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A Facile Preparation of 4-Thiazolone Derivatives from Thioamides and Various Haloacyl Halides in a Biphase System

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The reaction of thioamides (**1**) with various haloacyl halides (**2**, **7**, **11**, **14**, **17**, and **19**) was carried out in sat. $NaHCO_3$–CH_2Cl_2 and 5% NaOH–CH_2Cl_2 to give several kinds of 4-thiazolones (**3**—**5**, **10**, **12** and **15**), thiazin-4-one (**18**) and spiro compounds (**21**).

Keywords——4-thiazolone; thioamide; haloacyl halide; biphase system; spiro compound; phase-transfer catalyst

A thiazole ring moiety is contained in the structures of many drugs and biologically active compounds, and therefore the preparation of thiazoles is of considerable interest. Thiazoles have hitherto been prepared by a number of methods;[1] for example, 4-thiazolones have been prepared by the reaction of α-haloacetic acids with thioamides and thioureas,[1,2] the reaction of nitriles with α-halothioacetic acid,[3] the reaction of Schiff bases with α-mercaptoacetic acids,[4] and the reaction of thioureas with α-chloro-α-arylacetyl chlorides.[5] These reactions, however, require anhydrous conditions and refluxing in benzene, toluene or acetone. The preparation of 4-thiazolones has not been achieved under mild and aqueous conditions.

In this paper, we describe convenient syntheses of 4-thiazolone and related compounds from thioamides and various haloacyl halides in a biphase system (organic solvent–water).

First, we examined the reaction of thioamides (**1**) with several α-haloacyl halides (**2**). The reaction was successfully carried out by slowly adding **2** to a stirred solution of **1** in sat. $NaHCO_3$–CH_2Cl_2, followed by stirring for 10 h at room temperature to afford 4-thiazolones (**3** and **4**) in 51—87% yields. The results are summarized in Table I.

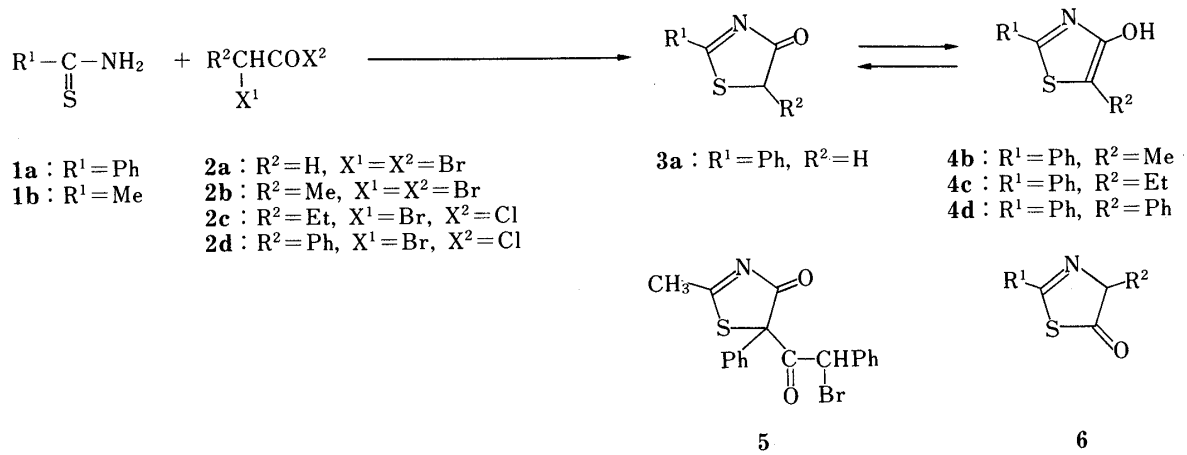


Chart 1

TABLE I. Preparation of 4-Thiazolones (**3**, **4** and **5**)

	mp (°C)	Yield (%)
3a	245—246 (lit.[a] 250)	62
4b	200—201 (lit.[a] 205)	53
4c	122—123	51
4d	214—216	87
5[b]	93—94	28

a) P. Chabrier, S. H. Renard, and K. Smarzewska, *Bull. Soc. Chim. Fr.*, **1949**, 237. [*Chem. Abstr.*, **44**, 5347*g* (1948)]. *b*) 5-(2-Bromo-2-phenylacetyl)-2-methyl-5-phenyl-4-thiazolone (**5**) was obtained.

