BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 3310—3313 (1969)

Synthetic Reactions by Complex Catalysts. XIV. Reaction of Isocyanide with Amine Catalyzed by Group IB and IIB Metal Compounds

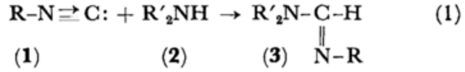
Takeo SAEGUSA, Yoshihiko ITO, Shiro KOBAYASHI, Kiwami HIROTA
and Hiroshi YOSHIOKA

Department of Synthetic Chemistry, Faculty of Engineering Kyoto University, Yoshida, Sakyo-ku, Kyoto

(Received May 17, 1969)

Group IB and IIB metal compounds catalyze the reaction of isocyanides (**1**) with amines (**2**) producing formamidines (**3**). In the reaction of cyclohexyl isocyanide with piperidine, the accelerating effect of catalyst was in the order $AgCl > CuCl \gg ZnCl_2$, $Cd(OAc)_2$, $HAuCl_4 \cdot 4H_2O$. 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 $HAuCl_4 \cdot 4H_2O > ZnCl_2 > AgCl \gg CuCl$. A ternary complex of $(CuCl)_2$ (cyclohexyl isocyanide)$_2$ (piperidine) was isolated, which was unstable and decomposed gradually at room temperature to give *N*-cyclohexyl-*N'*,*N'*-pentamethylene formamidine. A mechanism through a mixed ligand complex has been proposed, in which both isocyanide and amine are coordinated with the same metal ion and the reaction takes place in the sphere of complex ligand.

The reaction of aliphatic isocyanide with amine, which does not take place without catalyst, is induced effectively by copper,[1] silver, zinc, cadmium and gold salts. Aromatic isocyanides have been known to react with amine even in the absence of the metal salt catalyst.[2] In the reaction of aromatic isocyanide with amine, however, the accelerating effect of the above metal compounds is observed.



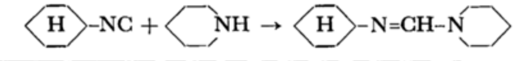
$$\underset{(\mathbf{1})}{R\text{-}N \rightleftarrows C:} + \underset{(\mathbf{2})}{R'_2NH} \rightarrow \underset{(\mathbf{3})}{R'_2N\text{-}\underset{\underset{N-R}{\|}}{C}\text{-}H} \qquad (1)$$

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 complex ligand.

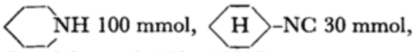
Results and Discussion

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 1).

TABLE 1. CATALYTIC ACTIVITIES OF METAL COMPOUNDS FOR CYCLOHEXYL ISOCYANIDE-PIPERIDINE REACTION



Cat.	Conditions (hr)*	Yield (%)
none	18	0
CuCl	1	96
AgCl	1	98
$ZnCl_2$	1	97
$Cd(OAc)_2$	1	97
$HAuCl_4 \cdot 4H_2O$	22	46
$Hg(OAc)_2$	6	5
$FeCl_3$	6	15
Ferrocene	17	2
$Fe(AA)_3$**	4	1
$AlCl_3$	7	1



* NH 100 mmol, -NC 30 mmol, Cat. 0.2 mmol, 110—120°C.
** AA=Acetylacetonate ligand

The catalytic activities of IB and IIB metal compounds except mercuric compound are conspicuously shown. Since the formamidines are obtained in high yields, the reaction can be utilized for the synthesis of the formamidine derivatives. Lewis acids such as ferric chloride and aluminum chloride are much less active. In the isocyanide-amine reaction, zinc chloride was used in an earlier work.[3] The results of an extended screening of the metal

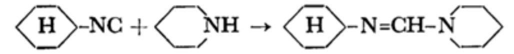
---

[1] T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota and H. Yoshioka, *Tetrahedron Letters*, **1966**, 6121.

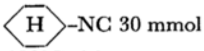
[2] J. U. Nef, *Liebigs Ann. Chem.*, **270**, 267 (1892).

