

SEVERAL REACTIONS  
OF  
ISOCYANIDE AND RELATED COMPOUNDS

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## P R E F A C E

In the present thesis are collected the author's studies which have been carried out under the direction of Professor Takeo Saegusa at Kyoto University during 1966 — 1969. The studies include new organic reactions of isocyanide, carbon monoxide and carbene, which are characterized by a carbon atom carrying lone-pair electrons. Reactions catalyzed by copper compounds as well as other Groups IB and IIB metal compounds constitute the central feature of the present studies. New organic reactions of isocyanide without catalysts are also presented.

The author expresses his deep gratitude to Professor Takeo Saegusa for his constant guidance and encouragement throughout the work. Grateful acknowledgement is also made to Dr. Yoshihiko Ito for his valuable advice and discussions during the course of studies.

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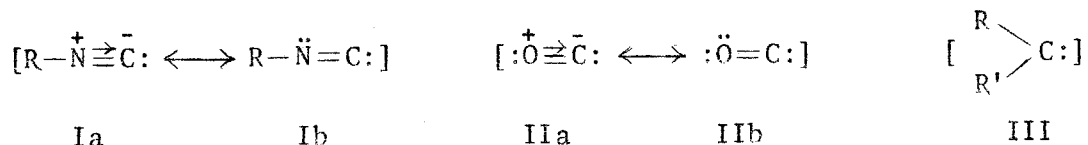
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## I N T R O D U C T I O N

Isocyanide (or isonitrile as it is sometimes called) is a well-known organic compound from old time which is formed by heating a primary amine with chloroform in the presence of alkali. Isocyanide is easily detected by its characteristic unpleasant odor, and this is applied to the detection of primary amine ("carbylamine test").<sup>1)</sup> Isocyanide was prepared more than one hundred years ago.<sup>2)</sup> Little attention, however, has been given to its chemical reactions except for Passerini reaction,<sup>3)</sup> because its preparation was of great difficulty. Since new preparative method of isocyanide has been presented by Ugi in 1960,<sup>4)</sup> much attention has been paid to its chemical behaviors, its increased reactivity and synthetic utility.

Isocyanide is a conspicuous example of stable organic compound which has a carbon atom carrying lone-pair electrons as indicated by the structure (I). Its stability can be rationalized on the basis of two resonance structures (Ia) and (Ib).

Carbon monoxide (II) and carbene (III) are characterized also by lone-pair electrons on a carbon atom. Especially, carbon monoxide has a closely related structure (II) with oxygen in the place of N-R of isocyanide (i.e., which is isoelectronic with isocyanide).



Carbene (III) is probably one of the most intensively studied metastable species at the present time.<sup>5)</sup> It should be noted that a part of reactions which were previously regarded to proceed via "carbene" intermediate has now been called "carbenoid" reaction. However, it is still equivocal to differentiate the term "carbenoid" from the term "carbene" in the strict sense, especially in the case of the so-called catalytic decomposition of diazo compounds. Therefore, the term "carbene" is tentatively used in this volume for the sake of simplicity.

Recently, studies upon synthetic reactions using metal complexes as catalysts have been developed, remarkably. The Fischer-Tropsch process for the conversion of water gas into hydrocarbons, Reppe reactions and "Oxo" process for syntheses of aldehydes or alcohols are based on the reactions of carbon monoxide by the catalysts of transition metal compounds. These reactions are recognized to proceed via metal carbonyl complex intermediates.<sup>6)</sup> This field is of great importance from an industrial view point and has attracted the attention of both industrial and academic chemists. Very few workers, however, have investigated the organic reactions by means of metal isocyanide complexes, although isocyanide are considered to exhibit similar chemical behaviors with carbon monoxide. The different natures as ligands between isocyanide and carbon monoxide are well demonstrated by the difference of the metals with which they are coordinated. The following transition metals have been reported to form isocyanide complexes.<sup>7)</sup> Among them, the

IB	IIB	VIA	VIIA	VIII		
Cu	Zn	Cr	Mn	Fe	Co	Ni
Ag	Cd	Mo	—	Ru	Rh	Pd
Au	Hg	W	Re	—	—	Pt

transition metals of groups VI, VII and VIII generally form more than one type of both isocyanide and carbonyl complexes. On the other hand, the elements of the B groups do not form pure metal carbonyls. Only the metal carbonyl halides of Groups IB elements are known. These facts can be taken to differentiate isocyanide from carbon monoxide. From this standpoint, Groups IB and IIB metal compounds may be expected to show specific catalytic behaviors which are different from other transition metal compounds.

Copper and its compounds are outstanding within Groups IB and IIB metal compounds for the variety and value of their applications as catalysts in several organic reactions, e.g., Ullmann coupling reaction<sup>9)</sup> and Sandmeyer reaction.<sup>10)</sup> The present author has been interested in the facts that isocyanide, carbon monoxide and carbene are coordinated with copper salts, that the decomposition of diazo compounds is catalyzed by copper compounds, and that amine, alcohol, thiol, and phosphine etc are known to coordinate to copper and other Groups IB and IIB metal compounds. The present studies are concerned with reactions of isocyanide, carbon monoxide and carbene from diazo compound in the presence and/or absence of catalysts.

In Part I, reactions of isocyanide with active hydrogen compounds such as amine, alcohol, thiol, silane, and phosphine have been investigated. It has been found that copper compounds as well as other IB and IIB metal



compounds catalyze effectively the reactions of isocyanide with these active hydrogen compounds. The carbon atom having lone-pair electrons of isocyanide is inserted into heteroatom-hydrogen linkages to produce the corresponding derivatives of formimidic acid in high yields and selectivities. These reactions are conveniently utilized for synthetic purposes. Catalytic behaviors of IB and IIB metal compounds, particularly of copper compounds, seem to be quite specific in the reactions of isocyanide with thiol or with silane. These reactions have been proposed to proceed via "mixed ligand complex" intermediates. In fact, ternary complex of cuprous chloride, isocyanide and amine was isolated as an unstable intermediate in the isocyanide-amine reaction.

In Part II, reactions of carbon monoxide and carbene have been studied. The catalytic activities of IB and IIB metal compounds, especially of copper compounds, for the carbonylation of primary and secondary amines to produce formamide derivatives have been investigated in Chapter 1. Copper compounds have been found to be excellent catalysts for the aliphatic amine carbonylation, while gold compound is a good catalyst for the aromatic amine carbonylation. Copper catalyzed insertions of carbene between N-H bond of amine and between S-H bond of thiol and O-H bond of alcohol have been described in Chapters 2 and 3, respectively. All of the products were isolated and the reaction processes have been discussed in detail. In Chapter 4, the reaction of ethyl diazoacetate with cupric chloride has been investigated. All products were explained by assuming unstable organocopper intermediates and subsequent chlorine ligand transfer processes.

In Part III, several reactions of isocyanide have been examined in

relation to the reactions by metal complex catalysts of Part I. Here, the catalytic reactions using transition metal complexes are not included in this Part. New radical reaction of isocyanide with thiol is described in Chapter 1. In the reaction of substituted phenyl isocyanide with thiol, the effect of substituent upon the reactivity was examined. From the Hammett plott, reaction mechanism was discussed. In Chapter 2, new reactions of isocyanide with nitroalkenes are given. Deoxygenation process of nitroalkenes by isocyanide is a quite interesting finding. In Chapter 3, oxidation reaction of isocyanide by nitric and nitrous oxides to produce isocyanate is described.

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## S Y N O P S E S

### Part I

#### Insertion Reactions of Isocyanide Catalyzed by Copper Compounds

New insertion reactions of isocyanide have been found. These reactions require catalysts, which are copper compounds as well as other Groups IB and IIB metal compounds. Reactions of isocyanide examined here are insertions of carbon atom of isocyanide between nitrogen-hydrogen of primary and secondary amine, oxygen-hydrogen of alcohol, sulfur-hydrogen of thiol, silicon-hydrogen of silane and phosphorus-hydrogen of phosphine.

In Chapter 1, reactions of isocyanide with primary and secondary amines producing formamidines catalyzed by Groups IB and IIB metal compounds, mainly by copper compounds, have been investigated. In the reaction of cyclohexyl isocyanide with piperidine, the order of catalytic activity was,  $\text{AgCl} > \text{CuCl} \gg \text{ZnCl}_2, \text{Cd}(\text{OAc})_2, \text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ . The AgCl catalyzed reaction proceeded almost quantitatively in 2.5 hr at 17°C. The reaction of aliphatic isocyanide with aromatic amine, e.g., N-methylaniline, required higher reaction temperatures (160°C) even in the presence of catalyst, in which the order of catalytic activity was,  $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O} > \text{ZnCl}_2 > \text{AgCl} \gg \text{CuCl}$ . A ternary complex of  $(\text{CuCl})_2$ - $(\text{cyclohexyl isocyanide})_2$ (piperidine) was isolated, which was unstable and

decomposed gradually at room temperature to give the formamidine product. A mechanism through a mixed ligand complex has been proposed, in which both isocyanide and amine are coordinated with the common metal ion and the reaction takes place in the sphere of complex ligand.

In Chapter 2, insertion reactions of isocyanide between oxygen and hydrogen bond of alcohols to produce formimidates have been studied in terms of the catalyst activities and of the reaction mechanism. The catalysts are classified into two groups. The first group includes metallic copper, and the oxides of copper ( $\text{Cu}^{\text{I}}$  and  $\text{Cu}^{\text{II}}$ ), silver and mercury, which induce the isocyanide reactions of various alcohols including saturated and unsaturated alcohols and aminoalcohol. The second group catalysts are the chlorides of copper ( $\text{Cu}^{\text{I}}$ ), silver, zinc and cadmium, which cause the reactions of isocyanide only with special alcohols having strong coordinating tendencies toward the catalyst, as being exemplified by allyl alcohol and  $\beta$ -N,N-dimethyl-aminoethanol. Among these catalysts, metallic copper and copper oxides are the most effective and give the products almost quantitatively. The difference in catalyst activity between the two groups of catalysts is well-explained by assuming a ternary complex consisting of the catalyst, isocyanide and alcohol as the site of reaction. It has been observed that copper is dissolved in liquid isocyanide to form a soluble complex. The coordination of isocyanide with copper catalysts has been examined by the shift of  $\nu_{\text{N}\equiv\text{C}}$  band of IR spectrum. The coordination of isocyanide with the first group catalysts (Cu and CuO) is weak (the magnitude of  $\Delta\nu_{\text{N}\equiv\text{C}}$  is small) whereas that with the second group catalysts (CuCl and CuCN) is strong ( $\Delta\nu_{\text{N}\equiv\text{C}}$  is large). From these findings it has been reasoned that the isocyanide ligand which is

loosely coordinated with the first group catalysts is readily replaced even by the alcohols of small coordinating tendencies such as saturated alcohols to form a ternary complex. On the other hand, the isocyanide ligand which is held rather tightly by the second group catalysts is partly replaced only by allyl alcohol and  $\beta$ -aminoethanol having strong coordinating tendencies. The strong coordinations of these special alcohols with CuCl have been demonstrated also by IR spectroscopy.

In Chapter 3, reactions of thiols and isocyanide have been investigated. The reaction of thiol with isocyanide proceeds in two directions. In the first reaction (course-a), the carbon atom of isocyanide having lone-pair electrons is inserted into the sulfur-hydrogen bond of thiol to produce thioformimidate. In the second reaction (course-b), isothiocyanate and the alkane from the alkyl group of thiol are formed. The proportion of the participation of two reactions depends upon the alkyl group of thiol and the reaction conditions including the employment of catalyst. Primary thiol prefers course-a to course-b, on the other hand tertiary thiol prefers course-b. In the reactions at 15°C, the Groups IB and IIB metal compounds, e.g., copper compounds, catalyze preferably the course-a reaction. At higher temperatures, e.g., 100°C, thiol reacts with isocyanide quite rapidly even in the absence of catalyst. However, the catalyst effect favoring course-a is seen even in the high temperature reactions. The mechanism of reaction, especially of course-b, has been discussed. Syn-anti structures of thioformimidate were also studied by NMR.

In Chapter 4, a new hydrosilation reaction of isocyanide is presented. The catalysts required for this reaction are copper compounds which seem

quite specific in catalytic activities. Chloroplatinic acid, which is known to be an efficient catalyst of hydrosilation of olefins, does not work as catalyst for the hydrosilation of isocyanide. Moreover, suitable solvent is necessary for this reaction. The reaction of cyclohexyl isocyanide with trimethylsilane by copper (II) acetylacetonate gave a new compound, formimidoylsilane, in high yield. Cyclohexyl isocyanide—triethylsilane and t-butyl isocyanide—trimethylsilane reactions have also been studied.

Chapter 5 is concerned with the reaction of dialkylphosphine with isocyanide in which the isocyanide carbon atom is inserted between phosphorus and hydrogen of dialkylphosphine. This is a new reaction to form the phosphorus—carbon bond by the  $\alpha, \alpha$ -addition of phosphine to the carbon atom of isocyanide. The product, N-substituted formimidoylphosphine may be regarded as a Schiff base of formylphosphine, which has not been known until now. Reactions of cyclohexyl isocyanide with diethylphosphine and with di-n-propylphosphine have been examined. The order of catalytic activity was,  $\text{Cu}_2\text{O} \gg \text{Cu}(\text{AA})_2, \text{ZnCl}_2, \text{CdCl}_2, \text{Hg}(\text{OAc})_2 \gg \text{AlCl}_3$ .

## Part II

### Reactions of Carbon Monoxide and of Diazo Compounds

Other species than isocyanide which have lone-pair electrons on carbon atom are carbon monoxide and carbenes generated by the decomposition of diazo compounds. From the isoelectronic relationship between carbon monoxide and isocyanide, catalytic reactions of carbon monoxide and amines have been

investigated. Also from a similar standpoint, reactions of carbene species with amine, with thiol and with alcohol have been examined. Finally, reactions of ethyl diazoacetate with metal salts involving ligand transfer reaction have been studied.

Chapter 1 describes the catalytic activities of Groups IB and IIB metal compounds, mainly of copper compounds, for the carbonylation of aliphatic and aromatic amines with carbon monoxide. At the same time, the catalytic activities of other metal compounds have also been examined. It was found that (i) copper compounds are excellent catalysts for the carbonylation of aliphatic amines to produce the corresponding formamides; (ii) the catalytic activities of copper compounds are enhanced by the addition of water; and (iii) chloroauric acid catalyzes the carbonylation of aromatic amine whereas copper compounds do not.

In Chapter 2, insertion reaction of carbenes between nitrogen and hydrogen of amine has been accomplished by copper compound catalysts. Copper compounds catalyzed the reaction of piperidine with ethyl diazoacetate, whereas the acid catalyst did not. Piperidine, morpholine and n-butylamine were used as amine in this reaction, and ethyl diazoacetate and diazomethane were the diazo compounds.

In Chapter 3, the reactions of thiols and alcohols with diazoacetate by copper compound catalyst have been examined, in which R of RSH (thiol) and ROH (alcohol) were n-C<sub>4</sub>H<sub>9</sub>, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub> and CH<sub>2</sub>=CHCH<sub>2</sub>. All the products were isolated and identified, the total yields of the products based on diazoacetate being almost quantitative. In the reaction with thiols, the carbene from ethyl diazoacetate was inserted into the sulfur-hydrogen linkage to



produce ethyl alkylthioacetate in a high yield and a high selectivity. In addition, diethyl alkylthiosuccinate (V) and diethyl thiodiglycolate (VI) were isolated as the by-products. On the other hand, the reaction of alcohol with ethyl diazoacetate afforded the insertion reaction products in low selectivity. The O-analogs corresponding to V and VI as well as triethyl 1-alkoxypropane-1,2,3-tricarboxylate, triethyl propene-1,2,3-tricarboxylate, diethyl fumarate and maleate were formed. In the allyl alcohol—diazoacetate reaction, the cyclopropane derivatives were also formed. Comparison of both reactions and some mechanistic discussions were also given.

In Chapter 4, the reaction of ethyl diazoacetate with  $\text{CuCl}_2$  has been investigated. In this reaction, ethyl chloroacetate, ethyl dichloroacetate and a mixture of ethyl dichloromaleate and ethyl dichlorofumarate were produced. These products were explained by assuming  $\alpha$ -chlorocarboethoxy-methylcopper complexes. The reactions of ethyl diazoacetate with  $\text{CoCl}_2$  and  $\text{HgCl}_2$  were examined in more detail as reference reactions from the mechanistic view point.

### Part III

#### Reactions of Isocyanide with Thiol, with Nitroalkene and with Nitric Oxide

The reactions of isocyanide of this Part do not use metal complex catalysts.

In Chapter 1, radical reaction of isocyanide with thiol has been

investigated. The reaction of isocyanide and thiol proceeds in two courses. Course-A is regarded as  $\alpha,\alpha$ -additions of thiyl group and hydrogen to the isocyanide carbon atom to produce thioformimidate. Course-B forms isothiocyanate from isocyanide and alkane from alkyl group of thiol. First, experimental findings supporting the radical chain mechanism involving thiyl radical are given. Radical reactions of primary and aromatic thiols take course-A, whereas those of  $\alpha$ -toluenethiol as well as tertiary thiols take course-B. The reaction with secondary thiol takes both courses. Copper catalyzed reaction, however, takes course-A exclusively, regardless of the nature of thiol alkyl group. The effect of substituent of aromatic isocyanide upon its reaction with thiyl radical is examined by means of a competitive reaction method. The result of Hammett plots is explained by assuming that the reaction rate is influenced by the polarity of isocyanide in its reaction with thiyl radical and by the resonance stabilization of the resultant formimidoyl radical.

In Chapter 2, new reactions of isocyanide with nitroalkenes are presented. In the nitroalkene--isocyanide reaction, 1-nitropropene and  $\omega$ -nitrostyrene were employed, which have a hydrogen at  $\alpha$ -carbon atom of nitro group. These nitroalkenes react with isocyanide to produce isocyanate and  $\alpha$ -cyano- $\alpha$ -substituted acetamide. The latter reacts with nitroalkene to form  $\alpha$ -cyano- $\alpha,\beta$ -disubstituted  $\gamma$ -nitrobutyramide as a by-product, which is considered to be a Michael addition product. The course of the reaction is explained by assuming that the first step of the reaction involves the nucleophilic attack of isocyanide on  $\beta$ -carbon from nitro group to form the 1,3-dipolar type intermediate followed by the deoxygenation by isocyanide.

In Chapter 3, the oxidation reaction of isocyanide with nitric oxide has been described. The reaction of isocyanide and nitric oxide produces isocyanate and nitrogen in high yields. Nitrous oxide also has the capacity of oxidizing isocyanide to isocyanate.

P A R T I

INSERTION REACTIONS OF ISOCYANIDE CATALYZED  
BY COPPER COMPOUNDS

## Chapter 1

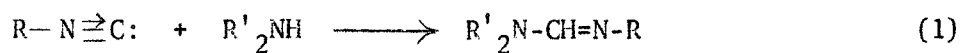
### Reaction of Isocyanide with Amine Catalyzed by Groups IB and IIB

#### Metal Compounds, mainly by Copper Compounds

Various synthetic reactions with copper compound catalysts have been known. Catalysis by copper compound in the reactions of nitrogen-containing compounds, e.g., amines, amino acid, acid amides, nitriles, and diazo compounds, constitutes one of catalysis features of copper, which may be due to a strong tendency of copper to form coordination complexes with nitrogen compounds.

In the present chapter, the reaction of amine with isocyanide was examined based upon the fact that isocyanide also forms a coordination complex with copper (I) compounds.<sup>1)</sup>

It has been found that copper compounds as well as other Groups IB and IIB metal compounds catalyze the reaction of isocyanide with primary and secondary amines, producing formamidine (I). The reaction of aliphatic



I

isocyanide with amine, which does not take place without catalyst, is induced quite effectively by the compounds of copper, silver, zinc, cadmium and gold.

On the other hand, aromatic isocyanides have been known to react with amine even in the absence of the metal compound catalyst.<sup>2)</sup> In the reaction of aromatic isocyanide with amine, however, the accelerating effect of the above metal compounds is observed.

A reaction mechanism through a mixed ligand complex has been proposed, in which both isocyanide and amine are coordinated with the common metal ion and the reaction takes place in the sphere of the complex ligand.

## 1. Results and Discussion

### 1.1. Catalytic Activities of Metal Compounds

The catalytic activities of various metal compounds were examined in the reaction of cyclohexyl isocyanide with piperidine producing N-cyclohexyl-N',N'-pentamethylene formamidine (Table I). The catalytic activities of IB and IIB metal compounds except for mercuric compound are conspicuously shown. The yield of the formamidine product is quite high, and this catalytic reaction can be conveniently utilized for the synthesis of the formamidine derivatives. In contrast to IB and IIB compounds, Lewis acids such as ferric chloride and aluminum chloride are much less active. In the isocyanide—amine reaction, zinc chloride was used in an old work.<sup>3)</sup> The results of an extended screening of the metal compounds in the present studies have indicated that the catalytic activity of zinc chloride is not ascribed to its function of the so-called Lewis acid. In the systems with typical transition metal salts such as cobalt and nickel chlorides the rapid polymerization of isocyanide

took place and hence no formamidine derivative was formed.

Table I. Catalytic Activities of Metal Compounds  
for Cyclohexyl Isocyanide—Piperidine Reaction

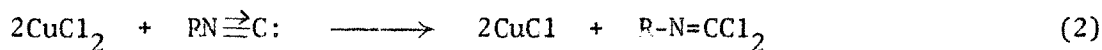


Catalyst	Conditions (hr) <sup>a</sup>	Yield (%)
none	18	0
CuCl	1	96
AgCl	1	98
ZnCl <sub>2</sub>	1	97
Cd(OAc) <sub>2</sub>	1	97
HAuCl <sub>4</sub> ·4H <sub>2</sub> O	22	46
Hg(OAc) <sub>2</sub>	6	5
FeCl <sub>3</sub>	6	15
Ferrocene	17	2
Fe(AA) <sub>3</sub>	4	1
AlCl <sub>3</sub>	7	1

<sup>a</sup> CyclohexylNH, 100 mmol; Cyclohexyl-NC, 30 mmol; Cat., 0.2 mmol;  
110 — 120°C.

Table II illustrates the catalytic activities of several copper compounds and metallic copper. Under these reaction conditions, the catalytic activity (the product yield) is not much affected by the valency of copper and the nature of anion ligand. It is to be mentioned, however, that the cupric chloride is reduced to cuprous chloride by isocyanide in a stoichiometric way

according to equation 2.<sup>4)</sup> Consequently it may be assumed that the cupric



species in Table II were reduced to the cuprous species which served as the real active catalyst.

Table II. Catalysis of Copper Compounds  
in Cyclohexyl Isocyanide—Piperidine Reaction<sup>a</sup>



Catalyst	Yield (%)
CuCl	94
CuCl <sub>2</sub>	86
CuCN	90
Cu(CN) <sub>2</sub>	94
Cu(AA) <sub>2</sub>	86
Cu	93

<sup>a</sup> C<sub>6</sub>H<sub>11</sub>NH, 100 mmol; C<sub>6</sub>H<sub>11</sub>NC, 30 mmol; Cat., 0.2 mmol;  
110 — 120°C., 1 hr.

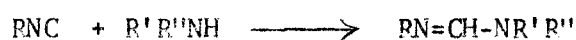
As to the catalyst activity of metallic copper, it is of interest that metallic copper dissolves in liquid isocyanide to form a soluble complex of copper isocyanide. Metallic copper powder was put in liquid cyclohexyl isocyanide and the mixture was centrifuged. The IR spectrum of the liquid phase showed a new band at 2180 cm<sup>-1</sup> in addition to the absorption band of cyclohexyl isocyanide. The new band is reasonably assigned to ν<sub>N=C</sub> of the isocyanide species which is coordinated with copper. Moreover, the correspond-

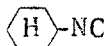

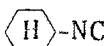
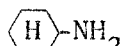
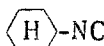
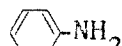
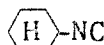
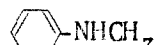
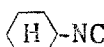



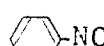



ing formamidine was formed when the liquid phase was treated with piperidine at room temperature. In the system of the metallic copper catalyzed reaction, the catalytic activity is thus ascribed to the soluble complex. (The actual valency of copper in liquid isocyanide must be the subject of future research.)

Table III shows the results of the reactions of three isocyanides with aliphatic and aromatic amines by cuprous chloride catalyst.

Table III. Cuprous Chloride Catalyzed Reaction of Isocyanide with Amine<sup>a</sup>



Isocyanide	Amine	Condition		Yield (%)
		(hr)	(°C)	
		5	25	90
		3	110—120	80
		24	140	85
		25	160	20
	 <sup>b</sup>	6	110—120	82 <sup>c</sup>
<u>n</u> -Bu-NC		3	110—120	90
<u>n</u> -Bu-NC		10	25	87
<u>n</u> -Bu-NC	<u>n</u> -Bu-NH <sub>2</sub>	5	110—120	88
		0.3	0	96

<sup>a</sup> Conditions: RNC, 30 mmol; R'R''NH, 100 mmol; CuCl, 0.2 mmol.

<sup>b</sup> As the reaction solvent, 10 ml of dioxane was employed.

<sup>c</sup> The product was bis-N,N'-(cyclohexylformimidoyl)piperazine.

The cuprous chloride catalyst causes the reaction of aliphatic isocyanide with aliphatic amine at considerable rates even at 25°C. The aliphatic isocyanide—aromatic amine reaction catalyzed by cuprous chloride requires higher reaction temperatures. As will be mentioned later, cuprous chloride is not a suitable catalyst for this combination of reaction.

Aromatic isocyanide reacts with amine without catalyst. For example, the reaction of phenyl isocyanide with piperidine proceeds at 25°C to give N-phenyl-N',N'-pentamethylene formamidine in a yield of 85 % after 48 hr. However, also in this case, the catalysis of cuprous chloride is clearly observed. In the presence of cuprous chloride, the reaction takes place instantaneously even at 0°C to produce the formamidine product almost quantitatively (the last run of Table III).

The catalyst activities of several salts of Groups IB and IIB metals are evaluated in a semiquantitative way by the time-conversion curves in the reactions of cyclohexyl isocyanide with piperidine at 17°C and with N-methylaniline at 160°C as shown in Figs. 1 and 2, respectively. The order of catalyst activity in the former reaction is  $\text{AgCl} > \text{CuCl} \gg \text{ZnCl}_2, \text{Cd}(\text{OAc})_2, \text{HAuCl}_4 \cdot 4\text{H}_2\text{O}$ , which is quite different from the order in the latter reaction of cyclohexyl isocyanide with aromatic amine,  $\text{HAuCl}_4 \cdot 4\text{H}_2\text{O} > \text{ZnCl}_2 > \text{AgCl} \gg \text{CuCl}$ . The specific activity of chloroauric acid in the aromatic amine—iso-cyanide reaction is of interest especially from the fact that it is also quite active as the catalyst in the reaction<sup>5)</sup> of aromatic amine with carbon monoxide which is isoelectronic to isocyanide.

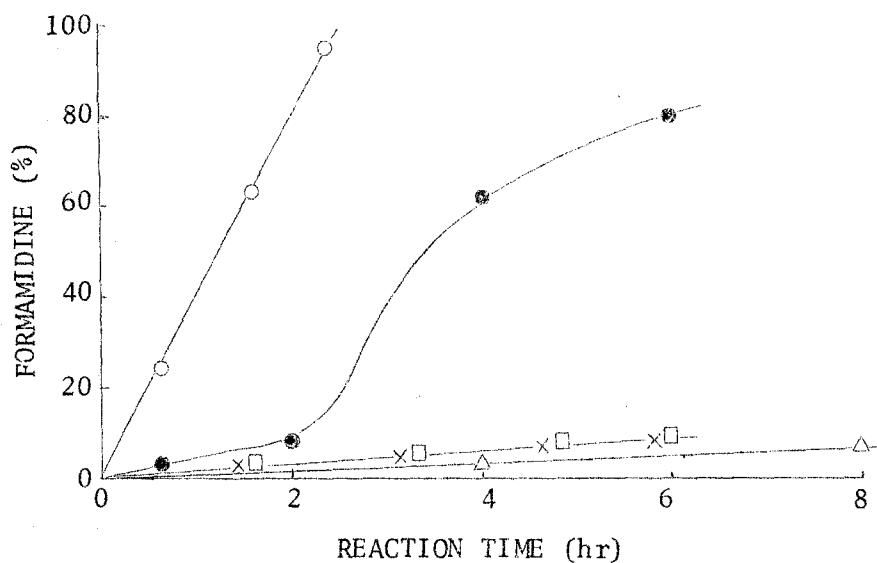


Fig. 1. Reaction of cyclohexyl isocyanide with piperidine (17°C).

—○— : AgCl.                      —●— : CuCl.                      —□— : ZnCl<sub>2</sub>.  
 —△— : HAuCl<sub>4</sub>·4 H<sub>2</sub>O.                      —x— : Cd(OAc)<sub>2</sub>.

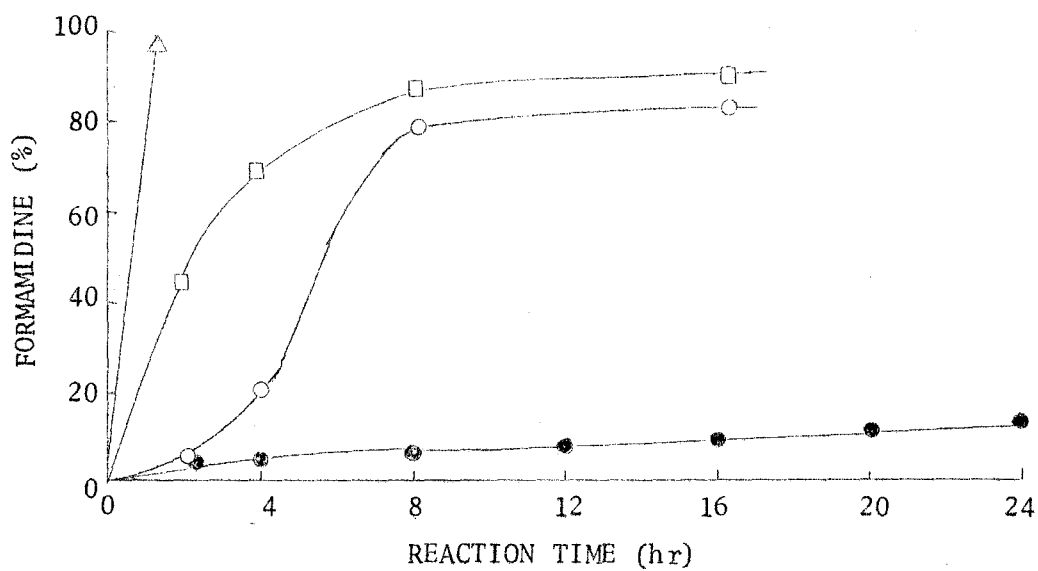


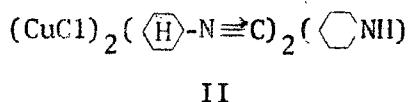
Fig. 2. Reaction of cyclohexyl isocyanide with N-methylaniline (160°C).

—○— : AgCl.                      —●— : CuCl.                      —□— : ZnCl<sub>2</sub>.                      —△— : HAuCl<sub>4</sub>·4 H<sub>2</sub>O.

## 1.2. Mechanism

The isocyanide—amine reaction of the present studies seems to proceed in the ligand sphere of a ternary complex consisting of metal ion, isocyanide and amine. The crystalline, binary complex of cyclohexyl isocyanide and cuprous chloride,  $[\text{Cu}(\text{C}\equiv\text{NC}_6\text{H}_{11})]\text{Cl}$ , was dissolved into liquid piperidine at  $0^\circ\text{C}$ . On standing the homogeneous solution at  $0^\circ\text{C}$ , a new crystalline solid separated out.

NMR spectrum of the new crystalline solid in deuterated chloroform showed two broad signals centered at  $\delta$  3.7 (2H,  $>\text{CH}-\text{N}\equiv\text{C}$ : of two mol. of cyclohexyl isocyanide) and  $\delta$  3.3 (4H,  $-\text{N}\begin{matrix} \text{CH}_2^- \\ \text{CH}_2^- \end{matrix}$  of one mol. of piperidine) and a complex signal at  $\delta$  1.0 — 2.1 (26H, 20H of  $-(\text{CH}_2)_5-$  of two mol. of cyclohexyl isocyanide plus 6H of  $-(\text{CH}_2)_3-$  of one mol. of piperidine). Together with the elemental analysis (Found: C, 45.92; H, 6.78; N, 8.75; Cl, 14.54. Calcd. for II: C, 45.51; H, 6.63; N, 8.38; Cl, 14.14), the composition of the new complex was determined as indicated by the formula,



The IR spectrum of the ternary complex showed two key bands at  $2176\text{ cm}^{-1}$  and  $3192\text{ cm}^{-1}$ , which were assigned to  $\nu_{\text{N}\equiv\text{C}}$  of the isocyanide ligand and  $\nu_{\text{N}-\text{H}}$  of the piperidine ligand. It is quite significant to compare these bands with those observed in three reference species, the isocyanide—CuCl binary complex, free isocyanide and free amine. The band of  $\nu_{\text{N}\equiv\text{C}}$  of the ternary complex is different from the corresponding  $\nu_{\text{N}\equiv\text{C}}$  of the binary complex at  $2192\text{ cm}^{-1}$  and from that of free isocyanide at  $2140\text{ cm}^{-1}$ . Variation of  $\nu_{\text{N}\equiv\text{C}}$  indicates that

the coordination of isocyanide in the ternary complex is influenced by the piperidine ligand. These observations show the formation of a mixed ligand complex in which the isocyanide and amine ligands are coordinated with the common cuprous ion.