TABLE II. Preparation of 2-Phenyl-4-thiazolone-5-spiroalkanes (**21**)

	mp (°C)	Yield (%)
21a	150—151	70
21b	116—117	54
21c	80—81	37

In this reaction, the formation of isomeric 5-thiazolone (**6**) is also possible. To clarify the structure of the product, 2-phenyl-4-thiazolone (**3a**) was alternatively prepared from thiobenzamide (**1a**) and chloroacetic acid,[2] and the product was confirmed to be identical with **3a** by comparison with their infrared (IR) spectra.

The IR spectra of the reaction products (**4**) of **1a** (R^1 = Ph) with **2b—d** did not show the carbonyl absorptions, and instead showed the absorptions of hydroxyl groups at 3100—2900 cm^{-1}. These results suggest that **4** are the tautomeric enol forms of **3**. The proton nuclear magnetic resonance (^{1}H-NMR) and mass spectra also supported these structures.

In the reaction of **1b** with **2d**, two molecules of **2d** reacted with **1b** to give 5-(2-bromo-2-phenylacetyl)-2-methyl-5-phenyl-4-thiazolone (**5**) in 36% yield. The IR spectrum of **5** showed carbonyl absorptions at 1720 and 1700 cm^{-1}, the ^{1}H-NMR spectrum exhibited the methine proton peak at 5.57 ppm (singlet), and the mass spectrum showed the parent ion.

The reaction of **1b** with other haloacyl halides (**2a—d**) under the same conditions, however, did not afford any of the expected compounds.

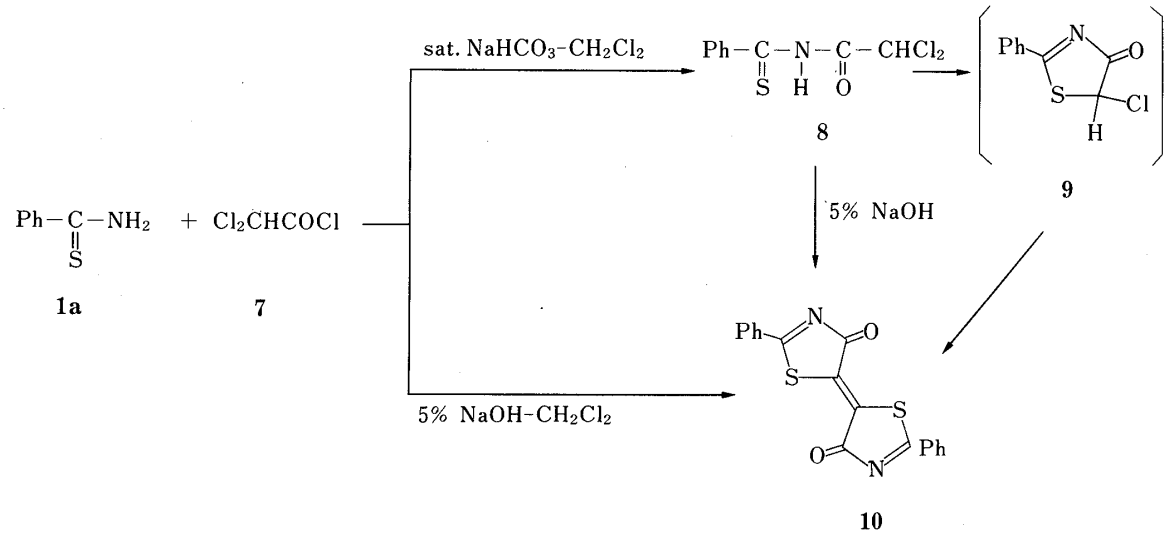
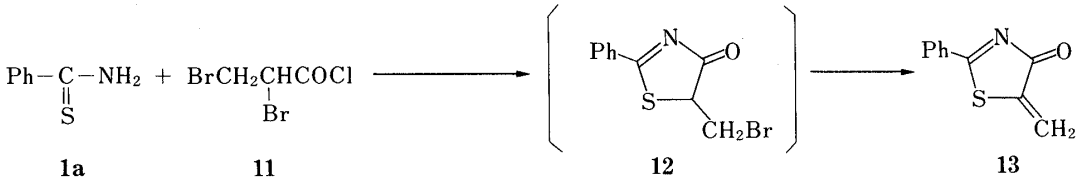


