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Synthetic Reactions by Complex Catalysts. XXIV. A New Catalyst of Copper-Isocyanide Complex for the Michael Addition

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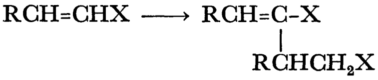
It has been found that some binary systems of a copper compound (or metallic compounds) and an isocyanide catalyze the Michael addition reaction. As the copper component, Cu_2O, metallic copper and copper acetylacetonate are effectual, whereas CuCl, $CuCl_2$, and CuO are ineffectual. The catalyst of copper isocyanide complex is characterized by the selective activation of cyano olefin compounds such as acrylonitrile. This was demonstrated by the competitive addition of an active hydrogen compound to acrylonitrile and methyl acrylate. Some results of kinetics and spectroscopic studies have been explained by assuming a scheme involving coordination of olefin onto copper-isocyanide complex.

This paper deals with the catalyst behavior of some binary systems of a copper compound and an isocyanide for the Michael addition reaction. We have concentrated on new catalyst activity of the copper-isocyanide complexes in the field of synthetic organic reactions, and found several new reactions with the catalytic aid of these complexes. Copper catalyzed formimidation of amine,[1a] phosphine,[1b] alcohol,[1c,d] thiol,[1e] and silane[1f] constitutes a series of new reactions of isocyanide. Dimerization of α,β-unsaturated nitriles and carbonyl compounds (Eq. (1)) is the second series of reactions catalyzed by the copper-isocyanide complexes, where the isocyanide ligand is not incorporated in the products.[2-4]



$$RCH{=}CHX \longrightarrow \underset{\displaystyle RCHCH_2X}{RCH{=}\overset{}{C}\text{-}X}$$

$$\begin{pmatrix} R=H,\ \text{primary and secondary alkyl groups} \\ X=CN,\ CO_2R',\ COR'' \end{pmatrix}$$

From the mechanistic consideration on the dimerization reaction, a nucleophilic addition of allyl and vinyl-copper complexes to α,β-unsaturated bond has been reasonably assumed as the key step.[3,4] This assumption prompted us to examine the catalysis of the copper-isocyanide complex in the Michael addition reaction. The expectation has been realized. In addition, the copper-isocyanide complex in the Michael addition is distinguished from the usual base catalysts by the selective activation of cyano olefins such as acrylonitrile.

Experimental

Materials. Commercial reagents diethyl malonate, acetylacetone, benzyl cyanide, malononitrile, *t*-butyl mercaptan, 2-nitropropane, indene, methyl crotonate, methyl acrylate, acrylonitrile, and triethylamine were purified by distillation. Methylacetylacetone (3-methylpentane-2,4-dione) was prepared from acetylacetone and methyl iodide using potassium carbonate catalyst.[5] Diethyl ethylmalonate was synthesized from diethyl malonate and ethyl bromide using sodium ethoxide catalyst.[6] Ethyl propiolate was prepared by the dehydrobromination of dibromosuccinic acid followed by decarboxylation and esterification.[7] Cyclohexyl isocyanide and *t*-butyl isocyanide were prepared according to Ugi's procedure.[8] Metal oxide and salts were all commercial reagents. Metallic copper powder was prepared by the reduction of cupric sulfate with zinc powder in acidic aqueous solution under nitrogen.[9]

Reaction of Diethyl Malonate with Methyl Crotonate. A mixture of diethyl malonate (1.6 g, 10 mmol), methyl crotonate (1.0 g, 10 mmol), cyclohexyl isocyanide (1.09 g, 10 mmol), and cuprous oxide (20 mg, 0.14 mmol) was heated under nitrogen at 90°C for 9 hr. The reaction mixture was subjected to fractional distillation. The fraction boiling at 152—153°C/4 mmHg was collected. The yield of the product was 2.46 g (95%). By IR and NMR spectra as well as elemental analysis, the structure of the product was shown to be $(EtO_2C)_2CHCH(CH_3)CH_2CO_2CH_3$ (I), an adduct of the Michael addition. Principal IR bands (neat) : 1730 (s), 1300—1150 (s) cm^{-1}. NMR of I in CCl_4 : τ 8.87 (d, CH_3–), 8.64 (t, $-CO_2CH_2CH_3$), 7.52 (d, $-\underset{|}{\overset{|}{C}}H-$), 7.30 (m, $CH_3\underset{|}{C}H$), 6.64 (d, $-CH_2CO_2CH_3$), 6.30 (s, $-CO_2CH_3$), and 5.79 (q, $-CO_2CH_2CH_3$).