[3] T. L. Davis and W. E. Yelland, *J. Am. Chem. Soc.*, **59**, 1998 (1937).

TABLE 2. CATALYSIS OF COPPER COMPOUNDS IN CYCLOHEXYL ISOCYANIDE-PIPERIDINE REACTION*



Cat.	Yield (%)
CuCl	94
$CuCl_2$	86
CuCN	90
$Cu(CN)_2$	94
$Cu(AA)_2$**	86
Cu	93

*  100 mmol,  30 mmol
Cat. 0.2 mmol; 110—120°C, 1 hr
** AA=Acetylacetonate ligand

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 2 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[4)]

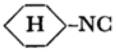
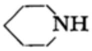
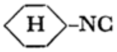
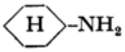
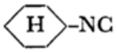
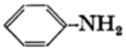
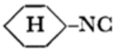
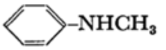
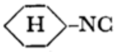
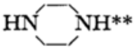
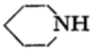
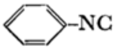
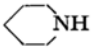
$$2CuCl_2 + RN \rightleftarrows C: \rightarrow 2CuCl + R-N=CCl_2 \qquad (2)$$

Consequently it may be assumed that the cupric species were reduced to the cuprous species which served as the real active catalyst.

As to the catalytic 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 in the liquid phase showed a new band at 2180 cm^{-1} in addition to the absorption band of cyclohexyl isocyanide. The new band is reasonably assigned to $\nu_{N\equiv C}$ of the isocyanide species which is coordinated with copper. Moreover, the corresponding formamidine was formed when the liquid phase was treated with piperidine at room temperature. In the metallic copper catalyzed reaction the catalytic activity is thus ascribed to the soluble complex. The actual valence state of copper in liquid isocyanide should be the subject of future research.

TABLE 3. CUPROUS CHLORIDE CATALYZED REACTION OF ISOCYANIDE WITH AMINE*

$$RNC + R'R''NH \rightarrow RN{=}CH{-}NR'R''$$

Isocyanide	Amine	Condition (hr)	Condition (°C)	Yield (%)
		5	25	90
		3	110—120	80
		24	140	85
		25	160	20
		6	110—120	82***
n-BuNC		3	110—120	90
n-BuNC		10	25	87
n-BuNC	n-$BuNH_2$	5	110—120	88
		0.3	0	96

* Conditions: RNC 30 mmol, R'R''NH 100 mmol, CuCl 0.2 mmol
** As the reaction solvent, 10 m*l* of dioxane was employed.
*** The product was bis-*N*,*N'*-(cyclohexylformimidoyl) piperazine.

Table 3 shows the results of the reactions of three isocyanides with aliphatic and aromatic amines by cuprous chloride catalyst. The cuprous chloride catalyzes 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. Cuprous chloride is not a suitable catalyst for this combination of reaction. This will be discussed later.

Aromatic isocyanide reacts with amine without catalyst. As an 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, the catalytic activity 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 almost quantitatively (the last run of Table 3).

The catalyst activities of several salts of group 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 $AgCl > CuCl \gg ZnCl_2$, $Cd(OAc)_2$, $HAuCl_4 \cdot 4H_2O$, which is quite different from that in the latter reaction of cyclohexyl isocyanide with aromatic amine, $HAuCl_4 \cdot 4H_2O > ZnCl_2 > AgCl \gg CuCl$. The specific activity of chloroautic acid in the aromatic amine-isocyanide reaction is of interest especially from the fact that it is

---

[4)] T. Saegusa, Y. Ito and S. Tomita, to be published.