The ternary, mixed ligand complex formed here was not stable and decomposed gradually even at room temperature. The decomposition product was just the formamidine product, N-cyclohexyl-N',N'-pentamethylene formamidine. Therefore, it is quite reasonable to assume that the cuprous chloride catalyzed reaction of isocyanide with amine proceeds in the ligand sphere of the mixed ligand complex.

## 2. Experimental

### Materials

Metal salts were commercially available, analytical reagent grade.

Metallic copper was prepared by reduction of cupric sulfate with zinc powder. In 600 ml of water, 100 g of cupric sulfate pentahydrate was dissolved, to which 15 g of zinc powder was added slowly with stirring below 70°C. The precipitate was washed several times with water and then with acetone. It was stored in acetone under nitrogen, and dried under nitrogen immediately prior to use.

Isocyanide was prepared by dehydration of N-substituted formamide with phosphorus oxytrichloride according to the Ugi's procedure.<sup>6)</sup>

### General Procedure

A mixture of isocyanide (30 mmol), amine (100 mmol) and metal compound

catalyst (0.2 mmol) was heated at the indicated temperature monitoring the reaction by the decrease of an infrared band  $\nu_{\text{N}=\text{C}}$  of isocyanide. The product of N,N'-disubstituted formamidine was isolated by distillation or by crystallization. Their structures were established by elementary analysis, IR and NMR spectra.

#### Identifications of the Formamidine Products

N-Cyclohexyl-N',N'-pentamethylene formamidine, b.p. 155 — 156°C (28 mm). Anal. Calcd for  $\text{C}_{10}\text{H}_{20}\text{N}_2$ : C, 74.17; H, 11.41; N, 14.42. Found: C, 74.40; H, 11.71; N, 14.53. IR (neat):  $1660\text{ cm}^{-1}$  ( $\nu_{\text{N}=\text{C}}$ ). NMR ( $\text{CDCl}_3$ ):  $\delta$  7.10 ppm (singlet,  $-\text{N}=\text{CH}-\text{N}<$ ).

N,N'-Dicyclohexyl formamidine, m.p. 100 — 101°C (recrystallization from *n*-hexane). Anal. Calcd for  $\text{C}_{13}\text{H}_{24}\text{N}_2$ : C, 74.94; H, 11.61; N, 13.45. Found: C, 74.61; H, 11.35; N, 13.64. IR (nujol):  $3280\text{ cm}^{-1}$  ( $\nu_{\text{N}-\text{H}}$ ),  $1650\text{ cm}^{-1}$  ( $\nu_{\text{N}=\text{C}}$ ).

N-Cyclohexyl-N'-methyl-N'-phenyl formamidine, b.p. 94 — 96°C (0.7 mm). Anal. Calcd for  $\text{C}_{14}\text{H}_{20}\text{N}_2$ : C, 77.73; H, 9.32; N, 12.95. Found: C, 77.61; H, 9.58; N, 13.11. IR (neat):  $1640\text{ cm}^{-1}$  ( $\nu_{\text{N}=\text{C}}$ ).

Bis-N,N'-(cyclohexylformimidoyl)piperazine, m.p. 99 — 101°C (recrystallization from *n*-hexane). Anal. Calcd for  $\text{C}_{18}\text{H}_{32}\text{N}_4$ : C, 71.00; H, 10.59; N, 18.40. Found: C, 71.16; H, 10.71; N, 18.68; Molecular weight (cryoscopic in benzene) Calcd for  $\text{C}_{18}\text{H}_{32}\text{N}_4$ : 304. Found: 294. IR (nujol):  $1630\text{ cm}^{-1}$  ( $\nu_{\text{N}=\text{C}}$ ).

N-*n*-Butyl-N',N'-pentamethylene formamidine, b.p. 118 — 120°C (27 mm). Anal. Calcd for  $\text{C}_{10}\text{H}_{20}\text{N}_2$ : C, 71.37; H, 11.98; N, 16.65. Found: C, 71.39; H, 12.08; N, 16.79. IR (neat):  $1640\text{ cm}^{-1}$  ( $\nu_{\text{N}=\text{C}}$ ). NMR ( $\text{CCl}_4$ ):  $\delta$  7.10 ppm (singlet,  $-\text{N}=\text{CH}-\text{N}<$ ).

### Preparation of Cyclohexyl Isocyanide—Cuprous Chloride (1:1) Complex

Cuprous chloride was added slowly to excess cyclohexyl isocyanide at room temperature, and the precipitation was collected by filtration. The white crystalline product was recrystallized from chloroform-ether, m.p. 95 — 96°C. Elementary analysis revealed that the crystalline product consisted of 1 mol cyclohexyl isocyanide and 1 mol cuprous chloride. Anal. Calcd for  $C_7H_{11}NCuCl$ : C, 40.40; H, 5.22; N, 6.60; Cl, 17.01. Found: C, 40.40; H, 5.29; N, 6.73; Cl, 17.07.

### Preparation of Ternary Complex

A mixture of piperidine (0.04 mol) and cyclohexyl isocyanide—cuprous chloride (1:1) complex (1 g) was stirred below 0°C. After several minutes a green homogeneous solution was obtained. On standing for further several minutes, a white crystalline was precipitated. The crystalline was washed with dry cold petroleum ether by decantation and dried in vacuo. This ternary mixed ligand complex is unstable at room temperature, and is readily decomposed to give N-cyclohexyl-N',N'-pentamethylene formamidine.

### References

- 1) L. Malatesta, "Progress in Inorganic Chemistry," Vol. 1, Interscience Publishers, New York, (1959), p. 283.
- 2) J. U. Nef, Ann, 270, 267 (1892).

- 3) T. L. Davis and W. E. Yelland, J. Am. Chem. Soc., 59, 1998 (1937).
- 4) To be published.
- 5) See Part II, Chapter 1.
- 6) I. Ugi and R. Meyr, Ber, 93, 239 (1960).



## Chapter 2

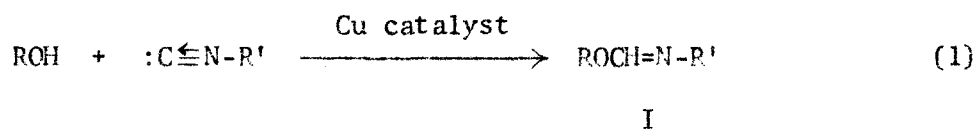
### Copper Catalyzed Reaction of Isocyanide with Alcohol

Based upon the fact that isocyanides form complexes with various transition metal salts, especially copper compounds, isocyanides are expected to react with alcohols as well as with amines<sup>1)</sup> as described in Chapter 1 in the presence of copper catalysts.

The present chapter describes the copper catalyzed reactions of isocyanides with alcohols, together with some results of infrared spectrum studies upon the interactions between copper catalyst and the reaction components.

#### 1. Results and Discussion

It was found that a new reaction of an isocyanide with an alcohol producing a formimidate, which was accomplished for the first time by means of catalysts of metallic copper and some copper compounds.



This reaction provides a convenient, highly selective method for the

preparation of formimidates. The product formimide may be regarded as being derived by the insertion of the isocyanide carbon bearing lone pair electrons between the oxygen and the hydrogen of the alcohol. In the absence of the copper catalyst, alcohol is quite inert toward isocyanides. Alcohol was sometimes employed as an inert solvent in several reactions of isocyanides.<sup>2)</sup>

### 1.1. Reactions of Isocyanides with Alcohols Catalyzed by Metallic Copper and Copper Oxides

Metallic copper and copper oxides ( $\text{Cu}^{\text{I}}$  and  $\text{Cu}^{\text{II}}$ ) catalyzed quite effectively the reactions of cyclohexyl isocyanide with various alcohols (Tables I and II).

Table I. Metallic Copper<sup>a</sup> Catalyzed Reactions of Cyclohexyl Isocyanide with Alcohols<sup>b</sup>

ROH	Product yield (%)	
	I	II
EtOH	99 <sup>c</sup>	1
<u>n</u> -BuOH	99 <sup>d</sup>	—
<u>sec</u> -BuOH	98 <sup>e</sup>	2
$\text{CH}_2=\text{CHCH}_2\text{OH}$	95 <sup>f</sup>	3

<sup>a</sup> Metallic copper was prepared by the reduction of  $\text{CuSO}_4$  with zinc powder according to the procedure given in "Organic Syntheses," Coll. Vol. 2, (1941), p. 432.

<sup>b</sup> Reaction conditions: Cyclohexyl isocyanide, 30 mmol; alcohol, 34 mmol; Cu, 3 mmol; 120°C; 5 hr.

<sup>c</sup> B.p. 85°C (27 mm).

<sup>e</sup> B.p. 90°C (21 mm).

<sup>d</sup> B.p. 81°C (21 mm).

<sup>f</sup> B.p. 90°C (26 mm).

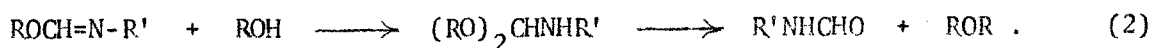
Table II. Copper Oxide Catalyzed Reaction  
of Cyclohexyl Isocyanide with Alcohols<sup>a</sup>

ROH	Cat.	Product yield (%)		
		I	II	III
EtOH	Cu <sub>2</sub> O	95	2	1
<u>n</u> -BuOH		95	1	
<u>sec</u> -BuOH		94	2	trace
<u>t</u> -BuOH		94 <sup>b</sup>		
CH <sub>2</sub> =CHCH <sub>2</sub> OH		92	5	
EtOH	CuO	87	1	
<u>n</u> -BuOH		81	—	
<u>sec</u> -BuOH		88	—	
<u>t</u> -BuOH		91	1	trace
CH <sub>2</sub> =CHCH <sub>2</sub> OH		89	3	

<sup>a</sup> Reaction conditions: Cyclohexyl isocyanide, 30 mmol; alcohol, 34 mmol; CuO (or Cu<sub>2</sub>O), 3 mmol; 120°C; 5 hr.

<sup>b</sup> B.p. 93°C (19 mm).

Several alkyl N-cyclohexylformimidates were produced in almost quantitative yields. In the reactions catalyzed by cuprous and cupric oxides, small amounts of two by-products, N-cyclohexylformamide (II) and alkyl N-cyclohexylcarbamates (III) were formed. II may possibly have been produced by the hydrolysis of the isocyanide or formimide (I) with water which was present as an impurity in the initial reaction mixture or was produced in situ by the etherification of alcohol. II may also be derived from the formimide according to



The formation of III is ascribed to the oxidation of isocyanide to isocyanate by the copper oxide catalysts. The reduction-oxidation between mercuric oxide and isocyanide is known, in which isocyanide is oxidized into isocyanate.<sup>3)</sup>



As expected, III was not formed in the reaction when metallic copper was the catalyst. As to the catalyst activity of metallic copper, it is very important to note that a small amount of metallic copper dissolved in cyclohexyl isocyanide to form a soluble complex. The complex formation from metallic copper and isocyanide will be described later. From these observations, it appears possible that copper oxide catalysts are reduced by isocyanide to form a copper(0)—isocyanide complex which is the actual active species responsible for their catalytic activities.

#### 1.2. Cuprous Chloride Catalyst in the Isocyanide—Alcohol Reaction

The catalysis of cuprous chloride in the alcohol—isocyanide reaction was somewhat different from that of metallic copper and of copper oxides. Cuprous chloride did not induce the isocyanide reactions with the usual saturated alcohols such as ethanol and n-butanol. It catalyzed only the reactions involving  $\beta$ -dimethylaminoethanol and  $\beta,\gamma$ -unsaturated alcohols such as allyl alcohol. As will be discussed later, these alcohols are characterized by a strong tendency of coordination onto cuprous chloride. The complexes of cuprous chloride and these alcohols are stable and can be isolated. These findings suggest that the coordination of isocyanide as well as alcohol onto cuprous chloride are essential for this reaction.

The reactions of cyclohexyl isocyanide with  $\beta,\gamma$ -unsaturated alcohols, and  $\beta$ -dimethylaminoethanol by cuprous chloride catalyst are shown in Table III.

Table III. Cuprous Chloride Catalyzed Reaction  
of Cyclohexyl Isocyanide with Alcohol<sup>a</sup>

ROH	Product yield (%)		
	I	II	IV
$\text{CH}_2=\text{CHCH}_2\text{OH}$	67	25	6
$\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2\text{OH}$	50 <sup>b</sup>	32	n.d. <sup>f</sup>
 - $\text{CH}=\text{CHCH}_2\text{OH}$	45 <sup>c</sup>	20	n.d.
 - $\text{CH}_2\text{OH}$	20 <sup>d</sup>	10	63
$(\text{CH}_3)_2\text{NCH}_2\text{CH}_2\text{OH}$	67 <sup>e</sup>	16	n.d.
$\text{C}_n\text{H}_{2n+1}\text{OH}$	no reaction		

<sup>a</sup> Reaction conditions: Cyclohexyl isocyanide, 40 mmol; alcohol, 70 mmol; CuCl, 8 mmol; 120°C; 5 hr.

<sup>b</sup> B.p. 116°C (27 mm).

<sup>c</sup> B.p. 130°C (3 mm).

<sup>e</sup> B.p. 85 — 86°C (5 mm).

<sup>d</sup> B.p. 155°C (3 mm).

<sup>f</sup> Not determined.

Benzyl alcohol is among the alcohols which react with isocyanide in the presence of cuprous chloride. Perhaps the phenyl group plays a role similar to that of  $\beta,\gamma$ -unsaturated group. In these reactions, N-cyclohexylformamide (II) and N-alkenyl-N-cyclohexylformamide (IV) were produced as the by-products. The amount of II, the product of the hydrolysis of cyclohexyl isocyanide, was much higher than that in the reactions with metallic copper and copper oxides catalysts. It may be attributed to a higher concentration of water formed in situ by the etherifications of these alcohols. It is known that  $\beta,\gamma$ -unsaturated alcohols are easily etherified by cuprous chloride catalyst.<sup>4)</sup>

The by-product IV was probably produced by the thermal rearrangement<sup>5)</sup> of I (Chapman rearrangement) which took place, at least partly, during the distillation of the reaction mixture. A higher yield of IV in the reaction with benzyl alcohol may be due in part to the higher distillation temperature.

In the cuprous chloride catalyzed reaction of cyclohexyl isocyanide with allyl alcohol, the decrease of isocyanide and the increases of the yields of products are plotted against the reaction time (Fig. 1). There is observed an induction period of 4 hr for the formation of I. The nature of the induction period has not yet been elucidated. As to the induction period, a possibility that the reaction is autocatalytic may be excluded. The addition of formamide or formimidate to the reaction system did not shorten the induction period. Cuprous chloride catalyst itself was not changed throughout the reaction. The hydrolysis of isocyanide to produce a by-product of II starts at the beginning of the reaction. Another by-product of IV, however, is produced only after the main product of I is accumulated in the reaction system.

### 1.3. Catalyst Behaviors of Other Copper Compounds

In the cupric chloride catalyzed reaction of isocyanide with saturated alcohols, only small amounts of N-substituted carbamate (III) and N-substituted formamide (II) were produced. The carbamate formation suggests the reduction-oxidation reaction between isocyanide and cupric chloride. A series of reactions of cyclohexyl isocyanide with increasing amounts of cupric chloride in the presence of excess ethanol was carried out (Fig. 2).

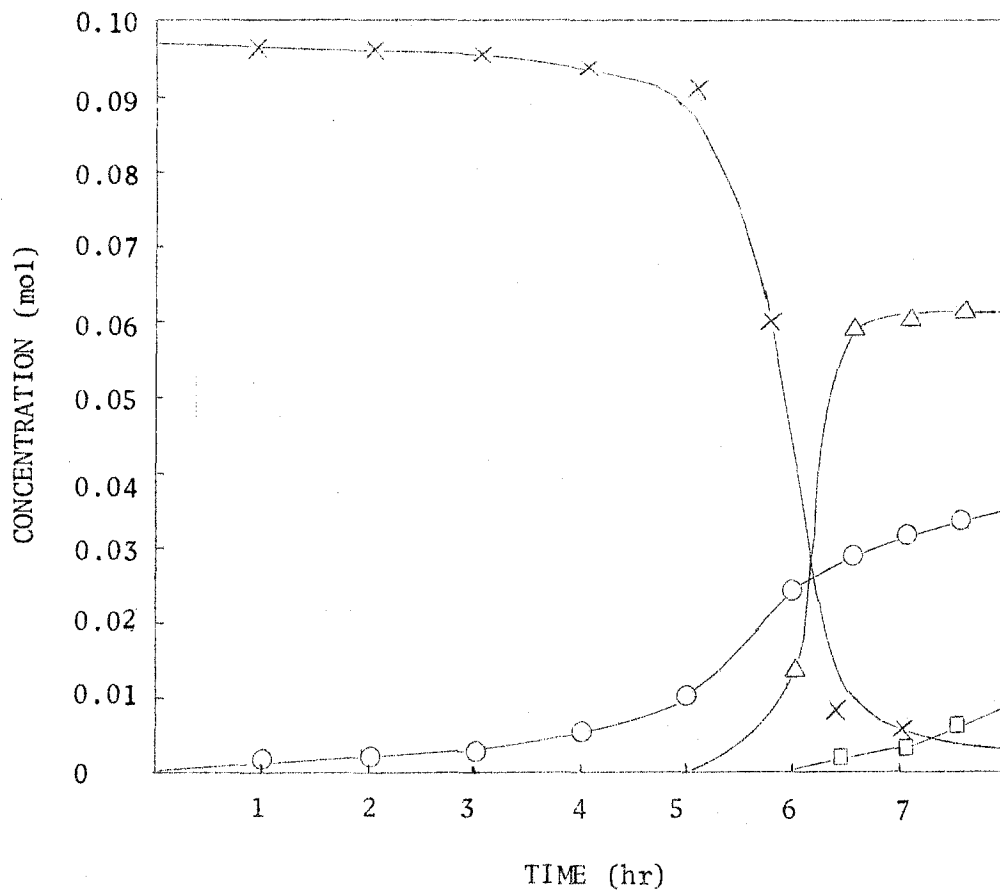


Fig. 1. CuCl catalyzed reaction of cyclohexyl isocyanide with allyl alcohol.

- x— : Cyclohexyl isocyanide.
- o— : N-Cyclohexylformamide.
- Δ— : Allyl N-cyclohexylformimidate.
- : N-Cyclohexyl-N-allylformamide.

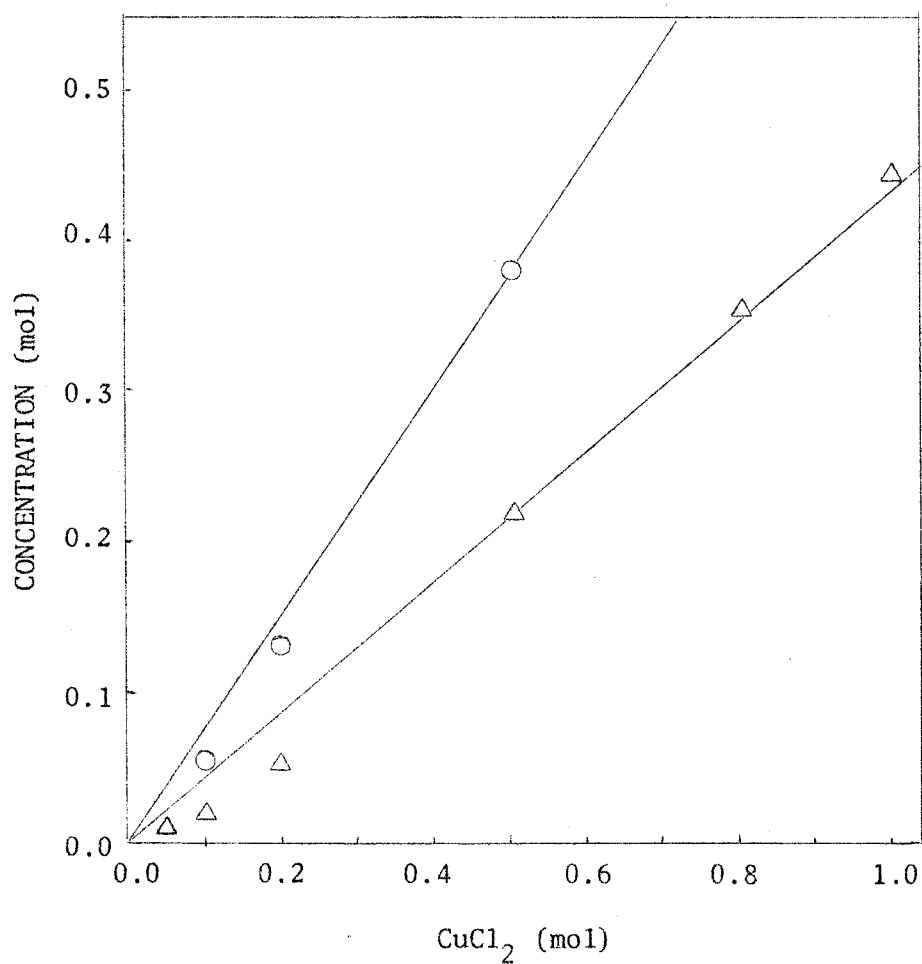


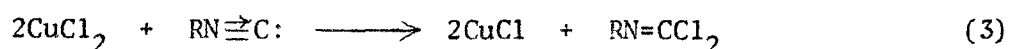
Fig. 2.  $\text{CuCl}_2$ —cyclohexyl isocyanide reaction in ethanol.

—○— :  $\text{CuCl}$  (formed by reduction of  $\text{CuCl}_2$ ).

—△— : Ethyl N-cyclohexylcarbamate.



It was found that cupric chloride was reduced to cuprous chloride, and the molar ratio of cuprous chloride and carbamate was about two. A separate study by us<sup>6)</sup> has shown that the isocyanide—cupric chloride reaction in the absence of alcohol produces cuprous chloride and N-substituted imidocarbonyl chloride, the precursor of carbamate.



The catalytic activity of cuprous cyanide was similar to that of cuprous chloride in the isocyanide—alcohol reaction. Cuprous cyanide induces the isocyanide—allyl alcohol reaction to form allyl formimidate but it does not promote the isocyanide reactions with the usual saturated alcohols.

#### 1.4. Catalytic Activities of Other Metal Compounds

Silver oxide and mercuric oxide also catalyzed the reaction of isocyanide with saturated alcohol. Two runs of the cyclohexyl isocyanide—ethanol reaction in the presence of silver oxide and mercuric oxide respectively were carried out under the same conditions as Table I, in which ethyl N-cyclohexylformimidate was formed in yields of 89 % and 51 %, respectively. However, oxides of zinc, cadmium and iron were inactive. Oxides of cobalt and nickel caused only the homopolymerization of isocyanide to produce brown colored, insoluble and infusible polymers.

Chlorides of silver, zinc and cadmium caused the reaction of isocyanide with allyl alcohol, but they did not induce that with the usual saturated alcohol. Mercuric chloride did not show catalyst activity even for the isocyanide—allyl alcohol reaction. Chlorides of nickel, cobalt, and

palladium did not induce the insertion reaction but caused the homopolymerization of isocyanide.

### 1.5. Mechanisms of Copper Catalysis

According to the catalysis behavior, copper catalysts are divided into two groups. The first group includes metallic copper and cuprous and cupric oxides, which catalyze the reactions of isocyanide with saturated and unsaturated alcohols. The second group of catalysts are cuprous chloride and cyanide which induce the reactions of isocyanide only with  $\beta,\gamma$ -unsaturated alcohol and  $\beta$ -aminoalcohol. The IR spectra of mixtures of cyclohexyl isocyanide and copper catalysts showed a new band at a frequency higher than  $2140\text{ cm}^{-1}$  of  $\nu_{\text{N}\equiv\text{C}}$  of free isocyanide. The new band has been assigned to  $\nu_{\text{N}\equiv\text{C}}$  of isocyanide coordinating to metal compound.<sup>7)</sup> From a Hammett relationship of the argentation constant of styrene derivatives,<sup>8)</sup> it is assumed that the contribution of the backdonation in the complex of  $d^{10}$  metal ion is small. The shift of  $\nu_{\text{N}\equiv\text{C}}$  to a shorter wave length is due to the donation of the electrons of isocyanide to  $d^{10}$  metal ion. Therefore, the magnitude of shift of  $\nu_{\text{N}\equiv\text{C}}$  caused by coordination may be utilized as a measure of the strength of the coordination of isocyanide onto copper catalysts. It follows that the coordination of isocyanide with the first group catalysts is weaker than that with the members of the second group.

The cyclohexyl isocyanide—metallic copper system for IR diagnosis was prepared at room temperature by the addition of metallic copper powder to liquid cyclohexyl isocyanide under nitrogen. Metallic copper was prepared by the reduction of cupric sulfate with zinc powder in aqueous solution. The

copper-isocyanide mixture was centrifuged. The IR spectrum of the liquid phase of copper-isocyanide showed a fairly strong absorption at  $2180\text{ cm}^{-1}$  as well as the band of  $\nu_{\text{N}\equiv\text{C}}$  of free isocyanide at  $2140\text{ cm}^{-1}$ . This finding indicates the formation of a soluble complex from metallic copper and isocyanide. On treating the centrifuged solution with alcohol, the formimidate was produced. This indicates that the metallic copper catalyzed reaction proceeds in a homogeneous solution phase, and the solid phase is merely the source of soluble catalyst complexes. The band of coordinating species of cyclohexyl isocyanide appeared at  $2181\text{ cm}^{-1}$  in the system of cuprous oxide with isocyanide.

On the other hand, the IR spectrum of the 1:1 complex of cuprous chloride with cyclohexyl isocyanide showed the band of coordinating isocyanide group at  $2192\text{ cm}^{-1}$ . The shifts of  $\nu_{\text{N}\equiv\text{C}}$  band of cyclohexyl isocyanide caused by copper catalysts are shown in Table IV.

Table IV. Shifts of  $\nu_{\text{N}\equiv\text{C}}$  Band of Cyclohexyl Isocyanide Caused by Copper Catalysts

Copper catalyst	$\Delta\nu_{\text{N}\equiv\text{C}}\text{ (cm}^{-1}\text{)}$
First group	
$\text{Cu}^0$	40
$\text{Cu}_2\text{O}$	41
Second group	
$\text{CuCl}$	52
$\text{CuCN}$	61

Thus, the magnitude of the shift of  $\nu_{N=C}$  caused by cuprous chloride is larger than that caused by metallic copper and cuprous oxide. These findings are taken to indicate that isocyanide coordinates more tightly with cuprous chloride than with the first group catalysts. Cuprous chloride is almost insoluble in the usual saturated alcohols, whereas it is quite soluble in allyl alcohol and in  $\beta$ -dimethylaminoethanol. This observation suggests a specific interaction between cuprous chloride and these particular alcohols. The complexing of cuprous chloride with these alcohols was indicated by IR spectroscopy. In comparison with the IR spectrum of allyl alcohol, the spectrum of cuprous chloride dissolved in allyl alcohol had additional bands at 1548 and 1010  $\text{cm}^{-1}$ , which are assigned to the olefin and alcohol groups, respectively, of the allyl alcohol—cuprous chloride complex (Fig. 3).<sup>9)</sup> The strong complexing tendency of  $\beta$ -dimethylaminoethanol with cuprous chloride was also demonstrated by IR spectroscopy. From cuprous chloride and  $\beta$ -dimethylaminoethanol, an 1:1 complex was successfully isolated, whose IR spectrum showed the shift of  $\nu_{C-O}$  band from 1039 to 1020  $\text{cm}^{-1}$  (Fig. 4).

On the basis of these IR spectroscopy studies, the difference in catalyst activity between the first group catalysts and those of the second group is explained by a hypothesis of mixed ligand complex. Isocyanide is held rather loosely by the first group catalysts, and hence a part of the isocyanide ligand will be replaced by alcohols including saturated alcohols of weak complexing tendency as well as the particular alcohols mentioned above. The first group catalysts will form a ternary, mixed ligand complex consisting of copper, isocyanide and various alcohols. On the other hand, isocyanide is held tightly by the second group catalyst, and the isocyanide

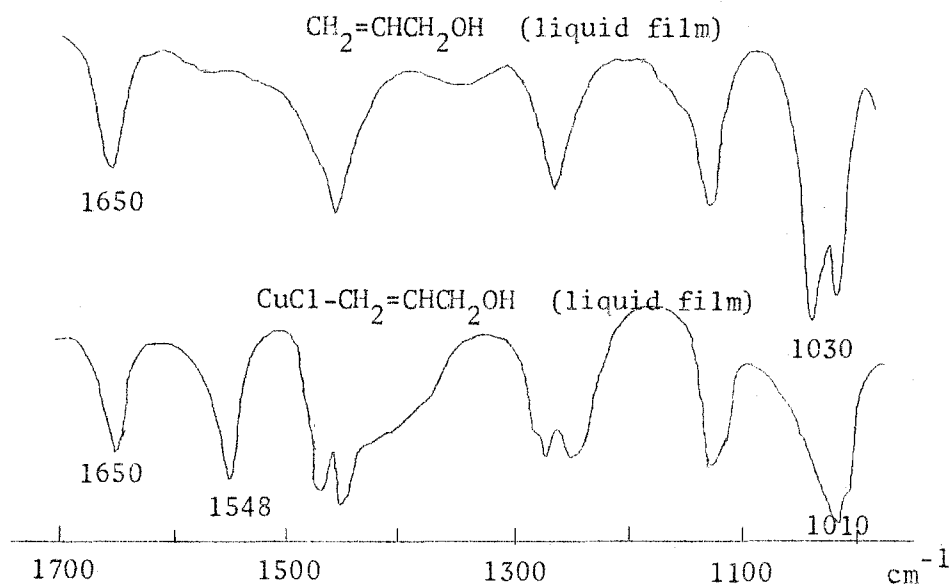


Fig. 3. IR spectra of allyl alcohol  
and  $\text{CuCl}$ —allyl alcohol complex

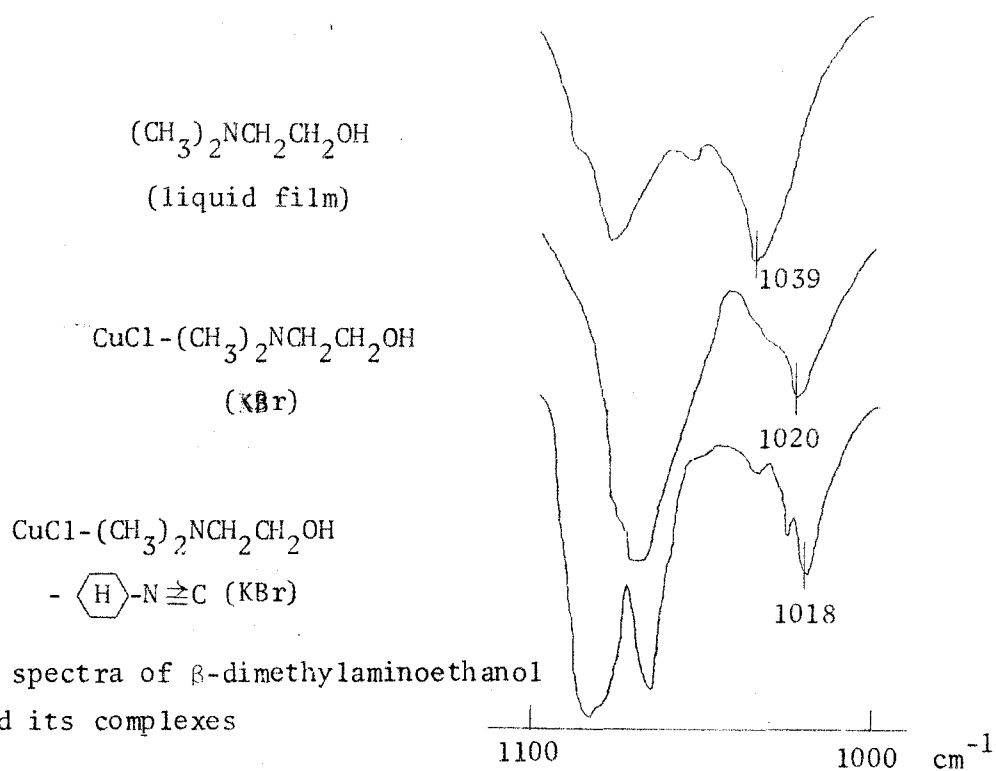


Fig. 4. IR spectra of  $\beta$ -dimethylaminoethanol  
and its complexes

ligand is partly replaced only by the special alcohols of strong coordinating tendencies. The ternary, mixed ligand complexes of the second group catalysts are feasible only for the special alcohols. It is assumed that the reaction between alcohol and isocyanide will take place in the ligand sphere of the mixed ligand complex. Thus, the formation of the mixed ligand complex is a prerequisite for the occurrence of the reaction.

