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SYNTHETIC REACTIONS BY COMPLEX CATALYSTS—XXI[1]

COPPER CATALYZED REACTIONS OF ALLYL ISOCYANIDE. ISOMERIZATION AND REACTIONS WITH AMIDE, AMINE AND ALCOHOL

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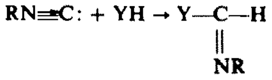
Abstract—Two groups of reactions of allyl isocyanide in the presence of copper (I), namely the double-bond isomerization of allyl isocyanide (AIC) to propenyl isocyanide (PPIC) (eq. 1), and formimidations of amide, amine and alcohol with AIC are described. The reaction of N-alkylamide with AIC gave the product by the insertion of the isocyanide carbon atom of PPIC into the $>$N—H bond of amide (eq. 3). In the formimidation of secondary amine with AIC, the AIC isomerization occurs concurrently, and two products (**13** and **14**) are formed. The reaction of alcohol with AIC gave the product by 1,4-addition of the second molecule of alcohol to the primary formimidation product.

THE PRESENT study is concerned with the Cu(I) catalyzed reaction of allyl isocyanide (AIC). Two groups of reactions are described here. The first is the double-bond isomerization of AIC (**1**) to propenyl isocyanide (PPIC, **2**) (eq. 1).

$$\underset{\mathbf{1}}{CH_2{=}CHCH_2N{\equiv}C{:}} \xrightarrow{Cu_2O} \underset{\mathbf{2}}{CH_3{-}CH{=}CH{-}N{\equiv}C} \qquad (1)$$

The second group is the Cu(I) catalyzed reactions of AIC with amide, amine and alcohol. During these reactions, the isomerization of AIC occurs concurrently, and the product due to PPIC is formed. In the Cu(I) catalyzed reactions with amide and alcohol, the behavior of PPIC differs from that of the usual saturated alkyl isocyanide.

Recently we have reported[1–5] a series of new reactions of isocyanide with Cu catalyst, in which the terminal carbon atom of isocyanide is inserted between Y—H bonds as shown below to produce the respective derivatives of a hypothetical "formimidic acid", HC(=NR)OH (eq. 2).



$$RN{\equiv}C{:} + YH \rightarrow Y{-}\underset{\underset{NR}{\|}}{C}{-}H \qquad (2)$$

$$(Y{=}R'_2N,\ R'_2P,\ R'O,\ R'S,\ R'_3Si)$$

These reactions are called "formimidation".[6] PPIC is an α,β-unsaturated isocyanide, and its specific reactivity in formimidation is given here.

RESULTS AND DISCUSSION

Isomerization of allyl isocyanide to propenyl isocyanide

In the presence of a catalytic amount of Cu_2O. AIC (**1**) isomerizes readily to PPIC at room temperature.

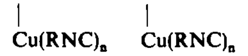
$$\underset{\mathbf{1}}{CH_2{=}CHCH_2NC} \xrightarrow{Cu_2O} \underset{\mathbf{2}}{CH_3CH{=}CHNC} \qquad (1)$$

Under N_2 a mixture of AIC (24 mmoles) and Cu_2O (0·7 mmole) was stirred for 3 hr. The IR band at 2150 cm^{-1} due to $\nu_{N\equiv C}$ of AIC disappeared rapidly in a few min even at 0° and a new band at 2120 cm^{-1} appeared. The lower frequency band is taken to suggest the formation of α,β-unsaturated isocyanide on the basis of the band of a reference compound. vinyl isocyanide whose $\nu_{N\equiv C}$ band is at 2128 cm^{-1}. By IR and NMR spectrum analysis, the distillate was shown to consist entirely of PPIC. The reverse isomerization of PPIC to AIC was not observed in the heat-treatment mixture of PPIC (24 mmoles) with Cu_2O (0·7 mmole) at 80° for 24 hr. As will be reported in a separate paper, however, the isomerization is not always irreversible.