Chart 2

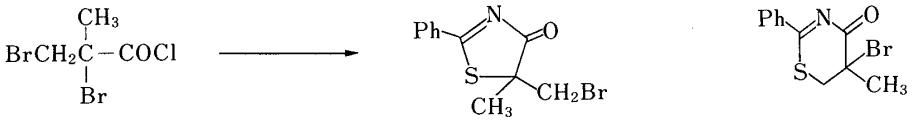
The reaction of **1a** with dichloroacetyl chloride (**7**) was also carried out in sat. $NaHCO_3$–CH_2Cl_2 to afford *N*-dichloroacetylthiobenzamide (**8**) in 73% yield, and this product was easily converted to 5,5′-bis(4-oxothiazolinyliene) (**10**) by stirring in 5% NaOH–CH_2Cl_2 at room temperature in 45% yield. Compound **10** was directly prepared from **1a** and **7** by stirring in 5% NaOH–CH_2Cl_2 at room temperature. The structure of **10** was confirmed by the IR, ^{1}H-

NMR and mass spectra. The formation of **10** from **8** is assumed to proceed *via* the intermediate **9** followed by self-condensation.

Next, the reaction between **1a** and α,β-dihaloacyl halide was examined. The reaction with 2,3-dibromopropionyl chloride (**11**) in sat. $NaHCO_3$–CH_2Cl_2 gave 5-methylene-4-thiazolone (**13**), probably *via* 5-bromomethyl-4-thiazolone (**12**), in 67% yield. The reaction with 2,3-dibromo-2-methylpropionyl bromide (**14**) afforded 5-bromomethyl-5-methyl-4-thiazolone (**15**) in 54% yield.



1a **11** **12** **13**

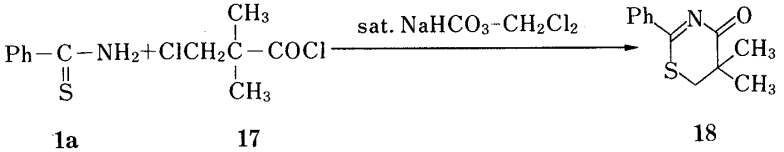


14 **15** **16**

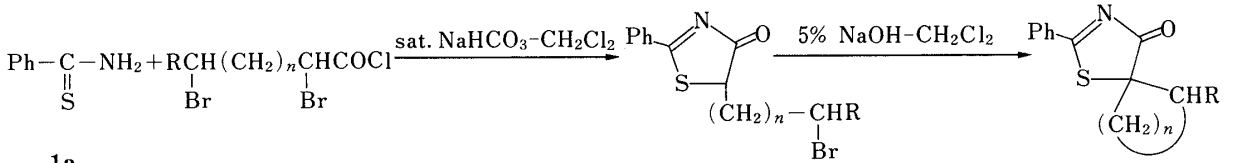
Chart 3

In the latter reaction, another structure (**16**) for the product is also possible. If the structure of the product is **16**, the nonequivalent geminal hydrogens at C-6 should show two doublet signals in the ^{1}H-NMR spectrum.[6] However, the methylene proton signal was seen as a singlet at 3.78 ppm. The IR spectrum exhibited the carbonyl absorption at the high frequency of 1718 cm^{-1}. These results strongly support the structure of **15**.

In the reaction of **1a** with a β-haloacyl halide, 2,2-dimethyl-3-chloropropionyl chloride (**17**), under the same conditions, dihydro-1,3-thiazin-4-one (**18**) was obtained in 49% yield.



1a **17** **18**



1a

19a : R=H, n=1
19b : R=Me, n=1
19c : R=H, n=3

20a : R=H, n=1
20b : R=Me, n=1
20c : R=H, n=3

21a : R=H, n=1
21b : R=Me, n=1
21c : R=H, n=3

Chart 4

Further, the reaction of **1a** (R^1=Ph) with α,ω-dihaloacyl chloride (**19**) was carried out in sat. $NaHCO_3$–CH_2Cl_2 and afforded 5-haloalkyl-4-thiazolone (**20**), which was readily converted to 2-phenyl-4-thiazolone-5-spirocycloalkane (**21**) by stirring in 5% NaOH–CH_2Cl_2 in the presence of a phase-transfer catalyst (PTC), benzyltriethylammonium chloride, in 37—70% yields.