Found: C, 55.43; H, 7.84%. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75%.

The reactions of other active hydrogen compounds and acceptor olefins were carried out similarly. The products were identified by IR and NMR spectra. The results are summarized in Table 1.

Effect of Metal Component of Catalyst System. A mixture of 1.60 g (10 mmol) of diethyl malonate, 1.00 g (10 mmol) of methyl crotonate, 1.09 g (10 mmol) of cyclohexyl isocyanide and metal compound (0.14—0.31 mmol) was heated at 90°C for 9 hr under nitrogen. The reaction mixture was subjected to glpc analysis to determine the yield of the Michael adduct, $(EtO_2C)_2CH(CH_3)CH_2CO_2Me$.

Relative Reactivities of Acrylonitrile (AN) and Methyl Acrylate

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[1] a) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and H. Yoshioka, *Tetrahedron Lett.*, **1966**, 6121; This Bulletin, **42**, 3310 (1969). b) T. Saegusa, Y. Ito, and S. Kobayashi, *Tetrahedron Letters*, **1968**, 935. c) T. Saegusa, Y. Ito, S. Kobayashi, N. Takeda, and K. Hirota, *ibid.*, **1967**, 1273: *Can. J. Chem.*, **47**, 1217 (1969). e) T. Saegusa, S. Kobayashi, Y. Ito, K. Hirota, and Y. Okumura, This Bulletin, **41**, 1638 (1968). f) T. Saegusa, Y. Ito, S. Kobayashi, and K. Hirota, *J. Amer. Chem. Soc.*, **89**, 2240 (1967).

[2] T. Saegusa, Y. Ito, S. Kobayashi, and S. Tomita, *Chem. Commun.*, **1968**, 273.

[3] T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *J. Org. Chem.*, **35**, 670 (1970).

[4] T. Saegusa, Y. Ito, H. Kinoshita, and S. Tomita, This Bulletin, **43**, 877 (1970).

[5] A. W. Johnson, E. Markham, and R. Price, "Organic Syntheses", Vol. 42, p. 75.

[6] N. Weiner, *ibid.*, Coll. Vol. II, p. 279.

[7] T. W. Abbot, R. T. Arnold, and R. B. Thompson, *ibid.*, Coll. Vol. II, p. 10.

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

[9] R. Q. Brewster and T. Groening, "Organic Syntheses", Coll. Vol. II, p. 446.

(MA) in the Michael Addition. The ratio of the reaction rates of AN and MA in the Michael addition reactions by copper-isocyanide catalyst and by the conventional base catalysts were determined by a method of competitive reaction. An equimolar mixture of AN and MA, if necessary with a reaction solvent (toluene), was subjected to the Michael addition with an active hydrogen compound in the presence of a catalyst, and the reaction was short-stopped at a lower conversion. The amounts of the two Michael adducts from AN and MA were determined by glpc. The molar ratio of the two adducts was taken to indicate the ratio of the rate constants of AN (k_{AN}) and MA (k_{MA}) on the basis of the assumption that the Michael addition reactions of AN and MA proceed *via* the same reaction mechanism. The extent of reaction was controlled by the feed concentrations of active hydrogen compound and catalyst and the time of reaction. The rate ratios with various catalysts were determined at the same reaction temperature. The feed compositions, reaction temperatures, reaction times and conversion percentage as well as the rate ratio values are shown in Table 3.

