Synthetic Reactions by Complex Catalysts. XXV.[1] The Copper-catalyzed Reaction of Allyl Isocyanide with Carbonyl Compounds and Olefins. Syntheses of 4-Vinyl-2-oxazoline and 5-Vinyl-1-pyrroline Derivatives

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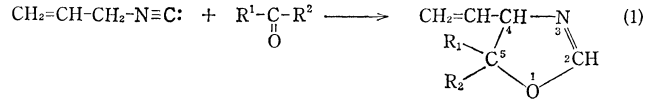
This paper describes two reactions of allyl isocyanide (AIC) by means of the Cu_2O catalyst; these reactions produce heterocyclic compounds with vinyl substituents. First, the reactions of AIC with such carbonyl compounds as ketones and aldehydes produce 4-vinyl-2-oxazoline derivatives (**1**) in good yields. Second, AIC also reacts with the C=C double bond of α,β-unsaturated nitriles and esters to produce 5-vinyl-1-pyrroline derivatives (**4**, **5**, and **6**). A mechanistic scheme involving an isocyanoallylcopper complex (**11**) has been assumed.

This paper will describe the Cu_2O-catalyzed reactions of allyl isocyanide (AIC) with carbonyl compounds (Eq. (1)) and with olefins (Eq. (2)). The products are 4-vinyl-2-oxazoline and 5-vinyl-1-pyrroline derivatives respectively. These synthetic reactions have been found



(1)

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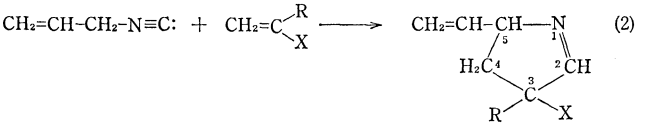
a. $R^1=R^2=CH_3$ **b.** $R^1=Me$, $R^2=Ph$
c. $R^1=R^2=-(CH_2)_4-$ **d.** $R^1=R^2=-(CH_2)_5-$
e. $R^1=H$, $R^2=Ph$ **f.** $R^1=H$, $R^2=i\text{-}Pr$



(2)

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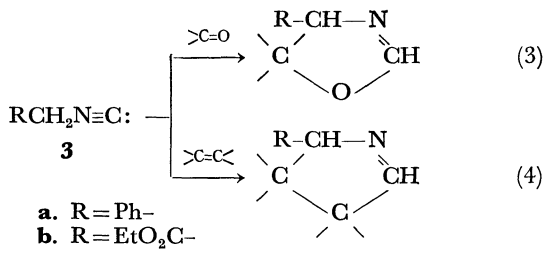
in a series of exploration studies of the catalytic behavior of the copper-isonitrile complexes.[2-4] Especially, they are closely related to our recent finding of oxazoline and pyrroline syntheses[4] in which benzyl isocyanide (**3a**) and carbethoxymethyl isocyanide (**3b**) are reacted with carbonyl compounds and with olefins respectively in the presence of Cu_2O as the catalyst (Eqs. (3) and (4)).



(3)

(4)

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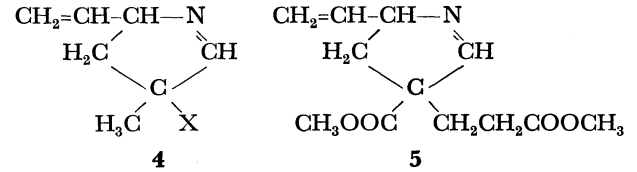
a. R=Ph-
b. $R=EtO_2C-$

Results and Discussion

Reaction of AIC with Carbonyl Compounds. Synthesis of 4-vinyl-2-oxazoline Derivatives. The results of the reaction of AIC with carbonyl compounds by means of the Cu_2O catalyst are shown in Table 1. 4-Vinyl-2-oxazoline derivatives (**1**) were obtained in high yields with high selectivities. Here, the oxazolines, **1b**, **1e**, and **1f**, are mixtures of the two diastereomers due to the 4-C and 5-C configurations. The ratios are given in Table 1.

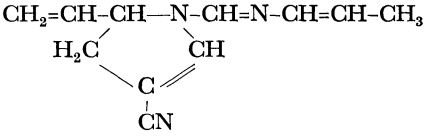
In this reaction, the isomerization of AIC to propenyl isocyanide (PPIC) takes place concurrently. After the reaction, the unreacted AIC was found to isomerize to PPIC. The IR spectrum of the lower-boiling fraction (at 5 mmHg, room temperature) from the reaction mixture showed an absorption at 2120 cm^{-1} of $\nu_{N\equiv C}$ of PPIC,[5] which differed from that of AIC ($\nu_{N\equiv C}$ at 2150 cm^{-1}). The isomerization from AIC to PPIC is, however, reversible. With the Cu_2O catalyst, PPIC was reacted with benzaldehyde to produce **1e** in an almost quantitative yield (Table 1). As will be mentioned later, the reversible isomerization of AIC⇄PPIC probably proceeds through the α-isocyano-organocopper complex (**11**), which is also the key intermediate in the reaction of AIC with carbonyl compounds to produce oxazoline derivatives.