## 2. Experimental

### Metallic Copper Catalyzed Reaction of Cyclohexyl Isocyanide with Ethanol

Metallic copper was prepared by treating an excess of aqueous solution of cupric sulfate maintained below 70°C with zinc powder under a nitrogen atmosphere. The metallic copper precipitate was collected and washed successively with water and dry acetone, and then dried.

A mixture of cyclohexyl isocyanide 3.27 g (0.030 mol), ethanol 1.56 g (0.034 mol), and metallic copper 0.43 g (0.003 g-atom) was heated at 120°C for 5 hr. After the insoluble catalyst was removed by filtration, the filtrate was subjected to glpc analysis (PEG 20,000 on celite). Two products, Ia and IIa, were detected. The product Ia was also isolated by distillation in vacuo, b.p. 42.5°C (5 mm).

On the basis of the following analyses, Ia was identified as ethyl N-cyclohexylformimidate. NMR (CCl<sub>4</sub>) of Ia:  $\delta$  1.21 (3H, triplet); 1.00 — 2.00 (10H, complex multiplet); 2.70 — 3.10 (1H, broad singlet); 3.98 (2H, quartet); 7.43 (1H, singlet). IR (Neat): 1650 cm<sup>-1</sup> (s), 1200 (s). The structure of Ia was further confirmed by comparisons of the glpc retention time and IR

spectrum with the authentic sample. The authentic sample of Ia was prepared as follows.<sup>10)</sup> N-Cyclohexylformamide (0.5 mol) was added dropwise to triethyloxonium fluoroborate (0.5 mol)<sup>11)</sup> in ether at room temperature. Ethyl N-cyclohexylformimidate hydrogen fluoroborate, separated as a viscous liquid in the lower layer, was treated with triethylamine to give ethyl N-cyclohexylformimidate.

IIa, b.p. 103°C (3 mm) was identified as N-cyclohexylformamide by comparison with the authentic sample prepared from cyclohexylamine and ethyl formate.

#### Cuprous Oxide Catalyzed Reaction of Cyclohexyl Isocyanide with *sec*-Butanol

A mixture of cyclohexyl isocyanide 3.27 g (0.030 mol), *sec*-butanol 2.52 g (0.034 mol) and cuprous oxide 0.43 g (0.003 mol) was heated at 120°C for 5 hr. Working up the mixture as described above, *sec*-butyl N-cyclohexylformimidate, b.p. 90°C (21 mm) (Ib), N-cyclohexylformamide and *sec*-butyl N-cyclohexylcarbamate (IIIb) were detected by glpc and identified. NMR (CCl<sub>4</sub>) of Ib:  $\delta$  0.87 (3H, triplet); 1.15 (3H, doublet); 1.00 — 2.00 (12H, complex multiplet); 2.70 — 3.10 (1H, broad singlet); 4.73 (1H, multiplet); 7.33 (1H, singlet). IR (Neat): 1650 cm<sup>-1</sup> (s), 1205 (s). The authentic sample of IIIb was prepared by the reaction of cyclohexyl isocyanate with *sec*-butanol.

#### Cupric Oxide-catalyzed Reaction of Cyclohexyl Isocyanide with *t*-Butanol

A mixture of cyclohexyl isocyanide 3.27 g (0.030 mol), *t*-butanol 2.52 g (0.034 mol), and cupric oxide 0.24 g (0.003 mol) was heated at 120°C for 5 hr. According to the same procedure, *t*-butyl N-cyclohexylformimidate, b.p. 93°C (19 mm) (Ic), N-cyclohexylformamide, and *t*-butyl N-cyclohexylcarbamate (IIIc)

were identified. NMR ( $\text{CCl}_4$ ) of Ic:  $\delta$  1.40 (9H, singlet); 1.00 — 2.00 (10H, complex multiplet); 2.70 — 3.10 (1H, broad singlet); 7.36 (1H, singlet). IR (Neat):  $1650\text{ cm}^{-1}$  (s), 1220 (s), 1170 (s).

#### Cuprous Chloride Catalyzed Reaction of Allyl Alcohol with Cyclohexyl

##### Isocyanide

A solution of cyclohexyl isocyanide 4.36 g (0.040 mol), allyl alcohol 4.06 g (0.070 mol) and cuprous chloride 0.80 g (0.008 mol) was heated at  $120^\circ\text{C}$  for 5 hr. Then the reaction mixture was subjected to glpc analysis and the products were identified. Allyl N-cyclohexylformimidate (Id), b.p.  $90^\circ\text{C}$  (26 mm), cyclohexylformamide, and N-allyl-N-cyclohexylformamide (IVd) were the products. NMR ( $\text{CCl}_4$ ) of Id:  $\delta$  1.00 — 2.00 (10H, complex multiplet); 2.70 — 3.20 (1H, broad singlet); 4.49 (2H, doublet); 4.90 — 6.20 (3H, multiplet); 7.53 (1H, singlet). IR (Neat):  $1650\text{ cm}^{-1}$  (s), 1190 (s), 990 (m), 910 (s). The authentic sample of Id was synthesized by the reaction of triallyloxonium fluoroborate with N-cyclohexylformamide. NMR ( $\text{CDCl}_3$ ) of IVd:  $\delta$  1.00 — 2.00 (10H, complex multiplet); 2.90 — 3.50 (1H, broad singlet); 3.84 (2H, doublet); 4.80 — 6.10 (3H, multiplet); 8.04 and 8.20 (1H, two singlet).

#### Cuprous Chloride Catalyzed Reaction of Cyclohexyl Isocyanide with Benzyl

##### Alcohol

A solution of cyclohexyl isocyanide 4.36 g (0.040 mol), benzyl alcohol 7.56 g (0.070 mol), and cuprous chloride 0.80 g (0.008 mol) was heated at  $120^\circ\text{C}$  for 5 hr. The whole product could not be analyzed by glpc. Distillation of the reaction mixture gave benzyl N-cyclohexylformimidate (Ie), b.p.



155°C (3 mm), cyclohexylformamide and N-benzyl-N-cyclohexylformamide (IVe), b.p. 133°C (3 mm). NMR ( $\text{CDCl}_3$ ) of Ie:  $\delta$  1.00 — 2.00 (10H, complex multiplet); 2.80 — 3.20 (1H, broad singlet); 4.49 (2H, singlet); 7.24 (5H, singlet); 7.60 (1H, singlet). NMR ( $\text{CCl}_4$ ) of IVe:  $\delta$  1.00 — 2.00 (10H, complex multiplet); 2.90 — 3.30 (1H, broad singlet); 4.28 and 4.40 (2H, two singlet); 7.15 (5H, singlet); 8.02 and 8.15 (1H, two singlet).

#### Cupric Chloride Catalyzed Reaction of Cyclohexyl Isocyanide with Ethanol

A solution of cyclohexyl isocyanide 4.36 g (0.040 mol), ethanol 5.52 g (0.0120 mol), and cupric chloride 2.69 g (0.020 mol) was heated at 120°C for 5 hr. The insoluble matter was separated by filtration, and the filtrate was analyzed by glpc. Ethyl N-cyclohexylcarbamate (0.0084 mol) was obtained in a yield of 42 % (based on  $\text{CuCl}_2$ ).  $\text{CuCl}$  in the insoluble portion was analyzed according to the thiocyanate method. It was found that 76 % of  $\text{CuCl}_2$  was reduced to  $\text{CuCl}$  (0.0152 mol).

#### Complex of Cyclohexyl Isocyanide—Cuprous Chloride (1:1)

Cuprous chloride was added slowly to excess cyclohexyl isocyanide at room temperature, and the precipitation was collected by filtration. The white crystalline product was recrystallized from chloroform-ether, m.p. 95 — 96°C. Elemental analysis revealed that the crystalline product consisted of 1 mol cyclohexyl isocyanide and 1 mol cuprous chloride. Anal. Calcd for  $\text{C}_7\text{H}_{11}\text{NCu}$ : C, 40.40; H, 5.22; N, 6.60; Cl, 17.01. Found: C, 40.40; H, 5.29; N, 6.73; Cl, 17.07.

#### Complex of $\beta$ -Dimethylaminoethanol—Cuprous Chloride (1:1)

A dark blue solution of cuprous chloride (0.01 mol) in  $\beta$ -dimethylaminoethanol (0.04 mol) was treated with excess petroleum ether, and the precipitating green crystalline mass was collected and dried, m.p. 144 — 145°C.

Anal. Calcd for  $(C_4H_{11}NOClCu)_2$ : C, 25.53; H, 5.86; N, 7.45; Cl, 18.88.

Found: C, 25.93; H, 5.42; N, 7.27; Cl, 18.78.

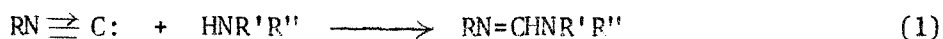
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## Chapter 3

### Reaction of Thiol with Isocyanide

Insertion reactions of isocyanide into nitrogen-hydrogen bond of amine,<sup>1)</sup> and oxygen-hydrogen bond of alcohol<sup>2)</sup> have been described in Chapters 1 and 2, respectively.

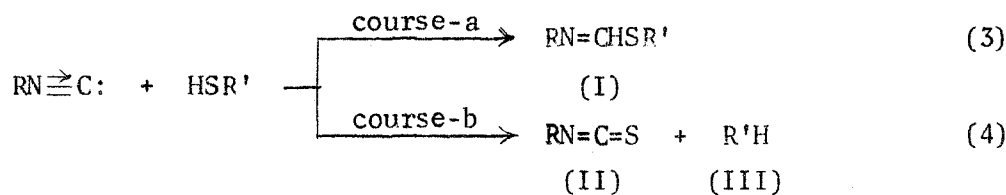


Both reactions are catalyzed by copper compounds to produce the corresponding derivatives of N-alkylformimidic acid. This chapter deals with the reaction of thiol with isocyanide. The syn-anti structures of thioformimidate were also examined by NMR.

### 1. Results and Discussion

#### 1.1. Reaction of Thiol with Isocyanide

The reaction of thiol with isocyanide proceeds in the following two directions.



In the first reaction (course-a, eq. 3), the carbon atom of isocyanide having lone-pair electrons is inserted into the sulfur-hydrogen bond of thiol to produce thioformimidate (I). In the second reaction (course-b, eq. 4), isothiocyanate (II) and alkane (III) from the alkyl group of thiol are formed by a process containing the transfer of sulfur atom from thiol to isocyanide. As will be discussed later, these reactions do not proceed consecutively, but they occur separately from each other.

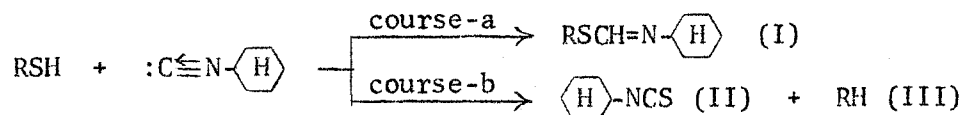
The proportion of participation of the two reactions depends on the alkyl group of thiol and the reaction conditions including the employment of catalyst.

The results of the reactions of thiol with cyclohexyl isocyanide are shown in Tables I and II 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 Groups IB and IIB metal compounds have been clearly demonstrated. However, at higher temperatures, e.g., 100°C, the reaction proceeds rapidly 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 I and II prefer course-a to course-b. On the other hand, tertiary thiols, e.g., VII, prefers course-b. 2-Methyl-2-heptanethiol also takes course-b preferably.

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

Table I. Reactions of Thiols with Cyclohexyl Isocyanide (Part 1)



RSH	Catalyst	Reaction		Yields <sup>d</sup>		
		Temp. (°C)	Time (hr)	I	II	III
C <sub>2</sub> H <sub>5</sub> SH (IV)	none	15	3	trace	3	n.d. <sup>e</sup>
	Cu(acac) <sub>2</sub> <sup>a</sup>	15	3	86	1	n.d.
	CuO	15	3	76	3	n.d.
	CuCl <sub>2</sub>	15	3	32	2	n.d.
	Cd(OAc) <sub>2</sub> <sup>b</sup>	15	3	67	4	n.d.
<u>i</u> -C <sub>3</sub> H <sub>7</sub> SH (V)	none	15	3	1	16	n.d.
	Cu <sub>2</sub> O	15	3	78	3	n.d.
	ZnCl <sub>2</sub>	15	3	45	10	n.d.
	Hg(OAc) <sub>2</sub> <sup>c</sup>	15	3	41	14	n.d.
<u>n</u> -C <sub>4</sub> H <sub>9</sub> SH (VI)	Cu <sub>2</sub> O	20	15	73	7	n.d.
	Cu	20	15	81	4	n.d.
<u>t</u> -C <sub>4</sub> H <sub>9</sub> SH (VII)	none	15	3	0	26	n.d.
	Cd(OAc) <sub>2</sub> <sup>b</sup>	15	3	13	68	n.d.
	CuCN	15	3	8	54	n.d.
	CuO	15	3	4	38	n.d.
C <sub>6</sub> H <sub>5</sub> SH (VIII)	none	20	15	89	0	0
	Cu <sub>2</sub> O	20	15	42	0	0

<sup>a</sup> Copper acetylacetonate.

<sup>b</sup> Cadmium acetate.

<sup>c</sup> Mercuric acetate.

<sup>d</sup> The yield of each product is based on the amount of cyclohexyl isocyanide.

<sup>e</sup> n.d., not determined.

Table II. Reactions of Thiols with Cyclohexyl Isocyanide<sup>a</sup> (Part 2)

RSH	Catalyst	Reaction time (hr)	Yields <sup>b</sup>		
			I	II	III
C <sub>2</sub> H <sub>5</sub> SH (IV)	none	3	85	8	n.d. <sup>c</sup>
	Cu <sub>2</sub> O	3	93	1	n.d.
<u>i</u> -C <sub>3</sub> H <sub>7</sub> SH (V)	none	1.5	23	64	60
	Cu <sub>2</sub> O	3	86	5	n.d.
<u>t</u> -C <sub>4</sub> H <sub>9</sub> SH (VII)	none	1.5	1	92	81

<sup>a</sup> The reactions were carried out at 100°C.

<sup>b</sup> The structures of the products are indicated in Table I.  
The yield of each product is based on cyclohexyl isocyanide.

<sup>c</sup> n.d., not determined.

The Groups IB and IIB metal compounds catalyze the thiol-isocyanide reaction and also increase preferably the relative participation of the course-a reaction. The effect of catalyst upon the relative participations of the two reactions is well demonstrated in the reaction of cyclohexyl isocyanide with 2-propanethiol. The uncatalyzed reaction is inclined towards course-b producing isothiocyanate, and the catalyzed reaction proceeds preferably through course-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 homogeneous system. The compounds of cadmium, zinc and mercury also accelerated the course-a reaction in preference to the course-b reaction. The catalyzed reaction of course-a proceeded at fairly

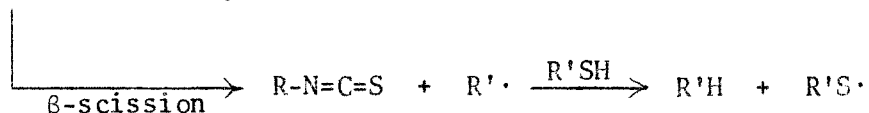
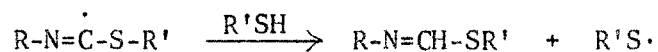
high rates. For example, the yield of ethyl N-cyclohexylthioformimidate in the reaction of ethanethiol—cyclohexyl isocyanide with copper acetylacetonate at 15°C was 30 % at 20 min, 55 % at 40 min, 65 % at 1 hr, and 86 % at 3 hr. As to the acceleration by catalyst it may be assumed that both isocyanide and thiol are coordinated with the catalyst metal ion to form a complex having the thiol and isocyanide ligands and the reaction proceeds within the sphere of ligand.

In addition to alkanethiol, aromatic thiol reacts with isocyanide. The reaction of benzenethiol (VIII) with cyclohexyl isocyanide, with or without 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 two courses occur separately, but not successively. 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 the course-b to produce cyclohexyl isothiocyanate and isobutane. But 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 unreacted under the same reaction conditions in the presence of catalyst.

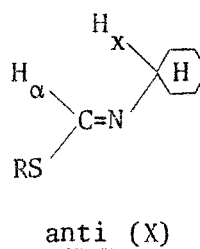
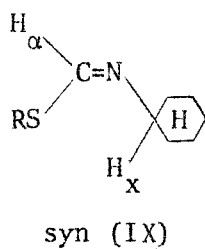
A mechanism involving a free radical may be considered to explain the over-all results of the reaction without any added catalyst.



As to the above scheme of a free radical mechanism, it has been observed that the addition of a radical inhibitor such as hydroquinone affects the reaction between thiol and isocyanide. Further studies on the reaction mechanism will be discussed later.<sup>4)</sup>

### 1.2. Syn-Anti Structures of Thioformimidate

For thioformimidate, syn (IX) and anti (X) forms are expected due to the restricted rotation of  $>C=N$ - bond.



In the NMR spectra of thioformimidates in deuteriochloroform and benzene, there were obtained two signals in the region of  $\tau$  1.7 — 2.1, both of which were assigned to  $H_{\alpha}$  of IX and X (Table III). In Figure 1, the NMR spectrum of ethyl N-cyclohexylthioformimidate is shown as an example. Two signals of  $H_{\alpha}$  have been ascribed to syn-anti isomerism on the basis of the solvent effect on the NMR spectrum.<sup>5,6)</sup>



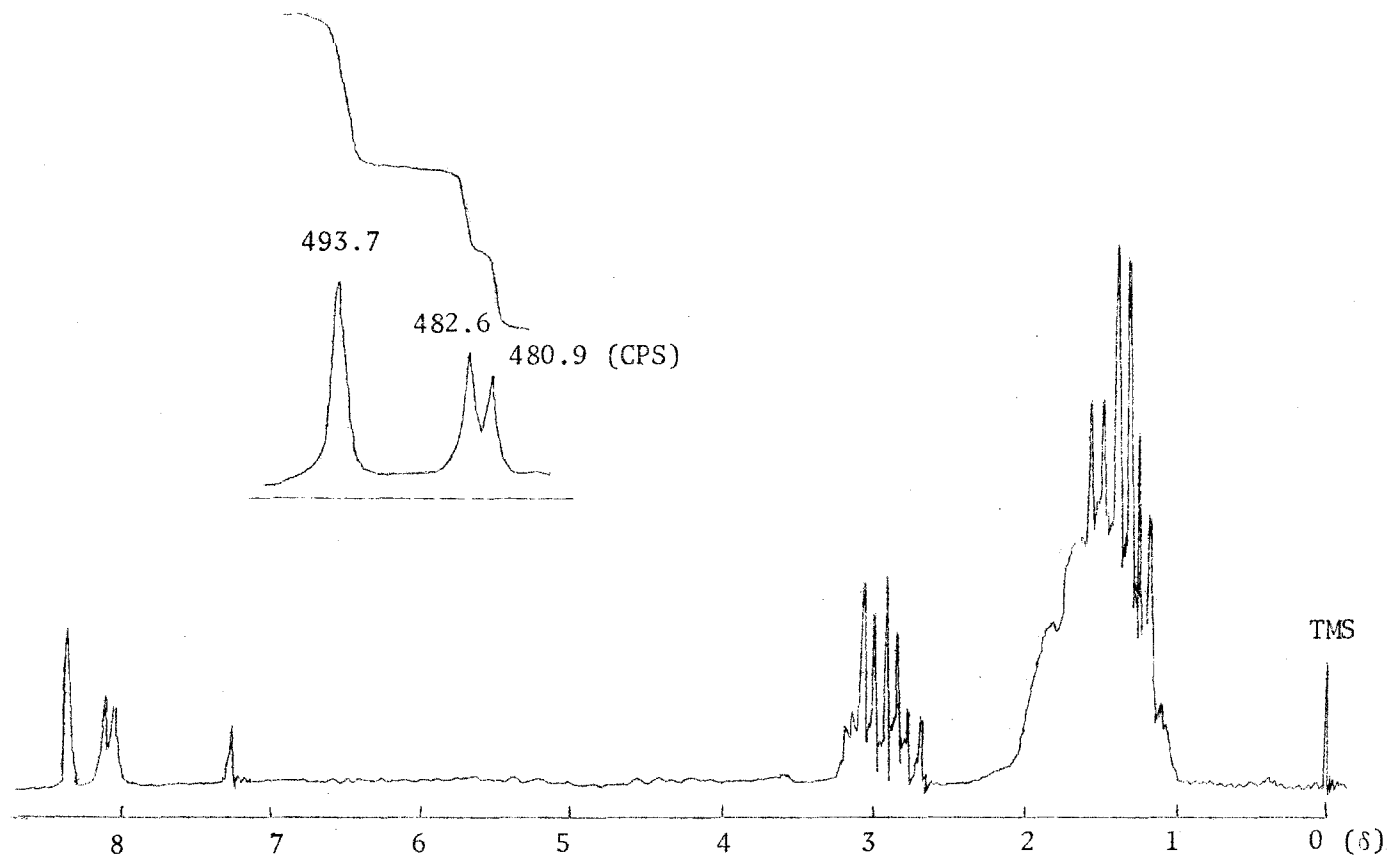
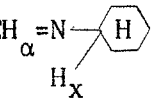
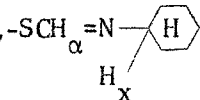
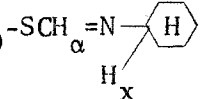
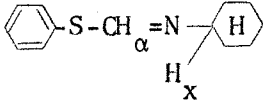
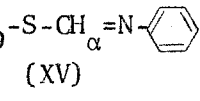


Fig. 1. NMR spectrum of ethyl N-cyclohexylthioformimidate (XI) (in deuteriochloroform)

Table III. NMR Data of  $-\text{SCH}_\alpha=\text{N}-$  of Thioformimidates<sup>a</sup>

Thioformimide	Solvent	$\text{H}_\alpha$ cps	$J_{\text{H}_\alpha\text{H}_x}$ cps	Ratio <sup>b</sup> (%)
$\text{C}_2\text{H}_5\text{SCH}_\alpha=\text{N}-$  (XI)	$\text{CDCl}_3$	<u>syn</u> 480.9, 482.6	1.7	47
		<u>anti</u> 493.7	0.0	53
	$\text{C}_6\text{H}_6$	<u>syn</u> 471.2, 472.9	1.7	—
		<u>anti</u> 476.7	0.0	—
$i\text{-C}_3\text{H}_7\text{-SCH}_\alpha=\text{N}-$  (XII)	$\text{CDCl}_3$	<u>syn</u> - 485.9, 487.5	1.6	56
		<u>anti</u> 495.1	0.0	44
	$\text{C}_6\text{H}_6$	<u>syn</u> 480.2, 481.8	1.6	—
		<u>anti</u> 477.6	0.0	—
$t\text{-C}_4\text{H}_9\text{-SCH}_\alpha=\text{N}-$  (XIII)	$\text{CDCl}_3$	<u>syn</u> 496.5, 498.2	1.7	73
		<u>anti</u> 506.7	0.0	27
	$\text{C}_6\text{H}_6$	<u>syn</u> 496.3, 498.0	1.7	—
		<u>anti</u> 487.0	0.0	—
 (XIV)	$\text{CDCl}_3$	<u>syn</u> 480.7, 482.6	1.9	72
		<u>anti</u> 500.4	0.0	28
	$\text{C}_6\text{H}_6$	<u>syn</u> 481.0, 482.6	1.6	—
		<u>anti</u> 486.6	0.0	—
$n\text{-C}_4\text{H}_9\text{-S-CH}_\alpha=\text{N}-$  (XV)	$\text{CDCl}_3$	<u>syn</u> 487.8	—	8
		<u>anti</u> 492.0	—	92

<sup>a</sup> All spectra were recorded at 60 Mc/sec on a modified JEOL JNM-3H-60 spectrometer for 10 — 15 %  $\text{CDCl}_3$  or  $\text{C}_6\text{H}_6$  solutions at 23°C.

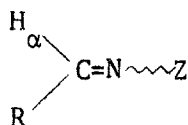
Chemical shifts values are in cps from TMS as an internal standard.

<sup>b</sup> No reliable value is obtained in benzene, because the signals of  $\text{H}_\alpha$  and benzene protons overlap each other.

Table IV. Solvent Effects on the Chemical Shifts of Protons ( $H_\alpha$ )

Thioformimidate	$\Delta\nu$ cps	value ( $\nu$ in $CDCl_3$ - $\nu$ in $C_6H_6$ )
XI		<u>syn</u> 9.7
		<u>anti</u> 17.0
XII		<u>syn</u> 5.7
		<u>anti</u> 17.5
XIII		<u>syn</u> 0.2
		<u>anti</u> 19.7
XIV		<u>syn</u> $\sim$ 0.0
		<u>anti</u> 13.8

Karabatsos et al.<sup>5,6)</sup> have presented a method for assigning syn and anti structures of hydrazone, semicarbazone and related compounds having the general formula:



It is based on the fact that in aromatic solvents  $H_\alpha$  hydrogens, cis and trans to Z, resonate at higher fields than they do in aliphatic solvents and that the degree of upfield shifts of cis hydrogen is larger than that of trans hydrogen. The shielding effect is ascribed to the benzene ring existing preferably in the vicinity of cis  $H_\alpha$ . The same reasoning is applied also to thioformimidate. Owing to the repulsion between the lone-pair electrons of nitrogen of thioformimidate and the  $\pi$  electrons of benzene ring, the shielding effect of benzene ring upon trans  $H_\alpha$  (syn form) is less than that upon

cis H<sub>α</sub> (anti form). In Table III, the assignment of two signals of H<sub>α</sub> hydrogen has been made based upon the above consideration. From the peak areas of two H<sub>α</sub> signals syn/anti ratio has been calculated. As indicated in Table III, syn H<sub>α</sub> gives a doublet whereas anti H<sub>α</sub> gives a singlet. The coupling of syn H<sub>α</sub> with the α-hydrogen (H<sub>x</sub>) of cyclohexane ring is more pronounced than that of anti H<sub>α</sub>. This observation corresponds with the fact that the coupling constant between trans hydrogens in olefin is larger than that between cis hydrogens. Table IV summarizes Δν values (Δν = ν in CDCl<sub>3</sub> - ν in C<sub>6</sub>H<sub>6</sub>) of four thioformimidates.

## 2. 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 catalyst (2 mmol) at the indicated reaction temperature. Then the reaction mixture was subjected to glpc, where ethyl N-cyclohexylthioformimidate (XI) and cyclohexyl isothiocyanate were identified and quantitatively analyzed. XI was isolated from the reaction mixture, by distillation, b.p. 110 — 112°C (20 mm). Anal. Calcd for C<sub>9</sub>H<sub>17</sub>NS: C, 63.10; H, 10.01. Found: C, 63.02; H, 10.05. The structure of XI was established by means of NMR (Fig. 1) and IR spectra (ν<sub>C=N</sub> at 1590 cm<sup>-1</sup>). The authentic sample of cyclohexyl isothiocyanate was prepared by the reaction of cyclohexyl isocyanide with sulfur.<sup>7)</sup>

### Reaction of V with Cyclohexyl Isocyanide

Reaction of V with cyclohexyl isocyanide was carried out in the same manner as the above. By glpc analysis, isopropyl N-cyclohexylthioformimide (XII) and cyclohexyl isothiocyanate were identified and quantitatively analyzed. XII was isolated by distillation of the reaction mixture, b.p. 135 — 136°C (20 mm). Anal. Calcd for C<sub>10</sub>H<sub>19</sub>NS: C, 64.81; H, 10.33; N, 7.56. Found: C, 64.67; H, 10.23; N, 7.62. The structure of XII was further established by IR ( $\nu_{\text{C=N}}$  1590 cm<sup>-1</sup>) and NMR spectra. In some experiments, 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.

#### Reaction of VII with Cyclohexyl Isocyanide

The same procedure as the preceding two reactions was adapted. In the glpc analysis of the reaction mixture, *t*-butyl N-cyclohexylthioformimide (XIII) and cyclohexyl isothiocyanate were identified and quantitatively analyzed. The gas evolved from the reaction system was identified by glpc and NMR as isobutane. XIII was isolated by distillation of the reaction mixture, b.p. 122 — 125°C (3 mm), m.p. 56 — 58°C. Anal. Calcd for C<sub>11</sub>H<sub>21</sub>NS: C, 66.27; H, 10.62; N, 7.03; S, 16.08. Found: C, 65.98; H, 10.63; N, 7.05; S, 15.53. The structure of XIII was further established by IR ( $\nu_{\text{C=N}}$  1590 cm<sup>-1</sup>) 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-cyclohexylthioformimide (b.p. 129 — 131°C (3 mm)) XVI and phenyl N-cyclohexylthioformimide (b.p. 120 — 122°C (0.1 mm)) (XIV), respectively. XVI and XIV were identified by means of their IR and NMR spectra as well as

by elemental analysis.

#### Reaction of VI with Phenyl Isocyanide

Following the same procedure as 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 %), b.p. 151 — 152°C (20 mm).  
Anal. Calcd for C<sub>11</sub>H<sub>15</sub>NS: C, 68.35; H, 7.82; N, 7.25; S, 16.59. Found: C, 68.18; H, 7.59; N, 7.11; S, 16.20. 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.

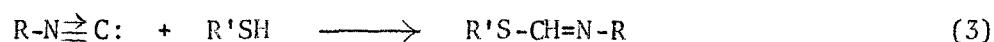
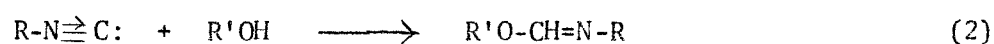
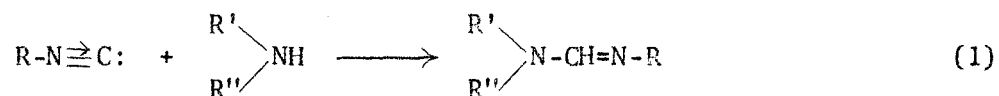
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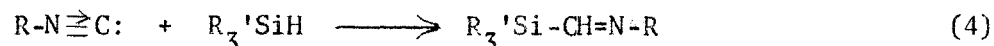
## Chapter 4

### A Novel Hydrosilation of Isocyanide by Copper Catalyst

In the foregoing chapters, it has been shown that isocyanide reacts with primary and secondary amines,<sup>1)</sup> alcohols,<sup>2)</sup> and thiols<sup>3)</sup> to produce the corresponding derivatives of formimidic acid. These reactions involve insertion of isocyanide into nitrogen-hydrogen, oxygen-hydrogen, and sulfur-hydrogen linkages, respectively; on the other hand, these are considered to be  $\alpha,\alpha$ -additions of amine, alcohol and thiol to the carbon atom of isocyanide.

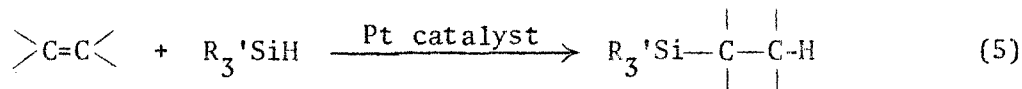


The present chapter describes the reaction of isocyanide with trialkylsilane by copper compound catalyst, in which the isocyanide carbon atom is inserted between silicon and hydrogen of the silane compound.



The product of formimidoylsilane is the adduct of  $\equiv\text{SiH}$  to isocyanide, and the reaction may be regarded as a novel hydrosilation, which is interestingly compared to the hydrosilation of olefins with group VIII metal complex

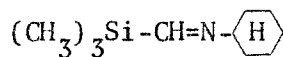
catalysts.<sup>4-8</sup>) The hydrosilation of olefins may be recognized as  $\alpha,\beta$ -addition of



silane to the olefin carbon atoms.

### 1. Results and Discussion

First of all, the reaction of trimethylsilane and cyclohexyl isocyanide was examined. Under nitrogen atmosphere, a mixture of 10.8 g (100 mmol) of cyclohexyl isocyanide, 0.89 g (120 mmol) of trimethylsilane, 0.52 g (2 mmol) of copper (II) acetylacetonate, and 10 ml of benzene (reaction solvent) was heated at 100°C for 5 hr in a sealed tube. As the temperature was raised, the catalyst was gradually dissolved into the reaction mixture to form a homogeneous system at 100°C. After the reaction, the mixture was distilled to isolate N-cyclohexylformimidoyltrimethylsilane (I), b.p. 118 — 120°C (40 mm). Anal. Calcd for C<sub>10</sub>H<sub>21</sub>NSi: C, 65.50; H, 11.54; N, 7.64. Found: C, 65.19; H, 11.89; N, 7.62. The yield of I based on cyclohexyl isocyanide was 86 %. The new silicon compound (I) is a colorless liquid and stable under dry nitrogen atmosphere, but vulnerable to moisture.