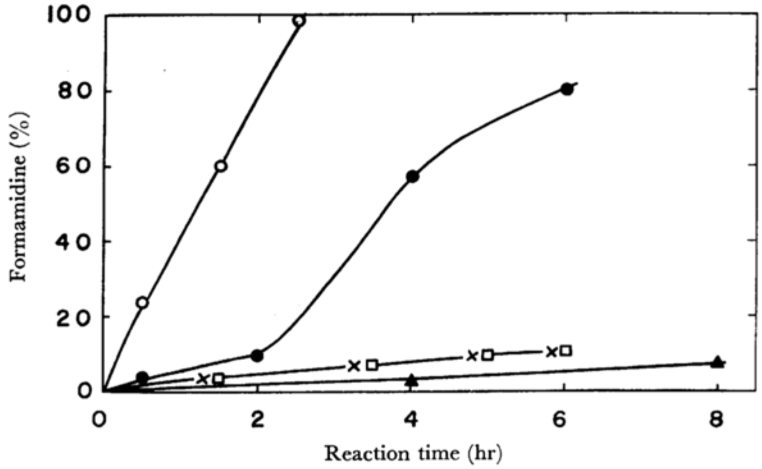


Fig. 1. Reaction of cyclohexyl isocyanide with piperidine (17°).
—○— AgCl —●— CuCl —□— $ZnCl_2$
—▲— $HAuCl_4\cdot 4H_2O$ —×— $Cd(OAc)_2$

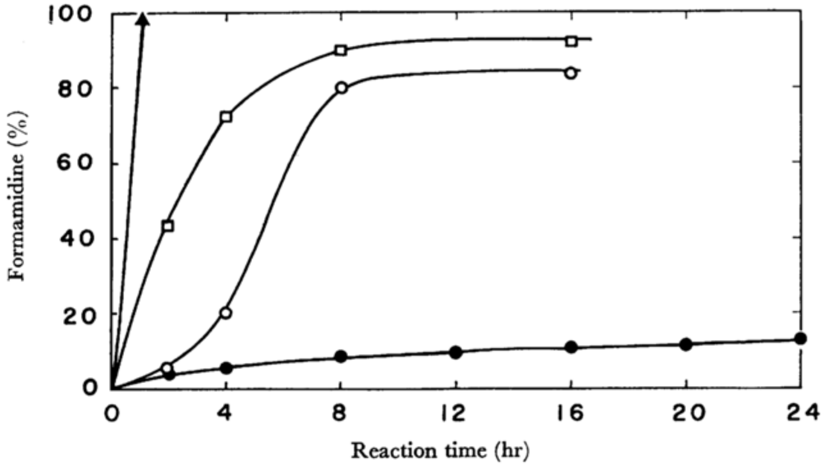


Fig. 2. Reaction of cyclohexyl isocyanide with *N*-methylaniline (160°).
—○— AgCl —●— CuCl
—□— $ZnCl_2$ —▲— $HAuCl_4\cdot 4H_2O$

also quite active as the catalyst in the reaction[5] of aromatic amine with carbon monoxide which is isoelectronic to isocyanide.

Metallation of aromatic compound with $AuCl_3$, as reported by Kharasch[6] may be cited in relation to the specific catalysis of chloroautic acid for these reactions.

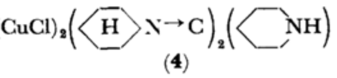
Mechanism. The isocyanide-amine reaction of the present studies seems to proceed in the ligand sphere of a ternary complex consisting of metal ion, isocyanide and amine. The crystalline, binary complex of cyclohexyl isocyanide and cuprous chloride, $[\mathrm{Cu}(\mathrm{C}\overset{\leftarrow}{=}\mathrm{NC_6H_{11}})]\mathrm{Cl}$, was dissolved into liquid piperidine at 0°C. On standing the homogeneous solution at 0°C, a new crystalline solid was separated.

NMR spectrum of the crystalline solid in deuterated chloroform showed two broad signals centered at δ 3.7 (2H, $\rangle\mathrm{CH{-}N}\overset{\rightrightarrows}{=}\mathrm{C}$: of two mol of cyclohexyl isocyanide) and δ 3.3 (4H, $-\mathrm{N}\langle\begin{smallmatrix}\mathrm{CH_2}-\\ \mathrm{CH_2}-\end{smallmatrix}$ of one mol of piperidine) and a complex signal at δ 1.0—2.1 (26H, 20H of $-(CH_2)_5-$ of two mol of cyclohexyl isocyanide plus 6H of $-(CH_2)_3-$ 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 **4**: C, 45.51; H, 6.63; N, 8.38; Cl, 14.14%), the composition of the complex was determined as indicated by the formula

---

[5] T. Saegusa, S. Kobayashi, K. Hirota and Y. Ito, This Bulletin, to be published.