Kinetic Study. An introductory kinetic study was carried out on the Michael addition of methylacetylacetone to MA in the presence of the copper acetylacetonate-cyclohexyl isocyanide system. A homogeneous catalyst solution was prepared by dissolving copper acetylacetonate in cyclohexyl isocyanide at room temperature.

1*) Rate Plot for Methylacetylacetone Concentration.* Under nitrogen, a mixture of MA (30.0 mmol) and methylacetylacetone (variable) was diluted with toluene to 10.0 m*l*, to which 10.0 m*l* of a toluene solution of catalyst containing 0.06 mmol of copper acetylacetonate and 6 mmol of cyclohexyl isocyanide was added. The reaction was carried out at room temperature. A small portion of the reaction mixture was taken out and analyzed by glpc. The initial tangent at time=0 of the time-conversion curve was taken as the rate. Several runs of reactions were performed with various amounts of methylacetylacetone. Fig. 1 shows the relationship between the rate and the concentration of methylacetylacetone.

2*) Rate Plot for MA Concentration.* The reaction was carried out in a similar way. The MA concentration was changed in a region from 1.03×10^{-1} mol l^{-1} to 5.00×10^{-1} mol l^{-1}. A linear relationship between the rate and the MA concentration was obtained as shown in Fig. 2.

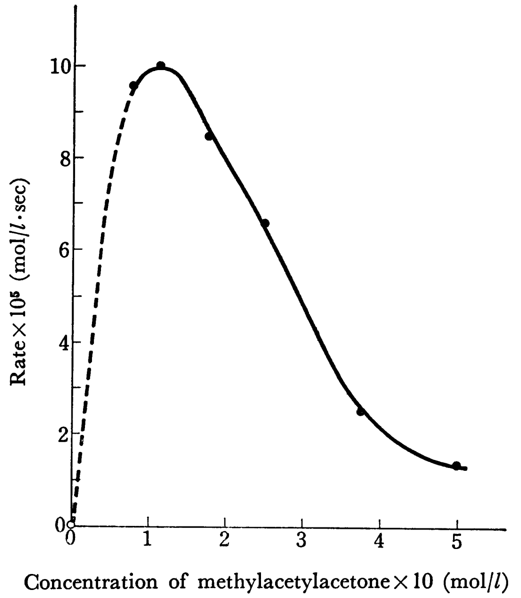


Fig. 1. Relation between the reaction rate and the concentration of methylacetylacetone.

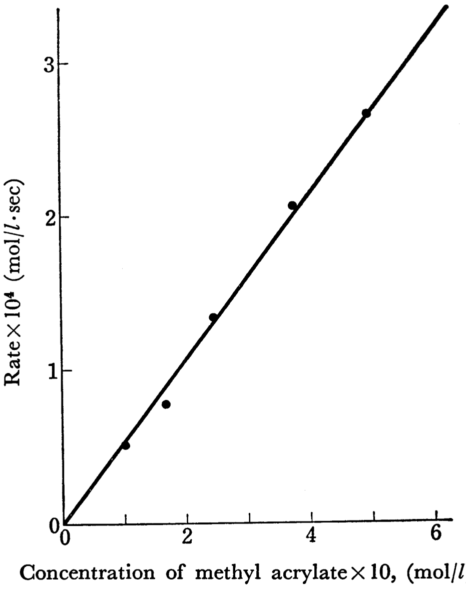


Fig. 2. Relation between the reaction rate and the concentration of methyl acrylate.

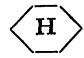
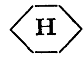
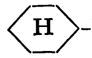
UV Examination on the Interaction of AN and MA with Cu_2O-Isocyanide System. 1*) AN - Cu_2O - Cyclohexyl Isocyanide System.* A mixture of 0.7 g (5 mmol) of Cu_2O, 2.18 g (20 mmol) of AN was diluted with acetonitrile to 10.0 m*l*. The mixture was stirred at room temperature for 1 hr. The insoluble Cu_2O was removed by decantation, and the clear homogeneous reddish-yellow solution was separated. This was diluted to AN and isocyanide concentrations of 6.6×10^{-4} mol l^{-1} with acetonitrile, and the diluted solution was subjected to UV spectroscopy examination (Shimadzu SV-50 spectrometer, Shimadzu Seisakusho, Japan). Two absorption bands were observed at λ_{max}=300 mμ and 360 mμ. The band at 300 mμ was assigned to the AN soluble oligomer formed during the course of preparation of the solution. The band at 360 mμ was observed only in the combination of the three components of AN, Cu_2O, and isocyanide. No single component and combination of two components showed absorption in this region.

