HETEROCYCLIZATIONS OF THIOSEMICARBAZONES WITH α-CHLOROACETYL CHLORIDE

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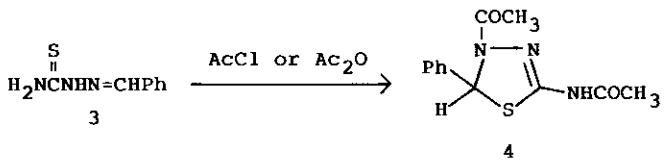
Abstract —— 4-Substituted thiosemicarbazones were allowed to react with α-chloroacetyl chloride to give two types of 1,3-thiazolin-4-ones which arose from the different cyclization depending on the substituents.

Thiosemicarbazides are widely used as versatile reagents in the preparation of heterocyclic compounds.[1] Although many reactions with carboxylic acids, ketones, and acyl halides have hitherto been reported to provide various kinds of heterocyclic compounds, studies on the reaction with halogeno-acyl halides have been reported only scarcely.[2]

We report here the reaction of 4-substituted thiosemicarbazones (**1**) with α-chloroacetyl chloride (**2**). In connection with this reaction, Kubota[3] has recently reported that the interesting novel reaction of benzaldehyde thiosemicarbazone (**3**) with acetyl chloride or acetic anhydride gives 2-acetamido-4-acetyl-5-phenyl-Δ^2-1,3,4-thiadiazoline (**4**) (Scheme 1).



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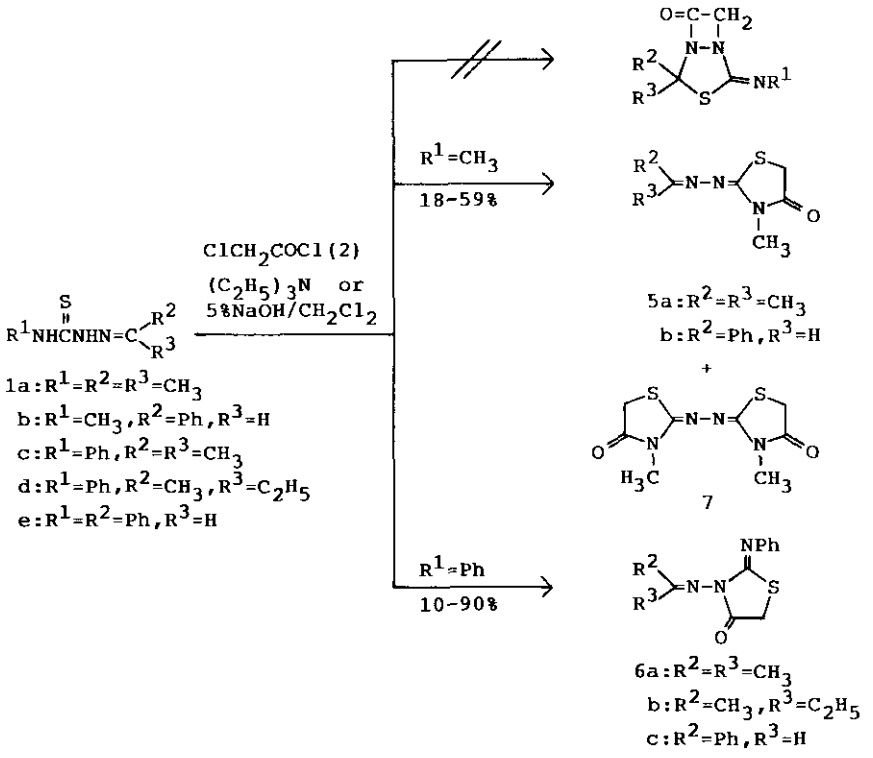
Scheme 1

The reaction between 4-substituted thiosemicarbazones (1) and α-chloroacetyl chloride (2) is expected to proceed analogously to yield 1,3,4-thiadiazolines. However, when **1** was allowed to react with an equivalent of **2** in dichloromethane in the presence of triethylamine or in a mixture of 5% aqueous sodium hydroxide and dichloromethane at room temperature, 1,3-thiazolines (**5** and **6**) were provided in low yields, without being isolated any anticipated thiadiazolines. In this reaction, the different direction of cyclization arising from the difference of the substituent at 4-position was observed. In the case that the substituent R^1 is the methyl group, the amino moiety adjacent to the methyl group is initially acylated, followed by the intramolecular S-alkylation to give the corresponding 1,3-thiazolines (**5**). On the other hand, in the case that the R^1 stands for phenyl group, the hydrazino moiety is first acylated, followed by cyclization by the intramolecular S-alkylation to provide another 1,3-thiazoline (**6**). Such a difference of the direction of cyclization may be due to the difference of the



Scheme 2

steric bulkiness between phenyl and methyl groups and the basicity between the anilino and methylamino groups. These two different thiazolines (**5** and **6**) were obviously discriminate by the characteristic infrared spectral pattern. In the reaction of acetone 4-methylthiosemicarbazone (**1a**) with **2**, thiazolin-4-one bishydrazone (**7**) was also isolated in 16% yield, along with 18% yield of the anticipated thiazoline (**5a**) (*Scheme 2*).