When the compounds **20** were treated with 5% NaOH–CH_2Cl_2 in the absence of PTC,

the yields of **21** were lower than those in the presence of PTC. These structures were consistent with the spectral data and elemental analyses.

Further applications of these reactions for 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-60H spectrometer and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were measured with a JEOL-FX-100 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were measured with a JEOL-01 SG mass spectrometer.

General Procedure for Preparation of 4-Thiazolones (3, 4, and 5)——An α-haloacyl halide **2** (5 mmol) was added dropwise to a stirred solution of a thioamide **1** (5 mmol) in sat. $NaHCO_3$ (10 ml) and CH_2Cl_2 (20 ml) under cooling with ice-water. After the addition was over, the reaction mixture was stirred for 10 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 recrystallized from EtOH. The IR, ^{1}H-NMR spectra and mass spectral data, and elemental analyses of the products are listed in Table III.

***N*-Dichloroacetylthiobenzamide (8)**——Compound **2** (0.29 ml, 3 mmol) was gradually added to a stirred solution of **1a** (0.41 g, 3 mmol) in sat. $NaHCO_3$ (8 ml) and CH_2Cl_2 (20 ml) under cooling with ice-water. The stirring was continued for 10 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 recrystallized from EtOH. mp 252—254 °C (dec.). Yield: 0.77 g (73%). IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1670 (C=O). *Anal.* Calcd for C_9H_7ClNOS: C, 43.56; H, 2.85; N, 5.65. Found: C, 43.42; H, 2.77; N, 5.53.

5,5′-Bis(4-oxo-2-phenylthiazolinylidene) (10)——1) From **8**: A mixture of **8** (0.5 g, 5 mmol) in 5% NaOH (8 ml) and CH_2Cl_2 (20 ml) was stirred overnight. The precipitated dark green solid was collected by filtration. Yield: 0.16 g (45%). mp >300 °C. IR ν_{max}^{KBr} cm^{-1}: 1740 (C=O), 1680 (C=N). MS *m/z*: 350 (M^+). *Anal.* Calcd for $C_{18}H_{10}N_2O_2S$: C, 61.70; H, 2.88; N, 7.99. Found: C, 61.90; H, 2.80; N, 7.43.

2) From **1** and **7**: Compound **7** (0.48 ml, 5 mmol) was added dropwise to a stirred solution of **1** (0.69 g, 5 mmol) in 5% NaOH (12 ml) and CH_2Cl_2 (20 ml) under cooling with ice-water. The mixture was stirred for 10 h, and the precipitated solid was filtered off. Yield: 0.46 g (26%).

5-Methylene-2-phenyl-4-thiazolone (13)——This compound was prepared from **1** (0.41 g, 3 mmol) and **11** (0.75 g, 3 mmol) by the the same procedure as described above, and recrystallized from $CHCl_3$ and EtOH. mp 211—213 °C. Yield: 0.38 g (67%). IR ν_{max}^{KBr} cm^{-1}: 1725 (C=O). MS *m/z*: 189 (M^+). *Anal.* Calcd for $C_{10}H_7NOS$: C, 63.47; H, 3.73; N, 7.40. Found: C, 63.62; H, 3.52; N, 6.92.

5-Bromomethyl-5-methyl-2-phenyl-4-thiazolone (15)——This compound was obtained from **1** (0.41 g, 3 mmol) and **14** (0.80 g, 3 mmol) by the same procedure as described above, and recrystallized from EtOH. mp 84—85 °C. Yield: 0.46 g (54%). IR ν_{max}^{KBr} cm^{-1}: 1718 (C=O). ^{1}H-NMR (δ) (DMSO-d_6): 1.89 (s, CH_3, 3H), 3.78 (s, CH_2, 2H), 7.33—7.73, 8.07—8.24 (m, Ph, 5H). MS *m/z*: 285, 283 (M^+). *Anal.* Calcd for $C_{11}H_{10}BrNOS$: C, 46.49; H, 3.55; N, 4.93. Found: C, 46.70; H, 3.59; N, 4.91.

