Thiocyanoacetate. IV. The Reaction of Ethyl Thiocyanoacetate with Aromatic Aldehydes in the Presence of Thioureas[1]

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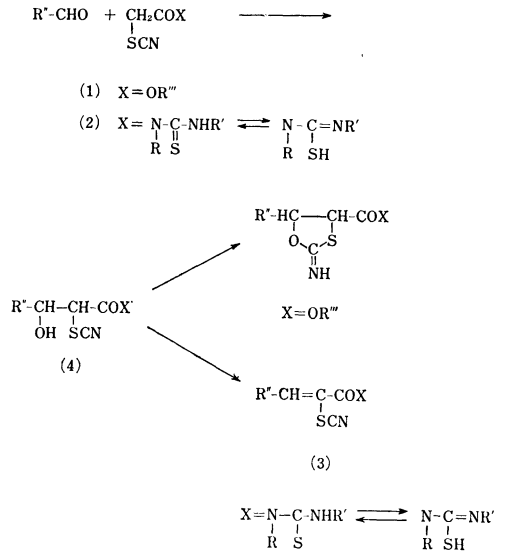
Ethyl thiocyanoacetate (**1**) reacts with anomatic aldehydes in the presence of *N,N'*-dialkylthiourea to give arylidene *N,N'*-dialkyl-*N*-thiocarbamoyl thiocyanoacetamides (**3**). On the other hand, the treatment of the ester (**1**) with benzaldehyde in the presence of thiourea or *N*-methylthiourea under the same conditions affords 5-benzylidene-2-imino-4-thiazolidinone (**5a**) or 5-benzylidene-3-methylthiazolidine-2,4-dione (**6a**).

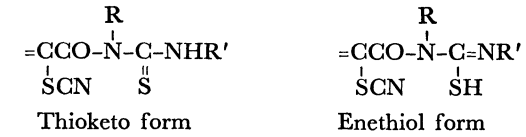
In the first paper of this series[2] it was shown that, in the presence of potassium carbonate or fluoride, thiocyanoacetic acid esters (**1**) and aldehydes undergo an Aldol-type condensation, followed by ring closure, to give *N*-carbamoyl-2-imino-1,3-oxathiolanes and α,β-unsaturated esters. However, we have found that *N,N'*-dialkyl-*N*-thiocarbamoyl thiocyanoacetamide (**2**) and aromatic aldehydes lead to a Knoevenagel-type condensation giving arylidene *N,N'*-dialkyl-*N*-thiocarbamoyl thiocyanoacetamides (**3**) in a good yield. This means that, in the case of the amide **2**, the dehydration rate of the intermediate **4** is larger than the rate of ring closure, whereas with the ester **1**, the reverse is true. It seems interesting that the modification of the ester group by the *N*-carbamoyl amide group causes a drastic change in the reaction course.



Scheme 1.

Results and Discussion

The reaction of the ester **1** with aromatic aldehydes in the presence of *N,N'*-dialkylthioureas gave arylidene *N,N'*-dialkyl-*N*-thiocarbamoyl thiocyanoacetamides (**3**), whose structures were confirmed on the basis of elemental analyses and spectral studies.

