SYNTHESIS OF NOVEL 1,3-THIAZOLIDINES AND 1,3,4-THIADIAZOLINES FROM THIOCARBOHYDRAZIDES

Shigeru Kabashima, Tadashi Okawara, Tetsuo Yamasaki, and Mitsuru Furukawa*

Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-hon-machi, Kumamoto 862, Japan

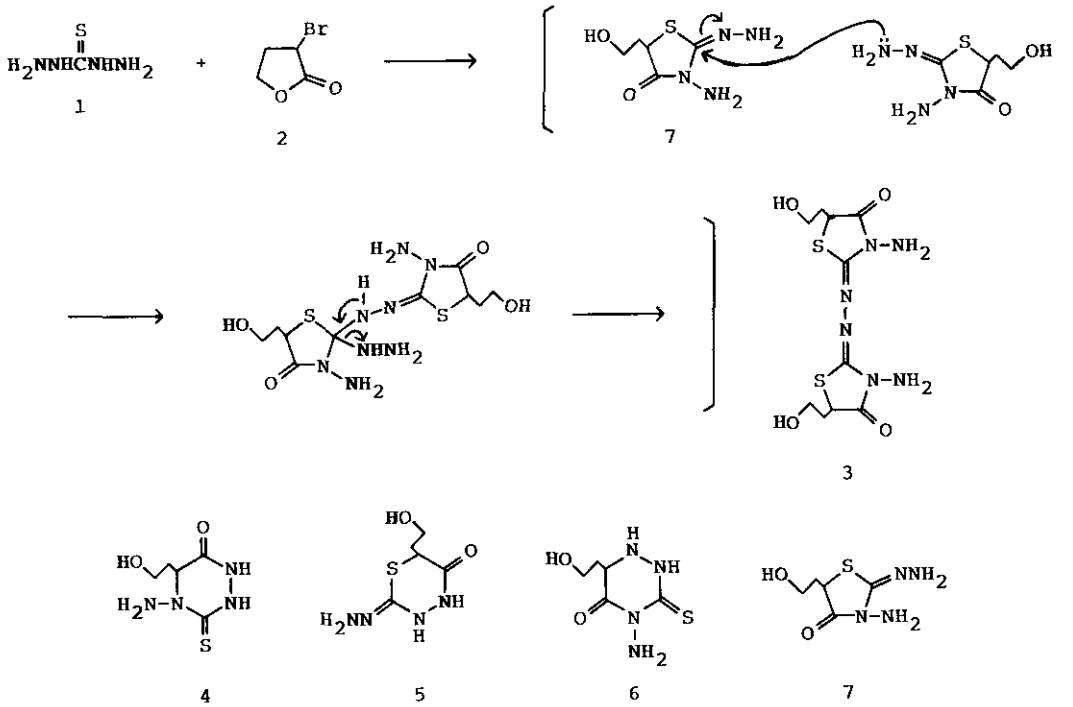
Abstract —— The reaction of thiocarbohydrazide (1) with α-bromo-γ-butyrolactone (2) provided the novel 1,3-thiazolidine (3). Alkylidenethiocarbohydrazides (8 and 13) were allowed to react with cyanogen bromide and acetyl chloride to give 4,5-dihydro-1,3,4-thiadiazoles (9 and 14).

Thiocarbohydrazides are significant as versatile materials in the synthesis of heterocycles, due to the structural similarity to thiosemicarbazides which are widely utilized for the preparation of a variety of heterocyclic ring systems.[1] Although the cyclization of thiocarbohydrazide with halogeno ketones has hitherto been known to provide thiadiazines,[2] pyrazoles,[3] and thiazolines,[4] there has been no report on cyclization with halogeno carboxylates. We now report the novel cyclization by the reactions of thiocarbohydrazides with α-bromo-γ-butyrolactone, cyanogen bromide, and acetyl chloride.

When thiocarbohydrazide (**1**) was treated with an equivalent of α-bromo-γ-butyrolactone (**2**) in boiling ethanol, a novel 1,3-thiazolidine (**3**) was provided in low yield.

