A Single-step Synthesis of 2-Substituted 2-Thiazolines[1]

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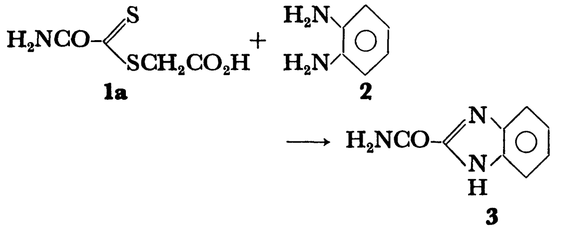
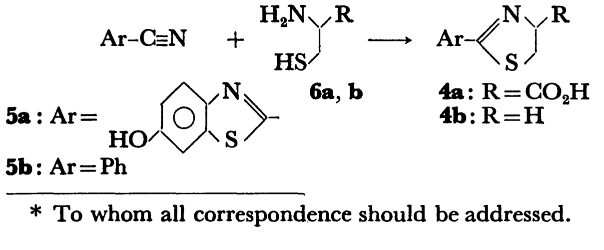
2-Phenyl-2-thiazoline (**4b**) and its derivatives: [4-carboxylic acid (**4c**), 4-carboxylic acid methyl ester (**4d**), and 5,5-dimethyl-4-carboxylic acid (**4e**)], 2-(*p*-chlorophenyl)-2-thiazoline (**4f**) and its 4-carboxylic acid (**4g**), and 2-methyl-2-thiazoline (**4h**) were obtained by treating $RCS_2CH_2CO_2H$ [R=Phenyl (**1b**), *p*-chlorophenyl (**1d**), or methyl (**1e**)] or $MeCS_2Et$ (**1f**) with the corresponding 2-aminoethane thiols, *i.e.*, cysteamine (**6a**), cysteine (**6b**), cysteine methy ester (**6c**), and/or penicillamine (**6d**). **4b** was also obtained from $PhCS_2Et$ (**1c**) and **6a** with a rate approximately equal to that from **1b** and **6a**. The attempted synthesis of 2-methyl-2-thiazoline-4-carboxylic acid (**4i**) using a similar method gave only *N*-acetylcysteine (**7**).

There have been numerous reports concerning the synthesis of 2-aryl- and 2-alkyl-2-thiazolines. The known synthetic methods can be classified as follows: (a) condensation of nitriles (R–C≡N)[2—4] or isonitriles (R–N=C:)[5a] with 2-aminoethane thiols (H_2N–CH_2CH_2–SH), or intramolecular cyclization of 2-mercapto isonitriles [R–CH(SH)CHR′–N=C:];[5b] (b) dehydration of *N*-acyl-2-aminoethane thiols (R–$CONHCH_2CH_2$–SH)[2,6] or *N*-thioacyl-2-aminoethanols (R–$CSNHCH_2$-CH_2–OH);[7] and (c) condensation of thioamides or imino thiols [R–(C=NH)SH] with 1,2-dihalides (X–CH_2CH_2–X) or 2-haloethylamines (H_2N–CH_2CH_2–X),[8] where R and R′=alkyl, aryl, or H, and X=Br or Cl. However, most of these require several steps and/or drastic conditions, such as high temperature and strongly acidic or basic media, to synthesize relatively unstable thiazolines.

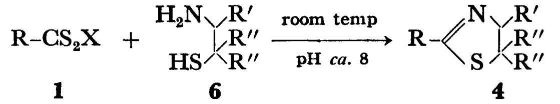
Suzuki and Goto have found in the course of the studies on the firefly bioluminescence[9] that (carbamoylthiocarbonylthio)acetic acid (**1a**)[10] readily condensed with *o*-phenylenediamine (**2**) at room temperature and pH *ca.* 8 to give 2-carbamoylbenzimidazole (**3**); similar reactions were expected to be applicable to the preparation of other five-membered heterocycles.


1a **2** **3**

White *et al.* reported an effective synthesis of an unstable thiazoline, firefly luciferin (**4a**), by condensation of 2-cyano-6-hydroxybenzothiazole (**5a**) with cysteine (**6b**) under mild conditions, *i.e.*, at room temperature at pH *ca.* 8.[4] However, we found that although 2-phenyl-2-thiazoline (**4b**) could be prepared by treating benzonitrile (**5b**) with cysteamine (**6a**) according to the above method (required reflux in EtOH), attempted condensation of the nitrile (**5b**) with other 2-aminoethane thiols (**6b**, **6c**, and **6d**) under similar conditions did not give the corresponding thiazolines (**4c**, **4d**, and **4e**).