[6] M. S. Kharasch and H. S. Isbell, *J. Am. Chem. Soc.*, **53**, 3053 (1931).



(**4**)

The spectrum of the ternary complex showed two key bands at 2176 and 3192, which were assigned to $\nu_{N\equiv C}$ of the isocyanide ligand and ν_{N-H} of the piperidine ligand. The band of $\nu_{N\equiv C}$ of the ternary complex is different from the corresponding $\nu_{N\equiv C}$ of the binary complex at 2192 cm^{-1} and from that of free isocyanide at 2140 cm^{-1}. Variation of $\nu_{N\equiv C}$ indicates that the coordination of isocyanide in the ternary complex is influenced by the piperidine ligand, whose ν_{N-H} band is also being shifted from that of free piperidine at 3280 cm^{-1}. These observations suggest 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 to produce 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.

Experimental

Meterials. Metal salts were of commercial, analytical reagent grade.

Metallic copper was prepared by reduction of cupric sulfate with zinc powder. In 600 m*l* 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 Ugi's procedure.[7]

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 $\nu_{N\equiv C}$ 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, bp 155—156°C/28 mmHg.

Found: C, 74.40; H, 11.71; N, 14.53%. Calcd for $C_{10}H_{20}N_2$: C, 74.17; H, 11.41; N, 14.42%. IR (neat): 1660 cm^{-1} ($\nu_{N=C}$), NMR (CDCl$_3$): δ 7.10 ppm (singlet, –N=CH–N<).

N,*N'*-Dicyclohexyl formamidine, mp 100—101°C (recrystallization from *n*-hexane).

Found: C, 74.61; H, 11.35; N, 13.64%. Calcd for $C_{13}H_{24}N_2$: C, 74.94; H, 11.61; N, 13.45%. IR (Nujol): 3280 cm^{-1} (ν_{N-H}), 1650 cm^{-1} ($\nu_{N=C}$).

N-Cyclohexyl-*N'*-methyl-*N'*-phenyl formamidine, bp 94—96°C/0.7 mmHg.

Found: C, 77.61; H, 9.58; N, 13.11%. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32; N, 12.95%. IR (neat): 1640 cm^{-1} ($\nu_{N=C}$).

Bis-*N*,*N'*-(cyclohexylformimidoyl) piperazine, mp 99—101°C (recrystallization from *n*-hexane).

Found: C, 71.16; H, 10.71; N, 18.68%. Calcd for $C_{18}H_{32}N_4$: C, 71.00; H, 10.59; N, 18.40%. Molecular weight (cryoscopic in benzene) Found: 294. Calcd for $C_{18}H_{32}N_4$: 304. IR (Nujol): 1630 cm^{-1} ($\nu_{N=C}$).

N-*n*-Butyl-*N'*,*N'*-pentamethylene formamidine, bp 118—120°C/27 mmHg.

Found: C, 71.39; H, 12.08; N, 16.79%. Calcd for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.65%. IR (neat); 1640 cm^{-1} ($\nu_{N=C}$). NMR (CCl$_4$): δ 7.10 ppm (singlet, –N=CH–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, mp 95—96°C. Elementary analysis revealed that crystalline product consisted of 1 mol cyclohexyl isocyanide and 1 mol cuprous chloride.

Found: C, 40.40; H, 5.29; N, 6.73; Cl, 17.07%. Calcd for $C_7H_{11}NClCu$: C, 40.40; H, 5.22; N, 6.60; Cl, 17.01%.

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 several minutes more, a white crystalline solid was precipitated. The crystalline solid 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.

---

[7] I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960).