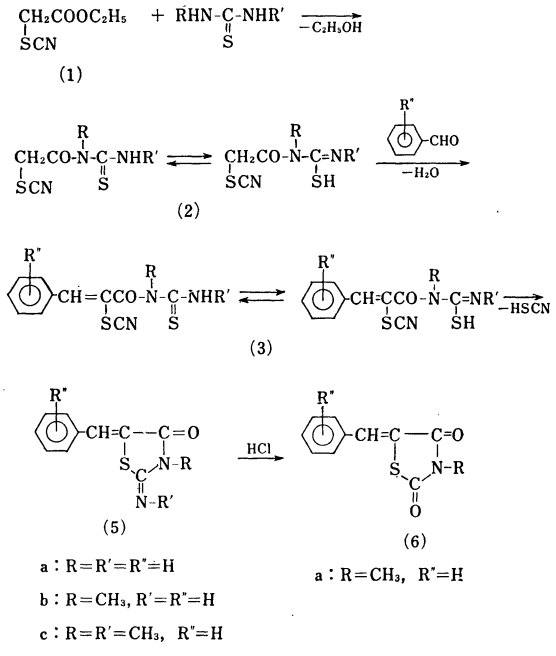


Thioketo form Enethiol form

Compounds **2** and **3** can exist in two tautomeric forms, the thioketo and enthiol forms, as is shown above. Product **3a**, for example, consisted of pale yellow needles with the structural formula $C_{13}H_{13}ON_3S_2$; mp 185—186°C. The IR spectrum of **3a** (KBr pellet) revealed the existence of the SH (near 2550 cm^{-1}), SCN (2050 cm^{-1}), C=O (1740 cm^{-1}), C=N (1640 cm^{-1}), and C=C (1600 cm^{-1}) groups. The NMR spectrum of **3a** (DMSO-d_6) showed the CH_3 proton signal δ at 3.25 and 3.30, =C<u>H</u> at 7.90, $C_6\underline{H}_5$ at 7.60, and a broad line with intensity of one proton at 8.85 ppm, a line which might be attributed to the SH proton. These facts suggest that **3** exists predominantly in the enethiol form.

The products (**3b—n**) could be obtained similarly from the reaction of substituted benzaldehyde with the ester **1** in the presence of *N,N'*-dialkylthiourea (see Table 1). However, the substituent effect was obscure in this case.

A plausible reaction sequence is illustrated in Scheme 2. Presumably, the reaction proceeds through the intermediacy of *N,N'*-dialkyl-*N*-thiocarbamoyl thio-



a : R=R'=R"=H
b : R=CH_3, R'=R"=H
c : R=R'=CH_3, R"=H

a : R=CH_3, R"=H

Scheme 2.

1) Part III of this series: S. Kambe and T. Hayashi, This Bulletin, **45**, 952 (1972).
2) S. Kambe, T. Hayashi, H. Yasuda, and H. Midorikawa, *ibid.*, **44**, 1357 (1971).

Table 1. Properties of arylidene *N,N*-dialkyl-*N*-thiocarbamoyl thiocyanoacetamides (**3**)

Product	R=R′	R″	Reaction time (hr)	Mp (°C)	Yield (%)	Formula	Analysis (%) Found (Calcd) C	H	N	S	SH str. (cm^{-1})	SCN str. (cm^{-1})	C=O str. (cm^{-1})	C=N str. (cm^{-1})	C=C str. (cm^{-1})
a	CH_3	H	2	185—186	65	$C_{13}H_{13}ON_3S$	53.48 (53.61)	4.44 (4.50)	14.35 (14.43)	21.90 (21.90)	2550 w	2050 s	1740 s	1640 s	1600 s
b	CH_3	*p*-CH_3	1.5	172—173	53	$C_{14}H_{15}ON_3S_2$	55.24 (55.08)	4.90 (4.95)	13.89 (13.77)	21.00 (20.96)	2550 w	2050 s	1750 s	1640 a	1610 sh
c	CH_3	*o*-OCH_3	1.5	196—197	47	$C_{14}H_{15}O_2N_3S_2$	52.38 (52.33)	4.76 (4.71)	13.10 (13.08)	19.28 (19.22)	2600 w	2050 s	1740 a	1640 s	1600 s
d	CH_3	*p*-OCH_3	2	180—181	43	$C_{14}H_{15}O_2N_3S_2$	52.42 (52.33)	4.55 (4.71)	13.50 (13.08)	19.34 (19.22)	2600 w	2050 s	1740 s	1640 s	1600 s
e	CH_3	*p*-$N(CH_3)_2$	2	236—237	56	$C_{15}H_{18}ON_4S_2$	53.90 (53.88)	5.48 (5.43)	16.72 (16.76)	19.18 (19.14)	2550 w	2050 s	1730 s	1630 a	1600 s
f	CH_3	*o*-OH	2	210—211	46	$C_{13}H_{13}O_2N_3S_2$	51.00 (50.81)	4.52 (4.26)	13.71 (13.68)	21.01 (20.82)	2600 w	2050 s	1730 s	1620 m	1590 s
g	CH_3	*p*-OH	2	219—221[a]	39	$C_{13}H_{13}O_2N_3S_2$	51.16 (50.81)	4.30 (4.26)	13.74 (13.68)	20.89 (20.82)	2600 sh	2050 s	1730 s	1640 s	1600 s
h	C_2H_5	H	2	169—170	62	$C_{15}H_{17}ON_3S_2$	56.82 (56.42)	5.40 (5.37)	13.20 (13.16)	20.10 (20.04)	2600 w	2050 s	1720 s	1620 sh	1600 s
i	C_2H_5	*p*-CH_3	2	157—158	65	$C_{16}H_{19}ON_3S_2$	57.67 (57.65)	5.78 (5.75)	12.64 (12.61)	19.15 (19.19)	2600 w	2050 s	1720 s	1640 s	1590 s
j	C_2H_5	*o*-OCH_3	1.5	164—165	59	$C_{16}H_{19}O_2N_3S_2$	55.09 (55.01)	5.50 (5.48)	12.10 (12.03)	18.45 (18.32)	2600 w	2050 s	1720 s	1640 s	1590 s
k	C_2H_5	*p*-OCH_3	1.5	174—175	45	$C_{16}H_{19}O_2N_3S_2$	55.29 (55.01)	5.48 (5.48)	12.22 (12.03)	18.49 (18.32)	2600 w	2050 s	1740 s	1650 s	1610 m
l	C_2H_5	*p*-$N(CH_3)_2$	2	201—202	45	$C_{17}H_{22}ON_4S_2$	56.39 (56.34)	6.18 (6.12)	15.41 (15.46)	17.61 (17.66)	2600 w	2050 s	1720 s	1640 s	1590 s
m	C_2H_5	*o*-OH	2	137—138	48	$C_{15}H_{17}O_2N_3S_2$	53.61 (53.73)	5.23 (5.11)	12.86 (12.53)	19.15 (19.08)	2550 w	2050 s	1730 s	1620 s	1590 s
n	C_2H_5	*p*-OH	2	98— 99	49	$C_{15}H_{17}O_2N_3S_2$	53.78 (53.73)	5.32 (5.11)	12.49 (12.53)	19.28 (19.08)	2550 w	2050 s	1730 s	1630 s	1590 s