5a: Ar= ; **5b**: Ar=Ph ; **6a, b** ; **4a**: R=CO_2H ; **4b**: R=H

In the present paper we wish to report on a convenient preparation of 2-substituted 2-thiazolines and their derivatives (**4b**—**4h**),[1] which were obtained by the condensation of dithioates (**1b**—**1f**) with the corresponding 2-aminoethane thiols (**6a**—**6d**) under slightly alkaline conditions; a probable reaction pathway is also discussed.



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	R	X
1b:	Ph	CH_2CO_2H
1c:	Ph	Et
1d:	*p*-Cl-Ph	CH_2CO_2H
1e:	Me	CH_2CO_2H
1f:	Me	Et

6

	R′	R″
6a:	H	H
6b:	CO_2H	H
6c:	CO_2Me	H
6d:	CO_2H	Me

4

	R	R′	R″
4b:	Ph	H	H
4c:	Ph	CO_2H	H
4d:	Ph	CO_2Me	H
4e:	Ph	CO_2H	Me
4f:	*p*-Cl-Ph	H	H
4g:	*p*-Cl-Ph	CO_2H	H
4h:	Me	H	H

Methods and Results

Syntheses of the 2-phenyl-2-thiazolines (**4b**—**4e**) which gave good yields were performed by the condensation of the dithioate (**1b**)[11] with the corresponding 2-aminoethane thiols (**6a**—**6d**) at room temperature in slightly alkaline media. **4b** was also obtained by the condensation of **6a** with **1c**[12] in place of **1b**.

Similarly, **4f** and **4g** were obtained from **1d**[13] and the corresponding 2-aminoethane thiols (**6a** and **6b**). Although 2-methyl-2-thiazoline (**4h**) was obtained in an unsatisfactory yield by the similar condensation of **1e**[11] or **1f**[12] with **6a**, the attempted synthesis of the 4-carboxylic acid (**4i**) by treating **1e** or **1f** with **6b** was unsuccessful; *N*-acetylcysteine (**7**), mp 106 °C,[14] as

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TABLE 1. SYNTHESIS OF THE 2-THIAZOLINES (**4b**—**4h**) AND **7**

Product	**4b**		**4c**	**4d**	**4e**	**4f**	**4g**	**4h**	**7**	
Reagents										
RCS_2X	**1b**	**1c**	**1b**	**1b**	**1b**	**1d**	**1d**	**1e**	**1e**	**1f**
2-Aminoethane thiols	**6a**	**6a**	**6b**	**6c**	**6d**	**6a**	**6b**	**6a**	**6b**	**6b**
Reaction Time (h)	5	5	23	3.5	22	22	20	22	48	28
Solvent[a)]	E(2:1)		E(2:1)	M	E(2:1)	E(1:1)	E(1:1)	E(1:1)	E(1:1)	
Isolation[b)]	A		B	C	C	C	D	C	C	
Recryst. Solvent[c)]	—		C	A	A	B	B	—	—	
Cryst. Form and Color[d)]	C-Liq.		C–N	C–FN	C–P	PY–L	C–FN	PY–Liq.	C–N	
Yield (%)	87	84	79	84	88	66	53	25	65	45
Mp (bp) (°C)	(129—130.5 °C/ 10 Torr)		121.5—122.5 °C	112—114 °C	120—121.5 °C	50—52 °C	169—171 °C	(144 °C)	106—108 °C	
[lit.]	(110 °C/5 Torr)		122 °C	113—114 °C	—	—	—	(143—145 °C)	107—107.5 °C	
Reference	2)		7a)	7a)	—	—	—	19)	14)	

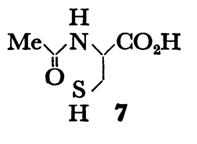
a) E (*n*: 1): EtOH–H_2O (*n*: 1); M: MeOH. b) A: Extd. with CH_2Cl_2 and ether, followed by distn.; B: Extd. with EtOAc and ether; C: Extd. with EtOAc; D: Collected by filtration. c) A: Ether; B: EtOH; C: Benzene–hexane. d) C: Colorless; PY: Pale yellow; N: Needles; L: Leaflets; FN: Fine needles.

