BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 1638—1642 (1968)

Synthetic Reactions by Complex Catalysts. IX. Reaction of Thiol with Isocyanide

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(Received October 19, 1967)

The reaction of a thiol with an isocyanide proceeds in two directions. In the first reaction (course a), the carbon atom of isocyanide with lone-pair electrons is inserted into the sulfur-hydrogen bond of thiol to produce thioformimidate (I). In the second reaction (course b), isothiocyanate (II) and the alkane (III) from the alkyl group of thiol are formed. The proportion of the participation of two reactions depends upon the alkyl group of thiol and upon the reaction conditions including whether or not a catalyst is employed. Primary thiol prefers course a to course b, whereas tertiary thiol prefers course b. In the reactions at 15°C, the Group IB and IIB metal compounds, *e. g.*, copper compounds, catalyzed the course a reaction preferably. At higher temperatures, *e. g.*, at 100°C, thiol reacts with isocyanide quite rapidly, even in the absence of a catalyst. However, the catalyst effect favoring course a is seen even in the high-temperature reactions. The mechanism of the reaction, especially course b, has been discussed. *Syn-anti* structures of thioformimidate were also studied by NMR.

We have reported a series of insertion reactions of isocyanide into the nitrogen-hydrogen bond of amine,[1] the oxygen-hydrogen bond of alcohol[2,3] and the silicon-hydrogen bond of silane.[4]

$$RN\rightleftarrows C: + HNR'R'' \longrightarrow RN{=}CHNR'R'' \quad (1)$$

$$RN\rightleftarrows C: + HOR' \longrightarrow RN{=}CHOR' \quad (2)$$

$$RN\rightleftarrows C: + HSiR'_3 \longrightarrow RN{=}CHSiR'_3 \quad (3)$$

These reactions are all catalyzed by copper compounds to produce the corresponding derivatives of *N*-alkylformimidic acid. This paper will describe our studies of the reaction of thiol with isocyanide. The structure of thioformimidate will also be examined by NMR.

Results and Discussion

Reaction of Thiol with Isocyanide. The reaction of a thiol with an isocyanide proceeds in the following two directions:

$$RN\rightleftarrows C: + HSR' \begin{cases} \xrightarrow{\text{Course a}} RN{=}CHSR' \quad (I) & (4) \\ \xrightarrow{\text{Course b}} RN{=}C{=}S \;(II) + R'H \;(III) & (5) \end{cases}$$

In the first reaction (course a, Eq. (4)), the carbon atom of isocyanide with lone-pair electrons is inserted into the sulfur-hydrogen bond of thiol to produce thioformimidate (I). In the second reaction (course

1) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota and H. Yoshioka, *Tetrahedron Letters*, **1966**, 6121.
2) T. Saegusa, Y. Ito, S. Kobayashi and K. Hirota, *ibid.*, **1967**, 521.
3) T. Saegusa, Y. Ito, S. Kobayashi, N. Takeda and K. Hirota, *ibid.*, **1967**, 1273.
4) T. Saegusa, Y. Ito, S. Kobayashi and K. Hirota, *J. Am. Chem. Soc.*, **89**, 2240 (1967).

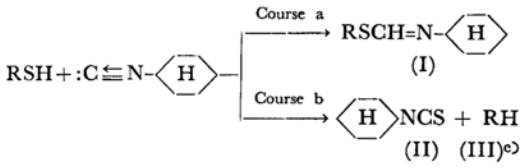
b, Eq. (5)), isothiocyanate (II) and alkane (III) from the alkyl group of thiol are formed by a process including the transfer of the sulfur atom from thiol to isocyanide. As will be discussed later, these reactions do not proceed consecutively, but they occur separately.

The proportion of the participation of the two reactions depends on the alkyl group of thiol and on the reaction conditions, including whether or not a catalyst is employed.

The results of the reactions of thiol with cyclohexyl isocyanide are shown in Tables 1 and 2, where the effects of the thiol alkyl group and of the reaction conditions are illustrated. In the reactions at 15°C, the catalyst activities of the Group IB and IIB metal compounds have been clearly demonstrated. However, at higher temperatures, *e. g.*, at 100°C, the reaction proceeds rapidly even without any added catalyst.