In this reaction, four reaction pathways are possible to give six-membered and five-membered ring compounds: The initial attack of the terminal amino group of the thiocarbohydrazide (**1**) to the carbonyl function of the lactone (**2**) provides the acyl intermediate by the cleavage of the lactone ring, followed by cyclization to 1,2,4-triazine (**4**) and 1,3,4-thiadiazine (**5**) by the intramolecular N- and

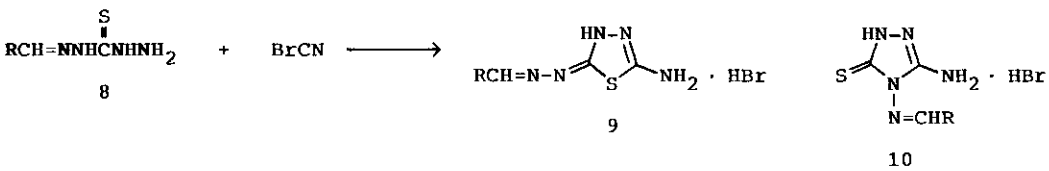
S-alkylations, respectively. On the other hand, initial N- and S-alkylations followed by the intramolecular N-acylation accompanying the cleavage of the lactone ring provide 1,2,4-triazine (6) and 1,3-thiazolidine (7), respectively.



Scheme 1

Concerning the reactivity of α-bromo-γ-butyrolactone (2), it is reported that anthranilic acid reacts with 2 to give N-alkylation product.[5] This result suggests that thiocarbohydrazide (1) may readily undergo the alkylation rather than the acylation by treating with 2. In general, S-alkylation occurs more readily than N-alkylation. In fact, thiosemicarbazide undergoes the S-alkylation with methyl iodide.[6] On the bases of these facts, it is presumed that the reaction of 1 with 2 initiates by the S-alkylation of 1 followed by cyclization to the compound (5) or (7) by the attack of either of two nitrogens of the hydrazino group. However, the practical product was the dimer (3), which was formed by dimerization of the initially formed compound (7) with elimination of hydrazine. The ir

spectrum of the product showed the absorption assignable to the carbonyl group at 1720 cm^{-1}, which supported the cyclic amido structure of the five-membered ring rather than that of the six-membered ring. The ^1H-nmr spectrum exhibited the multiplets corresponding to two methylene groups near 2.0 and 3.5 ppm, the multiplet assignable to the methine proton near 4.15 ppm, and the signals of OH and NH_2 at 4.72 and 5.13 ppm, which disappeared by deuterium exchange. The ms spectrum indicated the molecular ion peak at m/z 342. These spectral data supported the structural assignment of the product as **3**.



Scheme 2

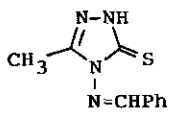
The reaction of alkylidenethiocarbohydrazides (**8**) with cyanogen bromide was also examined. The reaction was successfully carried out by adding cyanogen bromide into the stirred suspension of the compound (**8**), followed by stirring for 24 hours at room temperature to provide 2-amino-5-substituted methylideneimino-4,5-dihydro-4H-1,3,4-thiadiazoles hydrobromide (**9**) in good yields. The results are summarized in Tables 1 and 3.

Table 1 2-Amino-5-substituted methylideneimino-4,5-dihydro-4H-1,3,4-thiadiazoles hydrobromide (**9**)

Compd	R	Yield(%)	mp(°C)	Ir(KBr),cm^{-1}	Ms(M^+-HBr)
9a	phenyl	96	233-234	3350(NH) 3225(NH_3^+)	219

9b	2-thienyl	88	204-205	3482(NH) 3208(NH_3^+)	225
9c	2-furyl	94	222-223	3238(NH) 3190(NH_3^+)	209
9d	cinnamyl	79	218	3250(NH) 3204(NH_3^+)	245
9e	isopropyl	78	172-173	3204(NH) 3204(NH_3^+)	185

The product did not show the nitrile absorption in the ir spectra, and the ms spectra exhibited the molecular ion peak corresponding to the free base of the assigned structure. These data, however, could not distinguish between **9** and another possible isomeric structure (**10**). In order to discriminate these structures, the ^{13}C-nmr spectra of the product and the analogous functional compounds (**11** and **12**) were measured by adding aqueous sodium hydroxide. The signal of the thiocarbonyl carbon at the 5-position of **11** was little affected by the addition of aqueous sodium hydroxide and was slightly shifted from 161.156 ppm to 160.791 ppm. Whereas, the signal of the C=N carbon at the 2-position of **12** was considerably shifted from 154.082 ppm to 143.153 ppm. In the product, the similar shift from 164.055 ppm to 151.487 ppm was observed in the signal of the carbon at the 2-position. This supports the assigned structure (**9**) for the product.