TABLE 2. PHYSICAL PROPERTIES OF THE 2-THIAZOLINES (**4b**—**4h**) AND **7**

Compd	$\nu_{\max}^{\text{KBr}}$ (cm^{-1})		δ (ppm)			
	C=N	C=O	Solv.[b)]	C_4	C_5	Others
4b	1605S[a)]		C	4.42, t,[c)] *J* 8 Hz	3.35, t, *J* 8	7.45, 3H, m
						7.89, 2H, m
4c	1605S	1740sh	D	5.24, t, 9	3.56, d, 9	7.48, 3H, m
		1730S			3.65, d, 9	7.76, 2H, m
4d		1745S	C	5.26, t, 9	3.61, d, 9	7.40, 3H, m
		1225			3.66, d, 9	7.82, 2H, m
4e	1590	1735	D	4.81, s	1.44, s,	7.50, 3H, m
					1.72, s	7.78, 2H, m
4f	1605S		C	4.46, t, 8.4	3.44, t, 8.4	7.39, 2H, d, *J* 8.6
						7.79, 2H, d, 8.6
4g	1600S	1725S	D	5.32, t, 8.8	3.65, d, 8.8	7.56, 2H, d, 8.2
					3.68, d, 8.8	7.82, 2H, d, 8.2
4h	1630S		C	4.12, br. t	3.32, t, 10	2.16, 3H, t, 2
7		1720M	D	4.40, m	2.80, m	1.91, 3H, s
		1635S				8.11, 1H, d, 8.0(NH)

a) S: strong; M: medium. b) C: chloform-d_1; D: dimethyl-d_6 sulfoxide. c) s: singlet; d: doublet; t: triplet; m: multiplet; br: broad.

colorless crystals was however obtained in moderate yields (44% for **1e** and 65% for **1f**).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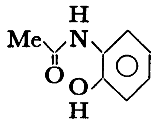
The results and the physical properties of the products are summarized in Table 1 and 2.

Discussion

To account for the observed products, especially *N*-acetylcysteine (**7**), a stepwise reaction pathway may be considered as the possible reaction scheme rather than a concerted reaction pathway. The product (**7**) is regarded as a rearrangement product of *S*-acetylcysteine derived from a hydrolysis of *S*-thioacetylcysteine;[14)] this is supported by the moderate stability of **4e** reported by Smith and Gorin.[14)] The production of *N*-acetyl-*o*-aminophenol (**8**) in the synthesis of 2-methylbenzoxazole (**9**)[15)] may also support the stepwise reaction pathway.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The first step in this reaction should be a nucleophilic attack of one of two nucleophiles, *i.e.*, the amino group or the sulfide anion.

$-SCH_2CO_2H$ **10** $-SEt$ **11**

It is well known that the carboxymethylthio group (**10**) is an effective leaving group in aqueous alkaline media. We expected to get some mechanistic information about the first step of the present reaction when the group **10** was replaced by the ethylthio group (**11**), which is supposed to be a less effective leaving group than **10**.16,17) When **1b** and **1c** were treated with **6a**, the disappearance rates of **1b** and **1c** were almost identical and the products were identified by GLC and IR spectra to be **4b**. This fact implies that there is little effect from the leaving groups on this reaction (see Fig. 1), and also that the sulfide anion is so strong a nucleophile that no significant effect from the leaving group could be determined.

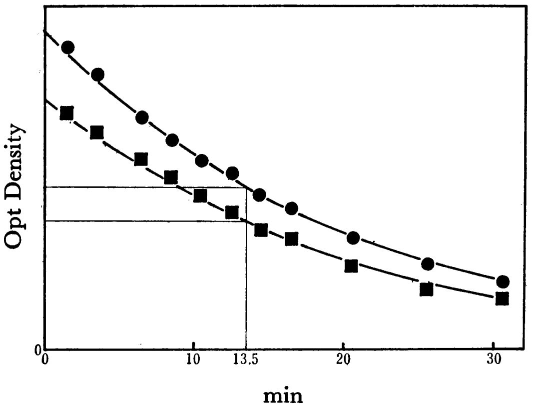

Fig. 1. Optical densities of **1b** and **1c** on treatments with **6a** at λ_{max} 488 nm in aqueous EtOH (1: 1).
—●—: **1b**, —■—: **1c**.