The isomerization of AIC is conveniently utilized for the synthesis of PPIC. PPIC is an ill-smelling liquid as is usual for isocyanides. On contact with air at room temp. it colors gradually and deposits a yellow insoluble polymeric material. PPIC can be kept unchanged at $-15°$ under N_2.

Besides Cu_2O, metallic Cu powder, CuO, $Cu(acac)_2$ and $Cu(OMe)_2$ are also effective. CuO is known to be easily reduced to Cu_2O by isocyanide. Therefore, the active species of the CuO catalyzed reaction may be Cu_2O. The valence of catalyst species in the metallic Cu catalyzed reaction has not been elucidated. CuCl. $CuCl_2$. $Cu(NO_3)_2 \cdot 3H_2O$. CuBr, CuI, CuSCN and CuCN, however, did not cause the isomerization even after one month at room temperature. When AIC was admixed with an equimolecular amount of CuCl in C_6H_6 at room temp, the specific smell of AIC was mostly lost probably by its coordination to CuCl. By treatment with KCN. AIC was recovered unchanged. In the presence of base, however, CuCl causes the isomerization as will be discussed later.

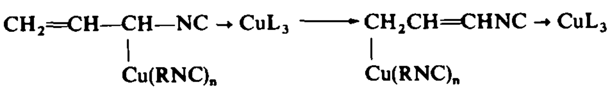
The isomerization of AIC to PPIC is interestingly compared with the isomerization of allyl cyanide (**3**) to crotononitrile (**4**) by the catalyst system of Cu_2O-alkyl isocyanide.[7] For the **3** to **4** isomerization, a mechanistic scheme involving cyanoallyl copper complexes (**5** and **6**) having an isocyanide ligand as the key intermediates has been presented.[7]



$$CH_2{=}CH{-}\underset{Cu(RNC)_n}{\underset{|}{CH}}{-}CN \longrightarrow \underset{Cu(RNC)_n}{\underset{|}{CH_2}}{-}CH{=}CHCN$$

5 **6**

In the AIC to PPIC isomerizaton, isocyanoallyl copper complexes (**7** and **8**) may also be assumed to be present.

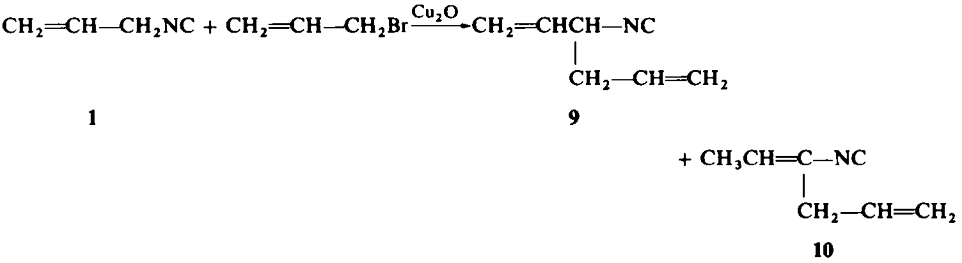


$$CH_2{=}CH{-}\underset{Cu(RNC)_n}{\underset{|}{CH}}{-}NC \to CuL_3 \longrightarrow \underset{Cu(RNC)_n}{\underset{|}{CH_2}}CH{=}CHNC \to CuL_3$$

(L: ligand)

7 **8**

The isocyano group of the isocyanoallyl ligand in these complexes is not free but is probably coordinated to another Cu ion. Treatment of AIC with Cu_2O in the presence of allyl bromide at room temp produced a mixture of 3-isocyano-1.5-hexadiene (**9**) and 4-isocyano-1.4-hexadiene (**10**).