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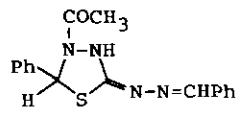

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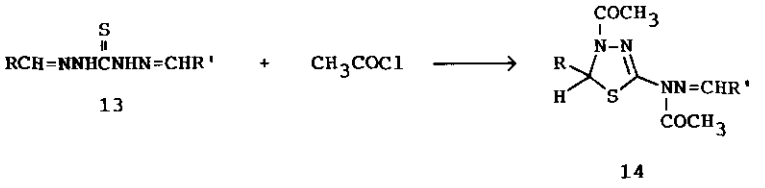
Scheme 3

The reaction of thiocarbohydrazide (**1**) with carboxylic acids is known to form triazoles,[7] though the treatment with acyl halides merely results in the acylation of the terminal amino function of **1**.[8]

It is reported that heterocyclization of thiosemicarbazones with acetyl chloride provides 4,5-dihydro-1,3,4-thiadiazoles.[9] Analogous cyclization of dithiocarbohydrazones (**13**) with acetyl chloride was examined and the expected 4,5-dihydrothiadiazoles (**14**) were successfully prepared in fairly good yields. The results are summarized in Tables 2 and 4. The structure (**14**) was confirmed by ir, ^{1}H-nmr and ms spectral data and elemental analysis.



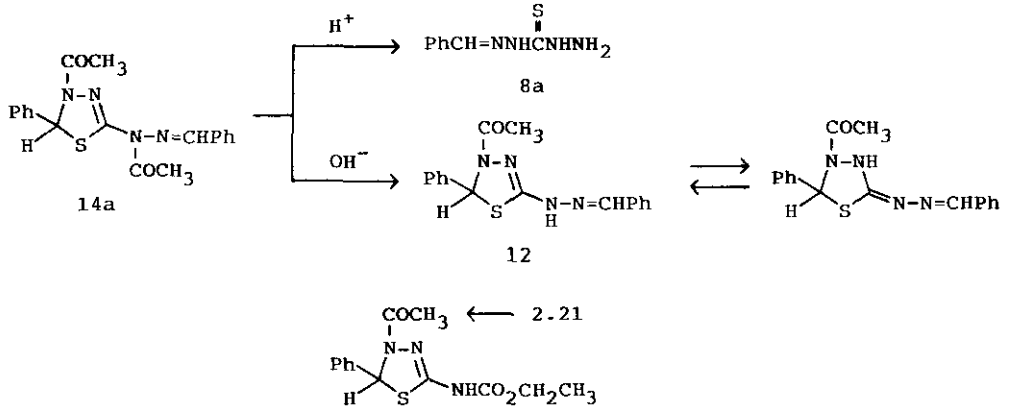
Scheme 4

Table 2 4-Acetyl-2-(1'-acetyl-2'-substituted methylidene)hydrazino-5-aryl-4,5-dihydro-1,3,4-thiadiazoles (**14**)

Compd	R	R'	Yield(%)	mp(°C)	Ir(KBr),cm^{-1}	Ms(M$^+$-HBr)
14a	phenyl	phenyl	97	168-168.5	1695(C=O) 1670(C=O)	366
14b	2-pyridyl	2-pyridyl	92	192-193	1700(C=O) 1670(C=O)	368
14c	3-pyridyl	3-pyridyl	63	187	1690(C=O) 1665(C=O)	368

14d	2-furyl	2-furyl	75	124	1705(C=O) 1675(C=O)	346
14e	2-thienyl	2-thienyl	26	150	1695(C=O) 1670(C=O)	378
14f	isopropyl	phenyl	58	93-94	1700(C=O) 1670(C=O)	332

Hydrolysis of the compound of **14a** gave benzylidenethiocarbohydrazide (**8a**) with cleavage of the 4,5-dihydrothiadiazole ring under acidic conditions and the deacetylated compound (**15**) under basic conditions.



Scheme 5

The ^{1}H-nmr spectrum of **12** exhibited the methyl signal of the acetyl group at 2.21 ppm. It is known that the similar compound (**15**) indicates the methyl signal of the acetyl group bonding to the ring nitrogen at 2.21 ppm.[6] On the basis of this result, it is reasonable to conclude that the deacylation occurred at the side

acetamide group.