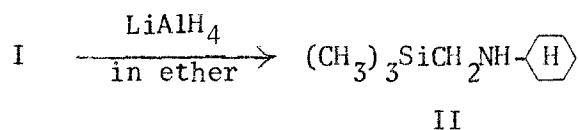


I

The structure of I was convincingly confirmed by IR, ultraviolet, and NMR spectra as well as by the reduction product. The IR spectrum of I

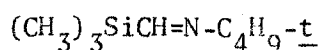


(neat) was consistent with the assigned structure, showing  $-\text{Si}(\text{CH}_3)_3$  at  $1246\text{ cm}^{-1}$  and  $842\text{ cm}^{-1}$ , and  $>\text{C}=\text{N}-$  at  $1601\text{ cm}^{-1}$ . The ultraviolet spectrum of I in cyclohexane had an absorption of  $\lambda_{\text{max}} = 285\text{ m}\mu$  ( $\epsilon$  70), which is assigned to  $n \rightarrow \pi^*$  transition of  $>\text{C}=\text{N}-$  group. The NMR spectrum in  $\text{CDCl}_3$  showed a singlet at  $1.67\ \tau$  (1H,  $-\text{CH}=\text{N}-$ ), two broad signals centered at  $7.2\ \tau$  (1H,  $=\text{N}-\text{CH}<$ ) and at  $8.5\ \tau$  (10H,  $-(\text{CH}_2)_5-$  of cyclohexane ring) and a singlet at  $9.87\ \tau$  (9H,  $-\text{Si}(\text{CH}_3)_3$ ). Further evidence supporting the structure (I) was obtained in the treatment of I with lithium aluminum hydride in ether at room temperature which afforded N-(trimethylsilylmethyl)-cyclohexylamine (II), b.p.  $208 - 210^\circ\text{C}$  (lit.<sup>9</sup> b.p.  $211^\circ\text{C}$ ),  $n_{\text{D}}^{25}$  1.4520 (lit.<sup>9</sup>  $n_{\text{D}}^{25}$  1.4519).



The structure of II was further confirmed by IR and NMR spectra. Similar results were obtained with cupric chloride as catalyst.

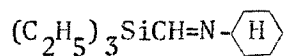
Similarly, the reaction of trimethylsilane and t-butyl isocyanide occurred in the presence of copper (II) acetylacetonate catalyst. The product, N-t-butylformimidoyltrimethylsilane (III) was obtained in 42 % yield, b.p.  $47 - 49^\circ\text{C}$  (150 mm).



III

Triethylsilane seems to be less reactive for hydrosilation of isocyanide. The reaction of triethylsilane with cyclohexyl isocyanide was carried out in benzene solvent with cupric chloride catalyst at  $130^\circ\text{C}$  for 18 hr. Distillation gave N-cyclohexylformimidoyltriethylsilane (IV) in a yield of 35 %,

b.p. 119°C (25 mm).



IV

The catalytic activity of copper compounds in reaction (4) seems quite specific. In the absence of copper catalyst both silane and isocyanide were recovered unchanged from the heat-treated reaction mixture. Further, no reaction was observed in the presence of chloroplatinic acid, which is known to be an efficient catalyst of hydrosilation of olefins,<sup>4-8</sup> as catalyst. Silver cyanide was also inactive as the catalyst for the present reaction between silane and isocyanide.

The reaction of silane toward isocyanide seems to depend upon the nature of R in  $\text{R}_3\text{SiH}$ . Trichloro, triphenyl and triethoxysilanes were found to be inert for the reaction with cyclohexyl isocyanide by cupric chloride catalyst in benzene at 100°C. These findings may be explained in terms of the nature of hydrogen of silane. Chemical shifts of hydrogen of  $\text{R}_3\text{SiH}$  in  $\tau$  value ( $\text{CDCl}_3$  solution) are 4.02 for  $\text{Cl}_3\text{SiH}$ , 4.52 for  $(\text{C}_6\text{H}_5)_3\text{SiH}$  and 5.84 for  $(\text{C}_2\text{H}_5\text{O})_3\text{SiH}$ , whereas 6.43 for  $(\text{CH}_3)_3\text{SiH}$  and  $(\text{C}_2\text{H}_5)_3\text{SiH}$ . From these facts, it may be said that the reaction of silane with isocyanide by copper catalyst can take place only in the silane compounds with electron donating R groups such as  $\text{CH}_3$  or  $\text{C}_2\text{H}_5$ , although the reaction mechanism is ambiguous at the present moment.

Finally, the presence of suitable solvent is indispensable for the present reaction. In the absence of solvent, the reaction system became heterogenous and product formation was quite low. Suitable solvents for the reaction examined here were dioxane, benzene, cyclohexane and tetrachloro-

ethylene.

## 2. Experimental

### Materials

Trimethylsilane was prepared by the reduction of trimethylsilyl chloride with lithium aluminum hydride, b.p. 6°C. Triethylsilane was obtained in 63 % yield by reaction of trichlorosilane and ethylmagnesium bromide according to the literature, b.p. 111°C (lit.<sup>10</sup>) 107°C (733 mm). Triethoxysilane was prepared by treating trichlorosilane with ethanol in benzene in a yield of 15 %, b.p. 133 — 135°C (lit.<sup>11</sup>) 132 — 135°C). Triphenylsilane was prepared by the action of phenyl magnesium bromide on trichlorosilane in 60 % yield, m.p. 32°C from 95 % ethanol (lit.<sup>12</sup>) 36 — 37°C).

### Reaction of Trimethylsilane and t-Butyl Isocyanide

In a 50 ml pressure tube, a mixture of 3.7 g (50 mmol) of trimethylsilane, 2.5 g (30 mmol) of t-butyl isocyanide, 0.26 g (1 mmol) of copper (II) acetylacetonate and 5 ml of benzene (reaction solvent) was heated at 110 — 120°C for 15 hr. After the reaction, III was isolated by fractional distillation to give 1.97 g (42 % yield), b.p. 47 — 49°C (150 mm). IR ( $\nu_{\text{N}=\text{C}}$  at  $1600 \text{ cm}^{-1}$ , very weak) and NMR (singlet at 1.65  $\tau$ : 1H, -CH=N) spectra supported the structure III.

### Reaction of Triethylsilane and Cyclohexyl Isocyanide

A reaction mixture consisting of 5.2 g (45 mmol) of triethylsilane, 3.3 g (30 mmol) of cyclohexyl isocyanide, 0.135 g (1 mmol) of cupric chloride and

4 ml of benzene was heated in a pressure tube at 130°C for 18 hr. Distillation gave 2.2 g (35 % yield) of IV, b.p. 119°C (25 mm). Anal. Calcd for  $C_{13}H_{27}NSi$ : C, 69.26; H, 12.07; N, 6.21. Found: C, 68.85; H, 11.82; N, 6.35. The structure of IV was further confirmed by IR and NMR spectra.

#### References

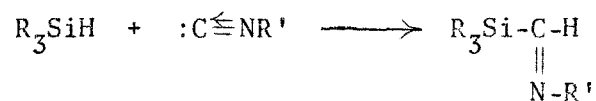
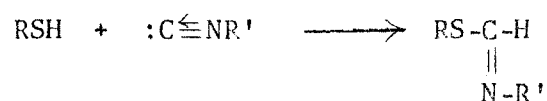
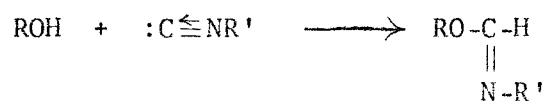
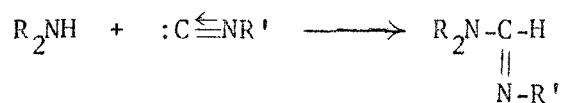
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- 4) J. L. Speier, L. A. Webster, and G. H. Barnes, *J. Am. Chem. Soc.*, 79, 974 (1957).
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## Chapter 5

### A New Insertion Reaction of Isocyanide

#### into Phosphorus-Hydrogen Bond

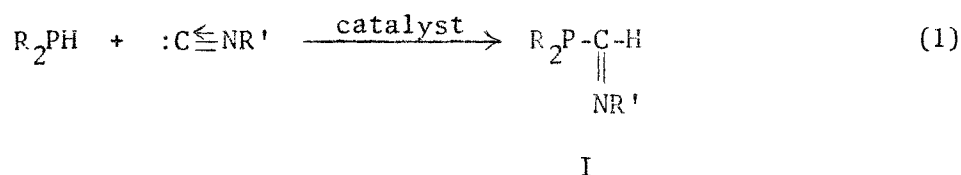
The preceding chapters have dealt with a series of insertion reactions of isocyanides into nitrogen-hydrogen of amine,<sup>1)</sup> oxygen-hydrogen of alcohol,<sup>2)</sup> sulfur-hydrogen of thiol,<sup>3)</sup> and silicon-hydrogen of silane<sup>4)</sup> to produce the corresponding derivatives of N-alkylformimidic acid in high yields.



All of these reactions are catalyzed by copper compounds.

This chapter describes the reaction of dialkylphosphine with isocyanide in which the isocyanide carbon atom is inserted between phosphorus and

hydrogen of dialkylphosphine.

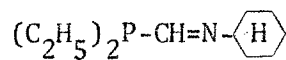


This is a new reaction to form the phosphorus-carbon bond by the  $\alpha,\alpha$ -addition of phosphine to the carbon atom of isocyanide, which is interestingly compared with the  $\alpha,\beta$ -addition of phosphine to olefin through radical mechanism.<sup>5)</sup> The product, N-substituted formimidoylphosphine (I) may be regarded as the Schiff base of formylphosphine, which has not been known until now. The new phosphine compound is stable under dry nitrogen at room temperature, but decomposes gradually in air. The present reaction (eq. 1) provides a new preparative method of such Schiff base.

### 1. Results and Discussion

The reaction of cyclohexyl isocyanide with diethylphosphine was examined at first. Under nitrogen atmosphere a mixture of 4.4 g (40 mmol) of cyclohexyl isocyanide, 2.7 g (30 mmol) of diethylphosphine and 0.021 g (1.5 mmol) of copper (I) oxide was heated in a sealed test tube at 110°C for 6 hr. Nearly complete conversion of diethylphosphine was indicated by the disappearance of  $\nu_{\text{P-H}}$  band at 2280  $\text{cm}^{-1}$  in the IR spectrum of the reaction mixture. Then the mixture was distilled to isolate N-cyclohexylformimidoyldiethylphosphine (II), b.p. 110 — 112°C (6 mm),  $n_{\text{D}}^{20}$  1.5059. Anal. Calcd for

$C_{11}H_{22}NP$ : C, 66.30; H, 11.13; N, 7.03; P, 15.54. Found: C, 65.94; H, 11.14; N, 7.07; P, 14.79. Mol. wt. calcd for II: 199. Found (cryoscopy in benzene): 202. The yield of II based on diethylphosphine was 81 %.



II

The structure of II was confirmed by IR and NMR spectra. The IR spectrum of II (neat) showed an absorption at  $1605\text{ cm}^{-1}$  ( $>C=N-$ ). The NMR spectrum in  $CDCl_3$  (Fig. 1) showed a doublet centered at  $\tau$  1.65 (1H,  $>P-CH=$ ,  $J_{P-H}$  32.9 cps), a broad signal centered at  $\tau$  7.1 (1H,  $=N-CH<$ ), and a multiplet (10H,  $-P(C_2H_5)_2$ ) and a broad signal (10H,  $-(CH_2)_5-$  of cyclohexane ring) in the region of  $\tau$  8.0 — 9.2.

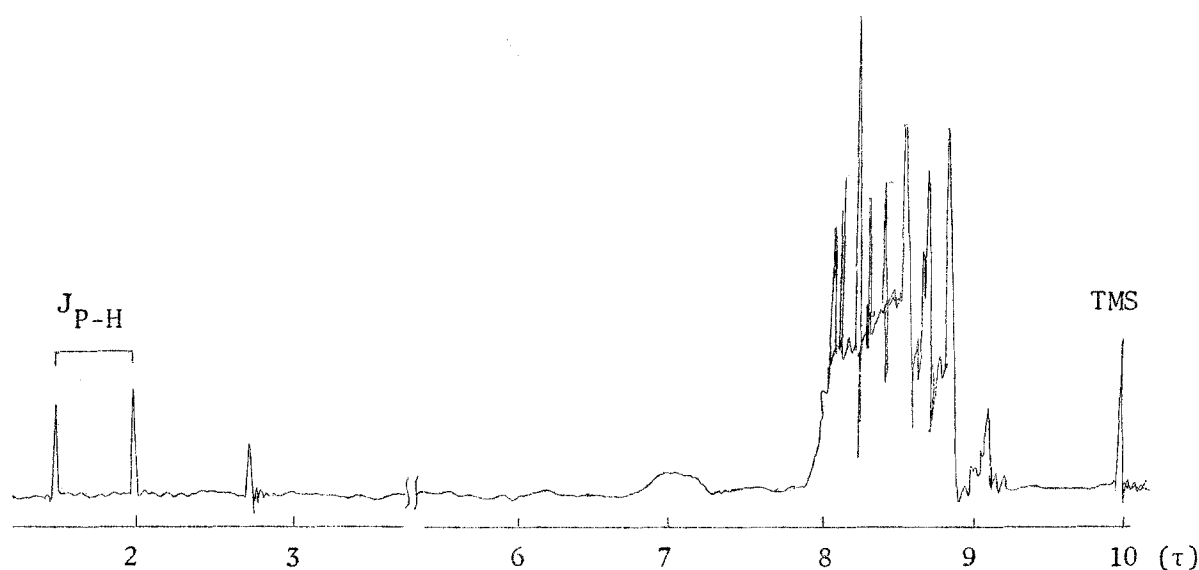
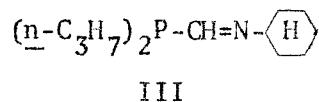


Fig. 1. NMR spectrum of N-cyclohexylformimidoyldiethylphosphine (II)  
(in deuteriochloroform)

Similarly, the reaction of cyclohexyl isocyanide and di-n-propylphosphine took place in the presence of copper (I) oxide catalyst. The product, N-cyclohexylformimidoyldi-n-propylphosphine (III) was obtained in a yield of 45 %.



The reaction (1) requires catalysts of the Group IB and IIB metal compounds. In the absence of catalyst, cyclohexyl isocyanide and diethylphosphine were recovered unchanged from the heat-treated reaction mixture. So far as we have examined, copper (I) oxide was excellent and copper (II) acetylacetonate, zinc chloride, cadmium chloride and mercury (II) acetate were fairly good. Typical Friedel—Crafts catalysts such as aluminum chloride were inactive. The Group VIII metal compounds such as nickel (II) and cobalt (II) chlorides caused exclusively the polymerization of isocyanide to form insoluble, light-brown solid.

## 2. Experimental

### Materials

Diethylphosphine was prepared according to the procedure described in literature.<sup>6)</sup> To a Grignard solution prepared from 36 g of magnesium, 163.5 g of ethyl bromide and 500 ml of absolute ether, 86 g of phosphorus thiochloride dissolved in 100 ml ether was added dropwise for 5 hr with stirring at 20 — 24°C. The ether solution was further warmed on a water-bath for 1 hr. Then, 10 % sulfuric acid was added carefully. The ether layer was



dried over sodium sulfate. After ether was distilled off, the solid material was precipitated, which was purified by recrystallization from acetone-water to give tetraethyldiphosphine disulfide, m.p. 76 — 77°C.

To 24 g of tetraethyldiphosphine disulfide suspended in 100 ml ether, 80 ml of ether solution containing 8 g of lithium aluminum hydride was added dropwise with stirring. After the addition, the ether solution was further refluxed for 1 hr. The reaction mixture was decomposed by the addition of water to form two layers. The ether layer was separated and dried over sodium sulfate. Distillation of the ether solution gave diethylphosphine in a yield of 60 %, b.p. 83 — 85°C.

Di-n-propylphosphine was prepared also by the above mentioned method.<sup>6)</sup>

#### Reaction of Cyclohexyl Isocyanide with Di-n-propylphosphine

To a mixture of 2.2 g (20 mmol) of cyclohexyl isocyanide and 2.4 g (20 mmol) of di-n-propylphosphine was added 0.014 g (1.0 mmol) of copper (I) oxide as catalyst. The mixture was heated at 110°C for 5 hr and then the reaction mixture was distilled in vacuo to isolate 1.2 g (46 %) of III, b.p. 124 — 125°C (4 mm). IR ( $\nu_{\text{C=N}}$  at  $1604 \text{ cm}^{-1}$ ) and NMR (a doublet centered at  $\tau$  1.62, 1H, P-CH=N,  $J_{\text{P-H}}$  32.2 cps) spectra were indicative of the structure III.

## References

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- 3) See Part I, Chapter 3.
- 4) See Part I, Chapter 4.
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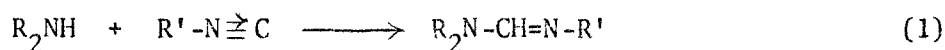
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REACTIONS OF CARBON MONOXIDE AND OF DIAZO COMPOUNDS

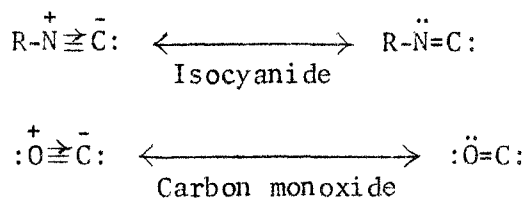
## Chapter 1

### Carbonylation of Amines by Copper Catalysts

It has been described in Chapter 1 of Part I that primary and secondary amines react with isocyanide in the presence of copper compound as catalyst to produce amidines in high yields.<sup>1)</sup>



In view of the fact that carbon monoxide is isoelectronic with isocyanide<sup>2)</sup> and forms coordination complexes with cuprous salts,<sup>3)</sup> the above finding prompted us to explore the possibility of the reaction of amine with carbon monoxide by copper catalyst.



In the present chapter, the catalytic activities of copper compounds as well as other Groups IB and IIB metal compounds for the carbonylation of amines have been investigated.

Various catalysts have hitherto been reported for the amine—carbon monoxide reaction. Transition metals of the Groups IV to VIII,<sup>4,5)</sup> their salts,<sup>5—8)</sup> their metal carbonyls,<sup>9—11)</sup> and corresponding organometallic

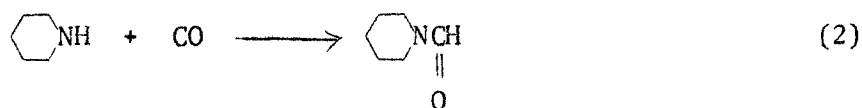
compounds<sup>12)</sup> catalyze this reaction to produce a mixture of formamide, urea, isocyanate and oxamide. The alkali metal alcoholate catalyzes the carbonylation of amine to produce the corresponding formamide.<sup>13)</sup> In addition, a patent claims the productions of N-methylformamide and N,N-dimethylformamide from methylamine and dimethylamine, respectively, by a catalyst selected from the group consisting of cuprous and cupric chlorides, ammonium chloride, potassium acetate and boron fluoride.<sup>14)</sup>

The purpose of the present investigation is to examine the catalytic activities of copper compounds along with other Groups IB and IIB metal compounds for the carbonylation of aliphatic and aromatic amines with carbon monoxide. New findings are that (i) copper compounds are excellent catalysts for the carbonylation of aliphatic amines to produce the corresponding formamides, (ii) the catalytic activities of copper compounds are enhanced by the addition of water, and (iii) chloroauric acid catalyzes the carbonylation of aromatic amine but copper compounds do not catalyze it.

## 1. Results and Discussion

### 1.1. Carbonylation of Piperidine

The Groups IB and IIB metal compounds were examined for catalyst activity for the carbonylation of piperidine. Their catalytic activities were also compared with



those of other metal compounds. The Groups IB and IIB metal compounds, especially copper compounds, are quite active.

Table I. Carbonylation of Piperidine in the Presence of Various Metal Compounds<sup>a</sup> (Method B)<sup>b</sup>

Exp. No.	Catalyst	Reaction conditions		Yield of N-formylpiperidine (%) <sup>c</sup>
		Temp. (°C)	Time (hr)	
1	CuCl	140	15	93
2	Cu(CN) <sub>2</sub>	110	15	72
3 <sup>d</sup>	CuCl <sub>2</sub>	120	14	17
4	CuCl—1,5-COD complex <sup>e</sup>	130	14	96
5	AgCl	140	14	25
6	HAuCl <sub>4</sub> ·4H <sub>2</sub> O	130	14	15
7	ZnCl <sub>2</sub>	135	16	18
8	Cd(OAc) <sub>2</sub>	140	14	15
9	Hg(OAc) <sub>2</sub>	130	14	60
10	AlCl <sub>3</sub>	120	15	5
11	Fe(AA) <sub>3</sub>	130	14	40
12	CoCl <sub>2</sub>	110	15	20
13	NiCl <sub>2</sub>	110	15	7
14	PdCl <sub>2</sub>	120	14	5

<sup>a</sup> 10 ml of piperidine and 1.0 g of a catalyst were used.

<sup>b</sup> See Experimental Section.

<sup>c</sup> Based on the initially charged piperidine.

<sup>d</sup> Ethanol (10 ml) was used as solvent.

<sup>e</sup> The cuprous chloride-1,5-cyclooctadiene complex was prepared according to the reference.<sup>15)</sup>

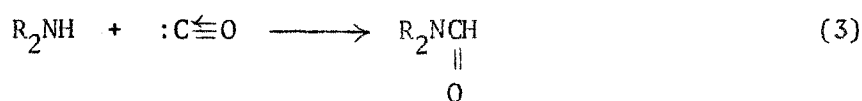
The typical transition metal salts of the Group VIII elements, e.g., Fe, Co, Ni, and Pd are less active than copper catalysts. Aluminum chloride, a strong Lewis acid, is a poor catalyst (Table I).

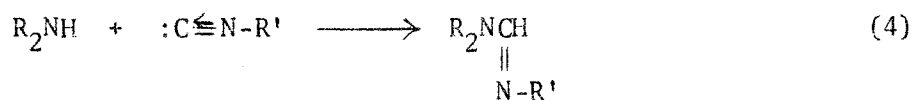
The catalytic behaviors of the copper compounds in the amine—carbon monoxide reaction are distinguished from the typical transition metal catalysts by their highly selective production of formamide. In the copper catalyzed reaction, a small amount (usually less than a few percent) of N,N'-dialkyl derivative of urea was formed as the sole by-product.

The amount of by-product is much smaller than that in the reaction with palladium<sup>8)</sup> and manganese<sup>11)</sup> catalysts. The piperidine—carbon monoxide reaction with catalysts of Ag, Au, Zn, Cd, and Hg salts produces also a trace amount of 1,1'-carbonyldipiperidine (less than a few percent) as by-product.

The coordination of carbon monoxide with cuprous salts in the presence of amine is well known.<sup>3)</sup> It is not unreasonable to assume that carbon monoxide coordination plays an important role in the catalysis. When cupric salts are used as catalysts, they may be reduced by carbon monoxide into cuprous species which may possibly be the real active species of the catalyst.

Copper compounds catalyze also the  $\alpha,\alpha$ -addition of nitrogen hydrogen bond of aliphatic amine to isocyanide.<sup>1)</sup> It is interesting to note that reaction with the aliphatic amine—carbon monoxide reaction of the present studies, since isocyanide and carbon monoxide are isoelectronic. These two reactions caused by copper catalysts are formulated in analogous manner.





## 1.2. Carbonylation of Dimethylamine

Copper compounds catalyze also the dimethylamine (DMA)—carbon monoxide reaction to produce N,N-dimethylformamide (DMA) (Table II).

Table II. Carbonylation of DMA with Copper Catalysts

Exp. No.	Catalyst	DMA (g)	DMA (ml)	Method <sup>a</sup>	Reaction conditions		Initial rate <sup>b</sup> (mmol/min)	Yield of DMF (%) <sup>c</sup>
					Temp. (°C)	Time (hr)		
15	CuCl	1.0	10	B	100	13	—	73
16	Cu(CN) <sub>2</sub>	1.0	10	B	100	13	—	52
17	CuCN	0.5	5	B	135	15	—	78
18	CuCl	2.0	30	A	180	28	—	96
19	none		60 <sup>d</sup>	A	145—150	2	—	18
20	CuCN	1.0	60 <sup>d</sup>	A	145—150	2	—	57
21	Cu(CN) <sub>2</sub>	2.0	60 <sup>d</sup>	A	120—130	10	—	85
22	CuCN	1.0	30 <sup>e</sup>	A	175	3.0	1.2	20
23	CuCN	1.0	30 <sup>f</sup>	A	175	3.0	5.7	84

<sup>a</sup> See Experimental Section.

<sup>b</sup> The rates of gas consumption during the initial 30 min are taken as a measure of the initial rate.

<sup>c</sup> Based on DMA.

<sup>d</sup> 40 % aqueous DMA solution (60 ml) was charged.

<sup>e</sup> Anhydrous DMA, dried with potassium carbonate, was employed.

<sup>f</sup> DMA containing 10 mol % of water was employed.



The by-product is N,N,N',N'-tetramethylurea, produced only in small amounts. It is quite interesting to observe that the catalytic activity of copper catalyst is enhanced by the addition of water. The accelerating effect of CuCl-CO complexization is favored by water.<sup>3)</sup>

The effect of a small amount of water is clearly demonstrated in the last two runs of Table II, where the carbonylation by CuCN catalyst was carried out in the absence (Exp. No. 22) and in the presence of water (Exp. No. 23). The addition of 10 mole % of water increases the rate and the conversion four to five fold. Furthermore, DMA carbonylation is efficiently carried out in an aqueous system (Exp. No. 19 to No. 21, Table II). Two possibilities may be pointed out to explain the effect of water. First, water molecule is incorporated into the copper-DMA complex as a ligand, which possibly modifies (increases) the catalyst activity. Second, water converts carbon monoxide to formic acid which may be responsible for the carbonylation reaction. In fact, it has been known that the addition of water to the reaction system without metallic catalyst increases the rate of carbonylation, although the actual rate itself is quite low.<sup>13)</sup>

### 1.3. Carbonylations of Miscellaneous Amines

Other aliphatic amines can also be carbonylated by means of copper compound catalysts (Table III). The carbonylation of secondary amines appears to be easier than that of primary amines.

The carbonylation of allylamine differentiates the copper catalyst from the cobalt carbonyl catalyst. The copper catalyzed carbonylation of allylamine yields only N-allylformamide, whereas the cobalt carbonyl catalyzed

reaction gives the cyclization product, 2-pyrrolidinone.

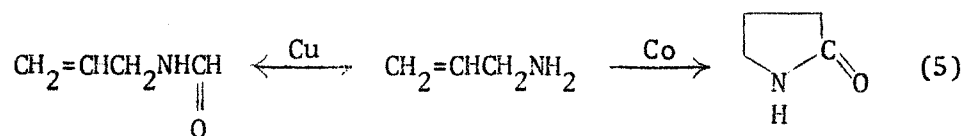



Table III. Carbonylation of Miscellaneous Aliphatic Amines  
with Copper Catalysts

Exp. No.	Amine	(ml)	Catalyst	(g)	Method <sup>a</sup>	Reaction conditions		Yield of formylated product (%) <sup>b</sup>
						Temp. (°C)	Time (hr)	
24	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> NH	50	Cu(OAc) <sub>2</sub>	2.5	A	170	20	46
25	 NH	10	Cu(CN) <sub>2</sub>	0.5	B	120	13	65
26	HOCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	20	CuCl <sub>2</sub>	1.0	B	105	20	23
27	n-C <sub>4</sub> H <sub>9</sub> NH <sub>2</sub>	10	CuCl	1.0	B	115	16	20
28	C <sub>2</sub> H <sub>5</sub> NH <sub>2</sub>	10	CuCN	1.0	B	165	20	25
29	CH <sub>2</sub> =CHCH <sub>2</sub> NH <sub>2</sub>	10	CuCl <sub>2</sub>	0.5	B	120	15	15

<sup>a</sup> See Experimental Section.

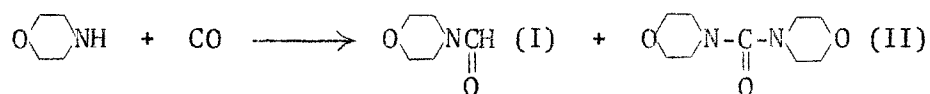
<sup>b</sup> Based upon the charged amine.

#### 1.4. Temperature Effects on Carbonylation of Morpholine

The rate of the carbonylation of morpholine is increased by raising the reaction temperature (Table IV). A small amount of 4,4'-carbonyldimorpholine by-product was formed at higher reaction temperature (Exp. No. 33). The urea may be produced by the copper catalyzed oxidation of morpholine with oxygen,<sup>16)</sup>

which is possibly present as a contaminant in the reaction system.

Table IV. Carbonylation of Morpholine  
with Cuprous Chloride Catalyst at Various Temperatures



Exp. No.	Temp. (°C)	Yield (%)	
		I	II
30	80	3	—
31	115	14	trace
32	150	42	trace
33	180	76	2

(Reaction conditions: Morpholine, 30 ml; CuCl, 2.0 g as catalyst; initial CO pressure 80 Kg/cm<sup>2</sup> at room temperature, with stirring for 6.5 hr.)

### 1.5. Carbonylation of Aromatic Amines

Copper compounds are inactive for the reaction of aromatic amines with carbon monoxide. On the other hand, chloroauric acid is active (Table V). From the isoelectronic relationship between carbon monoxide and isocyanide, it is also of interest to note that copper compounds do not work as effectively in the aromatic amine-isocyanide reaction as chloroauric acid does.<sup>1)</sup>

Table V. Formylation of Aniline and N-Methylaniline (Method B)<sup>a</sup>

Exp. No.	Amine	(mmol)	Catalyst	(mmol)	Reaction conditions		Yield of formanilide (%) <sup>b</sup>
					Temp. (°C)	Time (hr)	
34	C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	100	HAuCl <sub>4</sub> ·4H <sub>2</sub> O	1.0	180	15	17
35	C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	100	CuCl	1.0	180	15	0
36	C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	100	AgCl	1.0	180	15	0
37	C <sub>6</sub> H <sub>5</sub> NHCH <sub>3</sub>	100	HAuCl <sub>4</sub> ·4H <sub>2</sub> O	0.8	175	40	33

<sup>a</sup> See Experimental Section.

<sup>b</sup> Based on the charged amine.

## 2. Experimental

### Materials

All amines were distilled before use. Copper compounds and other metal salts were commercial reagents which were used as received. Carbon monoxide was reagent grade.

### Reaction Procedures

Method A. Amine and a catalyst were placed in a 200 ml stainless-steel autoclave equipped with a magnetic stirrer, to which carbon monoxide was charged up to a pressure of 60 — 80 Kg/cm<sup>2</sup> at room temperature. The autoclave was closed and heated at a given temperature for a given time. Then, the catalyst was separated by filtration if it was precipitated and the

reaction mixture was distilled or analyzed directly by glpc.

Method B. The reaction was carried out in a 50 ml stainless steel pressure tube without stirring. After-treatment of the reaction mixture was carried out in the same procedure as in Method A.

#### Identification and Analyses of the Products

The reaction products were identified by comparing their NMR and IR spectra and the glpc retention times with those of the respective authentic samples. The columns of glpc were PEG 6000 and Silicone DC 550. The yield of products was determined by glpc analyses and in some cases by fractional distillation.

#### Preparations of Authentic Samples

The authentic formamide derivatives were prepared by treating the respective amines with ethyl formate. The boiling points of these authentic samples were as follows: N-formylpiperidine, 90 — 92°C (9 mm); N,N-diethylformamide, 177 — 178°C; N-formylpyrrolidine, 97 — 98°C (15 mm); N-2-hydroxyethylformamide, 134 — 136°C (0.4 mm); N-n-butylformamide, 142 — 144°C (45 mm); N-allylformamide, 120 — 122°C (48 mm); N-ethylformamide, 109°C (30 mm); N-formylmorpholine, 121 — 124°C (15 mm); formanilide, 90 — 91°C (12 mm), (m.p. 47°C); and N-methylformanilide, 131 — 133°C (25 mm).

The authentic samples of 1,1'-carbonyldipiperidine and 4,4'-carbonyldimorpholine were prepared by the reaction of piperidine and morpholine with phosgene, the former, m.p. 42°C (lit.,<sup>16</sup>) m.p. 42 — 43°C) and the latter, m.p. 141 — 142°C (lit.,<sup>16</sup>) m.p. 143°C), respectively.

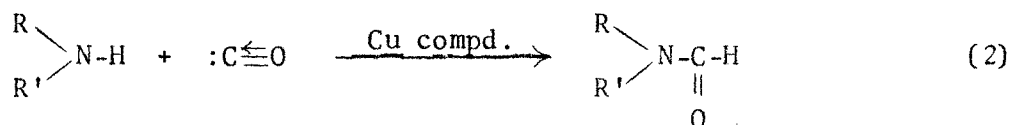
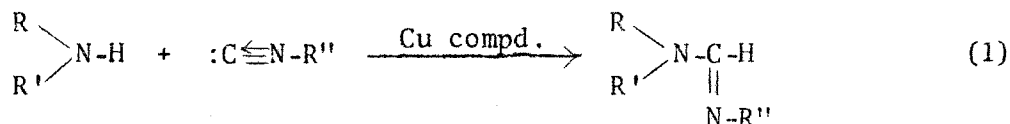
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## Chapter 2

### Copper Catalyzed N-Alkylation of Amine with Diazoalkane

Two reactions of amines by copper compound catalysts have been described in Chapter 1 of Part I and in Chapter 1 of Part II. The first is the reaction of amine with isocyanide (eq. 1)<sup>1)</sup> and the second is that with carbon monoxide (eq. 2),<sup>2)</sup> where formamidine and N-alkylformamide are formed, respectively.