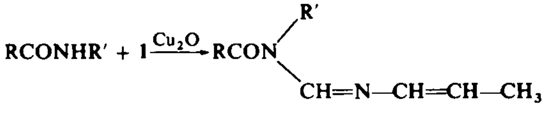
$$\mathrm{CH_2{=}CH{-}CH_2NC + CH_2{=}CH{-}CH_2Br \xrightarrow{Cu_2O} CH_2{=}CH\underset{\substack{|\\ CH_2-CH=CH_2}}{CH}{-}NC + CH_3CH{=}\underset{\substack{|\\ CH_2-CH=CH_2}}{C}{-}NC}$$

1 **9** **10**

In an experiment using 30 mmoles each of AIC and allyl bromide and 20 mmoles of Cu_2O in 10 ml of C_6H_6 at room temp for 24 hr, a mixture of **9** and **10** was obtained in 30% yield and **9**/**10** ratio was 74/26. This finding supports the mechanism of isomerization via the isocyanoallyl Cu complexes. Thus, the formation of **9** is reasonably explained by the coupling of an isocyanoallyl Cu complex **7** with allyl bromide. **10** is probably formed by the Cu_2O catalyzed isomerization of **9**.

Reaction of allyl isocyanide with amide

In the presence of Cu_2O, allyl isocyanide reacts with N-alkylamide to produce N—(N′-propenyl formimidoyl)amide (**11**) in fairly good yield (Table 1).

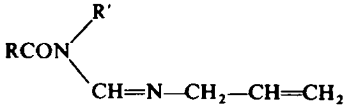


$$\mathrm{RCONHR' + 1 \xrightarrow{Cu_2O} RCON}\begin{matrix}\mathrm{R'}\\ \mathrm{CH{=}N{-}CH{=}CH{-}CH_3}\end{matrix} \qquad (3)$$

11

a: R = H. R′ = allyl
b: R – R′ = $-(CH_2)_5-$

By IR and NMR spectra as well as GLC analysis, the product **11** was shown to be a *cis*/*trans* mixture. The direct formimidation product having the structure **12** was not formed.



$$\mathrm{RCON}\begin{matrix}\mathrm{R'}\\ \mathrm{CH{=}N{-}CH_2{-}CH{=}CH_2}\end{matrix}$$

12

The formation of **11** is realized as the formimidation of amide with the isomerized isocyanide, PPIC. This assumption is quite consistent with the fact that the Cu(I) catalyzed formimidation of N-alkylamide is possible with vinyl isocyanide but not with saturated alkyl isocyanide.[6] The structure of α,β-unsaturated isocyanide is common to vinyl isocyanide and PPIC.

TABLE 1. FORMIMIDATION OF AMIDE, AMINE AND ALCOHOL BY ALLYL ISOCYANIDE

Reagent[a]	(mmole)	Cu_2O (mmole)	Solvent	(ml)	Time (hr)	Temp	Yield (%)	cis/trans ratio of[d] product
Amide								
$CH_2{=}CH{-}CH_2NHCHO$	12	0·35	Toluene	4	12	r.t.	67[b]	–
ε-caprolactam	12	0·7	CH_2Cl_2	4	12	80	69[b]	4·4:1
Amine								
piperidine	12	0·35	CH_2Cl_2	4	24	r.t.	100[c]	2·5:1 (2·7:1)[f]
morpholine	6	0·35	Toluene	2	24	r.t.	100[c]	3·1:1 (3·2:1)[f]
pyrrole	14·5	0·7	CH_2Cl_2	3	12	r.t.	72[b]	--
Alcohol								
CH_3OH	25	0·35	CH_2Cl_2	3	8	r.t.	16[b]	
CH_3OH	25	0·35	CH_2Cl_2	3	8	80	75[b]	
CH_3OH[e]	25	0·35	CH_2Cl_2	3	12	80	80[b]	

[a] An equimolecular amount of allyl isocyanide was employed except for the last run

[b] Yield was determined by distillation

[c] By GLC. the yield was shown to be quantitative

[d] The cis/trans ratio of the product was determined from GLC analysis data

[e] As isocyanide. propenyl isocyanide (9 mmoles) was used

[f] The values in parentheses were the cis/trans ratio in the CuCl catalyzed reactions

Reaction of AIC with amine

In the reaction of AIC with secondary amine, two isomeric formamidine derivatives. **13** and **14**. are produced.