EXPERIMENTAL

All the melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Ir spectra were recorded as KBr pellet on a JASCO IRA-1 grating infrared spectrophotometer. ^{1}H-Nmr spectra were determined with a HITACHI R-600 spectrometer using tetramethylsilane as an internal standard. Mass spectra were measured with a JEOL-01 SG mass spectrometer.

2,2'-Azino-3,3'-diamino-5,5'-hydroxyethyl-1,3-thiazolidine-4,4'-dione (3)

A solution of thiocarbohydrazide (1) (0.32 g, 3 mmol) and α-bromo-γ-butyrolactone (2) (0.25 ml, 3 mmol) in ethanol (15 ml) was heated for 24 h with stirring under reflux. The resulting precipitates deposited upon cooling were collected and recrystallized from water. Yield 0.14 g(25%). mp 271.5-272.5°C. Anal. Calcd for $C_{10}H_{16}N_6O_4S_2$: C,34.48; H,4.63; N,24.10. Found: C,34.47; H,4.42; N,24.42. Ir ν (KBr) cm^{-1}:3275(NH_2), 3165(OH), 1720(C=O). Ms m/z: 348(M^+). ^{1}H-Nmr(DMSO-d_6) δ : 1.60-2.17(4H, m, CH_2x2), 3.40-3.68(4H, m, CH_2x2), 4.05-4.28(2H, m, CHx2), 4.72(2H, t, J=4.8Hz, OHx2), 5.13(4H, s, NH_2x2).

Mono- and Dithiocarbohydrazones (8 and 13)

These compounds were prepared from thiocarbohydrazide and aldehydes according to Beyer[4] and Ried[10] methods.

2-Amino-5-substituted methylideneimino-4,5-dihydro-4H-1,3,4-thiadiazoles hydrobromide (9a-e)

To a stirred suspension of alkylidenethiocarbohydrazides (**8a-e**) (3 mmol) in THF (15 ml) was added cyanogen bromide (0.32 g, 3 mmol), and the mixture was stirred for 24 h at room temperature. The resulting precipitates were collected and recrystallized from ethanol. The results are summarized in Tables 1 and 3.

Table 3 2-Amino-5-substituted methylideneimino-4,5-dihydro-4H-1,3,4-thiadiazoles hydrobromide (9)

	Analysis

Compd	^{1}H-Nmr(DMSO-d_6), δ	Formula	Calcd(Found)		
			C	H	N
9a	5.23-9.42(4H, br, NH_3^+ and NH) 7.03-7.98(5H, m, Ph) 8.02(1H, s, CH=)	$C_9H_{10}N_5BrS$	36.01 (36.48)	3.36 (3.54)	23.33 (23.32)
9b	6.31-9.89(4H, br, NH_3^+ and NH) 6.96-7.89(3H, m, ArH) 8.29(1H, s, CH=)	$C_7H_8N_5BrS_2$	27.46 (27.57)	2.63 (2.73)	22.87 (22.54)
9c	6.47-7.84(3H, m, ArH) 7.94(1H, s, CH=) 5.23-9.42(4H, br, NH_3^+ and NH)	$C_7H_8N_5OBrS$	28.98 (29.09)	2.78 (2.79)	24.14 (23.94)
9d	7.04(2H, s, CH=x2) 7.18-7.80(5H, m, Ph) 7.90(1H, d, J=4.8Hz, CH=) 5.23-9.42(4H, br, NH_3^+ and NH)	$C_{11}H_{12}N_5BrS$	40.50 (40.99)	3.71 (3.57)	21.47 (21.08)
9e	0.92(6H, d, J=7.2Hz, CH_3x2) 2.40(1H, m, CH) 7.36(1H, d, J=6.0Hz, CH=) 5.23-9.42(4H, br, NH_3^+ and NH)	$C_6H_{12}N_5BrS$	27.08 (27.07)	4.55 (4.65)	26.31 (25.81)

4-Acetyl-2-(1'-acetyl-2'-substituted methylidene)hydrazino-5-aryl-4,5-dihydro-1,3,4-thiadiazoles (**14a-f**)

To a stirred suspension of dithiocarbohydrazone (**13a-f**) (1 mmol) in a mixture of pyridine (1.6 ml) and acetone (0.9 ml) was added dropwise a great excess of acetyl chloride (0.28 ml, 4 mmol) upon cooling with ice. After stirring was continued for 2 h at room temperature, H_2O (5 ml) was added to the reaction mixture. The

resulting precipitates were collected and recrystallized from ethanol. The results are summarized in Tables 2 and 4.