The structures of the compounds (**5**, **6**, and **7**) were assigned on the bases of the spectral data and elemental analyses. The ms indicated the molecular ions (M^+) corresponding to the assigned structures. The ^{1}H-nmr spectra exhibited singlet signals assignable to the ring methylene at 3.52~3.99 ppm and signals corresponding to the substituent groups. The ir spectra showed the carbonyl absorption at 1700-1730 cm^{-1}. The elemental analyses also supported the assigned structure. These data were summarized in Table 1.

Table 1 1,3-Thiazolines (**5**,**6**,and **7**)

Compound	R^1	R^2	R^3	Yield(%)	mp(°C)	Ir(KBr),cm^{-1}	^{1}H-Nmr($CDCl_3$) δ, J(Hz)
5a	CH_3	CH_3	CH_3	18	98-98.5	1700(C=O)	2.07(6H, s, CH_3x2) 3.26(3H, s, CH_3) 3.74(2H, s, CH_2)
5b	CH_3	Ph	H	59	141	1723(C=O)	3.09(3H, s, CH_3) 3.52(2H, s, CH_2) 6.99-7.76(5H, m, Ph) 8.22(1H, s, CH=)
6a	Ph	CH_3	CH_3	10	196-197	1723(C=O)	1.83(3H, s, CH_3) 2.02(3H, s, CH_3) 3.99(2H, s, CH_2) 7.20-7.50(5H, m, Ph)

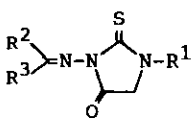
6b	Ph	CH_3	C_2H_5	12	171.5-172.5	1728(C=O)	1.11(3H, t, J=7.2, CH_3) 1.81(3H, s, CH_3) 2.32(2H, q, J=7.2, CH_2) 3.89(2H, s, CH_2) 7.16-7.62(5H, m, Ph)
6c	Ph	Ph	H	90	240	1730(C=O)	3.93(2H, s, CH_2) 7.20-7.87(10H, m, Phx2) 8.29(1H, s, CH=)
7	–	–	–	16	>300	1710(C=O)	3.27(3H, s, CH_3) 3.78(2H, s, CH_2)

Table 1 (Continued)

Compound	R^1	R^2	R^3	Ms(M^+)	Formula	Analysis (%) Calcd(Found) C	H	N
5a	CH_3	CH_3	CH_3	185	$C_7H_{11}N_3OS$	45.39 (45.75)	5.99 (5.92)	22.68 (22.52)
5b	CH_3	Ph	H	233	$C_{11}H_{11}N_3OS$	56.67 (56.63)	4.71 (4.75)	18.21 (18.01)
6a	Ph	CH_3	CH_3	247	$C_{12}H_{13}N_3OS$	58.28 (58.61)	5.30 (5.28)	16.99 (16.86)

6b	Ph	CH_3	C_2H_5	261	$C_{13}H_{15}N_3OS$	59.75	5.79	16.08
						(59.89)	(5.77)	(16.43)
6c	Ph	Ph	H	295	$C_{16}H_{13}N_3OS$	65.07	4.44	14.23
						(65.09)	(4.47)	(14.05)
7	–	–	–	258	$C_8H_{10}N_4O_2S_2$	37.20	3.90	21.69
						(37.47)	(3.83)	(21.51)

Regarding the structures of **5** and **6**, the other four isomeric structures (**8-9**) and (**10-11**) are also considered. Among them, the structures (**8** and **9**) are excluded, because of the absence of the absorption assignable to the thiocarbonyl group. In order to discriminate the assigned structures (**5**, **6**) and the possible structures (**10**, **11**), the product (**5b**) was hydrolyzed with a mixture of 5% aqueous sodium hydroxide and ethanol (1:1) and, as the result, 1-benzylidene-4-methylsemicarbazide (**12**) and dithioglycolic acid (**13**), which was formed by the