(4)

13 **14**

a: $-R- = (CH_2)_5$ (piperidine)
b: $-R- = (CH_2)_2O(CH_2)_2$ (morpholine)
c: $-R- = -CH{=}CH{-}CH{=}CH-$ (pyrrole)

Interestingly the ratio of the two products **13**/**14** is quite dependent upon the nature of the Cu. Table 2 illustrates the change of the product ratio by its nature. Cu_2O and $Cu(OMe)_2$ gave **14** exclusively in almost quantitative yields (Table 1 and 2). The AIC-morpholine reaction with CuCl produced **14** (37%). This result might be inconsistent with the fact that CuCl does not isomerize AIC to PPIC. However. it has been found that CuCl does isomerize AIC in the presence of amine. In Et_3N. CuCl isomerized AIC at room temp. In the formimidation. a reaction component of secondary amine itself may activate CuCl.

The product, **13** was not changed to **14** by heat treatment (80°) with CuCl. with Cu_2O. with CuCl–AIC and with Cu_2O–AIC. Namely, a possibility of the isomerization of **13** to **14** during the reaction has been eliminated. So the product ratio will be determined by the rate of the two competitive reactions of the formimidation with AIC and the isomerization of AIC catalyzed by Cu compounds. Since AIC to PPIC isomerization is irreversible and PPIC is much more reactive than AIC, the rate of formimidation with PPIC does not affect the product ratio.

TABLE 2. FORMIMIDATION OF MORPHOLINE WITH VARIOUS COPPER CATALYSTS[a]

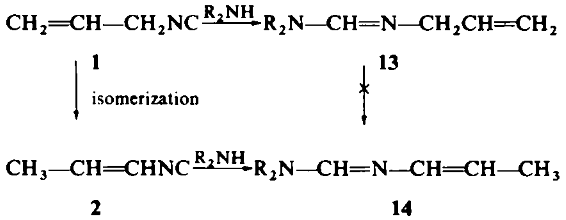
Catalysts	Yield	14/13 + 14[d]
Cu_2O	quantitative	1
$Cu(OMe)_2$	quantitative	1
$Cu(acac)_2$	quantitative	0·85
CuCl	quantitative	0·37
CuBr	quantitative	0·13
CuI	quantitative	0·093
CuSCN	quantitative	0·092
CuCN	41%[b]	0·090
CuCN[c]	quantitative	0·30

[a] A mixture of morpholine and AIC (each 6 mmoles) as well as a catalyst (0·3 mmole) in toluene (2 ml) was stirred at room temperature for 24 hr

[b] Yield determined by GLC analysis

[c] Performed at 80° for 12 hr

[d] Ratio determined from GLC analysis data



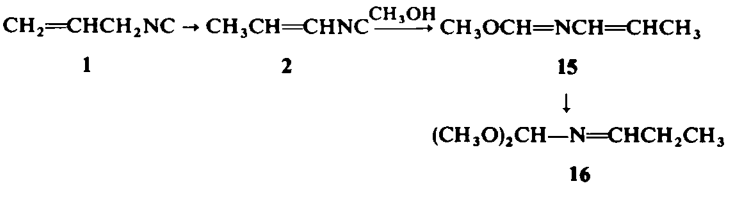
$$\begin{array}{ccc} \underset{\mathbf{1}}{CH_2{=}CH{-}CH_2NC} & \xrightarrow{R_2NH} & \underset{\mathbf{13}}{R_2N{-}CH{=}N{-}CH_2CH{=}CH_2} \\ \downarrow \text{isomerization} & & \not\downarrow \\ \underset{\mathbf{2}}{CH_3{-}CH{=}CHNC} & \xrightarrow{R_2NH} & \underset{\mathbf{14}}{R_2N{-}CH{=}N{-}CH{=}CH{-}CH_3} \end{array}$$