2*) MA - Cu_2O - Cyclohexyl Isocyanide System.* A mixture of 0.7 g (5 mmol) of Cu_2O, 2.18 g (20 mmol) of cyclohexyl isocyanide and 1.72 g (20 mmol) of MA was diluted with acetonitrile to 10.0 m*l*, and the mixture was stirred at room temperature for 4 hr. The insoluble Cu_2O was removed by decantation, and the clear yellowish solution was diluted to MA and isocyanide concentration of 2×10^{-2} mol l^{-1} with acetonitrile, and analyzed by UV. A weak absorption band was observed at λ_{max}=325 mμ. This band was observed only in the combination of these three components.

Results and Discussion

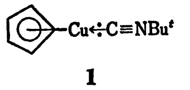
The catalyst activity of the Cu_2O-isocyanide system for the Michael addition reaction is demonstrated in Table 1. As active hydrogen compounds, acetylacetone, malonate, benzyl cyanide, malononitrile, 2-nitropropane, alcohol, thiol, and indene were employed. No single component of Cu_2O and isocyanide alone caused the reaction. Semi-quantitative com-

TABLE 1. MICHAEL ADDITION REACTION BY Cu_2O-ISOCYANIDE SYSTEM[a]

Active hydrogen		Olefin[b]	mmol	Catalysts (mmol)	Conditions		Adduct yield
Compound	mmol				°C	hr	%
$CH_2(CO_2Et)_2$	10	MC	10	-NC (10)—Cu_2O (0.2)	90	9	95
$CH_2(COMe)_2$	10	MC	10	-NC (10)—Cu_2O (0.2)	90	9	72
$PhCH_2CN$	10	MC	10	-NC (10)—Cu_2O (0.2)	90	9	53
$CH_2(CN)_2$	10	MC	10	-NC (10)—Cu_2O (0.2)	90	9	22
$MeCH(COMe)_2$	20	MA	20	-NC (10)—Cu_2O (0.2)	90	1	90
$MeCH(COMe)_2$	20	AN	20	-NC (10)—Cu_2O (0.2)	90	1	95
$EtCH(CO_2Et)_2$	20	MA	20	-NC (10)—Cu_2O (0.2)	90	2	50
$EtCH(CO_2Et)_2$	20	AN	20	-NC (10)—Cu_2O (0.2)	90	2	67
$PhCH_2OH$	30	MA	30	-NC (10)—Cu_2O (0.5)	90	5	50
$PhCH_2OH$	30	AN	30	-NC (10)—Cu_2O (0.5)	90	5	80
t-BuSH	30	AN	30	-NC (10)—Cu_2O (0.2)	70	1[e]	73
Me_2CHNO_2	30	MA	30	-NC (10)—Cu_2O (0.2)	80	1[f]	70
Indene	50	MA	50	*t*-BuNC (30)—Cu_2O (1)	90	4	50[c]
$MeCH(COCH_3)_2$	10	$CH{\equiv}CCO_2Et$	15	*t*-BuNC (5)—Cu_2O (0.2)	r.t.	24[g]	78[d]
$MeCH(COCH_3)_2$	20	AN	15	**1**[i] (1)	r.t.	6[h]	86

a) A mixture of an active hydrogen compound, α,β-unsaturated compound, isocyanide, and cuprous oxide was heated at 90°C otherwise e, f, g, h.
b) MC: Methyl crotonate, MA: Methyl acrylate, AN: Acrylonitrile.
c) The adduct was 3-(carbomethoxyethyl)indene.
d) The adduct was $(CH_3OC)_2C(CH_3)CH{=}CHCO_2Et$ (*cis*/*trans*=1/1).
i) **1** : $C_5H_5Cu(CN\text{-}Bu^t)$