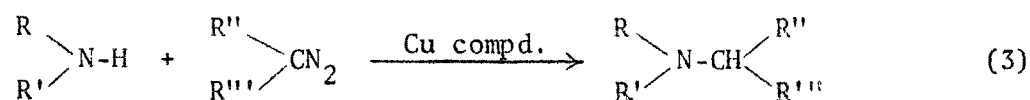
In both of these reactions, the carbon atoms having lone-pair electrons are inserted between nitrogen and hydrogen of amine.

On the other hand, carbene generated by the decomposition of diazoalkane is another species of carbon having lone-pair electrons,<sup>3)</sup> and it is well known that copper and its compounds catalyze the decomposition of diazoalkanes. In relation to the mechanism of the diazoalkane reaction, coordination complexes of carbene to copper compound<sup>4)</sup> (or an inverse ylid<sup>5,6)</sup> have been assumed.

This chapter describes the third of a series of the copper catalyzed reactions of amine, in which the reactions of amine with diazomethane and with ethyl diazoacetate have been investigated.

### 1. Results and Discussion

In the presence of copper compound catalyst, the carbon atom of carbene generated by the decomposition of diazo compound is also inserted between nitrogen and hydrogen of amine.



The reaction of this type was once performed by Müller et al.,<sup>7)</sup> who employed boron fluoride and borofluoric acid as catalyst.

The difference in catalytic activity between the acid catalyst and the copper compound is seen in the reaction of piperidine with diazoacetate, i.e., the former does not catalyze the reaction of this combination, whereas the latter does.

The reactions of amines with diazomethane and with diazoacetate are illustrated in Table I.

In the reaction of n-butylamine and ethyl diazoacetate, the aminolysis of ester group as well as the insertion reaction (eq. 3) occurs to give the corresponding N-n-butylamide.

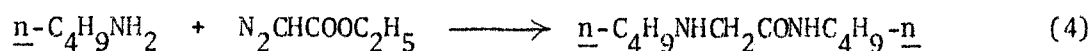







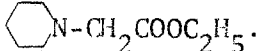
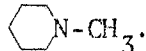
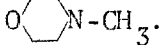


Table I. Copper Catalyzed Reaction of Amine  
with Diazoalkane<sup>a</sup>

Amine	Diazoalkane	Cu Catalyst	Products <sup>c</sup>	Yield <sup>d</sup> (%)
 NH	N <sub>2</sub> CHCOOC <sub>2</sub> H <sub>5</sub>	CuCN	I	72
 NH	N <sub>2</sub> CHCOOC <sub>2</sub> H <sub>5</sub>	CuCl	I	33
 NH	N <sub>2</sub> CH <sub>2</sub> <sup>b</sup>	CuCN	II	32
 NH	N <sub>2</sub> CH <sub>2</sub> <sup>b</sup>	CuCN	III	30
 NH	N <sub>2</sub> CH <sub>2</sub> <sup>b</sup>	CuCl	III	25
n-C <sub>4</sub> H <sub>9</sub> NH <sub>2</sub>	N <sub>2</sub> CHCOOC <sub>2</sub> H <sub>5</sub>	CuCN	IV	46

<sup>a</sup> Reaction conditions: 5 — 10°C, 5 hr, molar ratio of amine/diazoalkane = 3.0 — 4.0.

<sup>b</sup> Diazomethane was employed as an ether solution.

<sup>c</sup> Product I: . II: .  
III: . IV: n-C<sub>4</sub>H<sub>9</sub>NHCH<sub>2</sub>CONHC<sub>4</sub>H<sub>9</sub>-n.

<sup>d</sup> Based upon diazo compound.

## 2. Experimental

### Materials

Ethyl diazoacetate was prepared according to the usual method.<sup>8)</sup> A solution of 140 g (1 mol) of glycine ethyl ester hydrochloride and 3 g of sodium acetate in 150 ml of water was introduced into the 1 l flask and cooled to 0°C in an ice-salt bath. A cold solution of 80 g (1.15 ml) of

sodium nitrite in 100 ml of water was added and the mixture was stirred until the temperature became to 0°C. Ethyl ether (80 ml) and then cold 10 % sulfuric acid (3 ml) were added to the cold reaction mixture with stirring and cooling. The ether layer was washed with 50 ml of cold 10 % sodium carbonate solution. The ether solution was dried over anhydrous sodium sulfate. Distillation gave 65 g (56 %) of ethyl diazoacetate, b.p. 63°C (37 mm).

Diazomethane was obtained as an ethereal solution by the alkali decomposition<sup>9)</sup> of N-nitroso-N-methylurea prepared according to the reference.<sup>10)</sup> The amount of diazomethane in an ethereal solution was determined by treating it with excess benzoic acid and by titrating the unreacted benzoic acid with standard alkali.<sup>9)</sup> The concentration of diazomethane of ether solution was 1.2 mol/l.

#### General Procedure

A typical run is the reaction of piperidine with ethyl diazoacetate. To an ice-cold mixture of 17.9 g (0.21 mol) of piperidine and 1.57 g (0.017 mol) of cuprous cyanide, 7.98 g (0.07 mol) of ethyl diazoacetate was added dropwise with stirring at 5 — 10°C. After the addition, the reaction mixture was stirred for 5 hr at 5 — 10°C. During the reaction, the color change of the reaction mixture from green to brown was observed. After the removal of the insoluble catalyst, the reaction mixture was distilled in vacuo to yield 8.64 g (72 %) of ethyl 1-piperidineacetate, b.p. 108 — 110°C (20 mm).

NMR and IR spectra were indicative of the structure of ethyl 1-piperidineacetate.

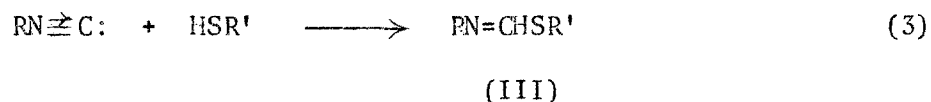
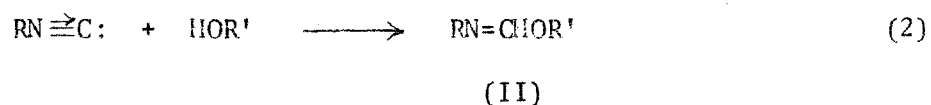
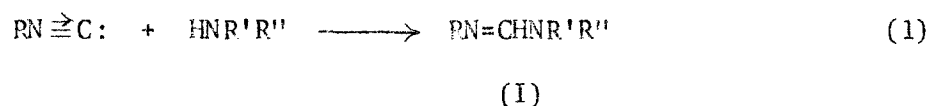
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## Chapter 3

### Copper Catalyzed Reactions of Thiol and Alcohol with Diazoacetate

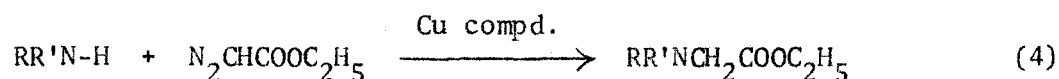
A series of reactions of isocyanide with amines,<sup>1)</sup> alcohols<sup>2)</sup> and thiols<sup>3)</sup> to produce formamidine (I), formimidate (II), and thioformimidate (III), respectively, has been described in previous chapters.



These reactions are all catalyzed by copper compounds and are characterized by the common feature that the isocyanide carbon atom having lone-pair electrons is inserted into N-H, O-H and S-H linkages.

The carbene produced by the decomposition of diazoalkane is another species having the lone-pair electrons of carbon, which resembles isocyanide also in the property of coordinating with copper compounds.<sup>4)</sup> These facts

prompted us to explore the copper catalyzed reactions of diazoacetate. It has been shown in the preceding chapter that the carbene carbon is inserted quite selectively into N-H linkage in the copper catalyzed reactions of ethyl diazoacetate with amines.<sup>5)</sup>



The present chapter describes the reactions of thiols and alcohols with ethyl diazoacetate in the presence of copper compounds as catalysts.

## 1. Results and Discussion

### 1.1. Reaction of Thiols with Ethyl Diazoacetate

The thiol-diazoacetate reaction without catalyst was once studied by Müller and Freytag,<sup>6)</sup> and it was reported that benzenethiol reacted with ethyl diazoacetate to form ethyl phenylthioacetate, whereas aliphatic thiols did not react even at 80°C. It has now been found that, in the presence of cuprous chloride as catalyst, aliphatic thiols (alkane and aralkane thiols) react satisfactorily with ethyl diazoacetate at 80 — 90°C to produce the corresponding thioacetate (IV) as the main product along with three by-products (V), (VI) and (VII).

Each product was isolated by means of preparative glpc and was identified by elemental analysis and IR and NMR spectra. Typical results are shown in Table I. Both diethyl maleate and fumarate were formed only in quite small yields in these reactions.

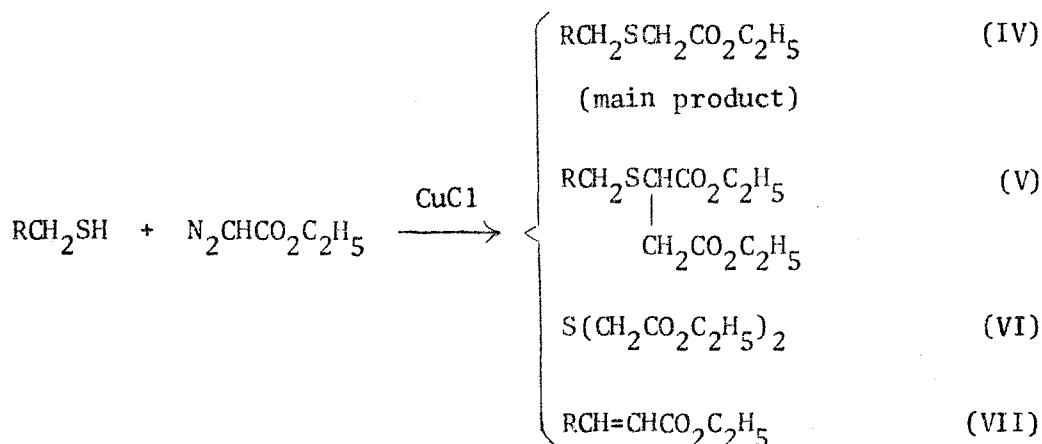


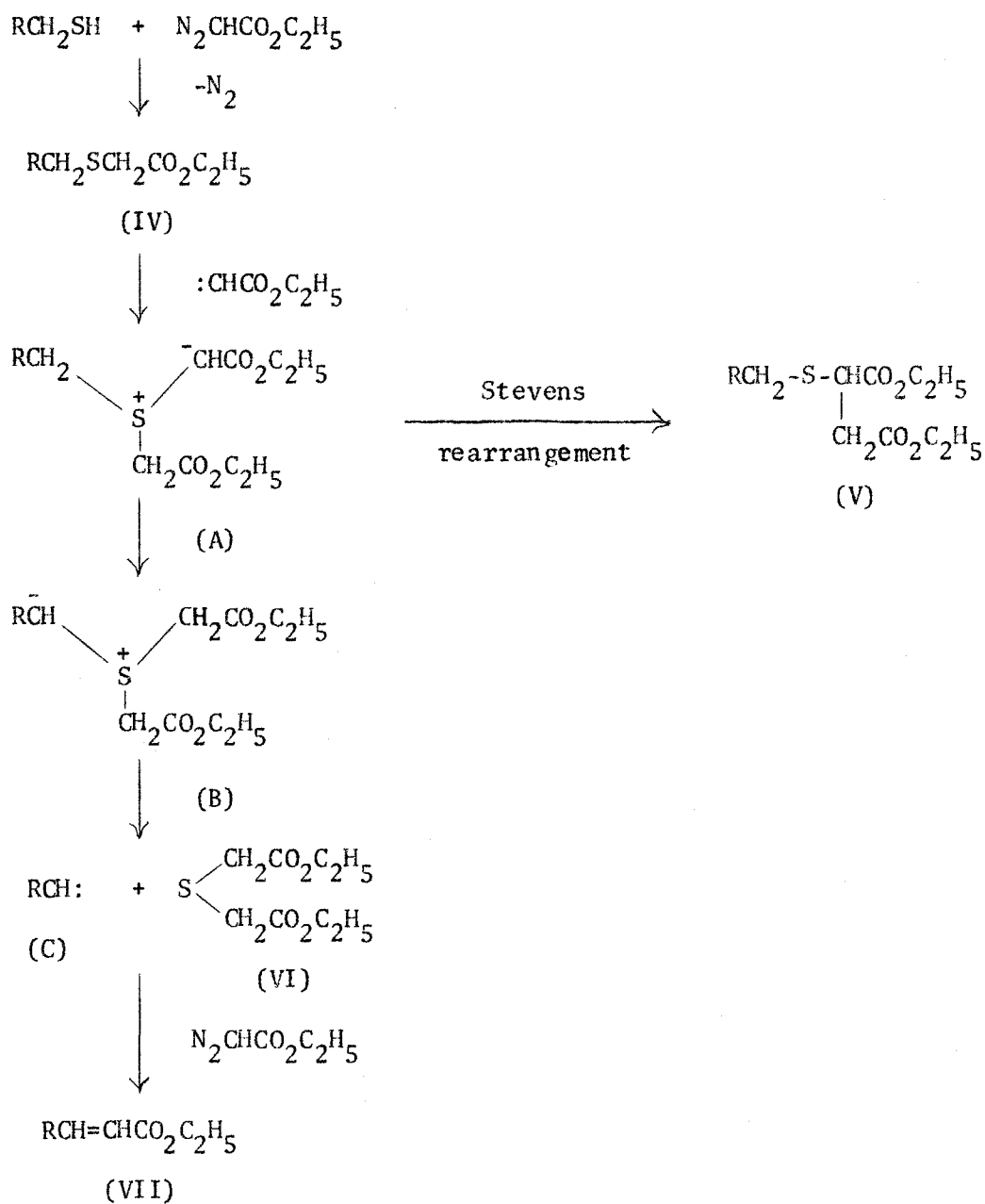
Table I. Reaction of Thiol with Ethyl Diazoacetate  
by Cuprous Chloride Catalyst<sup>a</sup>

Thiol (RCH <sub>2</sub> SH)	Reaction time (hr)	Products (yield %)			
		(IV)	(V)	(VI)	(VII)
<u>n</u> -C <sub>4</sub> H <sub>9</sub> SH	30	85	2	8	—
CH <sub>2</sub> =CHCH <sub>2</sub> SH	9	63	20	7	—
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SH	6	86	2	9	1

<sup>a</sup> A mixture of 60 mmol of thiol, 60 mmol of ethyl diazoacetate and 1 mmol of CuCl was heated at 80 — 90°C.

It is clearly indicated that the carbon having lone-pair electrons of the carbene from diazoacetate is inserted between sulfur and hydrogen of the thiol to form the main product (IV). The insertion of carbene into S-H linkage is interestingly compared with the corresponding insertions into O-H in the reactions of alcohol with diazoacetate. The selectivity of the formation of (IV) was much higher than that of the alkoxyacetate in the alcohol—diazoacetate reaction by copper catalyst, as will be described later.

The formations of three by-products may reasonably be explained by the following scheme of reactions.



The reaction of alkylthioacetate (IV) with the carbene from diazoacetate will lead to a S-ylid (A) whose rearrangement of Stevens type<sup>7)</sup> produces

alkylthiosuccinate (V). The proton shift in the S-ylid (A), on the other hand, will afford the carbene (C) and diethyl thiodiglycolate (VI) through the intermediate (B). The carbene (C) in turn reacts with diazoacetate to afford the third by-product (VII).

An alternative route would also be proposed for the formation of VI and VII. Proton abstract from thiol by S-ylid (A) and the subsequent attack of the resulting thiol anion on the resulting sulfonium ion will lead to the formation of VI. In this case, VII will be formed by the insertion of carbethoxy carbene into the methylene C-H bond of  $\alpha$ -toluenethiol followed by the loss of hydrogen sulfide.

It might be assumed that alkylthiosuccinate (V) resulted from the reaction of thiol with maleate or with fumarate which could be formed from diazoacetate. This possibility, however, has been eliminated by the reference experiments which have shown that thiol did not react with maleate and with fumarate under the same reaction conditions. As to the mechanism of the formation of VI, a possibility of the reaction of diazoacetate and hydrogen sulfide to form VI has also been denied by a reference experiment.

## 1.2. The Reaction of Alcohols with Ethyl Diazoacetate

The decomposition of diazoacetate catalyzed by cupric chloride was more quick in alcohols than in thiols and amines. At room temperature in alcohol, the evolution of nitrogen gas by the decomposition of diazoacetate ceased in 3 hr. The reaction products were analyzed and isolated by glpc techniques.

The results of the reactions of n-butanol, benzyl alcohol and allyl alcohol, respectively, with ethyl diazoacetate in the presence of cupric



chloride as catalyst are given in Tables II, III and IV.

Table II. Reaction of n-Butanol with Ethyl Diazoacetate  
by Cupric Chloride<sup>a</sup>

Products		Yield (%) <sup>b</sup>
$\underline{n}\text{-C}_4\text{H}_9\text{OCH}_2\text{CO}_2\text{C}_2\text{H}_5$	(VIIIb)	15
$\underline{n}\text{-C}_4\text{H}_9\text{OCHCO}_2\text{C}_2\text{H}_5$   $\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$	(IXb)	16
$\underline{n}\text{-C}_4\text{H}_9\text{OCHCO}_2\text{C}_2\text{H}_5$   $\text{CHCO}_2\text{C}_2\text{H}_5$   $\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$	(Xb)	14
$\text{O}(\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5)_2$	(XI)	7
<u>trans</u> - $\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$	(XIIb)	12
<u>cis</u> - $\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$	(XIIc)	11
$\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CCO}_2\text{C}_2\text{H}_5$   $\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$	(XIII)	16

(Total yield: 91)

<sup>a</sup>  $\underline{n}\text{-C}_4\text{H}_9\text{OH}$ , 35 mmol;  $\text{N}_2\text{CHCO}_2\text{C}_2\text{H}_5$ , 17 mmol;  
 $\text{CuCl}_2$ , 1 mmol at 25°C, 3 hr.

<sup>b</sup> Based on ethyl diazoacetate.

Table III. Reaction of Benzyl Alcohol  
with Ethyl Diazoacetate by Cupric Chloride<sup>a</sup>

Products		Yield (%) <sup>b</sup>
$C_6H_5CH_2OCH_2CO_2C_2H_5$	(VIIIc)	49
$C_6H_5CH_2OCHCO_2C_2H_5$   $CH_2CO_2C_2H_5$	(IXc)	13
$O(CH_2CO_2C_2H_5)_2$	(XI)	5
<u>trans</u> - $C_2H_5O_2CCH=CHCO_2C_2H_5$	(XIIb)	7
<u>cis</u> - $C_2H_5O_2CCH=CHCO_2C_2H_5$	(XIIc)	8
$C_2H_5O_2CCH=CCO_2C_2H_5$   $CH_2CO_2C_2H_5$	(XIII)	11

(Total yield: 93)

<sup>a</sup>  $C_6H_5CH_2OH$ , 35 mmol;  $N_2CHCOOC_2H_5$ , 17 mmol;  
 $CuCl_2$ , 1 mmol at 25°C, 3 hr.

<sup>b</sup> Based on ethyl diazoacetate.

Table IV. Reaction of Allyl Alcohol  
with Ethyl Diazoacetate by Cupric Chloride<sup>a</sup>

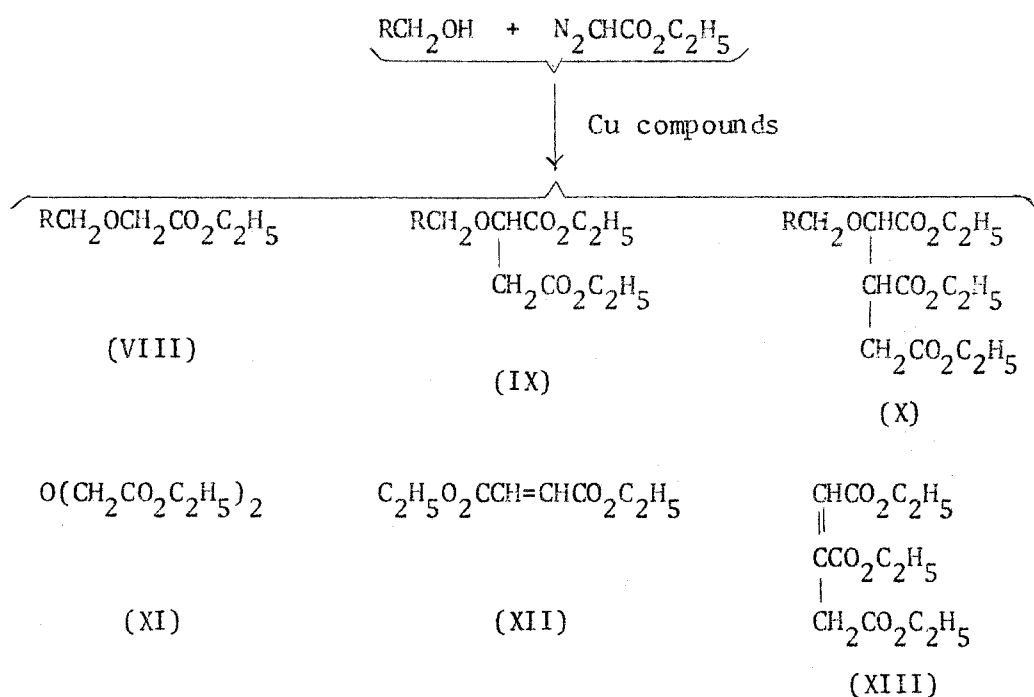
Products		Yield (%) <sup>b</sup>
$\text{CH}_2=\text{CHCH}_2\text{OCH}_2\text{CO}_2\text{C}_2\text{H}_5$	(VIII d)	17
$\text{O}(\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5)_2$	(XI)	9
<u>trans</u> - $\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$	(XI Ib)	15
<u>cis</u> - $\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CHCO}_2\text{C}_2\text{H}_5$	(XI Ic)	16
$\text{C}_2\text{H}_5\text{O}_2\text{CCH}=\text{CCO}_2\text{C}_2\text{H}_5$   $\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$	(XI II)	24
$\text{CH}_2-\text{CHCH}_2\text{OH}$   $\text{CHCO}_2\text{C}_2\text{H}_5$	(XIV)	8
$\text{CH}_2-\text{CHCH}_2\text{OCH}_2\text{CH}=\text{CH}_2$   $\text{CHCO}_2\text{C}_2\text{H}_5$	(XV)	5

(Total yield: 94)

<sup>a</sup>  $\text{CH}_2=\text{CHCH}_2\text{OH}$ , 17.6 mmol;  $\text{N}_2\text{CHCOOC}_2\text{H}_5$ , 8.8 mmol;  
 $\text{CuCl}_2$ , 1 mmol at 25°C, 3 hr.

<sup>b</sup> Based on ethyl diazoacetate.

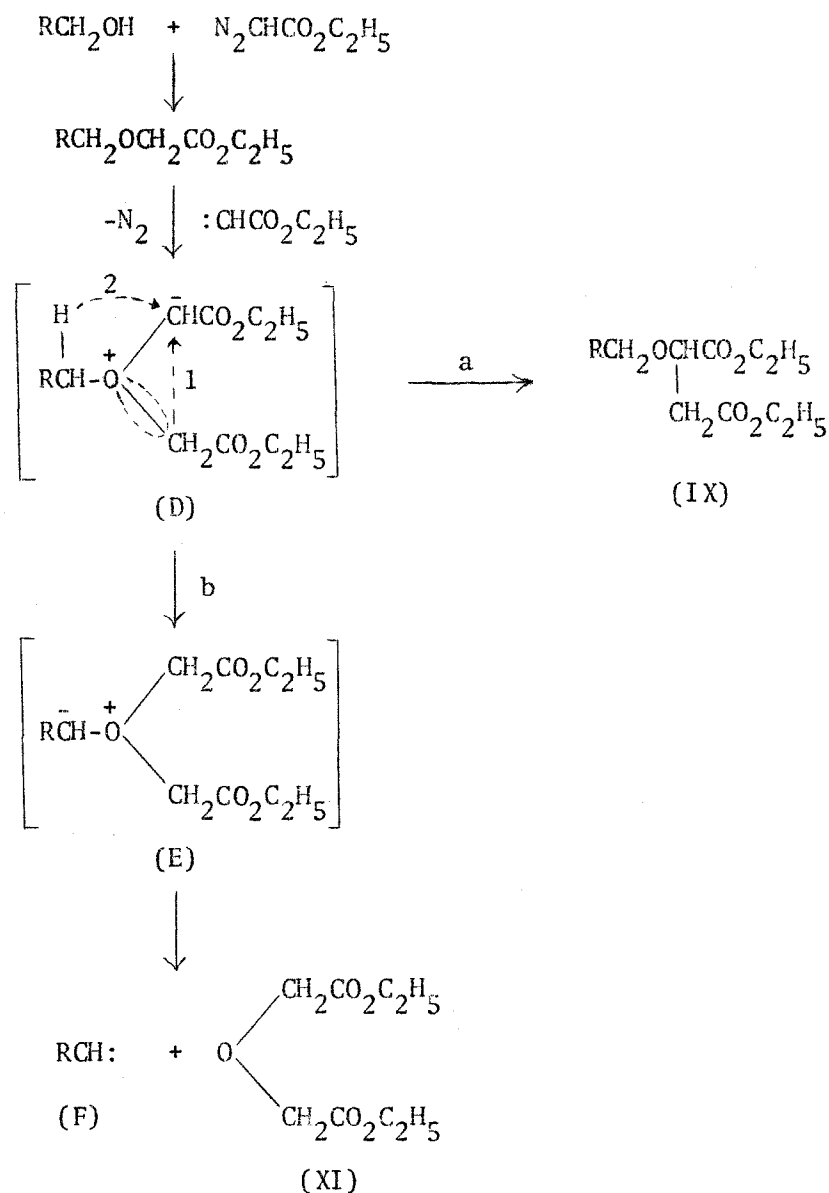
All the products were entirely identified. In addition, the total yield based on ethyl diazoacetate was almost quantitative. No distinguished difference in the catalyst activity was observed among cuprous and cupric compounds of various ligands. Except for the cyclopropane derivatives produced in the allyl alcohol—diazoacetate reaction, the products of the alcohol—diazoacetate reaction are summarized as follows:



In the thiol—diazoacetate reaction, the sulfur compounds of the structures corresponding to VIII, IX and XI were formed. The selectivity of the formation of VIII in the alcohol—diazoacetate reaction was, however, much lower than that of the alkylthioacetate in the thiol—diazoacetate reaction.

It has been shown in reference experiments that the reaction of VIII with ethyl diazoacetate actually affords IX and X. In a way similar to the thiol—diazoacetate reaction, the following mechanism via the intermediates

of O-ylids, D and E, may be postulated for the formations of IX and XI, i.e.,

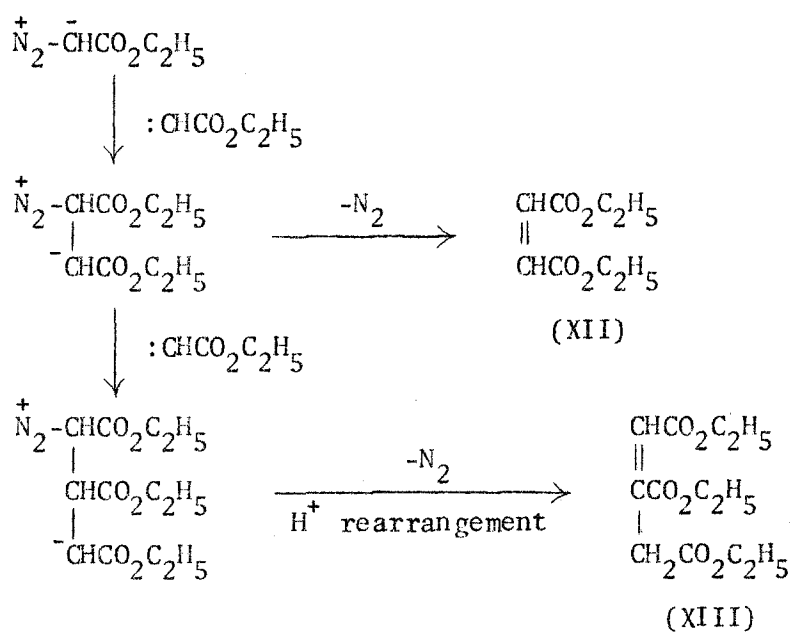


In the O-ylid (D), the transfer of  $\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5$  group to the carbanion center (reaction a) will afford IX, whereas the hydrogen migration will give another O-ylid (E) (reaction b). Then, E in turn gives XI. Alternatively, it may also be assumed that XI is formed by the reaction of diazoacetate with water

which is possibly produced in the condensation of two moles of alcohol to ether.

The by-products of X and XIII contain three units of the carbethoxy carbene group. Reference experiments have shown that X is actually formed in the reaction of VIII with ethyl diazoacetate but it is not formed in the reaction of XIII with alcohol under the same reaction conditions. The formation of X would be explained by considering an intermediate similar to that shown in the course of VIII — IX.

On referring to the mechanism proposed for the formations of diethyl fumarate and maleate from ethyl diazoacetate,<sup>8)</sup> the following scheme of reactions is now tentatively assumed to explain the production of XIII.



## 2. Experimental

### Reaction of 2-Propenethiol with Ethyl Diazoacetate

To a stirred mixture of 4.5 g (60 mmol) of 2-propenethiol and 0.1 g (1 mmol) of cuprous chloride, 6.9 g (60 mmol) of ethyl diazoacetate was added dropwise at room temperature during 30 min. Stirring was then continued for additional 9 hr at 80 — 90°C. After insoluble salt was removed by filtration, the filtrate was distilled in vacuo to give the distillate 9.2 g boiling at 55 — 120°C (26 mm). The distillate was analyzed by glpc. Three products were formed, which were isolated by preparative glpc.

Ethyl 2-propenylthioacetate (IVa). IR spectrum:  $\nu_{\max}$  1710 (vs), 1620 (w), 1270 (vs), 1120 (vs), 1020 (vs), 985 (s), and 910  $\text{cm}^{-1}$  (s). NMR with TMS (in  $\text{CDCl}_3$ ):  $\tau$  8.74 (3H, triplet,  $\text{CH}_3\text{CH}_2\text{O}-$ ), 6.90 (2H, singlet,  $\text{SCH}_2\text{CO}$ ), 6.78 (2H, doublet,  $=\text{CHCH}_2\text{S}$ ), 5.87 (2H, quartet,  $\text{CH}_3\text{CH}_2\text{O}-$ ), 4 — 5 (3H, multiplet,  $\text{CH}_2=\text{CH}-$ ). Anal. Calcd for  $\text{C}_7\text{H}_{12}\text{O}_2\text{S}$ : C, 52.47; H, 7.66. Found: C, 52.14; H, 7.48.

Diethyl- $\alpha$ -(2-propenyl)thiosuccinate (Va). NMR (in  $\text{CCl}_4$ ):  $\tau$  8.75 (6H, triplet,  $\text{CH}_3\text{CH}_2\text{O}-$ ), 7.56 (2H, multiplet,  $>\text{CH}-\text{CH}_2\text{CO}$ ), 6.78 (2H, doublet,  $=\text{CHCH}_2\text{S}-$ ), 6.65 (1H, triplet,  $\text{SCHCH}_2-$ ), 5.92 (4H, quartet,  $\text{CH}_3\text{CH}_2\text{O}-$ ), 4.0 — 5.2 (3H, multiplet,  $\text{CH}_2=\text{CH}-$ ). Anal. Calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_4\text{S}$ : C, 53.64; H, 7.37. Found: C, 53.48; H, 7.26.

Diethyl dithioglycolate (VI) was identified by the comparisons of glpc retention time and IR spectrum with the authentic sample.

In the reaction of  $\alpha$ -toluenethiol with ethyl diazoacetate, a small amount of trans ethyl cinnamate was formed in addition to the main product (IV) and

two by-products (V) and (VI).

#### Reaction of 2-Propenethiol with Diethyl Fumarate or Diethyl Maleate

A mixture of 1.5 g (20 mmol) of 2-propenethiol, 3.5 g (20 mmol) of diethyl fumarate or maleate and 30 mg (0.3 mmol) of cuprous chloride was stirred at 80 — 90°C for 9 hr. After the insoluble salt was removed by filtration, the filtrate was analyzed by glpc. Two starting compounds were recovered almost quantitatively and any trace of Va could not be detected.

#### Reaction of *n*-Butanol with Ethyl Diazoacetate

To a mixture of 2.6 g (35 mmol) of *n*-butanol and 0.13 g (1 mmol) of cupric chloride, 2.0 g (17 mmol) of ethyl diazoacetate was added dropwise with stirring at 25°C during 30 min. An exothermic reaction proceeded with the evolution of nitrogen gas. When the reaction mixture was stirred for additional 3 hr, the infrared absorption band of diazo group ( $\nu_{\text{N}=\text{N}}$  at 2100  $\text{cm}^{-1}$ ) disappeared. Then the reaction mixture was freed from insoluble residue by filtration and was distilled in vacuo to give 4.2 g of the distillate boiling from 40°C (18 mm) to 160°C (18 mm). The distillate was analyzed by glpc (PEG 20000, 200°C) and all the products were isolated by preparative glpc. Ethyl *n*-butoxyacetate (VIIIb), diethyl diglycolate (XI), diethyl fumarate (XIIb), and diethyl maleate (XIIc) were identified by the comparisons of the glpc retention times and the IR spectra with the corresponding authentic samples.