The fraction of **14** in **13** + **14** in Table 2 will give a qualitative measure of relative activity of Cu catalyst toward the AIC isomerization, and Cu compounds are arranged in the order of the value of **14/13** + **14**.

$$Cu_2O \approx Cu(OMe)_2 > Cu(acac)_2 \gg CuCl > CuBr > CuI \gtrsim CuSCN \gtrsim CuCN$$

Reaction of allyl isocyanide with alcohol

The AIC reaction with MeOH proceeds in the presence of Cu_2O to give N-propylidenedimethoxymethylamine (**16**). The reaction scheme involving an intermediate, **15**, the formimidation product of MeOH with PPIC, will reasonably explain



$$\underset{\mathbf{1}}{CH_2{=}CHCH_2NC} \rightarrow \underset{\mathbf{2}}{CH_3CH{=}CHNC} \xrightarrow{CH_3OH} \underset{\mathbf{15}}{CH_3OCH{=}NCH{=}CHCH_3} \qquad (5)$$
$$\downarrow$$
$$\underset{\mathbf{16}}{(CH_3O)_2CH{-}N{=}CHCH_2CH_3}$$

the formation of **16**. The 1,4-addition of MeOH to **15** gives rise to **16**. A reference experiment showed that **16** was actually produced in a quantitative yield in the Cu_2O catalyzed reaction of PPIC with MeOH. The same type of reaction was observed in the reaction of vinyl isocyanide with alcohol.[6]

TABLE 3. CHARACTERIZATION OF FORMIMIDATION PRODUCTS

Compd	b.p. (mm)	Formula	Anal. calcd % C	calcd % H	calcd % N	found % C	found % H	found % N	IR (neat) cm^{-1}	NMR. τ ($CDCl_3$)
11a	69 (1)	$C_8H_{12}N_2O$	63·13	7·95	18·41	62·56	7·93	18·44	1710 (C=O) 1650. 1625 (C=C. N=C)	1·50 (1H. s). 3·56 (1H. two sets of doublets). 8·15 (3H. two sets of doublets). 2·13 (1H. s. $\underline{\mathrm{H}}$CO—)
11b	101 (1)	$C_{10}H_{16}N_2O$	66·63	8·95	15·54	66·62	9·18	15·74	1687 (C=O) 1650. 1620 (C=C. N=C)	1·33 (1H. s). 3·32 (1H. two sets of doublets). 4·75 1H. p). 8·15 (3H. two sets of doublets)
13a	71 (1)	$C_9H_{16}N_2$	71·00	10·59	18·40	70·21	10·58	18·46	1650 (N=C) 3075. 995. 910 (C=C)	2·78 (1H. s). 4·2 (1H. m). 4·95 (2H. m). 6·15 (2H. d)
13b	83 (3)	$C_8H_{14}N_2O$	62·30	9·15	18·17	62·21	9·14	18·23	3178 (terminal olefin). 1653 (C=C. N=C)	2·68 (1H. s). 4·1 (1H. m). 4·8 (2H. m). 6·1 (2H. d)
14a	81 (1·5)	$C_9H_{16}N_2$	71·00	10·59	18·40	70·33	10·54	18·33	1623 (N=C) 1670. 1655 (C=C)	2·63 (1H. s). 3·53 (1H. two sets of doublets). 5·23 (1H. p). 8·17 (3H. two sets of doublets)
14b	75 (1)	$C_8H_{14}N_2O$	62·30	9·15	18·17	62·48	8·97	18·57	1650 (C=C) 1620 (N=C)	2·58 (1H. s). 3·4 (1H. two sets of doublets). 5·15 (1H. p). 8·17 (3H. two sets of doublets)
14c	96 ~ 97 (19)	$C_8H_{10}N_2$	71·61	7·51	20·88	71·76	7·57	21·13	1660 (C=C) 1630 (N=C)	1·95 (1H. s). 3·36 (1H. two sets of doublets). 4·66 (1H. p). 8·06 (3H. two sets of doublets)
16	116 ~ 120 (100)	$C_6H_{13}O_2N$	54·94	9·99	10·68	54·82	9·81	10·96	1665 (N=C) 1238 (—O—)	2·34 (1H. s). 5·78 (1H. t). 6·20. 6·71 (6H. s). 8·33 (2H. p). 9·11 (3H. t)