parison of the product yields between the reaction of acrylonitrile (AN) and methyl acrylate (MA) suggests that the olefin component having cyano group at the olefin carbon atom is more reactive than the one bearing carbomethoxyl group. Selective activation of cyano-olefin will be discussed later. As a reaction intermediate, an organic complex of copper derived from the active hydrogen compound might be postulated. Requisiteness of isocyanide for the catalyst activity suggests an organic complex of copper having an essential ligand of isocyanide. In the reaction of indene, a cyclopentadiene homologue, an indenyl copper complex can be assumed to be the intermediate. In fact, we have isolated a cyclopentadienyl copper isocyanide complex (**1**) from Cu_2O, cyclopentadiene and *t*-butyl isocyanide.[10]



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An organocopper complex **1** has been found to cause the Michael addition reaction (See Table 1).

Table 2 shows that Cu_2O, $Cu(acac)_2$ and metallic copper are effective as the metallic component in combination with isocyanide. CuO, CuCl, and $CuCl_2$ are much less effective. Besides copper compounds, $Co(acac)_2$ is shown to be fairly effective. The results of the competitive reaction between AN and MA well characterize the Cu_2O - isocyanide system. The rate ratio k_{AN}/k_{MA} changes according to the nature of the catalyst. In the reaction by the Cu_2O-isocyanide system, the rate of AN is much higher than that of MA. The high values of the rate ratio k_{AN}/k_{MA} may be explained by the preferential coordination of AN onto copper in a copper isocyanide complex of a key intermediate. It is reasonable to assume that the coordination of AN by means of the cyano group is stronger than the coordination of MA. The effect of coordination might be explained by the following scheme 1.

$$\underset{\mathbf{2}}{\mathrm{Cu^{I}(R^{1}NC)_{\mathit{a}}L_{\mathit{b}}}} \xrightleftharpoons{\mathrm{R^{2}H(-LH)}} \underset{\mathbf{3}}{\mathrm{R^{2}Cu(R^{1}NC)_{\mathit{c}}}} \xrightleftharpoons{\mathrm{Olefin}}$$

$$\underset{\mathbf{4}}{\mathrm{R^{2}Cu(Olefin)(R^{1}NC)_{\mathit{e}}}} \xrightarrow{\mathrm{R^{2}H}} \text{Michael adduct} + \mathbf{3} \qquad (1)$$

$$(a+b \leqq 4,\ 1 \leqq c \leqq 3,\ 1 \leqq e \leqq 2)$$

The complex of copper compound and isocyanide (**2**) reacts with an active hydrogen (R^2H) to form an

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[10] T. Saegusa, Y. Ito, and S. Tomita, *J. Amer. Chem. Soc.*, **93**, 5656 (1971).

TABLE 2. EFFECT OF METAL COMPONENT OF CATALYST SYSTEM[a)]

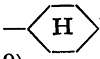
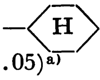
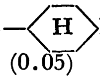
Copper component	(mmol)	Adduct yield (%)
Cu_2O	0.14	95
$Cu(acac)_2$	0.14	77
Cu	0.31	43
CuO	0.25	10
CuCl	0.22	trace
$CuCl_2$	0.14	trace
Other metal components	**(mmol)**	**Adduct yield (%)**
$Co(acac)_2$	0.20	27
Ag_2O	0.20	4
HgO	0.20	0
NiO	0.20	0

a) A mixture of diethyl malonate (10 mmol), methyl crotonate (10 mmol), cyclohexyl isocyanide (10 mmol), and the metal component was heated at 90°C for 9 hr.