The following three products were identified by IR and NMR spectra and elemental analysis.

Diethyl *n*-butoxysuccinate (IXb). IR spectrum:  $\nu_{\text{max}}$  1725 (vs), 1260



(vs), 1160 (vs), 1120 (vs), and 1020  $\text{cm}^{-1}$  (vs), NMR with TMS (in  $\text{CCl}_4$ ):  $\tau$  9.10 (3H, triplet,  $\text{CH}_3(\text{CH}_2)_3\text{O}$ ), 8.77 and 8.75 (6H, two triplets,  $\text{CH}_3\text{CH}_2\text{O}$ -), 7.49 (2H, doublet,  $>\text{CHCH}_2\text{CO}$ ), 6.58 (2H, multiplet,  $\text{CH}_3(\text{CH}_2)_2\text{CH}_2\text{O}$ ), 5.99 (1H, triplet,  $>\text{CHCH}_2$ -), 5.98 and 5.93 (4H, two quartets,  $\text{CH}_3\text{CH}_2\text{O}$ -). Anal. Calcd for  $\text{C}_{12}\text{H}_{22}\text{O}_5$ : C, 58.51; H, 9.00. Found: C, 58.26; H, 8.83.

Triethyl 1-(n-butoxy)propane-1,2,3-tricarboxylate (Xb). IR spectrum:  $\nu_{\text{max}}$  1730 (vs), 1300 — 1100 (broad, s), and 1020  $\text{cm}^{-1}$  (vs), NMR (in  $\text{CCl}_4$ ):  $\tau$  9.10 (3H, triplet,  $\text{CH}_3(\text{CH}_2)_3\text{O}$ -), 8.76, 8.75 and 8.73 (9H, three triplets,  $\text{CH}_3\text{CH}_2\text{O}$ -), 7.30 — 7.60 (2H, multiplet,  $>\text{CHCH}_2\text{CO}$ -), 6.30 — 7.00 (3H, multiplet,  $\text{CH}_3(\text{CH}_2)_2\text{CH}_2$ - and  $-\text{CH}_2\overset{1}{\text{CH}}-\text{CH}$ -), 5.97, 5.96 and 5.91 (6H, three quartets,  $\text{CH}_3\text{CH}_2\text{O}$ -), 5.80 — 6.10 (1H, doublet,  $\text{n-C}_4\text{H}_9\text{OCH-C}$ ). Anal. Calcd for  $\text{C}_{16}\text{H}_{28}\text{O}_7$ : C, 57.81; H, 8.49. Found: C, 57.68; H, 8.42.

Triethyl propene-1,2,3-tricarboxylate (XIII). IR spectrum:  $\nu_{\text{max}}$  1710 (vs), 1640 (w), 1270 (vs), 1170 (vs), 1090 (s), and 1020  $\text{cm}^{-1}$  (vs), NMR (in  $\text{CCl}_4$ ):  $\tau$  8.78, 8.73, 8.71 (9H, three triplets,  $\text{CH}_3\text{CH}_2\text{O}$ -), 6.21 (2H, singlet,  $=\text{C-CH}_2\text{CO}$ -), 5.70 — 6.20 (6H, three quartets,  $\text{CH}_3\text{CH}_2\text{O}$ -), and 3.20 (1H, singlet,  $=\text{CHCO}_2$ -). Anal. Calcd for  $\text{C}_{12}\text{H}_{18}\text{O}_6$ : C, 55.79; H, 7.30. Found: C, 55.49; H, 7.16.

#### Reaction of Ethyl n-Butoxyacetate with Ethyl Diazoacetate

To a stirred mixture of 3.2 g (20 mmol) of ethyl n-butoxyacetate and 0.07 g (0.5 mmol) of cupric chloride, 2.3 g (20 mmol) of ethyl diazoacetate was added dropwise at 25°C. After the evolution of nitrogen gas ceased, the reaction mixture was analyzed by glpc. In addition to the starting n-butoxyacetate, IXb and Xb were isolated in yields of 27 % and 19 %, respectively.

#### Reaction of Benzyl Alcohol with Ethyl Diazoacetate

The distillation of the reaction mixture gave 5.1 g of the distillate boiling from 80°C (18 mm) to 150°C (3 mm). By glpc, all the products were isolated. Ethyl benzyloxyacetate (VIIIc), diethyl diglycolate (XI), diethyl fumarate (XIIb), and diethyl maleate (XIIc) were identified by the comparisons of the glpc retention times and IR spectra with the authentic samples.

Diethyl benzyloxysuccinate (IXc) was identified by IR and NMR spectra and elemental analysis. IR spectrum:  $\nu_{\max}$  1740 (vs) and 1300 — 1000  $\text{cm}^{-1}$  (vs), NMR (in  $\text{CDCl}_3$ ):  $\tau$  8.78 and 8.71 (6H, two triplets,  $\text{CH}_3\text{CH}_2\text{O}-$ ), 7.19 (2H, doublet,  $>\text{CHCH}_2\text{CO}-$ ), 5.84 and 5.77 (4H, two quartets,  $\text{CH}_3\text{CH}_2\text{O}-$ ), 5.62 (1H, triplet,  $-\text{OCHCH}_2\text{CO}-$ ), 5.48 and 5.18 (2H, two doublets,  $\text{C}_6\text{H}_5\text{CO}-$ ,  $J_{\text{H-H}}^{\text{gem}}$  11.3 cps) and 2.68 (5H, singlet,  $\text{C}_6\text{H}_5-$ ). Anal. Calcd for  $\text{C}_{15}\text{H}_{20}\text{O}_5$ : C, 64.27; H, 7.19. Found: C, 64.37; H, 7.24.

#### Reaction of Allyl Alcohol with Ethyl Diazoacetate

At 25°C, the reaction was carried out using 1.0 g (17.6 mmol) of allyl alcohol, 1.0 g (8.8 mmol) of ethyl diazoacetate and 0.13 g (1 mmol) of cupric chloride. The vacuum distillation of the reaction mixture gave 1.5 g of distillate boiling in the range from 60°C (30 mm) to 150°C (30 mm).

Ethyl allyloxyacetate (VIIId) was identified as follows. IR spectrum:  $\nu_{\max}$  1730 (vs), 1630 (w), 1270 (vs), 1200 (s), 1120 (vs), 1020 (vs), 990 (s), and 910  $\text{cm}^{-1}$  (s). NMR (in  $\text{CCl}_4$ ):  $\tau$  8.73 (3H, triplet,  $\text{CH}_3\text{CH}_2\text{O}-$ ), 6.08 (2H, singlet,  $-\text{OCH}_2\text{CO}-$ ), 6.02 (2H, doublet,  $\text{CH}_2=\text{CHCH}_2\text{O}-$ ), 5.88 (2H, quartet,  $\text{CH}_3\text{CH}_2\text{O}-$ ), and 4.00 — 5.00 (3H, multiplet,  $\text{CH}_2=\text{CH}-$ ). Anal. Calcd for  $\text{C}_7\text{H}_{12}\text{O}_3$ : C, 58.32; H, 8.39. Found: C, 58.14; H, 8.30.

2-Carbethoxycyclopropylcarbinol (XIV). IR spectrum:  $\nu_{\max}$  3350 (vs),

1710 (vs), 1200 (s), 1180 (vs), and 1020  $\text{cm}^{-1}$  (vs). NMR (in  $\text{CCl}_4$ ):  $\tau$  8.30 — 9.30 (4H, multiplet, protons of cyclopropane ring), 8.71 (3H, triplet,  $\text{CH}_3\text{CH}_2\text{O}-$ ), 6.50 (2H, multiplet,  $>\text{CHCH}_2\text{OH}$ ), 6.18 (1H, singlet,  $-\text{OH}$ ), and 5.93 (2H, quartet,  $\text{CH}_3\text{CH}_2\text{O}-$ ). Anal. Calcd for  $\text{C}_7\text{H}_{12}\text{O}_3$ : C, 58.32; H, 8.39. Found: C, 58.57; H, 8.51.

Allyl 2-carbethoxycyclopropylmethyl ether (XV). NMR (in  $\text{CCl}_4$ ):  $\tau$  8.30 — 9.20 (4H, multiplet, protons of cyclopropane ring), 8.77 (3H, triplet,  $\text{CH}_3\text{CH}_2\text{O}-$ ), 5.70 — 6.20 (6H, multiplet,  $-\text{CH}_2\text{OCH}_2-$  and  $\text{CH}_3\text{CH}_2\text{O}-$ ), and 4.00 — 5.00 (3H, multiplet,  $\text{CH}_2=\text{CH}-$ ). Anal. Calcd for  $\text{C}_{10}\text{H}_{16}\text{O}_3$ : C, 68.15; H, 4.61. Found: C, 68.51; H, 4.92.

#### References

- 1) See Part I, Chapter 1.
- 2) See Part I, Chapter 2.
- 3) See Part I, Chapter 3.
- 4) H. Nozaki, S. Moriuchi, H. Tanaka, and R. Noyori, *Tetrahedron Letters*, 5239 (1966).
- 5) See Part II, Chapter 2.
- 6) E. Müller and A. Freytag, *J. Prakt. Chem.*, 146, 56 (1931).
- 7) T. Thompson and T. S. Stevens, *J. Chem. Soc.*, 69 (1932).
- 8) W. Kirmse, "Carbene Chemistry," Academic Press, (1964).

## Chapter 4

### Reaction of Ethyl Diazoacetate with Cupric Chloride

The reaction of diazo compounds, especially diazomethane, with metal halides has been extensively studied, which provides a convenient method for the preparation of  $\alpha$ -halomethylmetal compound.<sup>1)</sup> Studies upon the interaction between diazo compound and copper salts are confined entirely to those of the copper catalyzed decomposition of diazo compounds.<sup>2)</sup>

This chapter describes the reaction of ethyl diazoacetate (I) with  $\text{CuCl}_2$ . It has been found that  $\text{CuCl}_2$  is much distinguished from other copper salts. In equimolar reactions of I with cupric salts having negative groups of  $\text{CN}$ ,  $\text{SO}_4$  and  $\text{NO}_3$  as well as cuprous chloride, only a mixture of ethyl maleate and fumarate was produced. On the other hand, the reaction of I with  $\text{CuCl}_2$  produced ethyl chloroacetate (II), ethyl dichloroacetate (III), and a mixture of ethyl dichloromaleate (IV) and ethyl dichlorofumarate (V). These products were explained by assuming carboethoxy-substituted chloromethyl copper complexes, exemplified by X and XI, as unstable intermediates. The reactions of I with  $\text{CoCl}_2$  and  $\text{HgCl}_2$  are described in more detail as reference reactions from the mechanistic view point. The reaction of diphenyldiazomethane with cupric chloride was also examined as a complement to the mechanistic consideration.

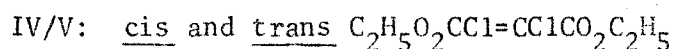
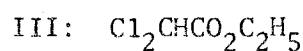
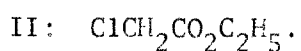
## 1. Results and Discussion

### 1.1. Reactions of Ethyl Diazoacetate (I) with Copper Compounds

An equimolar reaction of I with CuCl took place smoothly at room temperature. A mixture of ethyl maleate and ethyl fumarate was produced in a quantitative yield (Table I). Similarly, cupric salts having negative groups of CN, SO<sub>4</sub> and NO<sub>3</sub> gave the maleate—fumarate mixture. The formation of the maleate—fumarate mixture is explained by assuming the carboethoxy carbene.<sup>2)</sup>

Table I. Reaction of I with Copper Chlorides<sup>a</sup>

Ethyl diazoacetate (mmol)	Copper chloride (mmol)		Products <sup>b</sup> (%)			
			II	III	IV/V	maleate/fumarate
18	CuCl	18	0	0	0	97
16.4	CuCl <sub>2</sub>	16.4	16	40	3	30
10	CuCl <sub>2</sub>	20	8	82	6	0



<sup>a</sup> Reaction was carried out in 10 ml of acetonitrile at 15°C for 30 min.

<sup>b</sup> Products yields are calculated on the basis of the amount of ethyl diazoacetate.

The reaction of I with CuCl<sub>2</sub> is quite different from the reactions with other copper compounds. The products of an equimolar reaction at 15°C in acetonitrile were II (yield 16 %), III (40 %), a mixture of IV and V (3 %),

and the maleate—fumarate mixture (30 %). The maleate—fumarate mixture is probably produced also by the carbene reaction of I. In the I—CuCl<sub>2</sub> reaction of an 1:2 molar ratio, the maleate—fumarate mixture was not produced. Here, CuCl<sub>2</sub> was reduced completely to CuCl. These findings can be rationalized by the assumption that the reaction of I with CuCl<sub>2</sub> is much faster than the carbene reaction of I induced by CuCl. In other words, the maleate—fumarate mixture is produced, only after all CuCl<sub>2</sub> has been reduced to CuCl.

The production of considerable amounts of III is taken to differentiate CuCl<sub>2</sub> from other metal chlorides. Table II shows the reactions of I with CoCl<sub>2</sub> and HgCl<sub>2</sub>. These reactions produce predominantly II. In the case of HgCl<sub>2</sub> and CoCl<sub>2</sub>, the trace amounts of the IV/V mixture and ethyl trichloroacetate (IX) were formed.

Table II. Reaction of I with CoCl<sub>2</sub> and HgCl<sub>2</sub><sup>a</sup>

Metal chloride	Products (%) <sup>b</sup>			
	II	IV/V	IX	Organometal complex
CoCl <sub>2</sub>	31	trace	trace	35 <sup>c</sup>
HgCl <sub>2</sub>	41	trace	trace	40 <sup>d</sup>

<sup>a</sup> A mixture of 10.0 mmol of I 20.0 mmol of metal chloride and 20 ml of acetonitrile was refluxed for 4 hr.

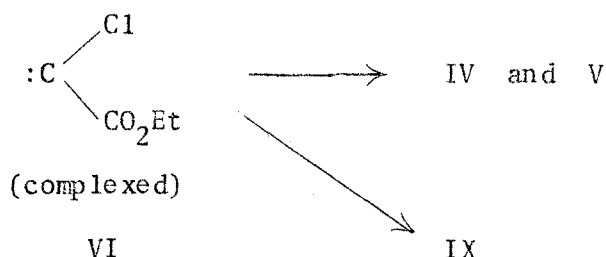
<sup>b</sup> The products yields are calculated on the basis of I.

<sup>c</sup> The essential constituent is assumed to be expressed by VIII.

<sup>d</sup> Organomercuric compound VII.

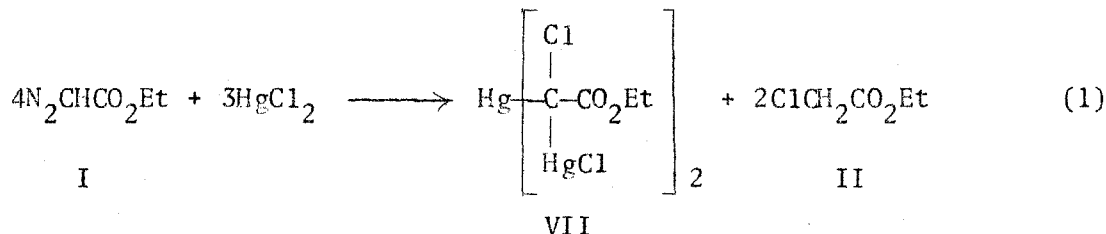
The formation of the IV/V mixture and IX in these reaction, although

their yields are not high, may be taken to suggest the transient production of carboethoxychlorocarbene complex (VI).



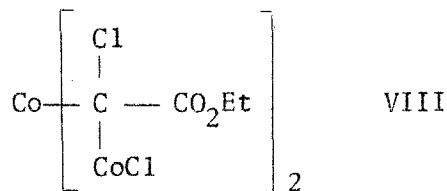
### 1.2. Reactions of Ethyl Diazoacetate (I) with $\text{CoCl}_2$ and $\text{HgCl}_2$

Nesmeyanov<sup>3)</sup> reported the reaction of I with  $\text{HgCl}_2$  which produced II and organomercuric compound (VII).



In order to characterize the I— $\text{CuCl}_2$  reaction and to elucidate its reaction mechanism, the reactions of I with  $\text{CoCl}_2$  and  $\text{HgCl}_2$  were examined as reference ones. At room temperature, these metallic chlorides reacted with I only very slowly. At reflux temperature (about  $80^\circ\text{C}$ ), the reactions proceeded at considerable rates. In the I— $\text{CoCl}_2$  reaction, the heat-treated reaction mixture was separated into liquid and solid parts. From the liquid part, II was isolated by distillation. By glpc analysis, the trace amounts of the IV/V mixture and IX were detected in the liquid part. The solid, insoluble part showed an IR spectrum which was almost the same as that of the organomercuric complex VII prepared according to Nesmeyanov's procedure.

Consequently, an organocobalt complex (VIII) may be assumed to be the essential constituent of the solid part of the I—CoCl<sub>2</sub> reaction mixture.



In the reaction of I with HgCl<sub>2</sub>, the trace amounts of the IV/V mixture and IX were detected in addition to the two products indicated in eq. (1). It is quite interesting that VII is comparatively inert towards CoCl<sub>2</sub> and HgCl<sub>2</sub> but easily decomposed by CuCl<sub>2</sub> to produce the IV/V mixture and IX. This finding has an important bearing upon the mechanism of the I—CuCl<sub>2</sub> reaction, especially the production of the IV/V mixture.

Table III. Reaction of VII with CuCl<sub>2</sub><sup>a</sup>

VII (mmol)	CuCl <sub>2</sub> (mmol)	Products (%) <sup>b</sup>	
		IV/V	IX
5	15	60	27

<sup>a</sup> Reaction was carried out in 10 ml of acetonitrile at 80°C for 1 hr.

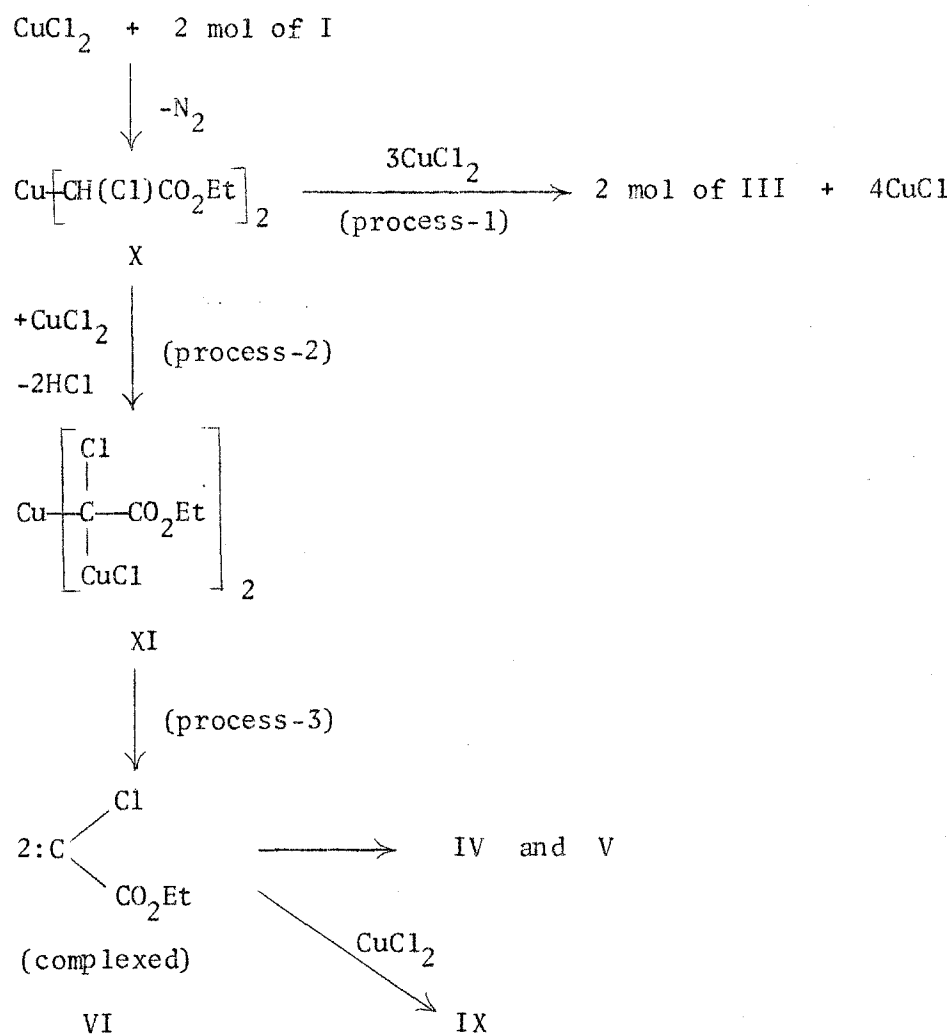
<sup>b</sup> Products yields are calculated on the basis of VII.

### 1.3. Mechanism of Reaction of Ethyl Diazoacetate (I) with CuCl<sub>2</sub>

The following scheme of reaction may explain the production of III and the IV/V mixture. As the first unstable intermediate, α-chlorocarboethoxymethylcopper complex (X) is postulated, whose reaction with CuCl<sub>2</sub> (process-1)

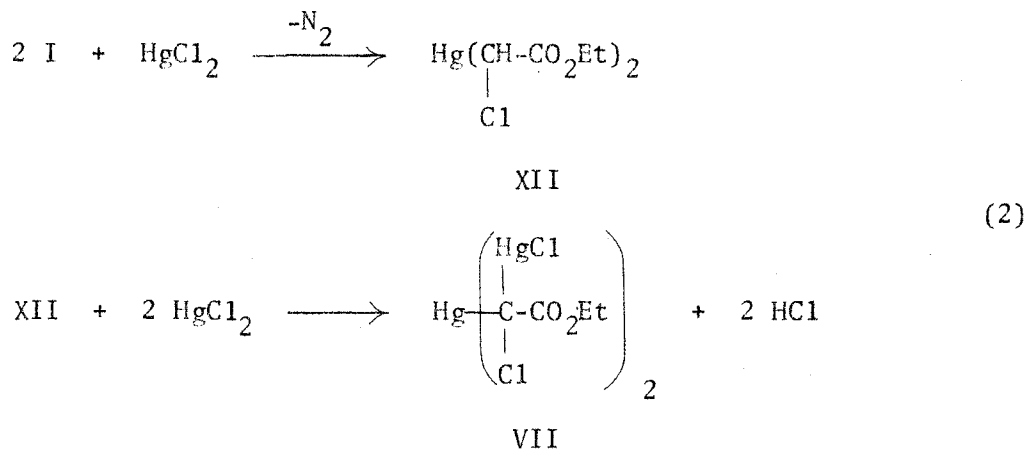


will produce III and CuCl. The process-1 is the process of the chlorine ligand transfer from CuCl<sub>2</sub> to α-chlorocarboethoxymethyl moiety, which may be taken to resemble the so-called ligand transfer<sup>4)</sup> between organic free radical and the ligand of metal salt. As to the production of II, the origin of the second α-hydrogen atom is an essential problem.



In the I—HgCl<sub>2</sub> reaction, Nesmeyanov<sup>3)</sup> proposed that II is produced from I and hydrogen chloride which is liberated by the mercuriation of the acidic

$\alpha$ -hydrogen of an organomercury compound (XII).



In the I—CuCl<sub>2</sub> reaction of the present study, an experiment using  $\alpha$ -deuterio diazoacetate (I-d) was carried out, and it has been established that the second hydrogen atom of II originates in another molecule of I. I-d of a degree of deuteration over 98 % was prepared from I and deuterium oxide in the presence of triethylamine catalyst. The products II and III in the reaction of I-d with CuCl<sub>2</sub> under the regular reaction conditions were of the same degree of deuteration over 98 % as that of I-d. Water as impurity and acetonitrile as solvent might be considered to be other hydrogen sources. These possibilities, however, have been excluded by the facts that extensive drying of the reaction system did not affect the amount of II and the reactions carried out in other solvents such as benzene, dioxane and carbon tetrachloride afforded similar results.

This conclusion has been supported by the reaction of diphenyldiazo-methane (XIII) with CuCl<sub>2</sub>. The products of the reaction of XIII with excess CuCl<sub>2</sub> (molar ratio 1:2) were dichlorodiphenylmethane (yield 48 %), tetraphenylketazine (34 %) and tetraphenylethylene (9 %). Here, diphenylchloro-

methane which corresponds to II in the reaction of I was not detected among the products.

In relation with the Nesmeyanov's mechanism for the reaction of  $\text{HgCl}_2$ , the conversion of X by  $\text{CuCl}_2$  to XI (process-2) liberating hydrochloride may be cited as one of possible mechanism of the elimination of hydrogen from I. In the reactions of I with  $\text{HgCl}_2$  and with  $\text{CoCl}_2$ , the species corresponding to XI were actually isolated. In the I— $\text{CuCl}_2$  reaction, XI was not isolated. This may be ascribed to the facts that XI is much less stable due to the weakness of copper-carbon bond and that XI is readily decomposed with  $\text{CuCl}_2$ . In addition, XI is assumed to be a key intermediate in the course of reaction leading to the IV/V mixture. The reaction of XI with  $\text{CuCl}_2$  producing the IV/V mixture has been supported by reference experiments in which the mercury species corresponding to XI was reacted with  $\text{CuCl}_2$  to give the IV/V mixture and IX. Although IX was not detected in the I— $\text{CuCl}_2$  reaction, IV/V mixture and IX would be derived from the common precursor VI. The process of the formation of IX seems to correspond to that of III in the I— $\text{CuCl}_2$  reaction.

## 2. Experimental

### Reaction of Ethyl Diazoacetate (I) with $\text{CuCl}$

To a stirred mixture of  $\text{CuCl}$  (18.0 mmol) and acetonitrile, I (18.0 mmol) was added dropwise at  $15^\circ\text{C}$ . The reaction proceeded smoothly, evolving  $\text{N}_2$  gas and ceased in 30 min. The reaction mixture was filtered to remove an insoluble copper salt, and then was subjected to distillation. A mixture of ethyl maleate and fumarate ( $80 - 85^\circ\text{C}$  (30 mm)) was obtained in 97 % yield.

### Reaction of Ethyl Diazoacetate (I) with $\text{CuCl}_2$

To a stirred mixture of  $\text{CuCl}_2$  (16.4 mmol) and acetonitrile (10 ml), I (16.4 mmol) was added dropwise at  $15^\circ\text{C}$ . The  $\text{N}_2$  gas evolution ceased in 30 min and the mixture turned to red-brown. The reaction mixture was filtered to remove the insoluble salt and subjected to distillation. The distillate of b.p.  $60 - 100^\circ\text{C}$  (20 mm) was analyzed by glpc. The products were ethyl chloroacetate (II) (16 %), ethyl dichloroacetate (III) (40 %), a mixture of ethyl dichloromaleate (IV) and ethyl dichlorofumarate (V) (3 %) and a mixture of ethyl maleate and fumarate (30 %). The products II, III, IV, V, ethyl maleate, and ethyl fumarate were identified by comparison of the glpc retention time and the IR spectrum with those of the corresponding authentic samples. On the other hand, the insoluble part was analyzed by IR and redox titration. The IR spectrum of the insoluble part showed no absorption band in the region of ordinary organic compounds. Thus, the salt did not contain any organic moiety. The valence of copper was measured by redox titration.  $\text{CuCl}_2$  was completely reduced to  $\text{CuCl}$  after the reaction.

### Reaction of Ethyl Diazoacetate (I) with $\text{CoCl}_2$

A mixture of  $\text{CoCl}_2$  (20 mmol), ethyl diazoacetate (I) (10 mmol) and acetonitrile (10 ml) was heated at  $80^\circ\text{C}$  for 4 hr. The solid and liquid parts were separated. From the liquid part, II was isolated by distillation (yield 31 %). The solid part did not dissolve in common solvents. The further purification without decomposition was impossible. The amount of solid part was 0.86 g, which corresponded to a yield of 35 % on the basis of the assumed structure VIII (IR (nujol):  $\nu_{\text{C=O}}$ ,  $1665\text{ cm}^{-1}$ ;  $\nu_{\text{C-O}}$ ,  $1205\text{ cm}^{-1}$ ;  $\nu_{\text{C-Cl}}$ ,  $770\text{ cm}^{-1}$ ).

### Reaction of Ethyl Diazoacetate (I) with HgCl<sub>2</sub>

To a mixture of HgCl<sub>2</sub> (20 mmol) and acetonitrile (10 ml), I (10 mmol) was added slowly at 15°C and then the reaction mixture was heated at refluxing temperature (80°C) for 4 hr. The reaction mixture was filtered to remove the insoluble solid. The filtrate was distilled to give ethyl chloroacetate (41 %). The organomercury compound (VII) was isolated from the insoluble part according to Nesmeyanov's<sup>3)</sup> procedure (yield 40 %). IR of VII (nujol):  $\nu_{C=O}$ , 1660 cm<sup>-1</sup>;  $\nu_{C-O}$ , 1200 cm<sup>-1</sup>;  $\nu_{C-Cl}$ , 775 cm<sup>-1</sup>.

### Reaction of Diphenyldiazomethane (XIII) with CuCl<sub>2</sub>

To a mixture of CuCl<sub>2</sub> (20 mmol) and acetonitrile (10 ml), a solution of XIII (10 mmol) in acetonitrile (5 ml) was added slowly at 15°C. The reaction proceeded smoothly evolving N<sub>2</sub> gas and ceased in about 15 min. The reaction mixture was filtered to remove a white solid. The filtrate was dried up in vacuo, and the residue was analyzed by column chromatography (silicagel, benzene-petroleum ether) to obtain dichlorodiphenylmethane (48 %), tetraphenylketazine (34 %) and tetraphenylethylene (9 %). These three products were identified by comparison of the IR spectra and/or the melting points with those of the corresponding authentic samples.

### Preparation of Ethyl $\alpha$ -Deuterio Diazoacetate (I-d)<sup>5)</sup>

A heterogeneous mixture of I (4 ml), deuterium oxide (15 ml) and triethylamine (0.1 ml) was stirred for 1 hr. The layer of diazoacetate was separated and treated with deuterium oxide again. Then the diazoacetate layer was dried with anhydrous Na<sub>2</sub>SO<sub>4</sub> and distilled to give ethyl  $\alpha$ -deuterio diazoacetate in 80 % yield. The NMR spectrum analysis revealed that the  $\alpha$ -

position was deuterated to an extent over 98 %.

Reaction of Ethyl  $\alpha$ -Deuterio Diazoacetate (I-d) with  $\text{CuCl}_2$

The reaction was carried out in the same way as that of the I— $\text{CuCl}_2$  reaction. The products of II, III and the IV/V mixture were isolated by preparative glpc. By NMR spectrum, the extents of deuteration at  $\alpha$ -hydrogen of II and III were found to be over 98 %.

Reaction of  $\begin{array}{c} \text{Hg}(\text{C}(\text{Cl})\text{CO}_2\text{Et})_2 \\ | \\ \text{HgCl} \end{array}$  (VII) with  $\text{CuCl}_2$

A mixture of VII (5 mmol),  $\text{CuCl}_2$  (15 mmol) and acetonitrile (10 ml) was heated at 80°C for 1 hr. Then the reaction mixture was filtered to remove the solid part. The filtrate was concentrated in vacuo and analyzed by glpc. The products were the IV/V mixture (60 %) and trichloroacetate (IX) (27 %).

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- 1) D. Seyferth, Chem. Revs., 55, 1155 (1955).
- 2) a) W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, (1964).  
b) See Part II, Chapter 3.
- 3) A. N. Nesmeyanov and G. S. Powich, Ber., 67, B, 971 (1934).
- 4) a) J. K. Kochi and D. D. Davis, J. Am. Chem. Soc., 86, 5264 (1964).  
b) J. K. Kochi, Science, 155, 415 (1967).
- 5) G. W. Robinson and M. McCarty, Jr., J. Am. Chem. Soc., 82, 1859 (1960).

P A R T    I I I

REACTIONS OF ISOCYANIDE WITH THIOL, WITH NITROALKENE,

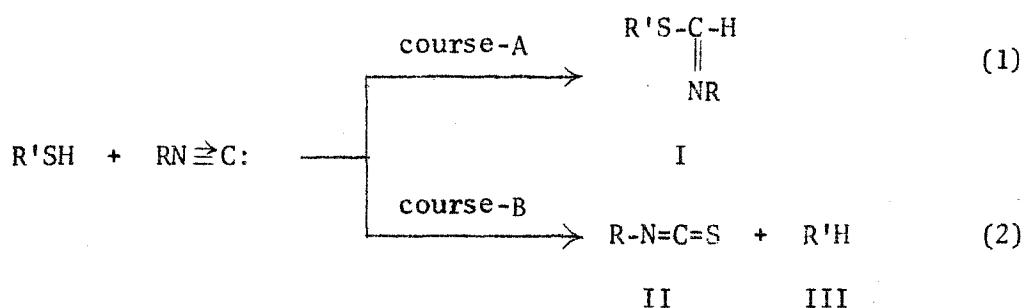
AND WITH NITRIC OXIDE

## Chapter 1

### Radical Reaction of Isocyanide with Thiol

There have been described a set of reactions of isocyanide, which are the insertions of the isocyanide carbon atom into the nitrogen—hydrogen bond of amine,<sup>1)</sup> oxygen—hydrogen bond of alcohol,<sup>2)</sup> sulfur—hydrogen bond of thiol,<sup>3)</sup> phosphorus—hydrogen bond of phosphine<sup>4)</sup> and silicon—hydrogen bond of silane.<sup>5)</sup> All these reactions are catalyzed by copper compound and produce the corresponding derivatives of formimidic acid in high yields.