The alkyl group of thiol controls the relative participations of the two reactions. Primary thiols, *e. g.*, IV and VI in Tables 1 and 2, prefer course a to course b. On the other hand, tertiary thiols,

Table 1. Reactions of thiols with cyclohexyl isocyanide[a] (part 1)



RSH	Catalyst	Yield[g] (%) I	II
C_2H_5SH (IV)	None	trace	3
	$Cu(acac)_2$[d]	86	1
	CuO	76	3
	$CuCl_2$	32	2
	$Cd(OAc)_2$[e]	67	4
i-C_3H_7SH (V)	None	1	16
	Cu_2O	78	3
	$ZnCl_2$	45	10
	$Hg(OAc)_2$[f]	41	14
n-C_4H_9SH[b] (VI)	Cu_2O	73	7
	Cu	81	4
t-C_4H_9SH (VII)	None	0	26
	$Cd(OAc)_2$[e]	13	68
	CuCN	8	54
	CuO	4	38
C_6H_5SH[b] (VIII)	None	89	0
	Cu_2O	42	0

a) The reactions were carried out at 15°C, for 3 hr, unless otherwise indicated.
b) Reaction conditions; at 20°C for 15 hr.
c) The yield of III was not determined.
d) Copper acetylacetonate.
e) Cadmium acetate.
f) Mercuric acetate.
g) The yield of each product is based on the amount of cyclohexyl isocyanide.

Table 2. Reactions of thiols with cyclohexyl isocyanide[a] (part 2)

RSH	Catalyst	Reaction time (hr)	Yield[b] (%) I	II	III
C_2H_5SH (IV)	None	3	85	8	n. d.[c]
	Cu_2O	3	93	1	n. d.
i-C_3H_7SH (V)	None	1.5	23	64	60
	Cu_2O	3	86	5	n. d.
t-C_4H_9SH (VII)	None	1.5	1	92	81

a) The reactions were carried out at 100°C.
b) The structures of the products are indicated in Table 1. The yield of each product is based on cyclohexyl isocyanide.
c) n. d.; not determined.

e. g., VII, prefer course b. 2-Methyl-2-heptanethiol also takes course b preferably.

Propane and isobutane are, respectively, the alkane products of the course b reactions of 2-propanethiol and 2-methyl-2-propanethiol with isocyanide. No olefinic hydrocarbon was detected in the products of these reactions by NMR analysis.

The Group IB and IIB metal compounds catalyze the thiol-isocyanide reaction and also increase the relative participation of the course a reaction. The effect of the catalyst upon the relative participations of two reactions is well demonstrated in the reaction of cyclohexyl isocyanide with 2-propanethiol. The uncatalyzed reaction is inclined towards course b, producing isothiocyante, whereas the catalyzed reaction preferably proceeds through course a. A similar tendency is seen in the reactions of isocyanide with other thiols. Copper compounds, such as cuprous and cupric oxides and copper acetylacetonate, dissolve in the thiol-isocyanide mixture at room temperature to form a homogeneous system. The compounds of cadmium, zinc, and mercury also accelerate the course a reaction in preference to the course b reaction. Catalyzed reactions (course a) proceeded at fairly high rates. For example, the yield of ethyl *N*-cyclohexylthioformimidate in the reaction of ethanethiol-cyclohexyl isocyanide with copper acetylacetonate at 15°C was 30% at 20 min, 55% at 40 min, 65% at 1 hr, and 86% at 3 hr.

Aromatic thiol also reacts with isocyanide through course a. The reaction of benzenethiol (VIII) with cyclohexyl isocyanide, with or without a catalyst, gave phenyl *N*-cyclohexylthioformimidate exclusively.

Aromatic isocyanides react with thiols to produce the corresponding thioformimidates. For example, *n*-butyl *N*-phenylthioformimidate was produced in a yield of 90% by the reaction of phenyl isocyanide with *n*-butanethiol.