a) Decomp. All IR spectra were measured in KBr pellets.

cyanoacetamide (**2**), which subsequently condenses with aromatic aldehyde to give **3**.

Support for this may be supplied by the fact that the ester **1** reacted easily with *N,N'*-dialkylthiourea to give the amide **2**, and that the amide **2** thus isolated condensed with an aromatic aldehyde in the presence of *N,N'*-dialkylthiourea as a basic catalyst to give the product **3**. In contrast with the above reaction, when thiourea was used instead of *N,N'*-dialkylthiourea, the reaction of the ester **1** with benzaldehyde led to the formation of 5-benzylidene-2-imino-4-thiazolidinone (**5a**).[3]

The reaction of ester **1** with benzaldehyde in the presence of *N*-methylthiourea afforded 5-benzylidene-3-methylthiazolidine-2,4-dione (**6a**).[3] This compound is considered to be produced by the hydrolysis of 5-benzylidene-2-imino-3-methylthiazolidin-4-one (**5b**), which may be formed as an intermediate. Compound **6a** was obtained by the hydrolysis of the **3a** product with hydrochloric acid–ethanol. In addition, the reaction of the ester **1** with *N*-methylthiourea gave the corresponding amide (**2a**) (R=CH_3, R=H), but not 2-imino- or oxothiazolidinone. On the other hand, the treatment of **3a** with potassium carbonate or fluoride gave 5-benzylidene-2-methylimino-3-methyl-4-thiazolidinone (**5c**), which was identical with the authentic sample prepared by the alternative synthesis from benzaldehyde and 2-methylimino-3-methyl-4-thiazolidinone.[4] Furthermore, this compound (**5c**) was also obtained by the reaction of the amide **2b** (R=R'=CH_3) with benzaldehyde in the presence of potassium carbonate or fluoride. These facts suggest that, in the reaction of the amide **2** with aromatic aldehyde, the formation of a 4-thiazolidinone ring occurs after the condensation between the amide **2** and aromatic aldehyde has taken place. It is interesting that the ring closure of **3** might occur with the elimination of hydrogen thiocyanide, as is shown in Scheme 2.

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a Shimadzu IR-27G spectrometer. The NMR spectra obtained on a Nihondenshi JNM-C-60 high-resolution NMR spectrometer (60 MHz). Tetramethylsilane was used as the internal standard. The chemical shifts of the protons are presented in terms of δ values.

General Procedure for the Reaction of Ethyl Thiocyanoacetate. (1) With Aromatic Aldehyde in the Presence of N,N'-*Dialkylthiourea*: A mixture of the ester **1** (0.02 mol), an aldehyde (0.02 mol), and an *N,N'*-dialkylthiourea (0.02 mol) in ethanol (20 m*l*) was refluxed for a suitable period. After the reaction mixture had then been cooled, the resulting precipitates were filtered and washed with water. They were recrystallized from ethanol to give arylidene *N,N'*-dialkyl-*N*-thiocarbamoyl thiocyanoacetamide (**3**). The results are summarized in Table 1.