Among these reactions, the isocyanide—thiol reaction differs from others, i.e., the isocyanide—thiol reaction is induced also by a radical initiator. This chapter describes the radical reaction of isocyanide with thiol. The reaction of isocyanide with thiol proceeds in two courses:



Course-A (eq. 1) is regarded as  $\alpha,\alpha$ -additions of thiyl group and hydrogen to the isocyanide carbon atom carrying lone-pair electrons, which produces



thioformimidate (I). In course-B (eq. 2), isothiocyanate (II) and alkane (III) are formed. The course of reaction is determined by the nature of the thiol alkyl group, i.e., primary and aromatic thiols take course-A exclusively, whereas  $\alpha$ -toluenethiol as well as tertiary thiols take course-B. The reaction with secondary thiol proceeds in both courses.

In the present chapter, experimental supports for the radical chain mechanism are first given, and the effect of substituent of aromatic isocyanide upon its reaction with thiyl radical is discussed. The difference between the radical reaction of isocyanide with thiol and the copper catalyzed one is also mentioned.

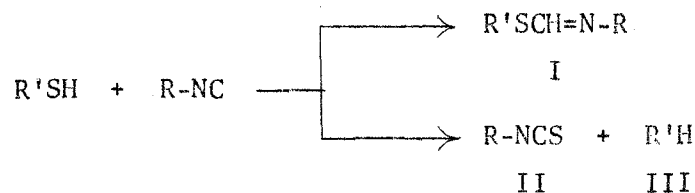
## 1. Results and Discussion


### 1.1. Supports for Radical Chain Mechanism

When a mixture of thiol and isocyanide is heated without any added catalyst, the reaction occurs between them. This reaction has been shown to be a radical chain reaction by a set of the following findings: (i) the reaction is accelerated by radical initiators such as azobisisobutyronitrile (AIBN) and by ultra-violet irradiation and (ii) the reaction is suppressed by radical inhibitors such as hydroquinone (HQ), t-butylcatechol and p-benzoquinone (p-BQ).

Table I illustrates the radical initiated reaction of isocyanide with thiol. The reactions with primary and aromatic thiols by radical initiators proceed via course-A.

Table I. Radical and Cupric Oxide—Catalyzed Reactions of Thiols with Isocyanides



Exp. No.	R-NC (mmol)	R'SH (mmol)	Additive (mmol)	Reaction		Product yield (%) <sup>a</sup>		
				Temp. (°C)	Time (hr)	I	II	III
1	<u>t</u> -C <sub>4</sub> H <sub>9</sub> NC (IV) (5.0)	C <sub>2</sub> H <sub>5</sub> SH (VII) (5.0)	AIBN (0.01)	35	4.0	60	0	0
2	IV (5.0)	C <sub>6</sub> H <sub>5</sub> SH (VIII) (5.0)	AIBN (0.01)	80	2.0	82	0	0
3	IV (12.0)	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> SH (IX) (10.0)	AIBN (0.02)	100	0.2	0	93	96
4	IV (12.0)	IX (10.0)	CuO (0.1)	100	2.0	91	0	0
5	 -NC (V) (5.0)	<u>sec</u> -C <sub>4</sub> H <sub>9</sub> SH (X) (5.0)	b	0	0.1	83	11	n.d. <sup>c</sup>
6	C <sub>6</sub> H <sub>5</sub> NC (VI) (6.0)	<u>t</u> -C <sub>4</sub> H <sub>9</sub> SH (XI) (20.0)	AIBN (0.05)	75	0.2	0	97	n.d. <sup>c</sup>
7	V (5.0)	XI (7.0)	CuO and <u>p</u> -BQ (0.1) (0.5)	90	3.0	64	6	n.d. <sup>c</sup>

<sup>a</sup> Determined by glpc.

<sup>b</sup> Irradiated by UV in 2 ml of diethyl ether under nitrogen.

<sup>c</sup> n.d: Not determined.

Copper catalyzed reactions of these combinations take the same course. The isocyanide—secondary thiol reactions, both copper catalyzed and photo-induced

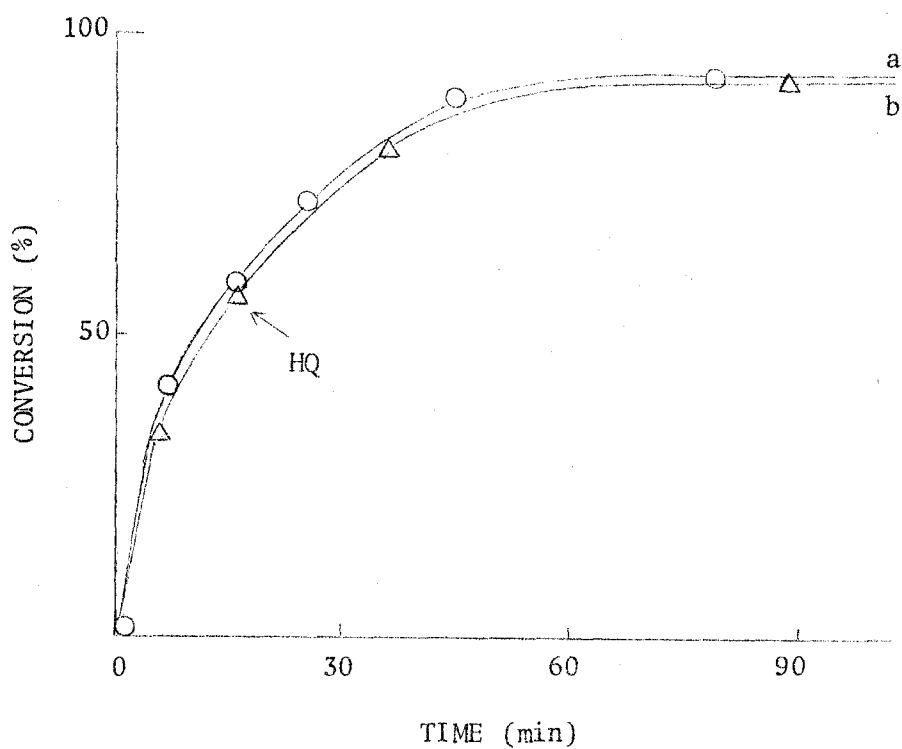


Fig. 1. Reaction of cyclohexyl isocyanide with 2-propanethiol in the presence of cupric oxide (2 mol %) catalyst.

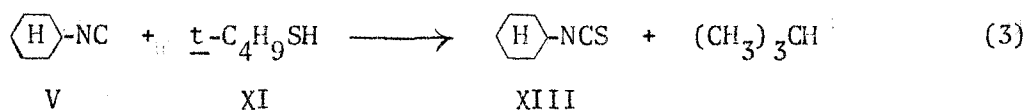
(a) without hydroquinone.

(b) with 10 mol % of hydroquinone after 13 min at 70°C.

ones, give the products of the two courses. The course of the reactions of  $\alpha$ -toluenethiol and tertiary thiols, however, is determined by the nature of catalyst, i.e., those by radical initiator take course-B, whereas those catalyzed by copper compound take course-A.

The mechanism of radical initiated reaction of isocyanide with thiol obviously differs from that of copper catalyzed one. Fig. 1 indicates that the copper catalyzed reaction of cyclohexyl isocyanide (V) with 2-propanethiol (XII) is not affected by the addition of hydroquinone (Fig. 1). As will be described in the following parts, the radical initiated reaction of isocyanide with thiol is suppressed by the so-called radical inhibitors. The difference of the products (Table I, Exp. Nos. 3 and 4) also distinguishes the radical initiated reaction from the copper catalyzed one.

The effects of radical initiator and inhibitor upon the reaction of V with 2-methyl-2-propanethiol (XI) giving cyclohexyl isothiocyanate (XIII) and isobutane are shown in Fig. 2.



The progress of reaction was followed by the glpc determination of XIII at several times of reaction. The reaction of an equimolar mixture (neat) of V and XI was heated at 60°C under nitrogen is shown by curve a, in which a small amount of oxygen due to incomplete exclusion of air may cause the radical reaction. The addition of AIBN (1 mol %) much enhanced the reaction (curve b), whereas the addition of hydroquinone, suppressed it (curve c). The addition of hydroquinone at a halfway point (at 20 min) to the reaction system

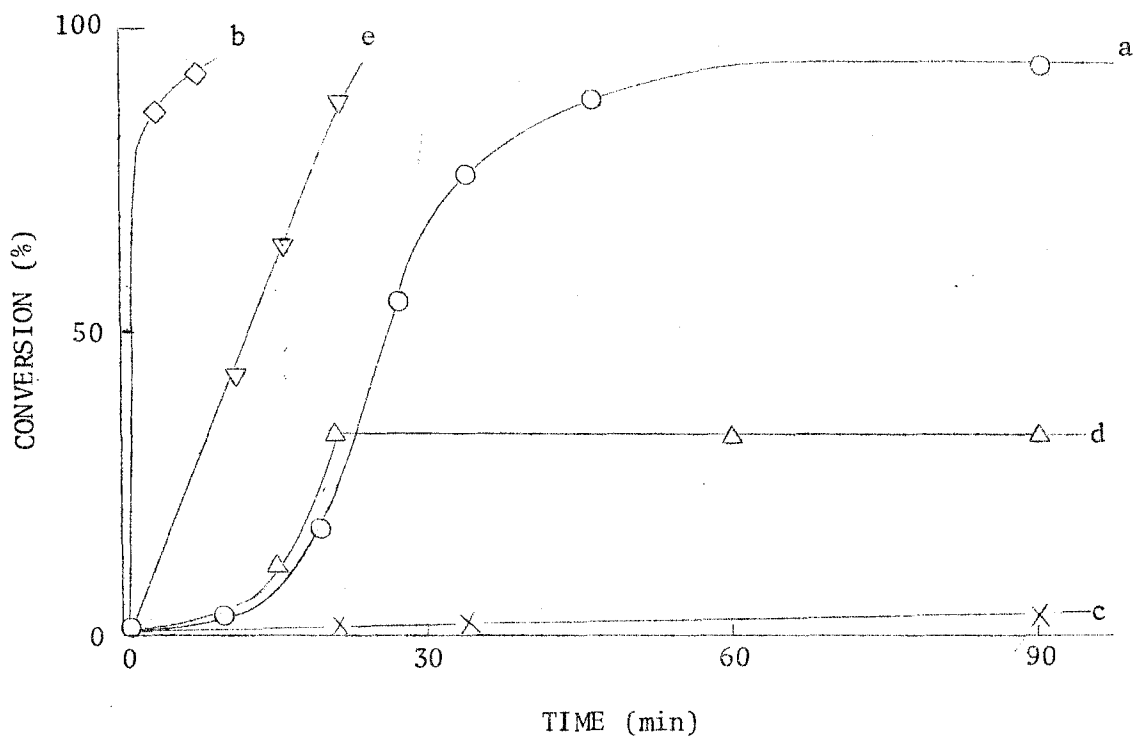


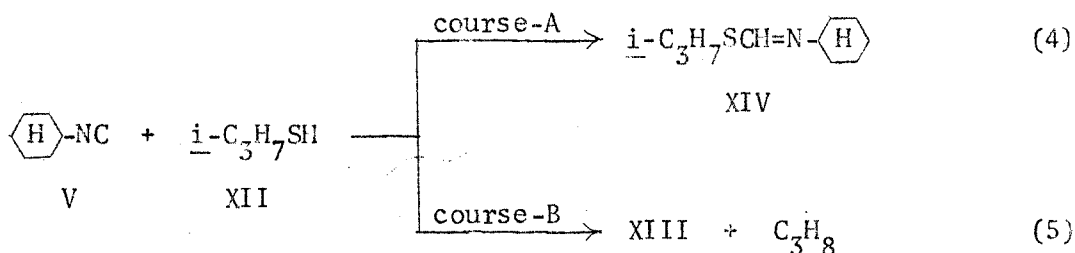
Fig. 2. Reaction of cyclohexyl isocyanide with 2-methyl-2-propanethiol.

Effects of radical initiator and inhibitor.

- (a) without added catalyst at 60°C.
- (b) with 1 mol % of AIBN at 60°C.
- (c) with 5 mol % of hydroquinone at 60°C.
- (d) with addition of 2 mol % of hydroquinone after 20 min at 60°C.
- (e) irradiated in diethyl ether at 0°C.

without any added catalyst interrupted the reaction completely (curve d). In addition, the reaction was accelerated also by UV-irradiation. A mixture of V, XI and diethyl ether (solvent) in a Pyrex tube was irradiated at 0°C under nitrogen (curve e). Here, no reaction was observed at all in dark at 0°C in diethyl ether solvent.

In the combination of isocyanide and secondary thiol, two modes of reactions, courses-A and -B, take place. The reaction of V with 2-propane-thiol (XII) was carried out under various conditions (Fig. 3).



The total yield of the two products, XIII and XIV, and the yield of XIII at several times of reaction without any added catalyst at 100°C are shown by curves a and a', respectively. The addition of 2 mol % of hydroquinone at a time of 2.2 hr interrupted both courses of reactions (curves b and b'). The reaction was accelerated by AIBN (reaction at 70°C curves c and c'). It is quite significant that the ratio of the final yields of the two products, XIII/XIV, was 3/2 throughout these three reactions. Furthermore, 1 mol % of *t*-butylcatechol was enough to inhibit the reaction completely. The results of the reactions of secondary thiols with cyclohexyl isocyanide induced by irradiation were also indicative of the acceleration effects.

The reaction with primary thiol proceeds through course-A. In Fig. 4, the acceleration by AIBN (curve b) and by UV-irradiation (curve d) as well as

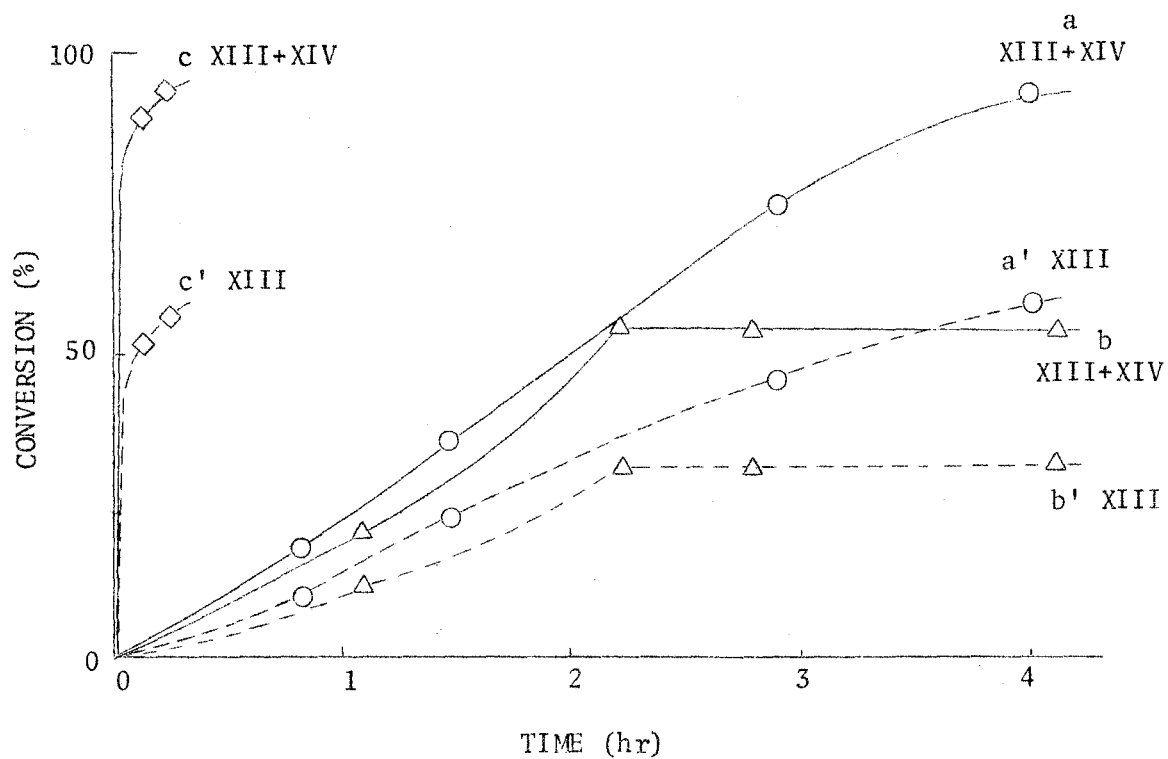


Fig. 3. Reaction of cyclohexyl isocyanide with 2-propanethiol.

(a) and (a') without added catalyst, at 100°C.

(b) and (b') with addition of 2 mol % of hydroquinone after 2.2 hr at 100°C.

(c) and (c') with 0.5 mol % of AIBN at 70°C.

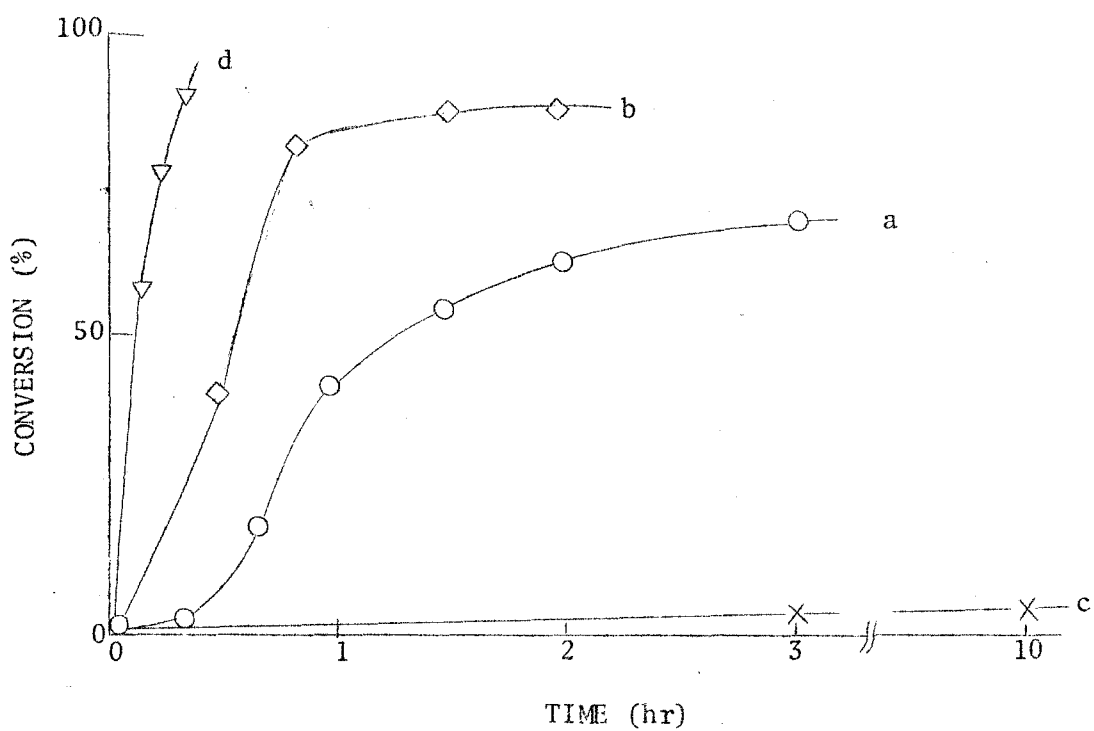


Fig. 4. Reaction of cyclohexyl isocyanide with ethanethiol.

(a) without added catalyst at 40°C.

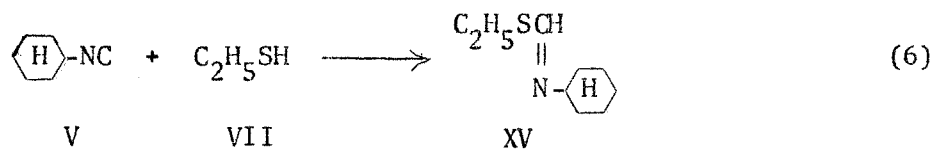
(b) with 0.1 mol % of AIBN at 40°C.

(c) with 10 mol % of P-BQ at 40°C.

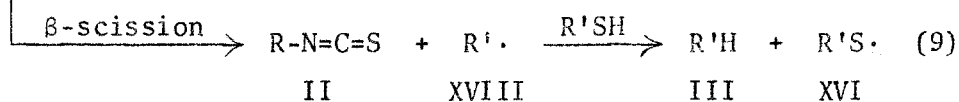
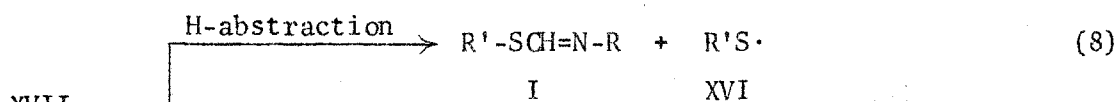
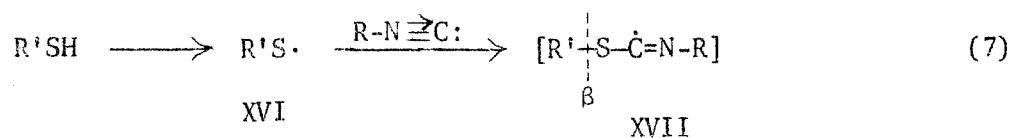
(d) irradiated in diethyl ether at 0°C.



the inhibition by p-benzoquinone are demonstrated in the reaction of V with ethanethiol (VII).



These several findings are taken to support a radical chain mechanism, which may be explained by the following scheme involving thiyl radical XVI.

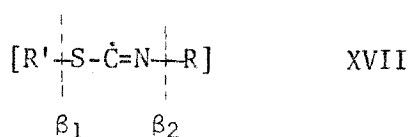


Thiyl radical (XVI) is first formed from thiol by radical initiator or by irradiation, which then attacks isocyanide to produce the intermediate formimidoyl radical (XVII). The formimidoyl radical (XVII) may undergo two reactions, i.e., hydrogen abstraction from thiol (eq. 8) and  $\beta$ -scission (eq. 9). The hydrogen abstraction gives thioformimidate (I) and XVI. On the other hand, the  $\beta$ -scission at the alkyl (or benzyl) group—sulfur bond leads to isothiocyanate (II) and alkyl (or benzyl) radical (XVIII). The second hydrogen abstraction of XVIII from thiol produces hydrocarbon (III) and XVI. Relative degrees of participation of the two courses are determined by the nature of R'. When R' is easily cleft from R—S bond as a radical,  $\beta$ -scission predominates (eq. 9). This is the case for the reactions with

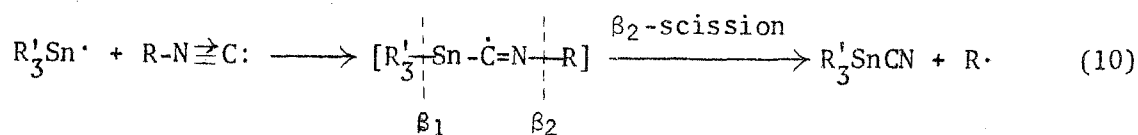
$\alpha$ -toluenethiol and tertiary thiols. On the other hand, when the homolytic cleavage of R'-S bond is slow, XVII prefers to abstract hydrogen from thiol (eq. 8). The reactions with primary and aromatic thiols take this course. The case of secondary thiol is between these two extremes.

In the above scheme, the both courses involve thiyl radical as the common chain carrier. The coupling of two thiyl radicals constitutes the chain termination, which produces the corresponding disulfide. A small amount of dialkyl disulfide was actually detected in the reaction mixture. For instance,  $3.5 \times 10^{-5}$  mol of di-t-butyl disulfide was detected by glpc in the mixture of the V—XI reaction (Fig. 2, curve a). Assuming that di-t-butyl disulfide is formed only by the termination reaction, the chain length is calculated at 140.

In the intermediate formimidoyl radical XVII, the R—N bond is located at another beta position ( $\beta_2$ ), which may possibly suffer from  $\beta$ -scission reaction especially when R is a good leaving group as a free radical.

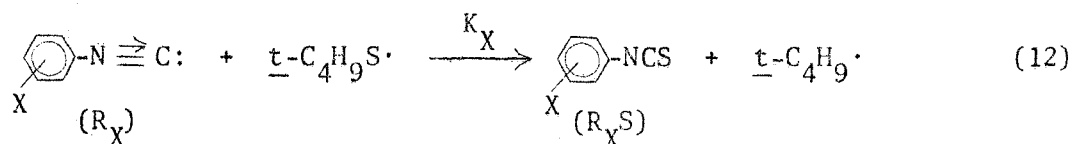
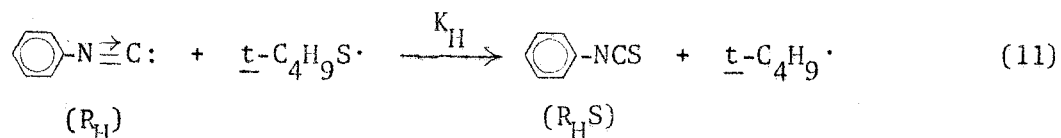


The isocyanide—thiol reaction, however, does not involve the  $\beta_2$ -scission at the R—N bond, i.e., in the first two reactions of Table I using IV, any product which is to be derived from the  $\beta_2$ -scission of XVII was not detected. This is quite different from the radical reaction of isocyanide with tri-alkylstannane which involves the scission at  $\beta_2$ -position (eq. 10).<sup>6)</sup>



1.2. Relative Reactivities of Substituted Phenyl Isocyanides with  
2-Methyl-2-propanethiol (XI)

By means of a competitive reaction method, the effect of substituent of benzene ring upon the reactivity of aromatic isocyanide was investigated. A mixture of substituted and unsubstituted phenyl isocyanides,  $R_X$  and  $R_H$ , was subjected to the reaction with XI, and the reaction was stopped at a low conversion. The amounts of the two products, substituted and unsubstituted phenyl isothiocyanates were determined by glpc. On the basis of the reaction scheme from eq. 7 to 9, the ratio of the relative consumptions of isocyanides corresponds to the ratio of the rate constants of the reactions of two isocyanides with common thiyl radical,



$$\frac{\log[R_X]_0 - \log[R_X]}{\log[R_H]_0 - \log[R_H]} = \frac{K_X}{K_H} \quad (13)$$

where  $[R_X]_0$  and  $[R_X]$  are the initial and final concentrations of substituted phenyl isocyanide, and  $[R_H]_0$  and  $[R_H]$  are the corresponding ones of phenyl isocyanide. Since the competitive reaction was stopped at a very low conversion, the rate ratio can be expressed by

$$\frac{K_X}{K_H} = \frac{[R_X\text{S}]}{[R_X]_0} \cdot \frac{[R_H]_0}{[R_H\text{S}]} \quad (14)$$

where  $[R_X S]$  and  $[R_H S]$  are the amounts of substituted and unsubstituted phenyl isothiocyanates,  $R_X S$  and  $R_H S$ , respectively. In the competitive reaction, two reaction conditions, A and B, were adapted. In Method A, a mixture of phenyl isocyanide and a substituted phenyl isocyanide (a few milimoles each) was subjected to the reaction with XI (less than 20 mol % to the combined amount of isocyanides) in the presence of 2 mol % of AIBN in benzene at 75°C for 30 min. In Method B, a mixture of two isocyanides (a few milimoles each) and XI (less than 20 mol %) in diethyl ether was irradiated under nitrogen at 0°C for 1 hr. In both methods, the amounts of two isothiocyanates were analyzed by glpc.

Six substituted phenyl isocyanides were prepared and their reactivities were compared with the reactivity of phenyl isocyanide as the reference. The reproducibility of the ratio of rate constants is indicated by the data in the competitive reaction (Method A) of the combination of phenyl isocyanide and *p*-methoxyphenyl isocyanide, where the molar ratio of initial charges of two isocyanides is varied in the range of 0.65 to 2.04 (Table II).

Table II. Relative Reactivities of *p*-Methoxyphenyl Isocyanide toward XI and Reaction Conditions<sup>a</sup>

$\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{NC}$ (mmol)	$\text{C}_6\text{H}_5-\text{NC}$ (mmol)	$\frac{[R_X]_0}{[R_H]_0}$	$\frac{K_X}{K_H}$ <sup>b</sup>
2.48	3.79	0.65	1.18
3.06	2.51	1.21	1.19
4.00	3.02	1.32	1.22
4.37	2.14	2.04	1.16

<sup>a</sup> Method A.

<sup>b</sup> From eq. 14.

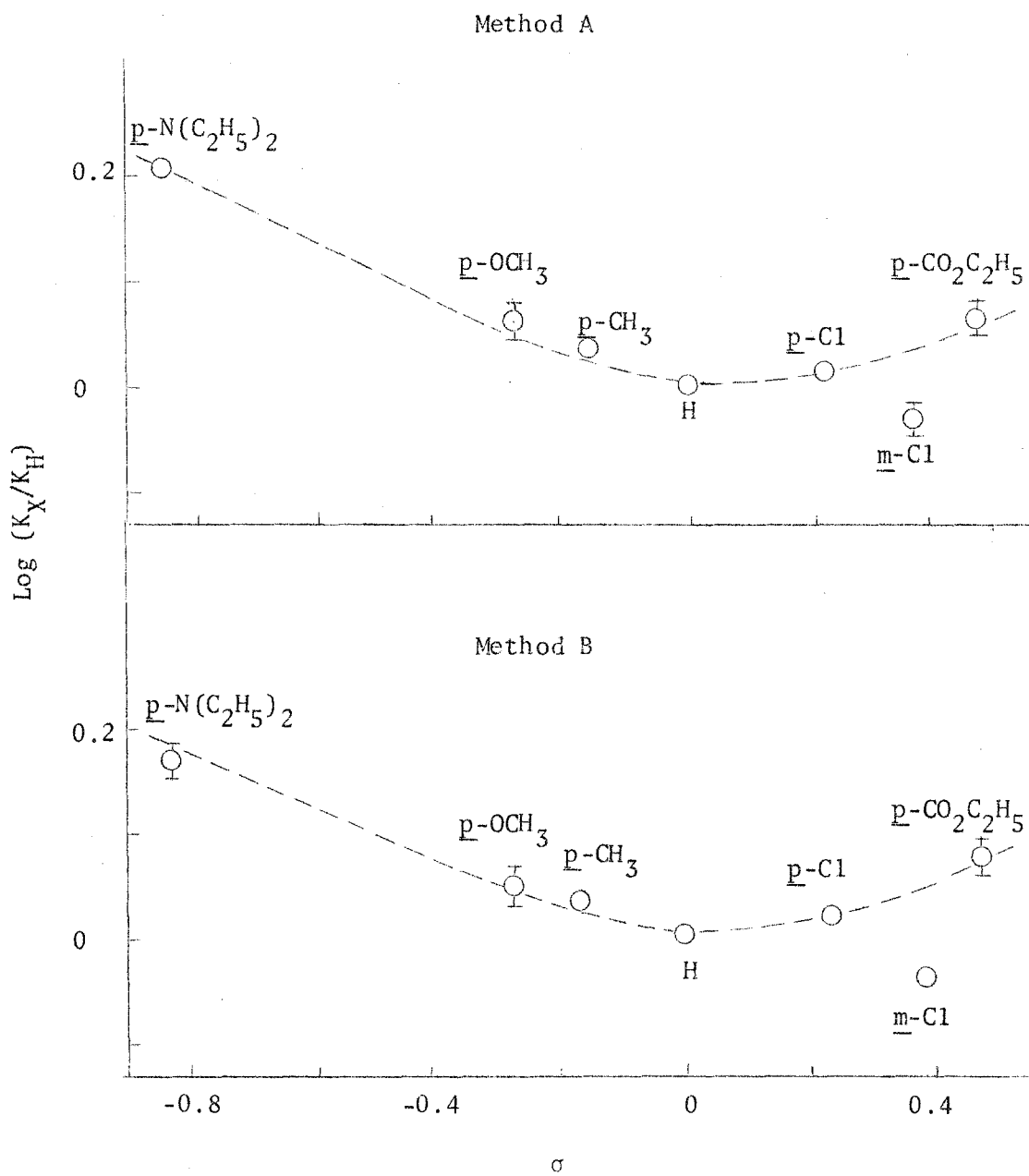
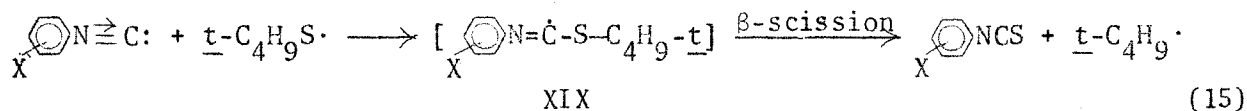


Fig. 5. Plots of  $\log(K_X/K_H)$  vs. Hammett's  $\sigma$  value

In Fig. 5, the values of  $\log(K_X/K_H)$  are plotted against the Hammett  $\sigma$  constants of the substituents.\* Two curves of Methods A and B are similar in shape to each other, and this indicates the same reaction mechanism. The shapes of two Hammett plots may be explained by polar and resonance effects of the substituents. In other words, the reaction rate is influenced by the polarity of isocyanide in its reaction with thiyl radical and by the resonance stabilization of the resultant formimidoyl radical (XIX).