The reactions of the two courses occur separately, but not consecutively. In other words, isothiocyanate (II) and alkane (III) are not formed

by the decomposition of thioformimidate. The reaction between 2-methyl-2-propanethiol and cyclohexyl isocyanide occurs preferably along course b, producing cyclohexyl isothiocyanate and isobutane. However, these products are not formed by the decomposition of *t*-butyl *N*-cyclohexylthioformimidate. It was observed that *t*-butyl *N*-cyclohexylthioformimidate, which was prepared by the thiol interchange between isopropyl *N*-cyclohexylthioformimidate and 2-methyl-2-propanethiol, remained unchanged under the same reaction conditions in the presence of a catalyst.

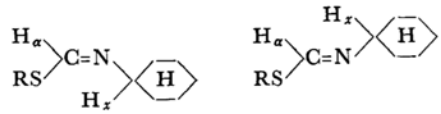
A mechanism involving a free radical may be considered to explain the over-all results of the reactions without any added catalyst.

$$\mathrm{RSH} \xrightarrow{\mathrm{R'\cdot}} \mathrm{RS\cdot} \xrightarrow{\mathrm{R''\text{-}N\rightleftarrows C}} \mathrm{RS\text{-}\dot{C}(=NR'')\text{-}} \xrightarrow{\mathrm{RSH}} \mathrm{RSCH{=}NR''} + \mathrm{RS\cdot}$$

$$\mathrm{RS\text{-}\dot{C}(=NR'')\text{-}} \xrightarrow[\beta\text{-scission}]{} \mathrm{R''\text{-}N{=}C{=}S} + \mathrm{R\cdot} \xrightarrow[\mathrm{RSH}]{} \mathrm{RH} + \mathrm{RS\cdot}$$

As to the above scheme of a free radical mechanism, it has been observed that the addition of a radical inhibitor such as hydroquinone does not affect the reaction between thiol and isocyanide. Further work is now in progress to elucidate the reaction mechanism, especially the function of the metal catalyst.

***Syn-anti* Structures of Thioformimidate.** For thioformimidate, the *syn* (IX) and *anti* (X) forms are expected as a result of the restricted rotation of the >C=N–bond.

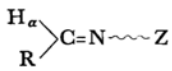


syn (IX) *anti* (X)

In the NMR spectra of thioformimidates in deuteriochloroform and benzene, two signals were obtained in the region of τ 1.7—2.1; both signals were assigned to H_α of IX and X (Table 3).

In Fig. 1, the NMR spectrum of ethyl *N*-cyclohexylthioformimidate is shown as an example. The two signals of H_α have been ascribed to *syn-anti* isomerism on the basis of the solvent effect on the NMR spectrum.[5,6]

Karabatsos *et al.*[5,6] have presented a method for assigning the *syn* and *anti* structures of hydrazone, semicarbazone, and related compounds with this general formula:



This method has been applied to thioformimidate in the present study. Because of the repulsion between the lone-pair electrons of the nitrogen of thioformimidate and the π-electrons of the benzene ring of the solvent, the shielding effect of the benzene ring upon *trans* H_α (*syn* form) is less than that upon *cis* H_α (*anti* form). In Table 3, the two signals of H_α hydrogen have been assigned on the basis of the above consideration. From the peak areas