Reaction of AIC with Olefins. Synthesis of 5-Vinyl-1-pyrroline Derivatives. The results of the Cu_2O-catalyzed reaction of AIC with α,β-unsaturated esters and nitriles are shown in Table 2. The derivatives of 1-



4 **5**

a. $X=COOCH_3$
b. X=CN



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1) Part XXIV: T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, This Bulletin, **45**, 496 (1972).
2) T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *J. Org. Chem.* **35**, 670 (1970).
3) T. Saegusa, Y. Ito, H. Kinoshita, and S. Tomita, This Bulletien, **43**, 877 (1970).
4) T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *J. Org. Chem.*, **36**, 3316 (1971).
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Table 1. Reactions of allyl isocyanide with carbonyl compounds[a]

Carbonyl compds (mmol)		Cu_2O (mmol)	Solvent toluene (ml)	Time (hr)	Yield[b] (%) of **1**	Isomers ratio[c]
Ketones						
acetone	(20)	0.7	5[d]	12	**a** ≈69	—
acetophenone	(20)	0.35	5	12[e]	**b** ≈60	66:34
cyclopentanone	(12)	0.7	4	24[e]	**c** ≈23	—
cyclopentanone	(12)	0.35	4	12	**c** ≈65	—
cyclohexanone	(12)	0.35	3	12	**d** ≈60	—
Aldehydes						
benzaldehyde	(20)	0.35	5	6	**e** ≈77	62:38
2-methylpropanal	(20)	0.35	5	12	**f** ≈75	66:40
benzaldehyde	(6)[f]	0.35	3	12	**e** ≈95	—

a) In the presence of Cu_2O, an equimolar mixture of allyl isocyanide and carbonyl compound in toluene was heated at 80°C unless otherwise described.
b) Determined by distillation.
c) Determined by NMR.
d) Benzene was used as solvent.
e) Reaction at room temperature.
f) Propenyl isocyanide instead of allyl isocyanide was used.

Table 2. Reaction of allyl isocyanide with olefins[a]

Olefins (mmol)		Cu_2O (mmol)	Solvent (ml)	Time (hr)	Yield[b] (%)	Isomers ratio[c]
Methyl methacrylate	(20)	0.35	C_6H_6 (3)	12	≈34	54:46
	(6)	0.35	C_6H_6 (3)	96	≈36	
	(6)[d]	0.35	C_6H_6 (3)	12	**4a** ≈ 9.8	
	(6)[d]	0.35	C_6H_6 (3)	96	≈33	
	(6)[d]	0.35	CH_2Cl_2 (3)	12	≈ 1.7	
Methacrylonitrile	(20)	0.7	C_6H_6 (5)	12	**4b** ≈24	55:45
Methyl acrylate	(20)	0.7	DMF (5)	12	**5** ≈73[e]	69:31
Crotononitrile	(20)	0.7	CH_3Ph (5)	12	**8** ≈62[f]	
					6 ≈23[f]	
Acrylonitrile	(10)	0.35	DMF (5)	24	**10** ≈trace	

a) An equimolecular mixture of allyl isocyanide and olefin was heated at 80°C.
b) Determined by glpc.
c) Determined by NMR.
d) Propenyl isocyanide instead of allyl isocyanide was employed.
e) Calculated on the basis of methyl acrylate.
f) Calculated on the basis of crotononitrile.

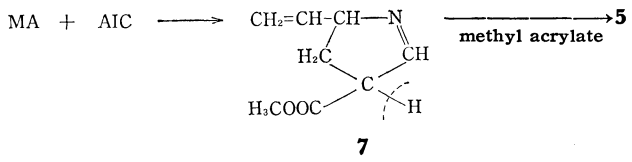
pyrroline, **4**, **5**, and **6**, were produced. In this reaction, **4a**, **4b**, and **5** were obtained as mixtures of the two isomers due to the 3-C and 5-C configurations (The ratios are given in Table 2).