These results are summarized by the following equation, a modified Hammett equation

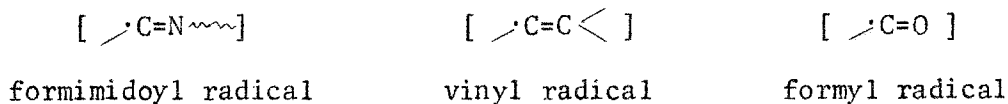
$$\log(K_X/K_H) = \rho\sigma + E_R \quad (16)$$

where  $E_R$  is an extra term due to the resonance stabilization involving the substituent.<sup>7)</sup> The reaction constant,  $\rho$ , is reasonably assumed to be negative, because *m*-chlorophenyl isocyanide is less reactive than phenyl isocyanide. The value of  $\rho$  is estimated to be about -0.1 provided that  $E_R$  is zero in the case of *m*-chlorophenyl isocyanide. This conclusion is quite compatible with the electrophilic nature of thiyl radical which has been established in the reaction of substituted stilbenes with  $\cdot\text{SCH}_2\text{CO}_2\text{H}$  and that of substituted  $\alpha$ -methylstyrenes with  $\cdot\text{SCH}_2\text{CO}_2\text{CH}_3$ .<sup>8)</sup>

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\* The  $\sigma$  constants are taken from C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 2, 334 (1964). The  $\sigma$  value, -0.83 of *p*-N(CH<sub>3</sub>)<sub>2</sub> was used as a  $\sigma$  value of *p*-N(C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>.

The formimidoyl radical is assumed to possess  $\sigma$  character, because it is isoelectronic with vinyl<sup>9,10)</sup> and formyl radicals<sup>11)</sup> of  $\sigma$ -character.



It is of interest to note that the resonance stabilization in the formimidoyl radical of  $\sigma$ -character is considerable.

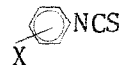
## 2. Experimental

### Materials

All thiols were commercial samples of pure grade, which were purified by rectification under nitrogen prior to use. Isocyanides were prepared from the corresponding formamides according to Ugi's procedure.<sup>12)</sup> *m*-Chlorophenyl isocyanide was a new compound, which was prepared in a yield of 12 %, b.p. 60 — 63°C (6 mm). Calcd for  $\text{C}_7\text{H}_4\text{NCl}$ : C, 61.11; H, 2.93. Found: C, 61.23; H, 2.86, IR spectrum  $\nu_{\text{N}=\text{C}}$  at 2120  $\text{cm}^{-1}$ . *p*-Ethoxycarbonylphenyl isocyanide was also a new isocyanide, which was prepared similarly and isolated by preparative glpc (column, Silicon DC 550). Anal. Calcd for  $\text{C}_{10}\text{H}_9\text{NO}_2$ : C, 68.56; H, 5.18. Found: C, 68.31; H, 5.02. The structure of *p*-ethoxycarbonylphenyl isocyanide was confirmed by NMR and IR spectra.

### Preparation of Isothiocyanates

The glpc authentic samples of substituted phenyl isothiocyanates were prepared by the reaction of the corresponding substituted phenyl isocyanides with XI and identified by elemental analysis, and IR and NMR spectra.

Table III. Substituted and Unsubstituted Phenyl Isothiocyanates, 

X	M.p. or b.p. (°C)	Lit. m.p. or b.p. (°C)	Calcd (%)			Found (%)		
			C	H	N	C	H	N
H	b.p. 75—77 (5 mm)	b.p. 102—103 (15 mm) <sup>13)</sup>	62.19	3.73	10.36	62.27	3.65	10.30
<u>p</u> -CH <sub>3</sub>	b.p. 113—115 (16 mm)	b.p. 115 (15 mm) <sup>13)</sup>	64.39	4.73	9.39	64.28	4.57	9.44
<u>p</u> -CH <sub>3</sub> O	b.p. 120—123 (7 mm)	b.p. 144—145 (15 mm) <sup>13)</sup>	58.16	4.27	8.48	58.18	4.26	8.51
<u>p</u> -N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	b.p. 162—167 (3 mm)	b.p. 148 (1.2 mm) <sup>14)</sup>	64.03	6.84	13.58	64.41	7.09	13.63
<u>p</u> -Cl	m.p. 43—44	m.p. 44 <sup>15)</sup>	49.56	2.38	8.26	49.37	2.45	8.03
<u>m</u> -Cl	b.p. 104—107 (5 mm)	b.p. 131 (15 mm) <sup>13)</sup>	49.56	2.38	8.26	49.29	2.40	8.23
<u>p</u> -CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	m.p. 50—51	m.p. 58 <sup>15)</sup>	57.95	4.38	6.76	58.21	4.60	6.63



Data of m.p. and b.p. as well as elemental analysis are given in Table III.

Reactions of Cyclohexyl Isocyanide (V) with 2-Methyl-2-propanethiol (XI)

(Fig. 2)

Curve a reaction. A mixture of 0.90 g (10 mmol) of XI and 1.08 g (10 mmol) of V was heated at 60°C under nitrogen atmosphere without added catalyst. The progress of reaction was followed by glpc determination of XIII at several times of reaction (column, Silicon DC 550 and PEG 20000).

Curve b reaction. A ternary mixture of 0.90 g (10 mmol) of XI, 1.08 g (10 mmol) of V and 17 mg (0.1 mol) of AIBN was heated at 60°C. Curve c reaction.

As a radical inhibitor, 55 mg (0.5 mmol) of hydroquinone was added at the beginning of curve a reaction. Curve d reaction. After the reaction

proceeded for 20 min in the same conditions as curve a reaction, 22 mg (0.2 mmol) of hydroquinone was added to the reaction system. Curve e reaction.

A solution of 0.45 g (5 mmol) of XI, 0.54 g (5 mmol) of V and 2 ml of diethyl ether (solvent) in a Pyrex test tube cooled in an ice bath was irradiated using a high-pressure mercury lamp under nitrogen atmosphere.

Reactions of Cyclohexyl Isocyanide (V) with 2-Propanethiol (XII), Ethanethiol (VII), and 2-Butanethiol (X)

The time-conversion curves of the reactions of V with XII (Fig. 3) and V with VII (Fig. 4) were made by the same procedures as the above. The structures of XIV and XV were established already.<sup>3)</sup> sec-Butyl N-cyclohexylthioformimidate was produced in the V—X reaction, b.p. 99 — 100°C (4 mm),  $n_D^{25}$  1.5012. Anal. Calcd for  $C_{11}H_{21}NS$ : C, 66.27; H, 10.62; N, 7.03. Found: C, 66.03; H, 10.51; N, 7.11. NMR and IR ( $\nu_{C=N}$  at 1595  $cm^{-1}$ ) spectra supported

its structure.

Reaction of t-Butyl Isocyanide (IV) with Benzenethiol (VIII)

A mixture of 0.55 g (5 mmol) of VIII and 0.42 g (5 mmol) of IV was heated in the presence of 1.7 mg (0.01 mmol) of AIBN at 80°C for 2 hr. Distillation gave 0.65 g (67 %) of phenyl N-t-butylthioformimidate: B.p. 99 — 101°C (3 mm),  $n_D^{25}$  1.5514. Anal. Calcd for  $C_{11}H_{15}NS$ : C, 68.34; H, 7.82. Found: C, 68.22; H, 7.95. The structure was further confirmed by NMR and IR ( $\nu_{C=N}$  at  $1597\text{ cm}^{-1}$ ) spectra.

Reaction of t-Butyl Isocyanide (IV) with Ethanethiol (VII)

Similarly, the IV—VII reaction by AIBN was carried out at 35°C for 4 hr, which gave ethyl N-t-butylthioformimidate: B.p. 75 — 76°C (70 mm),  $n_D^{25}$  1.4654, Anal. Calcd for  $C_7H_{15}NS$ : C, 57.90; H, 10.34. Found: C, 57.60; H, 10.20.

Competitive Reactions of Substituted and Unsubstituted Phenyl Isocyanides with 2-Methyl-2-propanethiol (XI)

Method A: In a typical experiment, a reaction mixture consisting of 0.368 g (3.14 mmol) of p-tolyl isocyanide, 0.340 g (3.30 mmol) of phenyl isocyanide, 0.08 g (0.9 mmol) of XI, 3.4 mg (0.02 mmol) of AIBN and 3.0 ml of benzene as solvent was heated at 75°C under nitrogen atmosphere for 30 min. The conversion was about 3 % for both isocyanides. The products ratio,  $[R_{p-CH_3}S]/[R_H S]$  of eq. 14 was determined by glpc (Column PEG 20000) with hydrogen as carrier gas. Using the authentic samples, calibration curves were made by means of the half-height width method. Method B: A mixture of 0.304 g (2.28 mmol) of p-methoxyphenyl isocyanide, 0.251 g (2.44 mmol) of phenyl isocyanide, 0.12 g (1.3 mmol) of XI and 1.0 ml of diethyl ether as

solvent was irradiated at 0°C under nitrogen. Irradiation was continued for 1 hr when the conversion percents of both isocyanides were in a range of 3 %. The ratio of the two isothiocyanates,  $[R_{\text{p-OCH}_3}\text{S}]/[R_{\text{H}}\text{S}]$  of eq. 14 was determined using calibration curves.

#### Reactions of t-Butyl Isocyanide (IV) with $\alpha$ -Toluenethiol (IX)

Radical reaction. Radical reaction of IV with IX by AIBN at 80°C gave 93 % of t-butyl isothiocyanate and 96 % of toluene.

Copper catalyzed reaction. To a mixture of 1.24 g (10 mmol) of IX and 1.00 g (12 mmol) of IV was added 8.0 mg (0.1 mmol) of cupric oxide as a catalyst. The reaction system became homogeneous soon at room temperature. When the reaction mixture was heated at 100°C for 2.0 hr, 91 % of IX disappeared. Benzyl N-t-butylthioformimidate was isolated by preparative glpc.  $n_{\text{D}}^{25}$  1.5435. Anal. Calcd for  $\text{C}_{12}\text{H}_{17}\text{NS}$ : C, 69.51; H, 8.26; N, 6.76. Found: C, 69.78; H, 8.37; N, 6.52.

#### Reaction of Cyclohexyl Isocyanide (V) with 2-Methyl-2-propanethiol (XI) in the Presence of Cupric Oxide and p-Benzoquinone

A mixture of 0.63 g (7 mmol) of XI, 0.54 g (5 mmol) of V, 8 mg (0.1 mmol) of cupric oxide and 55 mg (0.5 mmol) of p-benzoquinone was refluxed at 90°C for 3 hr. By the glpc analysis of the reaction mixture, t-butyl N-cyclohexylthioformimidate<sup>3)</sup> (64 %) and XIII (6 %) were formed.

## References

- 1) See Part I, Chapter 1.
- 2) See Part I, Chapter 2.
- 3) See Part I, Chapter 3.
- 4) See Part I, Chapter 5.
- 5) See Part I, Chapter 4.
- 6) T. Saegusa, S. Kobayashi, Y. Ito, and N. Yasuda, *J. Am. Chem. Soc.*, 90, 4182 (1968).
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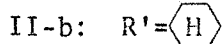
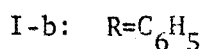
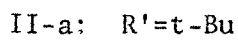
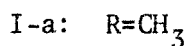
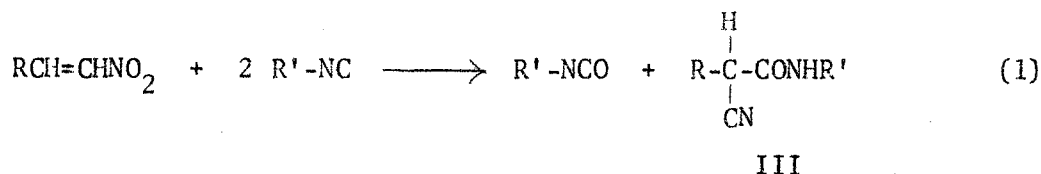
## Chapter 2

### Reaction of Isocyanide with Nitroalkene

This chapter deals with the reaction of isocyanide with  $\alpha,\beta$ -unsaturated nitro compounds, which was explored in the course of studies upon the reactions of isocyanide. As nitroalkene, 1-nitropropene (I-a) and  $\omega$ -nitrostyrene (I-b) were employed, which have a hydrogen at  $\alpha$ -carbon atom of nitro group.

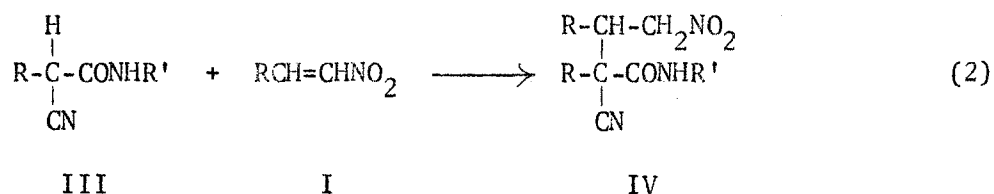
#### 1. Results and Discussion

Isocyanide reacts with nitroalkene to produce isocyanate and  $\alpha$ -cyano- $\alpha$ -substituted acetamide (III) as shown by the following eq. 1.













The latter product (III) has an acidic hydrogen and reacts further with

nitroalkene to form  $\alpha$ -cyano- $\alpha,\beta$ -disubstituted  $\gamma$ -nitrobutyramide (IV) in a mode of the Michael reaction.



Some results are shown in Table I.

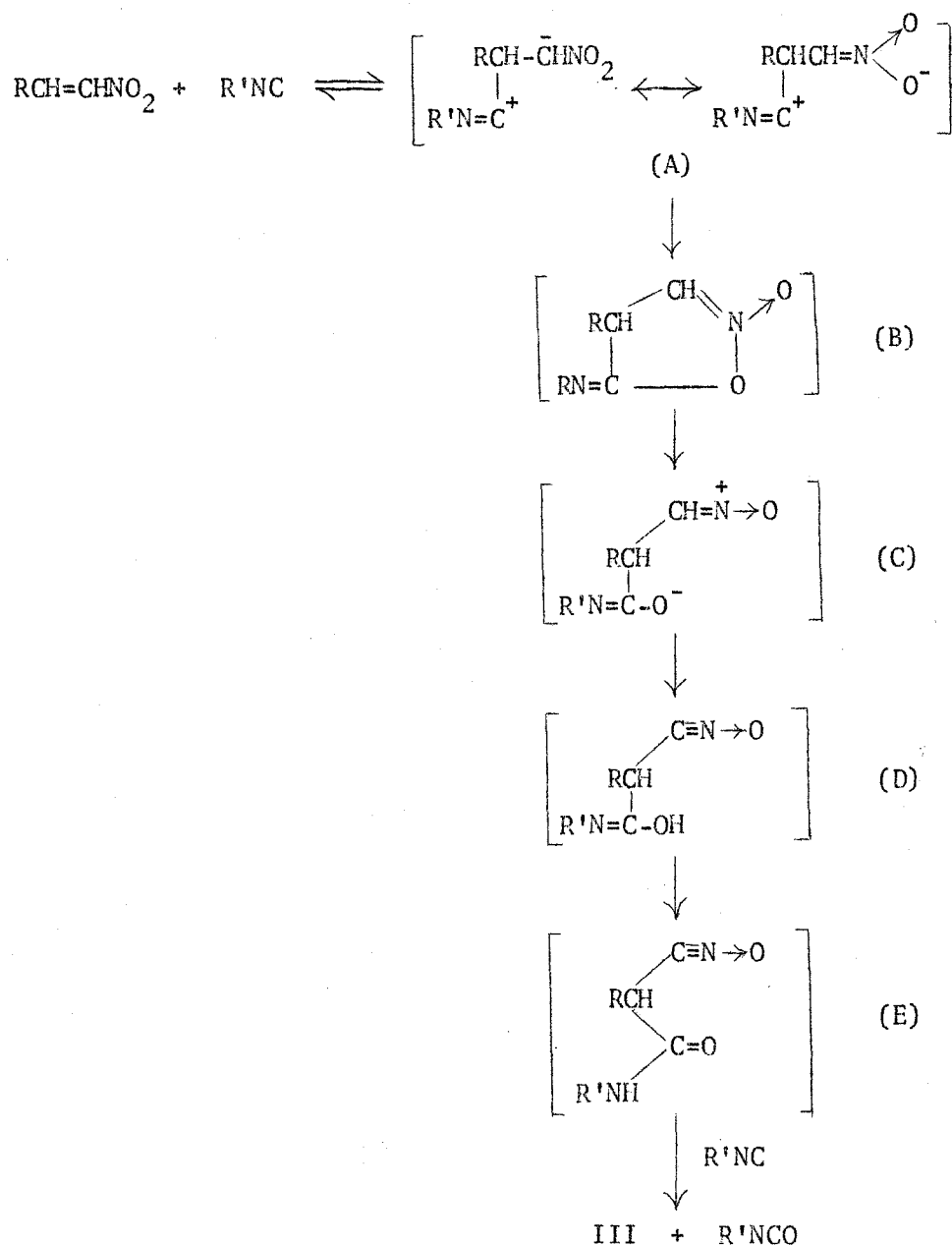
Table I. Reaction of Nitroalkene with Isocyanide

R of RCH=CHNO <sub>2</sub> (mmol)	R' of R'-NC (mmol)	Solvent (ml)	Reaction condition		Product	(mmol)
			(°C)	(hr)		
CH <sub>3</sub> (I-a) 20	t-Bu (II-a) 40	—	60	3	t-BuNCO III-a-a (R=CH <sub>3</sub> , R'=t-Bu)	10.7 11.0
CH <sub>3</sub> (I-a) 10	 (II-b) 20	C <sub>6</sub> H <sub>6</sub> 3	60	3	 -NCO III-a-b, (R=CH <sub>3</sub> , R'=  )	7.0 7.3
C <sub>6</sub> H <sub>5</sub> (I-b) 10	 (II-b) 30	C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub> 10	100	5	 -NCO <sup>a</sup> III-b-b (R=C <sub>6</sub> H <sub>5</sub> , R'=  ) IV-b-b (R=C <sub>6</sub> H <sub>5</sub> , R'=  )	3.4 2.8 0.6
C <sub>6</sub> H <sub>5</sub> (I-b) 20	 (II-b) 20	C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub> 10	100	8	 -NCO <sup>a</sup> IV-b-b (R=C <sub>6</sub> H <sub>5</sub> , R'=  )	6.2 5.8

<sup>a</sup> Isolated as N,N'-dicyclohexylurea.

In the reactions of 1-nitropropene, any Michael addition product was not detected under the reaction conditions given in Table I. However,  $\omega$ -nitro-

styrene gave two products, III and IV. Reaction of equimolar amounts of I-b and II-b produced exclusively the Michael addition product. The following scheme may be taken to explain the formation of III.



The first step of the reaction is the electrophilic attack of isocyanide on  $\beta$ -carbon atom to form the 1,3-dipolar type intermediate (A). The intermediate

(A) will be converted into an unstable ring intermediate (B), whose ring opening reaction gives rise to the nitrile oxide species (E) through (C) and (D). The deoxidation of (E) with the second molecule of isocyanide will give the product III. In this step, the second isocyanide molecule is converted into the corresponding isocyanate. The deoxidation of nitrile oxide by isocyanide has been established.<sup>1)</sup>

In the Michael addition of III to nitroalkene may have been catalyzed by isocyanide which has a character of base. In a separate experiment, the Michael addition of this combination was smoothly carried out in the presence of triethylamine catalyst, i.e., a mixture of 10 mmol of III-b-b and 15 mmol of I-b catalyzed by 1 mmol of triethylamine in toluene at 60°C for 0.5 hr, gave IV-b-b quantitatively.

## 2. Experimental

### Materials

$\omega$ -Nitrostyrene was prepared according to the ordinary method<sup>2)</sup> by dehydration of benzaldehyde and nitromethane with alkali, m.p. 57°C.

1-Nitropropene was prepared by dehydration of 2-nitroisopropyl alcohol prepared according to the reference,<sup>3)</sup> with phthalic anhydride at reduced pressure.<sup>4)</sup>

### Reaction of 1-Nitropropene (I-a) and t-Butyl Isocyanide (II-a)

A mixture of 1.74 g (20 mmol) of I-a and 3.32 g (40 mmol) of II-a was heated at 60°C for 3 hr. After the reaction, 0.86 g (8.7 mmol) of t-butyl



isocyanate was trapped by distillation at reduced pressure, whose structure was determined by comparing its IR spectrum with that of the authentic sample. The distillation residue was extracted with hot ligroin to give 1.70 g (11.0 mmol) of N-t-butyl- $\alpha$ -cyanopropionamide (III-a-a), m.p. 85 — 86°C (from ligroin).

III-a-a was identified by IR and NMR spectra as well as elemental analysis. The IR spectrum showed bands at  $\nu_{\max}$  3250 (s), 2280 (w) and 1650 (vs); NMR (in  $\text{CDCl}_3$ ) peaks appeared at  $\tau$  8.62 (9H, singlet, t-Bu), 8.44 (3H, doublet,  $\text{CH}_3\text{-CH(CN)}$ ), 6.68 (1H, quartet,  $\text{CH}_3\text{-CH(CN)}$ ) and 3.8 — 4.3 (1H, broad, NH). Anal. Calcd for  $\text{C}_8\text{H}_{14}\text{N}_2\text{O}$ : C, 62.30; H, 9.15; N, 18.17. Found: C, 62.01; H, 9.15; N, 18.02.

A part of t-butyl isocyanate was converted to N-N'-di-t-butylurea (1.0 mmol), which was isolated from the extract of ligroin by recrystallization.

#### Reaction of 1-Nitropropene (I-a) and Cyclohexyl Isocyanide (II-b)

A mixture of 0.87 g (10 mmol) of I-a, 2.18 g (20 mmol) of II-b and 3 ml of benzene (solvent) was heated at 60°C for 3 hr. The vacuum distillation of the reaction mixture gave 3.7 g of distillate boiling at 30 — 76°C (40 mm), which was analyzed by glpc to contain 0.87 g (7.0 mmol) of cyclohexyl isocyanate. The distillation residue was extracted several times with chloroform—ligroin mixture to give 1.31 g (7.3 mmol) of crude N-cyclohexyl- $\alpha$ -cyanopropionamide (III-a-b), m.p. 80 — 81°C (from ligroin).

The IR spectrum of III-a-b showed bands at  $\nu_{\max}$  3260 (s), 2270 (w) and 1650 (vs); NMR (in  $\text{CDCl}_3$ ) showed peaks at  $\tau$  8.42 (3H, doublet,  $\text{CH}_3\text{CH(CN)}$ ), 7.9 — 9.1 (10H, broad,  $-(\text{CH}_2)_5-$ ), 6.62 (1H, quartet,  $\text{CH}_3\text{CH(CN)}$ ), 6.0 — 6.6

(1H, broad, N-CH<), and 3.6 — 4.1 (1H, broad, NH-). Anal. Calcd for  $C_{10}H_{16}N_2O$ : C, 66.64; H, 8.95; N, 15.54. Found: C, 66.83; H, 9.14; N, 15.26.

Reaction of  $\omega$ -Nitrostyrene (I-b) and Cyclohexyl Isocyanide (II-b)

To a mixture of 1.49 g (10 mmol) of I-b and 3.27 g (30 mmol) of II-b, 10 ml of toluene was added as solvent and the reaction mixture was heated at 100°C for 5 hr. After the reaction, a small amount of wet ligroin was added to the reaction mixture and kept standing at room temperature for one day. Then, crystalline material precipitated out which was collected by filtration. On recrystallization, the crystalline material gave rise to two crystalline compounds. One was shown to be N,N'-dicyclohexylurea (1.7 mmol) by its IR spectrum. The urea was recognized as the reaction product of cyclohexyl isocyanate and water. The other crystalline (0.68 g), m.p. 118°C, was identified to be N-cyclohexyl- $\alpha$ -cyano- $\alpha$ -phenylacetamide (III-b-b) (2.8 mmol) by IR and NMR spectra as well as elemental analysis. The IR spectrum showed  $\nu_{\max}$  3260 (s), 2280 (w) and 1650 (vs); NMR (in  $CDCl_3$ ) peaks appeared at  $\tau$  7.9 — 9.0 (10H, broad,  $-(CH_2)_5-$ ), 6.1 — 6.6 (1H, broad, N-CH<), 5.33 (1H, singlet, CH(CN)), 3.6 — 4.0 (1H, broad, -NH-), and 2.57 (5H, singlet,  $C_6H_5-$ ). Anal. Calcd for  $C_{15}H_{18}NO$ : C, 74.35; H, 7.49; N, 11.56. Found: C, 74.57; H, 7.63; N, 11.51.

Further addition of petroleum ether to the filtrate gave the third crystalline compound, which was identified to be N-cyclohexyl- $\alpha$ -cyano- $\alpha,\beta$ -diphenyl- $\gamma$ -nitrobutyramide (IV-b-b) (0.6 mmol), m.p. 154 — 155°C (from ligroin), by IR and NMR spectra, elemental analysis and molecular weight. The IR spectrum showed bands at  $\nu_{\max}$  3360 (s), 2280 (w), 1690 (vs), 1530 (vs),

and 1370 (s); NMR (in  $\text{CDCl}_3$ ) peaks appeared at  $\tau$  7.8 — 9.0 (10H, broad,  $-(\text{CH}_2)_5-$ ), 6.0 — 6.5 (1H, broad, N-CH<), 5.35 and 5.55 (1H, two doublets,  $-\text{CH}(\text{C}_6\text{H}_5)-\text{CH}_2\text{NO}_2$ ), 4.98 and 4.87 (2H, two doublets,  $\text{CH}-\text{CH}_2\text{NO}_2$ ), 3.8 — 4.2 (1H, broad, NH-), and 2.98 and 2.73 (10H, two singlets,  $\text{C}_6\text{H}_5-\text{CH}$  and  $\text{C}_6\text{H}_5-\text{C}(\text{CN})$ ); molecular weight (VPO in benzene). Calcd for IV-b-b: 391.5. Found: 391.5. Anal. Calcd for  $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_3$ : C, 70.57; H, 6.44; N, 10.74. Found: C, 70.35; H, 6.26; N, 10.75.

The reaction of 2.98 g (20 mmol) of I-b with 2.18 g (20 mmol) of II-b in 10 ml of toluene at  $100^\circ\text{C}$  for 8 hr, gave 3.1 mmol of N,N'-dicyclohexylurea and 5.8 mmol of N-cyclohexyl- $\alpha$ -cyano- $\alpha,\beta$ -diphenyl- $\gamma$ -nitrobutyramide (IV-b-b). A large amount of tarry materials was also formed in this case.

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- 1) P. V. Finzi and M. Arbasino, *Tetrahedron Letters*, 4645 (1965).
- 2) D. E. Worrall, "Organic Syntheses," Coll. Vol. 1, (1941), p. 413.
- 3) N. Leavy and C. W. Scaife, *J. Chem. Soc.*, 1096 (1946).
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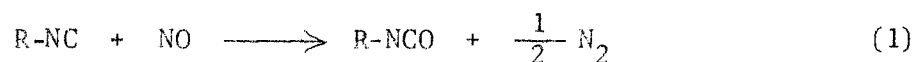
## Chapter 3

### Reaction of Isocyanide with Nitric Oxide

In the course of the mechanistic studies on reactions of isocyanide and nitro compounds,<sup>1)</sup> new reaction of isocyanide with nitric oxide has been found. This chapter describes the oxidation reaction of isocyanide with nitric oxide to produce isocyanate.



#### 1. Results and Discussion

Some results are shown in Table I. Isocyanates were obtained in high yields. The main gaseous product was nitrogen, whose amount roughly satisfies the following stoichiometric relation:



Small amounts of nitrous oxide (below 10 % of nitrogen) and carbon dioxide (less than a few percent) were formed as by-products. The production of carbon dioxide may be attributed to the hydrolysis of the product isocyanate with water which is present as an impurity. The amine from the isocyanate hydrolysis may have been converted by the second molecule of isocyanate into

Table I. Reaction of Isocyanide with Nitric Oxide

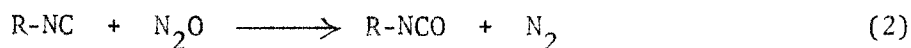
Exp. No.	R-NC	(mmol)	Solvent	Reaction		Yield of R-NCO <sup>a</sup> (%)	N <sub>2</sub> (mmol)
				Temp. (°C)	Time (hr)		
1	 -NC	10	C <sub>6</sub> H <sub>6</sub>	80	5	77	3.3
2	t-Bu-NC	20	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	120	8	50	—
3	n-C <sub>6</sub> H <sub>13</sub> -NC	10	C <sub>6</sub> H <sub>6</sub>	100	8	62	—
4	 -NC	10	C <sub>2</sub> H <sub>5</sub> OH	110	8	80 <sup>b</sup>	—

<sup>a</sup> Based on the isocyanide initially charged.

<sup>b</sup> Isolated as ethyl N-cyclohexylurethane which is the reaction product of N-cyclohexyl isocyanate and ethanol (solvent).

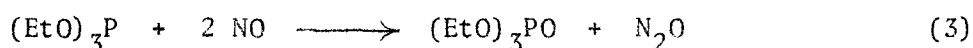
the corresponding urea. In fact, small amount of urea was isolated from the reaction mixture. The nitric oxide— isocyanide reaction proceeded even at atmospheric pressure. Nitric oxide gas was passed at a rate of 1.5 l/hr through a mixture of 50 mmol of cyclohexyl isocyanide and 10 ml of toluene (solvent) at 95°C for 10 hr. Cyclohexyl isocyanate was produced in 56 % yield.

Nitrous oxide also oxidized isocyanide into isocyanate. To a mixture of cyclohexyl isocyanide (13 mmol) and benzene (3 ml, solvent) in a 50 ml stainless-steel pressure tube, nitrous oxide was compressed to 20 kg/cm<sup>2</sup> at room temperature. The content of the tube was heated at 120 — 130°C for 16 hr. Only 22 % of cyclohexyl isocyanide was converted into isocyanate.

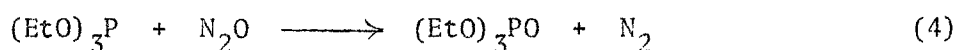


Judging from the reaction conditions and the conversion rate, the oxidizing reactivity of nitrous oxide is much lower than that of nitric oxide. This finding, however, is not taken to support a mechanism of stepwise reduction of nitric oxide to nitrogen through the intermediate stage of nitrous oxide.

The reaction of phosphite with nitric oxide is interestingly compared with that of isocyanide. It has been reported that nitric oxide reacts with triethyl phosphite to produce triethyl phosphate and nitrous oxide in liquid phase at room temperature and that nitrous oxide has no tendency to oxidize triethyl phosphite under the same reaction conditions.<sup>2)</sup> However, it was found,



in connection with the present reaction, that nitrous oxide also has the capacity of oxidizing triethyl phosphite to triethyl phosphate at higher temperatures and pressures. Thus, triethyl phosphate was obtained in more than 80 % yield by the triethyl phosphite—nitrous oxide reaction under



the same reaction conditions as described in the cyclohexyl isocyanide—nitrous oxide reaction.

## 2. Experimental

### General Procedure

A typical run is the reaction of cyclohexyl isocyanide and nitric oxide.

A mixture of 1.09 g (10 mmol) of cyclohexyl isocyanide and 3 ml of benzene (solvent) was placed in a 50 ml stainless-steel pressure tube, to which nitric oxide was compressed to 20 kg/cm<sup>2</sup> at room temperature. The pressure tube was closed and the content was heated for 5 hr without shaking and stirring. After the reaction, the gaseous products were trapped and analyzed by glpc with a column of silica gel (column temperature, -78°C for nitrogen and nitric oxide and 40°C for nitrous oxide and carbon dioxide). Isocyanide and isocyanate were analyzed by glpc (columns of Silicone DC 550 and PEG 6000).

#### References

- 1) See Part III, Chapter 2.
- 2) L. P. Kuhn, J. O. Doali, and C. Wellman, J. Am. Chem. Soc., 82, 4792 (1960).

## LIST OF PUBLISHED PAPERS

### Part I

- Chapter 1. Reaction of Isocyanide with Amine.  
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- Chapter 2. Copper Catalyzed Reaction of Isocyanide with Alcohol.  
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Chapter 4. Reaction of Ethyl Diazoacetate with Cupric Chloride.

To be published in J. Org. Chem.

### Part III

Chapter 1. Radical Reaction of Isocyanide with Thiol.

To be published in J. Am. Chem. Soc.

Chapter 2. Reaction of Isocyanide with Nitroalkene.

To be published in J. Org. Chem.

Chapter 3. Reaction of Isocyanide with Nitric Oxide.

To be published in Chem. Commun.

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