-ammonium chloride readily provided the spiro compounds **9** ($n=2$) in fairly good yields.

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




9

Chart 2

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

| 9 | $R^1$ | $R^2$ | $n$ | Condition | mp (°C) | Yield (%)[c] |
|---|---|---|---|---|---|---|
| **a** | $C_6H_5$ | $C_6H_5CH_2$ | 2 | 5% NaOH–$CH_2Cl_2$, BTEAC[b] | 131—132 | 51 |
| **b** | $C_6H_5$ | $CH_3$ | 2 | 5% NaOH–$CH_2Cl_2$, BTEAC | 115—117 | 57 |
| **c** | $C_6H_5$ | $C_6H_5$ | 2 | 5% NaOH–$CH_2Cl_2$, BTEAC | 154—155 | 92 |
| **d**[a] | $C_6H_5$ | $C_6H_5$ | 4 | NaOEt–EtOH | 105—106 | 54 |
| **e**[a] | $C_6H_5$ | $C_6H_5CH_2$ | 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 $^1$H-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. $^1$H-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 $SOCl_2$.[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)–$CH_2Cl_2$ (20 ml) under cooling with ice-water. After the addition was over, the reaction mixture was stirred for 12 h at room temperature. The $CH_2Cl_2$ layer was separated, washed with $H_2O$ (10 ml × 2), dried over anhydrous $MgSO_4$ and evaporated to dryness. The residue was purified by recrystallization from EtOH or by silica-gel column chromatography ($CHCl_3$). The IR, $^1$H-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) ($R^1=R^2=$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 $Et_2O$ (15 ml × 2). The extracts were evaporated to yield diphenylurea (**6**). The alkaline filtrate was acidified with 6 N HCl and extracted with $Et_2O$ (10 ml × 3). The ethereal extract was dried over anhydrous $MgSO_4$ and evaporated to dryness to afford the oily 2-thiacyclohexanecarboxylic acid (**8**). Yield 0.16 g (44%). IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1710 (C=O). MS (*m/z*): 146 ($M^+$). $^1$H-NMR ($\delta$) ($CDCl_3$): 1.00—2.32 (6H, m, $-(CH_2)_3-$), 2.32—3.17 (2H, m, $\underline{CH_2}$-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), $CH_2Cl_2$ (10 ml), and benzyltriethylammonium chloride (20 mg) was stirred for 10 h. The $CH_2Cl_2$ layer was separated, washed with $H_2O$ (10 ml × 2), dried over

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

| 3 | IR $\nu_{max}^{KBr}$ cm$^{-1}$ | $^1$H-NMR ($\delta$) in $CDCl_3$ | $m/z$ ($M^+$) | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **a** | 1730 (C=O)<br>1630 (C=N) | 2.66 (2H, m, $CH_2$, $J$=6.0 Hz)<br>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) | 388<br>400 | $C_{18}H_{17}BrN_2OS$ | 55.54<br>(55.79 | 4.40<br>4.37 | 7.20<br>7.07) |
| **b** | 1730 (C=O)<br>1650 (C=N) | 2.47 (2H, m, $CH_2$, $J$=6.0 Hz)<br>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) | 312<br>314 | $C_{12}H_{13}BrN_2OS$ | 46.01<br>(46.55 | 4.18<br>4.09 | 8.94<br>8.76) |
| **c** | 1725 (C=O)<br>1630 (C=N) | 2.60 (2H, m, $CH_2$)<br>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, Ph×2) | 374<br>376 | $C_{17}H_{15}BrN_2OS$ | 54.41<br>(54.41 | 4.03<br>3.88 | 7.46<br>7.26) |
| **d** | 1730 (C=O)<br>1640 (C=N) | 2.60 (2H, m, $CH_2$)<br>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) | 326<br>328 | $C_{13}H_{15}BrN_2OS$ | 47.72<br>(47.72 | 4.62<br>4.45 | 8.56<br>8.62) |
| **e** | 1730 (C=O)<br>1640 (C=N) | 1.77—2.47 (4H, m, $CH_2$×2)<br>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) | 402<br>404 | $C_{19}H_{19}BrN_2OS$ | 56.58<br>(56.85 | 4.75<br>4.57 | 6.95<br>7.26) |
| **f** | 1730 (C=O)<br>1640 (C=N) | 1.80—2.43 (4H, m, $CH_2$×2)<br>3.12 (3H, s, $CH_3$), 3.43 (2H, m, $CH_2$), 4.26 (1H, m, CH), 7.10—7.56 (5H, m, Ph) | 326<br>328 | $C_{18}H_{15}BrN_2OS$ | 47.71<br>(47.72 | 4.62<br>4.64 | 8.56<br>8.88) |
| **g** | 1730 (C=O)<br>1630 (C=N) | 1.75—2.37 (4H, m, $CH_2$×2)<br>3.42 (2H, m, $CH_2$), 4.27 (1H, m, CH), 6.85—7.57 (10H, m, Ph×2) | 388<br>390 | $C_{18}H_{17}BrN_2OS$ | 55.53<br>(55.55 | 4.40<br>4.37 | 7.20<br>7.21) |
| **h** | 1710 (C=O)<br>1650 (C=N) | 1.77—2.30 (4H, m, $CH_2$×2)<br>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) | 340<br>342 | $C_{14}H_{17}BrN_2OS$ | 49.27<br>(48.98 | 5.02<br>4.92 | 8.21<br>8.18) |
| **i** | 1730 (C=O)<br>1650 (C=N) | 1.66—2.27 (6H, m, $CH_2$×3)<br>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) | 416<br>418 | $C_{20}H_{21}BrN_2OS$ | 57.56<br>(57.46 | 5.07<br>5.10 | 6.71<br>6.71) |
| **j** | 1730 (C=O)<br>1650 (C=N) | 1.63—2.33 (6H, m, $CH_2$×3)<br>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) | 340<br>342 | $C_{14}H_{17}BrN_2OS$ | 49.27<br>(49.29 | 5.02<br>5.01 | 8.21<br>8.40) |
| **k** | 1720 (C=O)<br>1630 (C=N) | 1.66—2.32 (6H, m, $CH_2$×3)<br>3.40 (2H, t, $CH_2$, $J$=6.0 Hz), 4.23 (1H, m, CH), 6.83—7.50 (10H, m, Ph×2) | 402<br>404 | $C_{19}H_{19}BrN_2OS$ | 56.58<br>(57.02 | 4.75<br>4.80 | 6.95<br>6.89) |
| **l** | 1705 (C=O)<br>1650 (C=N) | 1.43—2.13 (6H, m, $CH_2$×3)<br>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) | 354<br>356 | $C_{15}H_{19}BrN_2OS$ | 50.71<br>(50.91 | 5.39<br>5.45 | 7.89<br>7.63) |