The Reaction of Ethyl Thiocyanoacetate (1) with Benzaldehyde in the Presence of N-*Methylthiourea.* A mixture of the ester **1** (0.02 mol), benzaldehyde (0.02 mol), and *N*-methylthiourea (0.02 mol) in ethanol (20 m*l*) was refluxed for 5 hr. After cooling, the resulting precipitate was filtered and washed with water. Recrystallization from ethanol gave 5-benzylidene-3-methylthiazolidine-2,4-dione (**6a**); yield, 48%; mp 133—134°C (lit,[3] 134—135°C).

The Reaction of Ethyl Thiocyanoacetate (1) with Benzaldehyde in the Presence of Thiourea. A mixture of the ester **1** (0.02 mol), benzaldehyde (0.02 mol), and thiourea (0.02 mol) in ethanol (20 m*l*) was refluxed for 3 hr. A crystalline precipitate was deposited during the reaction; this was collected on a filter and washed with ethanol. Recrystallization from dimethyl sulfoxide gave 5-benzylidene-2-imino-4-thiazolidinone (**5a**); yield, 37%; decomp. 282—284°C (lit,[3] decomp. 282—284°C).

The Reaction of Ethyl Thiocyanoacetate (1) with N-*Methylthiourea.* The ester **1** (0.02 mol) was added, drop by drop at approximately 60°C, to a mechanically-stirred solution of *N*-methylthiourea (0.02 mol) in 20 m*l* of ethanol. Stirring was continued for 3 hr. After the solvent had then been removed with a vacuum evaporater, the residue was allowed to stand overnight. The precipitate which thus formed was separated by filtration, washed with water, and recrystallized to give *N*-methyl-*N*-thiocarbamoyl thiocyanoacetamide (**2a**); yield, 25%; decomp. 175—178°C.

IR (KBr): near 3300 (NH), near 2500 (SH), 2050 (SCN), 1670 (C=O), 1650 (C=N) cm^{-1}.

Found: C, 31.71; H, 3.69; N, 21.43; S, 33.81%. Calcd for $C_5H_7ON_3S_2$: C, 31.75; H, 3.73; N, 22.22; S, 33.83%.

The Reaction of Ethyl Thiocyanoacetate (1) with N,N-*Dimethylthiourea.* A mixture of the ester **1** (0.02 mol) and *N,N'*-dimethylthiourea (0.02 mol) in ethanol (20 m*l*) was refluxed for 2 hr. The resulting precipitate was collected on a filter and washed with water. Recrystallization from ethanol gave *N,N'*-dimethyl-*N*-thiocarbamoyl thiocyanoacetamide (**2b**); yield, 68%; mp 174—175°C.

IR (KBr): near 2550 (SH), 2050 (SCN), 1750 (C=O, 1640 (C=N) cm^{-1}.

Found: C, 35.51; H, 4.50; N, 20.89; S, 31.67%. Calcd for $C_6H_9ON_3S_2$: C, 35.47; H, 4.47; N, 20.69; S, 31.50%.

The Reaction of Ethyl Thiocyanoacetate (1) with N,N'-*Diethylthiourea.* A solution which contained the ester **1** (0.02 mol) and *N,N'*-diethylthiourea (0.02 mol) in ethanol (20 m*l*) was refluxed for 4 hr. After the solvent had then been removed with a vacuum evaporator, the residue was allowed to stand for several days. The crystalline matter thus formed was collected, washed with water, and air-dried. Recrystallization from ethanol–water gave *N,N'*-diethyl-*N*-thiocarbamoyl thiocyanoacetamide (**2c**); yield, 21%; mp 96—97°C.

Found: C, 41.52; H, 5.66; N, 18.31; S, 27.73%. Calcd for $C_8H_{13}ON_3S_2$: C, 41.56; H, 5.67; N, 18.18; S, 27.73%.

The Reaction of Ethyl Thiocyanoacetate (1) with Thiourea. Thiourea (0.02 mol) was stirred in ethanol (20 m*l*) at approximately 60°C; the stirring was then continued until the thiourea was completely dissolved. To a stirred alcoholic solution there was then added, drop by drop, the ester **1** (0.02 mol) over a 0.5-hr period. After this addition, stirring was continued for an additional 4 hr, and then the reaction mixture was allowed to stand for several hours. The crystalline matter thus formed was collected and washed with ethanol. Recrystallization from acetic acid gave 2-imino-4-thiazolidinone; yield, 19%; decomp. 232—235°C (lit,[5] 233—238°C).

3) S. Kambe, T. Hayashi, H. Yasuda, and A. Sakurai, *Nippon Kagaku Zasshi*, **92**, 867 (1971).