5,6-Dihydro-5,5-dimethyl-2-phenyl-1,3-thiazin-4-one (18)——This compound was prepared from **1** (0.69 g,

TABLE III. Spectral and Elemental Analysis Data for 4-Thiazolones (**4** and **5**)

	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR (δ)	M^+ (*m/z*)	Analysis (%) Calcd (Found)		
				C	H	N
4c	3100—2900 (OH)	1.15 (t, CH_3, 3H, J=6.0 Hz), 2.12 (q, CH_2, 2H, J=6.0 Hz), 7.40—8.12 (m, Ph, 5H), 9.6 (br, OH, 1H) ($CDCl_3$)	205	64.36 (64.29	5.40 5.22	6.82 6.50)
4d	3100—3000 (OH)	7.42—7.96 (m, Ph × 2, and OH, 11H) (CF_3COOD)	253	71.12 (70.99	4.38 4.42	5.38 5.56)
5	1720 (C=O) 1700 (C=O)	2.65 (s, CH_3, 3H), 5.57 (s, CH, 1H), 7.23—7.66 (m, Ph × 2, 10H) ($CDCl_3$)	387 389	55.68 (55.86	3.63 3.55	3.61 3.89)

TABLE IV. Spectral and Elemental Analysis Data for 2-Phenyl-4-thiazole-5-spiroalkanes (**21**)

	IR ν_{max}^{KBr} cm^{-1}	^{1}H-NMR (δ) in $CDCl_3$	M$^+$ (m/z)	Analysis (%) Calcd (Found)		
				C	H	N
21a	1700 (C=O)	1.66—1.83 (m, $CH_2 \times 2$, 4H), 7.43—7.66 and 8.00—8.17 (m, Ph, 5H)	202	65.00 (65.13	4.46 4.49	6.89 6.91)
21b	1710 (C=O)	1.36 (d, CH_3, 3H, J=6.0 Hz), 1.33—1.47 (m, CH_2, 2H), 2.00 (q, CH, 1H, J=6.0 Hz), 7.47—7.66 and 8.03—8.26 (m, Ph, 5H)	217	66.33 (66.41	5.10 5.21	6.45 6.25)
21c	1710 (C=O)	1.83—2.50 (m, $CH_2 \times 4$, 8H), 7.43—7.67 and 8.02—8.18 (m, Ph, 5H)	231	67.50 (67.65	5.66 5.70	6.06 6.11)

a) ^{13}C-NMR ($CDCl_3$/TMS): δ=20.5 (-CH_2-), 38.3 (-$\overset{|}{C}$-), 135.8, 136.5, 140.1, 142.4 (Ph), 205.4 (C=O).

5 mmol) and **17** (0.77 g, 5 mmol) by the same procedure as described above, and recrystallized from EtOH. mp 101—102 °C. Yield: 0.42 g (38%). IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O). ^{1}H-NMR (δ) ($CDCl_3$): 1.37 (s, $CH_3 \times 2$, 6H), 3.20 (s, CH_2, 2H), 7.21—8.13 (m, Ph, 5H). MS m/z: 219 (M$^+$). *Anal.* Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39. Found: C, 65.70; H, 5.98; N, 6.24.

5-(4-Bromobutyl)-2-phenyl-4-thiazolone (20, R=H, *n*=3)——This compound was obtained from **1** (0.41 g, 3 mmol) and **19** (R=H, n=3) (0.88 g, 3 mmol) and recrystallized from EtOH. mp 78—79 °C. Yield: 0.58 g (62%). IR ν_{max}^{KBr} cm^{-1}: 1728 (C=O). ^{1}H-NMR (δ) ($CDCl_3$) 1.67—2.17 (m, $CH_2 \times 3$, 6H), 3.38 (m, CH_2Br, 2H), 6.33 (m, CH, 1H), 7.33—7.63, 8.00—8.20 (m, Ph, 5H). *Anal.* Calcd for $C_{13}H_{14}BrNOS$: C, 50.00; H, 4.52; N, 4.49. Found: C, 50.35; H, 4.51; N, 4.71.

General Procedure for Preparation of 2-Phenyl-4-thiazolone-5-spirocycloalkane (21)——An α,ω-haloacyl halide (**19**, 5 mmol) was added dropwise to a stirred solution of **1** (0.69 g, 5 mmol) in 5% NaOH (10 ml) and CH_2Cl_2 (30 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 stirring was continued for 10 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 results are summarized in Table II, and the spectral data and elemental analyses are summarized in Table IV.

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