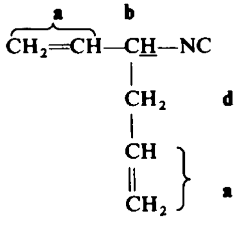
EXPERIMENTAL

Cu salts were commercial analytical reagents. Cupric methoxide[8] was prepared according toWicholas. Cu catalysts were dried under N_2 before use. Allyl isocyanide was prepared from allylformamide and phosgene according to Ugi.[9] and dried with molecular sieves 4A. bp 101 ~ 101·5°. ε-Caprolactam was a commercial reagent. Piperidine, morpholine and pyrrole were all commercial reagents, distilled over KOH.

Isomerization of AIC to PPIC. AIC (24 mmoles) and a catalytic amount of Cu_2O (0·7 mmole) were stirred under N_2 atm at room temp for 3 hr subjected to vac distillation (3 mm) at room temp and volatile material trapped at −78°. The condensate consisted of a single compound (GLC) shown by IR and NMR spectra to be PPIC. On redistillation, PPIC (80·5 ~ 81°, 60 ~ 70%) was obtained. IR (neat) 2120 (N≡C), 1650 cm^{-1} (C=C); NMR ($CDCl_3$) τ *ca.* 4·25 (2H, m, vinyl proton), 8·10 (3H, d, —$\underline{C}H_3$).

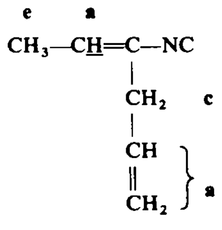
Reaction of AIC with amide, amine and alcohol. Reactions were carried out in a sealed tube under N_2. Products were isolated by vac distillation and purified by prep GLC. Structure was determined by IR and NMR spectra and elemental analysis. Identification data of products are summarized in Table 3.

Allylation of AIC by allyl bromide (**9** *and* **10**). A mixture of 20 mmoles Cu_2O, 30 mmoles of allyl bromide and 10 ml of C_6H_6 was stirred under N_2 at room temp for 5 min, then 30 mmoles of AIC added and the mixture stirred for 24 hr. Excess Cu_2O was filtered and washed with 20 ml of CH_2Cl_2 (unreacted Cu_2O 1·56 g). The filtrate was treated twice with 30 cc of 4N KCNaq. The organic layer was distilled and the fraction boiling at 80 ~ 85° 87 mm collected (0·96 g). By IR and NMR analysis, the distillate was shown to be a mixture of two isomeric isocyanides, **9** and **10**. IR: 2139 cm^{-1} (N≡C of **9**), 2118 cm^{-1} (N≡C of **10**), 1645 ~ 40 cm^{-1} (C=C of **9** and **10**), 990 and 925 cm^{-1} (terminal C=C of **9** and **10**).



$CH_2{=}CH{-}\underline{C}H(NC){-}CH_2{-}CH{=}CH_2$

9



$CH_3{-}\underline{C}H{=}C(NC){-}CH_2{-}CH{=}CH_2$

10

NMR ($CDCl_3$): **a**, τ = 4 ~ 5 (olefin proton of **9** and **10**); **b**, τ = 5·75 (methine proton of **9**); **c**, τ = 7·10 (CH_2 proton of **10**); **d**, τ = 7·65 (CH_2 proton of **9**); **e**, τ = 8·25 (doublet, Me proton of **10**). The peak area ratio of **b**:**d** = 1:2 and **c**:**e** = 2:3 were observed. The ratio of **a**:(**b** + **c** + **d** + **e**) = 10:8 was confirmed. From the peak area ratio of **d**:**c**, the product ratio of **9**/**10** = 74/26 was obtained.

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