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

| 9 | IR $\nu_{max}^{KBr}$ cm$^{-1}$ | $^1$H-NMR ($\delta$) in $CDCl_3$ | $m/z$ ($M^+$) | Formula | Analysis (%) Calcd (Found) | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **a** | 1735 (C=O)<br>1640 (C=N) | 1.37 (2H, m, $CH_2$)<br>1.77 (2H, m, $CH_2$), 4.25 (2H, s, $CH_2$), 7.27 (5H, s, Ph), 7.15—7.70 (5H, m, Ph) | 308 | $C_{18}H_{16}N_2OS$ | 71.10<br>(70.72 | 5.23<br>5.20 | 9.08<br>8.99) |
| **b** | 1720 (C=O)<br>1640 (C=N) | 1.33 (2H, m, $CH_2$)<br>1.73 (2H, m, $CH_2$), 3.08 (3H, s, $CH_3$), 7.37 (5H, m, Ph) | 232 | $C_{12}H_{12}N_2OS$ | 62.04<br>(62.43 | 5.21<br>5.25 | 12.06<br>11.83) |
| **c** | 1730 (C=O)<br>1630 (C=N) | 1.34 (2H, m, $CH_2$)<br>1.75 (2H, m, $CH_2$), 6.60—7.83 (10H, m, Ph×2) | 294 | $C_{17}H_{14}N_2OS$ | 69.36<br>(69.35 | 4.79<br>4.81 | 9.52<br>9.35) |
| **d** | 1725 (C=O)<br>1625 (C=N) | 1.50—2.90 (8H, m, $CH_2$×4)<br>6.55—7.83 (10H, m, Ph×2) | 322 | $C_{19}H_{18}N_2OS$ | 70.78<br>(71.12 | 5.63<br>5.75 | 8.69<br>8.51) |
| **e** | 1725 (C=O)<br>1625 (C=N) | 1.52—2.66 (8H, m, $CH_2$×4)<br>5.05 (2H, s, $CH_2N$), 6.85—7.67 (5H, m, Ph), 7.45 (5H, s, $PhCH_2$) | 336 | $C_{20}H_{20}N_2OS$ | 71.40<br>(71.71 | 5.99<br>6.21 | 8.33<br>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-($\delta$-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×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) ($R^1=R^2=$Ph, $n=2$)**——$\alpha,\gamma$-Dibromobutyryl chloride (**2**, $n=2$) (1.32 g, 5 mmol) was gradually added to a solution of diphenylthiourea (**1**, $R^1=R^2=$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).