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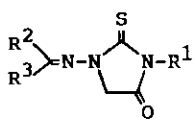

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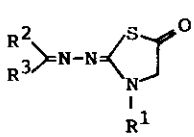

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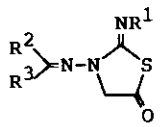

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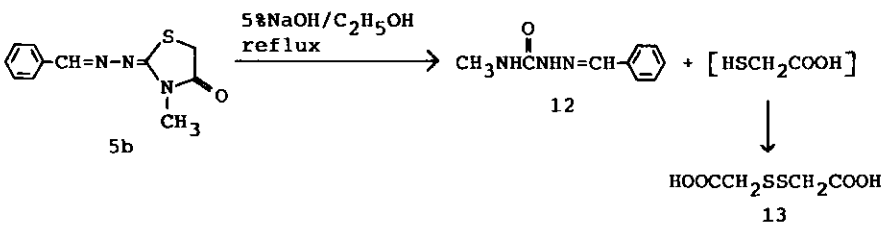

Scheme 3

oxidative dimerization of intermediately formed thioglycolic acid[4] were isolated (Scheme 3).

This result denies the other possible structure (10 and **11**), from which dithioglycolic acid (13) is not able to form directly by hydrolysis. The discrimination between **5** and **6** was defined by the fact that the N-N bond of hydrazones is readily cleaved, whereas that of N-amino heterocycles is stable and difficult to cleave. Thus, the product formed together with dimer (7) is presumed to be **5**. Further extensions and developments of this work are in progress.

EXPERIMENTAL

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. The ^{1}H-nmr measurements were obtained on a JEOL-60H spectrometer using tetramethylsilane as an internal standard. The ir spectra were determined with a JASCO IR A-1 grating ir spectrophotometer. The mass spectra were measured with JEOL-01SG mass spectrometer.

Reaction of 4-Substituted Thiosemicarbazones (**1a-e**) with Chloroacetyl Chloride (**2**)

1. To a stirred solution of **1a, c, d** (5 mmol) in dichloromethane (30 ml) containing triethylamine (1.39 ml, 10 mmol) was added **2** (0.40 ml, 5 mmol) upon cooling with ice. After stirring was continued overnight, the solution was washed with water (50 mlx3), dried over anhydrous magnesium sulfate, and evaporated to dryness. The residue was recrystallized from ethanol to give 2-isopropylidenehydrazino-3-methyl-1,3-thiazolidin-4-one (**5a**), 3-isopropylideneamino-2-phenylimino-1,3-thiazolidin-4-one (**6a**), and 3-isobutylideneamino-2-phenylimino-1,3-thiazolidin-4-one (**6b**), respectively.

The washing aqueous layer was evaporated under reduced pressure, and to the residue was added a small amount of water. The insoluble crystals were collected and recrystallized from benzene to give 2,2'-azinodi-3,3'-dimethyl-1,3-thiazolidine-4,4'-dione (**7**).

2. To a stirred solution of **1b, e** (10 mmol) in dichloromethane (60 ml) was alternately added 5% aqueous sodium hydroxide (16 ml, 20 mmol) and **2** (0.80 ml, 10 mmol) upon cooling, and stirring was continued for additional 24 h at room

temperature. The dichloromethane layer was separated, washed with water (20 mlx2), dried over anhydrous magnesium sulfate, and evaporated. The residue was recrystallized from ethanol or ethyl acetate to give 2-benzylidenehydrazino-3-methyl-1,3-thiazolidin-4-one (**5b**) and 3-benzylideneamino-2-phenylimino-1,3-thiazolidin-4-one (**6c**).

These data are summarized in Table 1.

Hydrolysis of 2-Benzylidenehydrazino-3-methyl-1,3-thiazolidin-4-one (**5b**)

A mixture of **5b** (1.17 g, 5mmol) in a mixture of 5% aqueous sodium hydroxide and ethanol (1:1) (30 ml) was heated for 6 h under reflux. The mixture was distilled to remove ethanol and extracted with ether. The etheral layer was dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was recrystallized from ethanol to give 1-benzylidene-4-methylsemicarbazide (**12**). Ir (KBr), cm^{-1}: 1680(C=O). Ms m/z: 177 (M^+). Anal. Calcd for $C_9H_{11}N_3O$: C, 61.87; H, 6.10; N, 23.50. Found: C, 61.00; H, 6.26; N, 23.71.

The aqueous layer was acidified with hydrochloric acid and distilled off to give dithioglycolic acid, of which structure was confirmed by comparison of the ir spectrum with that of Aldrich.[5]

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