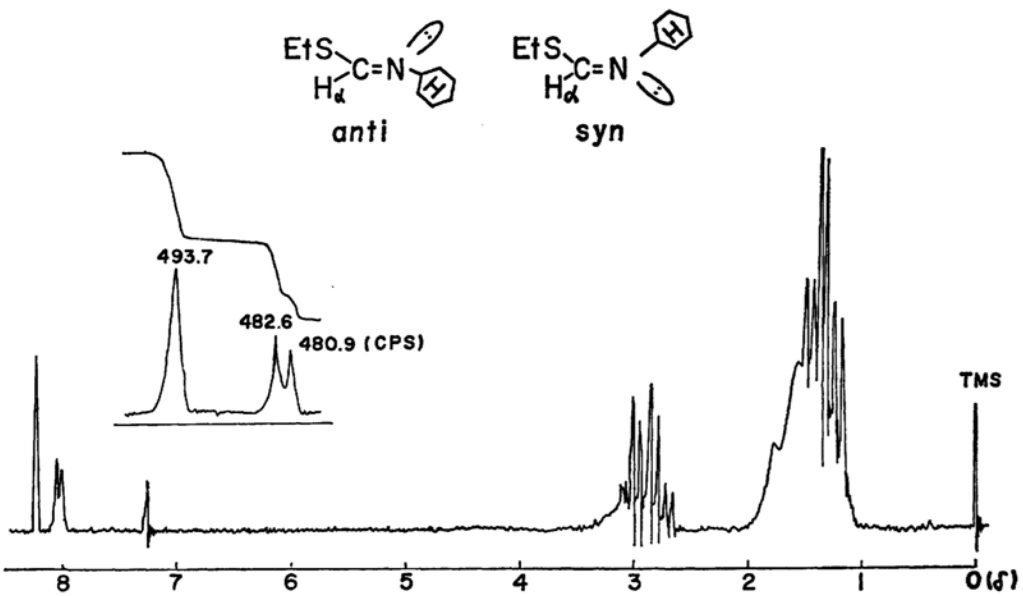


Fig. 1. NMR spectrum of ethyl *N*-cyclohexylthioformimidate (XI) (in deuteriochloroform).

5) G. J. Karabatsos, R. A. Taller and F. M. Vane, *ibid.*, **85**, 2326 (1963).

6) G. J. Karabatsos and R. A. Taller, *ibid.*, **85**, 3624 (1963).

TABLE 3. NMR DATA OF $-SCH_\alpha=N-$ OF THIOFORMIMIDATES[a)]

Thioformimidate	Solvent		H_α cps	$J_{H_\alpha H_x}$ cps	Ratio[b)] (%)
$C_2H_5SCH_\alpha=N-$  (XI)	$CDCl_3$	*syn*	480.9, 482.6	1.7	47
		anti	493.7	0.0	53
	C_6H_6	*syn*	471.2, 472.9	1.7	—
		anti	476.7	0.0	—
i-C_3H_7-$SCH_\alpha=N-$  (XII)	$CDCl_3$	*syn*	485.9, 487.5	1.6	56
		anti	495.1	0.0	44
	C_6H_6	*syn*	480.2, 481.8	1.6	—
		anti	477.6	0.0	—
t-C_4H_9-$SCH_\alpha=N-$  (XIII)	$CDCl_3$	*syn*	496.5, 498.2	1.7	73
		anti	506.7	0.0	27
	C_6H_6	*syn*	496.3, 498.0	1.7	—
		anti	487.0	0.0	—
 (XIV)	$CDCl_3$	*syn*	480.7, 482.6	1.9	72
		anti	500.4	0.0	28
	C_6H_6	*syn*	481.0, 482.6	1.6	—
		anti	486.6	0.0	—
n-C_4H_9-$S-CH_\alpha=N-$  (XV)	$CDCl_3$	*syn*	487.8	—	8
		anti	492.0	—	92

a) All spectra were recorded at 60 Mc/sec on a modified JEOL JNM-3H-60 spectrometer for 10—15% $CDCl_3$ or C_6H_6 solutions at 23°C. Chemical shifts values are in cps from TMS as an internal standard.
b) No reliable value is obtained in benzene, because the signals of H_α and benzene protons overlap each other.

TABLE 4. SOLVENT EFFECTS ON THE CHEMICAL SHIFTS OF PROTONS (H_α)

Thioformimidate		$\Delta\nu_{cps}$ value (ν in $CDCl_3$ $-$ ν in C_6H_6)
XI	*syn*	9.7
	anti	17.0
XII	*syn*	5.7
	anti	17.5
XIII	*syn*	0.2
	anti	19.7
XIV	*syn*	~0.0
	anti	13.8

of the two H_α signals, the *syn*/*anti* ratio has been calculated. As is indicated in Table 3, *syn* H_α gives a doublet, whereas *anti* H_α gives a singlet. The coupling of *syn* H_α with the α-hydrogen (H_x) of the cyclohexane ring is more pronounced than that of *anti* H_α. This observation corresponds to the fact that the coupling constant between *trans* hydrogens in olefin is larger than that between *cis* hydrogens. Table 4 summarizes the $\Delta\nu$ values ($\Delta\nu=\nu$ in $CDCl_3$ $-\nu$ in C_6H_6) of four thioformimidates.