Table 4 4-Acetyl-2-(1'-acetyl-2'-substituted methylidene)hydrazino-5-aryl-4,5-dihydro-1,3,4-thiadiazoles (**14**)

Compd	^{1}H-Nmr, δ	Formula	Analysis Calcd(Found) C	H	N
	solvent:DMSO-d_6				
14a	2.15(3H, s, CH_3)	$C_{19}H_{18}N_4O_2S$	62.28	4.95	15.29
	2.34(3H, s, CH_3)		(62.68)	(5.11)	(14.95)
	7.16(1H, s, CH)				
	7.25-7.67(10H, m, Phx2)				
	8.41(1H, s, CH=)				
	solvent:$CDCl_3$				
14b	2.34(3H, s, CH_3)	$C_{17}H_{16}N_6O_2S$	55.41	4.39	22.80
	2.54(3H, s, CH_3)		(55.68)	(4.45)	(22.97)
	7.14-8.95(10H, m, ArH, CH and CH=)				
	solvent:DMSO-d_6				
14c	2.26(3H, s, CH_3)	$C_{17}H_{16}N_6O_2S$	55.41	4.39	22.80
	2.48(3H, s, CH_3)		(55.43)	(4.49)	(23.03)
	7.26-8.72(9H, m, ArH and CH)				
	8.98(1H, s, CH=)				
	solvent:$CDCl_3$				
14d	2.27(3H, s, CH_3)	$C_{15}H_{14}N_4O_4S$	52.02	4.07	16.17
	2.46(3H, s, CH_3)		(52.38)	(4.05)	(16.25)
	6.20-7.55(7H, m, ArH and CH)				

	8.45(1H, s, CH=)				
	solvent:$CDCl_3$				
14e	2.19(3H, s, CH_3)	$C_{15}H_{14}N_4O_2S_3$	47.60	3.73	14.80
	2.42(3H, s, CH_3)		(47.53)	(3.82)	(14.75)
	6.88-7.51(7H, m, ArH and CH)				
	8.71(1H, s, CH=)				
	solvent:$CDCl_3$				
14f	0.84(3H, d, J=7.2Hz, CH_3)	$C_{16}H_{20}N_4O_2S$	57.81	6.07	16.85
	0.96(3H, d, J=7.2Hz, CH_3)		(58.01)	(6.05)	(16.76)
	2.23(3H, s, CH_3)				
	2.42(3H, s, CH_3)				
	2.80(1H, m, CH)				
	6.18(1H, d, J=4.8Hz, CH)				
	7.03-7.89(5H, m, Ph)				
	8.18(1H, s, CH=)				

Acid Hydrolysis of 4-Acetyl-2-(1'-acetyl-2'-benzylidene)hydrazino-5-phenyl-4,5-dihydro-1,3,4-thiadiazole (**14a**)

To a solution of **14a** (0.37 g, 1 mmol) in a mixture of H_2O (5 ml) and ethanol (10 ml) was added 1N hydrochloric acid (5 ml), and the mixture was heated under reflux over night. The resulting precipitates deposited upon cooling were collected and recrystallized from dioxane to give benzylidenethiocarbohydrazide (**8a**). Yield 0.25 g(77%). mp 191-192°C.

Alkaline Hydrolysis of 4-Acetyl-2-(1'-acetyl-2'-benzylidene)hydrazino-5-phenyl-4,5-dihydro-1,3,4-thiadiazole (**14a**)

Aqueous 2N sodium hydroxide solution (2.1 ml) was added into a suspension of **14a** (0.73 g, 2 mmol) in a mixture of H_2O (10 ml) and ethanol (10 ml) and the reaction mixture was heated over night under reflux. The resulting precipitates deposited upon cooling were collected and recrystallized from ethanol to give 4-acetyl-2-

(2'-benzylidene)hydrazino-5-phenyl-4,5-dihydro-1,3,4-thiadiazole (**12**). Yield 0.55 g (85%). mp 240 °C. Ir ν (KBr) cm^{-1} : 3135(NH), 1640(C=O). ^{1}H-Nmr (DMSO-d_6) δ : 2.21(3H, s, CH_3), 7.00(1H, s, CH), 7.17-7.85(10H, m, Phx2), 7.95(1H, s, CH=), 12.03(1H, br, NH). Ms m/z: 324 (M^+).

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