organic complex of copper **3**. Replacement of a ligand of **3** by olefin gives rise to the formation of key intermediate **4**, in which the nucleophilic attack of R^2 ligand onto the coordinated olefin occurs in the sphere of ligands. In **4**, the coordination of olefin by means of cyano group will decrease the electron density of olefin bond and increase the electrophilic nature of olefin. In the competitive reaction, the higher rate of AN is due to the fact that the concentration of the complex species **4** of AN is higher than that of the corresponding species of MA. The coordination of olefin to copper/isocyanide complex has not been well established. However, UV absorption bands at 360 mμ of AN - Cu_2O - isocyanide system and at 325 mμ of MA - Cu_2O - isocyanide system might be due to the corresponding complexation. These absorptions were not observed in any single component system or in any combination of two components. Exact assignment of these bands requires further studies. Scheme-1 has been partly supported by some kinetics characters. Preliminary kinetic study was carried out on the reaction of MA with methylacetylacetone (MeAc) in the presence of the $Cu(acac)_2$ - cyclohexyl isocyanide system. As a copper component, copper acetylacetonate was employed in order to insure the homogeneousness of the reaction system. Kinetics has not been fully analyzed, and some fragmentary results which fit Scheme-1 are mentioned. Fig. 1 illustrates a strange dependence of the reaction rate upon the concentration of active hydrogen compound of MeAc. As the concentration of MeAc is increased, the rate first increases and then decreases after reaching a maximum. This exhibits a striking contrast to the corresponding relation in the base catalyzed Michael addition.[11)] Anomalous change of the rate in Fig. 1 may be explained by the scheme involving coordination complexes. According to Scheme-1, the concentration of methylacetylacetonyl ligand will increase with the increase of the concentration of MeAc. However, the increase of MeAc concentration will be unfavorable to the coordination of olefin onto copper, and hence it decreases the concentration of the key intermediate of **4**. The decrease of concentration of **4** gives rise to the decrease of rate. The first order dependence of the rate upon the MA concentration is shown in Fig. 2, which is explained by an assumption that the equilibrium constant of the MA coordination onto copper is small and the concentration of **4** is regarded as being nearly proportional to the initial feed concentration of MA.

$$\mathbf{3} + \text{Olefin} \rightleftarrows \mathbf{4} + \text{isocyanide}$$

TABLE 3. RELATIVE REACTION RATES OF ACRYLONITRILE (AN) AND METHYL ACRYLATE (MA) IN THE MICHAEL REACTION WITH VARIOUS CATALYSTS

Feed composition					Reaction condition			
Active hydrogen compd.	(mmol)	Catalyst (mmol)	AN, MA[c)] (mmol)	Toluene (ml)	Temp. (°C)	Time (min)	Conv.[d)] (%)	k_{AN}/k_{MA}[e)]
$MeCH(COMe)_2$	15	Cu_2O (0.3)—NC (4.5)	15	20	80	5	0.91	5.47
	15	EtONa (0.9)	15	20		7	1.65	0.198
	3	Et_3N (10)	30	0		15×60	2.10	0.855
$EtCH(CO_2Et)_2$	2	Cu_2O (0.5)—NC (20)	40	0	room temp.	60	<2.5	15.8
	2	*t*-BuOK (0.05)[a)]	40	0		2	<2.5	1.70
	2	*t*-BuONa (0.1)[b)]	40	0		2	<2.5	0.536
$PhCH_2OH$	2	Cu_2O (0.5)—NC (20)	40	0	room temp.	10	<2.5	7.80
	2	$PhCH_2OK$ (0.05)	40	0		7	<2.5	2.51
	2	$PhCH_2ONa$ (0.1)	40	0		2	<2.5	0.95

a) 0.05 mmol of *t*-BuOK in 0.3 m*l* of *t*-BuOH.
b) 0.1 mmol of *t*-BuONa in 0.23 m*l* of *t*-BuOH.
c) An equimolar amount of AN and MA was used.
d) Conversion percent was based on the consumption of combined amount of AN and MA.
e) The ratio of AN and MA.

[11)] K. T. Finley, D. R. Call, G. W. Solovocool, and W. J. Hayles, *Can. J. Chem.*, **45**, 571 (1967).