Lawson and Searle have shown that in the absence of any steric hindrance to the approach of the amino-nitrogen atom to the thion-carbon atom of **1b**, the ease of thiobenzoylation of amino compounds depends largely on the nucleophilicity of the amino-nitrogen atom.7b) Thus, the lower yield of 2-methyl derivative (**4h**) and the unsuccessful attempt to prepare **4i** may be explained by the lowering of the electrophilicity of the thion-carbon atom caused by an electronic effect of the methyl substituent in the second step of the present reaction.

Some of the cyclizations to yield 2-thiazolines were reported to be acid catalysed.2,5b,7a–c,12) The cyclization in the present reaction, however, occurs in basic conditions.

Provided that the present reaction proceeds through a stepwise mechanism, and since the acidities of -SH and -NH$_2$ are

$$\text{-SH} \gg \text{-NH}_2,^{18)}$$

we suggest that the cyclization may proceed as follows:

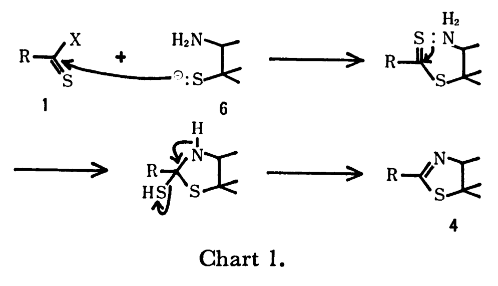

Chart 1.

Experimental

All mps and bps were uncorrected. The following spectrometers were used for spectral measurements: UV: Shimadzu UV-200; IR: JASCO IR-G; NMR: JEOL JNM-MH-100 (100 MHz); MS: JEOL JMS-D-100. The spectral data are presented as follows: UV: in nm and ε in parentheses; IR in cm^{-1}; NMR: chemical shifts (δ) in ppm from int. TMS and coupling constants (J) in Hz (accuracy$\pm$0.5 Hz); the solvents used are given in parentheses. GLC conditions used were as follows: Yanagimoto Yanaco G-1800F; Silicone SE-GE-31 (10%) on Diasolid L (60—80 mesh), in stainless steel column (2 m$\times\phi$ 2.25 mm); col. temp 215 °C, inj. temp 170 °C, carrier gas (N$_2$) 20 ml/min. TLC conditions used were as follows: Silica gel PF$_{254}$-gipshaltig (E. Merck A. G.); thickness: 2.2 mm, 20 cm×20 cm, hexane.

Benzonitrile (**5b**), acetonitrile, cysteine (**6b**), cysteine methyl ester (**6c**), penicillamine (**6d**), and *N*-acetyl-L-cysteine (**7**) were purchased from Nakarai Chem. Co., and cysteamine (**6a**) was from Tokyo Kasei Chem. Co.

*Carboxymethyl dithiobenzoate (**1b**)*11) and *carboxymethyl p-chlorodithiobenzoate (**1d**)*13) were prepared according to the method of Kurzer *et al.*11) **1b**: Red fine prisms; mp 121—123 °C [lit,11) 125 °C], λ_{max} [EtOH–H$_2$O (1: 1)] 487 nm (ε 120), 294 (12000), no change occurred after the addition of 1 M NaOH. **1d**: Reddish orange leaflets; mp 120—121 °C [lit,13) 115—117 °C]; Found: C, 44.09; H, 2.76%. Calcd for C$_9$H$_7$ClO$_2$S$_2$: C, 43.81; H, 2.86%.

*Ethyl dithioacetate (**1f**)*,12) *ethyl dithiobenzoate (**1c**)*,12) and *carboxymethyl dithioacetate (**1e**)*13) were prepared according to the methods of Meijer *et al.*12) **1c**: Red liq.; bp 113—118 °C/1.2 mmHg [lit,13) 164 °C/12 Torr], λ_{max} [EtOH–H$_2$O (1: 1)] 488 nm (100), 298 (10800), no change occurred after the addition of 1 M NaOH. **1e**: Yellow needles; mp 76—79 °C [lit,7a) 80—81 °C]. **1f**: Orange-yellow liq.; bp 47—50 °C/12 mm [lit,12) 52 °C/12 mm].