4) R. Andreasch, *Monatsh. Chem.*, **39**, 417 (1918).

5) H. R. Snyder and E. X. Werber, "Organic Syntheses" Vol. 27, p. 71 (1947).

The Reaction of N,N′-*Dimethyl*-N-*thiocarbamoyl Thiocyanoacetamide (***2b***) with Benzaldehyde in the Presence of* N,N′-*Dimethylthiourea.* A solution of the amide **2b** (0.01 mol) benzaldehyde (0.01 mol), and *N,N′*-dimethylthiourea (0.0025 mol) in ethanol (30 m*l*) was refluxed for 4 hr. After cooling, a crystalline matter separated; this was recrystallized from ethanol to afford benzylidene *N,N′*-dimethyl-*N*-thiocarbamoyl thiocyanoacetamide (**3a**); yield, 65%.

The Reaction of N,N′-*Dimethyl*-N-*thiocarbamoyl Thiocyanoacetamide (***2b***) with Benzaldehyde in the Presence of Potassium Carbonate or Fluoride.* To a solution of the (**2b**) amide (0.01 mol) and benzaldehyde (0.01 mol) in ethanol (20 m*l*), potassium carbonate or fluoride (0.01 mol) was added, after which the mixture was refluxed for a suitable period. After standing overnight, the resulting precipitate was collected on a filter and washed with water. Recrystallization from ethanol gave 5-benzylidene-2-methylimino-3-methyl-4-thiazolidinone (**5c**); mp 109—110°C.

When potassium carbonate was used as the catalyst, the reaction time was 2 hr and the yield was 54%.

When potassium was used as the catalyst, the reaction time was 7 hr and the yield was 58%.

IR (Nujol): 1750 (C=O), 1660 (C=N), 1620 (C=C) cm^{-1}.

NMR (DMSO-d_6): δ 3.20, 3.40 (CH_3), 6.05 (C_6H_5), 6.15 (=CH) ppm.

Found: C, 61.89; H, 5.20; N, 12.04; S, 13.74%. Calcd for $C_{12}H_{12}ON_2S$: C, 62.06; H, 5.21; N, 12.06; S, 13.77%.

The Reaction of Benzylidene N,N′-*Dimethyl*-N-*thiocarbamoyl Thiocyanoacetamide (***3a***) in the Presence of Potassium Carbonate or Fluoride.* A mixture of the amide **3a** (0.01 mol) in ethanol (20 m*l*) containing potassium carbonate or fluoride (0.01 mol) was refluxed for a suitable period. After the mixture had then stood overnight, the precipitate formed was separated by filtration, washed with water, and recrystallized from ethanol to afford 5-benzylidene-2-methylimino-3-methyl-4-thiazolidinone (**5c**).

When potassium carbonate was used as the catalyst, the reaction time was 2 hr and the yield was 56%.

When potassium fluoride was used as the catalyst, the reaction time was 6 hr and the yield was 58%.

The Hydrolysis of Benzylidene N,N′-*Dimethyl*-N-*thiocarbamoyl Thiocyanoacetamide (***3a***).* To a solution containing concentrated hydrochloric acid (10 m*l*) and ethanol (10 m*l*), we added the amide **3a** (0.01 mol), and then the mixture was refluxed for 6 hr. After cooling, the reaction mixture was poured onto cracked ice. The crystalline matter thus formed was collected, washed with water, and air-dried. Recrystallization from ethanol gave 5-benzylidene-3-methylthiazolidin-2,4-dione (**6a**); yield, 52%; mp 133—134°C (lit,[3] 134—135°C).

The Hydrolysis of 5-Benzylidene-2-methylimino-3-methyl-4-thiazolidinone. The procedure used was essentially the same as that described above; yield, 53%; mp 133—134°C.

The Reaction of 2-Methylimino-3-methyl-4-thiazolidinonew ith Benzaldehyde. 2-Methylimino-3-methyl-4-thiazolidinone was prepared according to the procedure described in the literature.[4]

A mixture of 2-methylimino-3-methyl-4-thiazolidinone (0.01 mol) and benzaldehyde (0.01 mol) in ethanol (10 m*l*) containing potassium acetate (0.01 mol) was refluxed for 4 hr. After the solvent had been removed, the residue was allowed to stand overnight. The resulting crystals were collected on a filter. Recrystallization from ethanol gave 5-benzylidene-2-methylimino-3-methyl-4-thiazolidinone (**5c**); yield, 56%; mp 109—110°C.

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