Experimental

Reaction of IV with Cyclohexyl Isocyanide. A mixture of 6.2 g (0.1 mol) of IV and 8.8 g (0.08 mol) of cyclohexyl isocyanide was stirred, with or without a catalyst (2 mmol), at the indicated reaction temperature. Then the reaction mixture was subjected to glpc, whereby ethyl *N*-cyclohexylthioformimidate (XI) and cyclohexyl isothiocyanate were identified and quantitatively analyzed. XI was isolated from the reaction mixture by distillation, bp 110—112°C/20 mmHg.

Found: C, 63.02; H, 10.05%. Calcd for $C_9H_{17}NS$: C, 63.10; H, 10.01%.

The structure of XI was established by means of NMR (Fig. 1) and infrared spectroscopy ($\nu_{C=N}$ at 1590 cm^{-1}). The authentic sample of cyclohexyl isothiocyanate was prepared by the reaction of cyclohexyl isocyanide with sulfur.[7)]

Reaction of V with Cyclohexyl Isocyanide. The reaction of V with cyclohexyl isocyanide was carried out in the same manner as the above. By glpc analysis, isopropyl *N*-cyclohexylthioformimidate (XII) and cyclohexyl isothiocyanate were identified and quantitatively analyzed. XII was isolated by the distillation of the reaction mixture, bp 135—136°C/20 mmHg.

Found: C, 64.67; H, 10.23; N, 7.62%. Calcd for $C_{10}H_{19}NS$: C, 64.81; H, 10.33; N, 7.56%.

The structure of XII was further established by infrared ($\nu_{C=N}$ 1590 cm^{-1}) and NMR spectra studies. In some experiments, the gas evolved during the reaction was collected in a gas burette and quantitatively analyzed. The evolved gas was identified as propane by glpc and NMR.

7) A. J. Weith, *Ber.*, **6**, 210 (1873).

Reaction of VII with Cyclohexyl Isocyanide. The procedure of the preceding two reactions was adopted. In the glpc analysis of the reaction mixture, *t*-butyl *N*-cyclohexylthioformimidate (XIII) and cyclohexyl isothiocyanate were identified and quantitatively analyzed. The gas evolved from the reaction system was identified as isobutane by glpc and NMR. XIII was isolated by the distillation of the reaction mixture, bp 122—125°C/3 mmHg, mp 56—58°C.

Found: C, 65.98; H, 10.63; N, 7.05; S, 15.53%. Calcd for $C_{11}H_{21}NS$: C, 66.27; H, 10.62; N, 7.03; S, 16.08%.

The structure of XIII was further established by infrared ($\nu_{C=N}$ 1590 cm^{-1}) and NMR spectra studies.

Reaction of Other Thiols with Cyclohexyl Isocyanide. Similarly, VI and VIII were treated with cyclohexyl isocyanide to give *n*-butyl *N*-cyclohexylthioformimidate (bp 129—131°C/3 mmHg) (XVI) and phenyl *N*-cyclohexylthioformimidate (bp 120—122°C/0.1 mmHg) (XIV) respectively. XVI and XIV were identified by means of their infrared and NMR spectra as well as by elemental analysis.

Reaction of VI with Phenyl Isocyanide. Following the procedure described above, a mixture of 9.0 g (0.1 mol) of VI, 8.3 g (0.08 mol) of phenyl isocyanide, and 0.28 g (2 mmol) of cuprous oxide was stirred at 20°C. Then the mixture was distilled to yield *n*-butyl *N*-phenylthioformimidate (XV) (14 g, 90%), bp 151—152°C/20 mmHg.

Found: C, 68.18; H, 7.59; N, 7.11; S, 16.20%. Calcd for $C_{11}H_{15}NS$: C, 68.35; H, 7.82; N, 7.25; S, 16.59%.

The structure of XV was further established by a study of its NMR spectrum.

Exchange of Alkylthio Group of Thioformimidate. A mixture of 5.5 g (0.03 mol) of XII and 9.0 g (0.1 mol) of VII was stirred at 15°C for 1 hr. It was shown by glpc analysis that XII was converted quantitatively into XIII.