Authentic samples of **4c**, **4d**, **4h** were prepared by the methods described in the lit. **4c**: Colorless needles; mp 116—117 °C [lit,7a) mp 122 °C]. **4d**: Colorless fine needles; mp 112—114 °C [as HCl salt; lit,7a) mp 113—114 °C]. **4h**: Pale-yellow liq. bp 142—144 °C [lit,19) bp 143—145 °C].

General Synthetic Procedure of the Thiazolines. The dithioate (**1b**—**f**) (1.0 mmol) and the aminothiol (**6a**—**d**) (1.1 mmol) were dissolved in aqueous MeOH or aqueous EtOH (1: 1; 25 ml); the pH was adjusted to *ca.* 8 with aqueous 1 M NaOH. The mixture was stirred at room temp under slightly reduced pressure (aspirator) to remove H$_2$S generated until the red color of the dithioate disappeared. The reaction was also monitored by TLC (E. Merck A. G.; Silica gel PF$_{254}$-gipshaltig, *ca.* 0.25 mm, hexane–acetone, 3: 1). The pH of the mixture was checked occasionally and kept *ca.* 8 by intermittent additions of the aqueous alkali. After the mixture was acidified (pH *ca.* 3) with aqueous 1 M HCl and concentrated *in vacuo* below 40 °C, the resulting aqueous mixture was extracted with CHCl$_3$ or EtOAc. Evaporation of the extracts and/or crystallization gave a liquid (**4b** or **4h**) or crystalline product (**4c**, **4d**, **4e**, **4f**, or **4g**) in good yield. The results and their properties are shown in Tables 1 and 2. The products of each condensation were checked with GLC and/or TLC before and after the acidification of the reaction mixtures. The products were identical before and after the work-up.

The thiazoline (**4b**) synthesized was identical with that from **5b** and **6a** (IR and NMR), and its bp was identical with that which appears in the lit.11) The carboxylic acid (**4c**) and its methyl ester (**4d**) were identified by comparing with mp, IR, and NMR of the authentic samples.7a) 2-Methyl-2-thiazoline

(**4h**) synthesized was identical with that of the authentic sample.[19] The *N*-acetylcysteine (**7**) obtained was assigned by comparing its mp, IR, and NMR with the authentic sample.[14]

2-Phenyl-5,5-dimethyl-2-thiazoline-4-carboxylic Acid (4e). Found: C, 61.39; H, 5.58%. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57%. Its IR spectrum was very similar to that of **4c**; MS showed a molecular peak at *m/e* 235 and NMR spectral data showed two methyls (1.44s and 1.72s), a methine (4.81s), and monosubstituted benzene protons (7.50 m and 7.78 m), which support the structure assignment (**4e**).

*2-(*p*-Chlorophenyl)-2-thiazoline (4f).* Found: C,54.44; H, 3.79%. Calcd for C_9H_8ClNS: C, 54.68; H, 4.08%. Its IR spectrum was very similar to that of **4b**; MS showed a molecular peak at *m/e* 197 and its NMR spectrum showed two methylenes (3.44 t and 4.46 t), and *p*-disubstituted benzene protons (7.39 d and 7.79 d), which support the structure assignment (**4f**).

*2-(*p*-Chlorophenyl)-2-thiazoline-4-carboxylic Acid (4g).* Found: C, 49.82; H, 3.23; N, 5.64%. Calcd for $C_{10}H_8ClNO_2S$: C, 49.70; H, 3.34; N, 5.80%. Its IR spectrum was very similar to that of **4c**; MS showed a molecular peak at *m/e* 241 and its NMR spectrum showed two methylene protons (3.65 d and 3.68 d), a methine (5.32 t), and *p*-disubstituted benzene protons (7.56 d and 7.82 d), which support the structure assignment (**4g**).

*Relative Rate of Reaction of **1b** or **1c** with **6d**.* Into the aqueous ethanolic (1:1; 3 ml) solutions of **1b** or **1c** (0.1 mmol/15 ml) were added an aqueous 1 M NaOH (60 μl) and then an aqueous ethanolic solution (2 ml) of **6a** (0.11 mmol/10 ml). Their optical densities at *ca.* 488 nm were measured at intervals (16 °C). The relative reaction rate was calculated based on the results to be about unity ($\tau_1/_2=13.5$ min). The generation of **4b** was confirmed by GLC. (See Fig. 1).

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