As is shown in Table 2, the selectivity of the pyrroline synthesis by the AIC-olefin reaction is generally lower than that of the oxazoline synthesis shown in Table 1. The dimerization and polymerization of olefin by the Cu_2O-isonitrile system occur simultaneously, and together they decrease the pyrroline yield.

Similarly to the case of the reaction with carbonyl compounds, the isomerization of AIC to PPIC occurred concurrently. Sometimes PPIC was isolated from the reaction mixture of AIC by vacuum distillation (5 mmHg) at room temperature. Furthermore, the reversibility of AIC⇄PPIC isomerization was also demonstrated in tnis reaction; *i.e.*, **4a** was produced in the reaction of PPIC with methyl methacrylate. The conversion of PPIC to a dark tarry material disturbed the pyrroline formation. In the PPIC-olefin reaction, only a trace of unreacted PPIC remained, and the PPIC was converted mostly to a dark-brown tar. The strong tendency of PPIC to polymerize to a dark tar was observed also in an experiment isomerizing AIC to PPIC.[5]

As has been mentioned previously, the AIC-olefin reaction is not always clean. In the reaction of AIC with methyl acrylate, **5** was isolated as the main product; it was thought of as being formed by the Michael addition[3,4] of the first pyrroline product, **7**, to another molecule of olefin. Here, the first pyrroline product was not isolated. Probably the rate of the formation of **7** is slower than that of the Michael reaction of **7** with methyl acrylate.

In the case of crotononitrile, the main reaction was its dimerization. The dimerization of crotononitrile by the Cu_2O-isonitrile system has already been found by us.[2] In the AIC-crotononitrile-Cu_2O mixture, the crotononitrile dimerization suppressed the pyrroline formation (Table 2). In addition, the pyrroline product of



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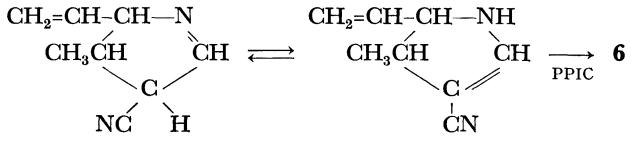
$$CH_3\text{-}CH{=}CH\text{-}CN \xrightarrow{Cu_2O/RNC} CH_3\text{-}CH{=}C(CH_3)\text{-}CH_2CN$$

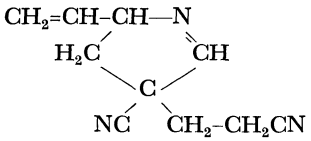
8

this reaction was **6**, which was explained as being derived from the primary product (**9a**) by the copper-catalyzed formimidation[6] of this tautomer (**9b**) with PPIC. The tautomerization of **9a**⇄**9b** has been found in our previous study of the pyrroline synthesis;[4] the copper-catalyzed formimidation of the >NH bond has also been reported.[6]



9a **9b**

In the reaction of AIC with acrylonitrile in benzene and DMF, only a trace of the pyrroline product, **10**, was detected by glpc (silicones; column temperature, 200°C). This was due to the polymerization of acrylonitrile by Cu_2O-isonitrile.[7] The polymerization of acrylonitrile by the Cu_2O-isonitrile system as well as the Cu_2O-isonitrile-active hydrogen compound system has been reported by us.[7]



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Reaction Scheme

On the basis of the scheme for the reactions of benzyl and carbethoxymethyl isocyanide with carbonyl and olefinic compounds, the following scheme may be presented for the reactions of AIC in the present study. First, the isocyanoallylcopper-isonitrile complex (**11**) is formed by the abstraction of α-hydrogen from AIC by Cu_2O. Probably, the coordination of the isocyano group of AIC to another copper complex facilitates the hydrogen abstraction by decreasing the electron density of the α-carbon atom. The α-isocyanoallylcopper complex (**11**) adds to the >C=O or >C=C< group to produce a new-formed copper species (Step 2), and the intramolecular reaction between the copper species and the isocyano group in **12** gives rise to the ring closure, thus producing **13** (Step 3). The abstraction of the α-hydrogen of another AIC molecule by **13** produces **11** and the final product, **14** (Step 4). Thus, the organocopper species is regenerated and the reactions proceed catalytically.

The α-isocyanoallylcopper complex acts as the key intermediate in the AIC⇄PPIC isomerization[5] also as is indicated in the scheme. The formation of **11** is supported by the fact that when the AIC-Cu_2O mixture was treated with allyl bromide, 3-isocyano-1,5-hexadiene (**15**) was isolated.[5]

$$\mathbf{11} + CH_2CH\text{-}CH_2Br \longrightarrow CH_2{=}CH(CH_2CH{=}CH_2)\text{-}NC$$

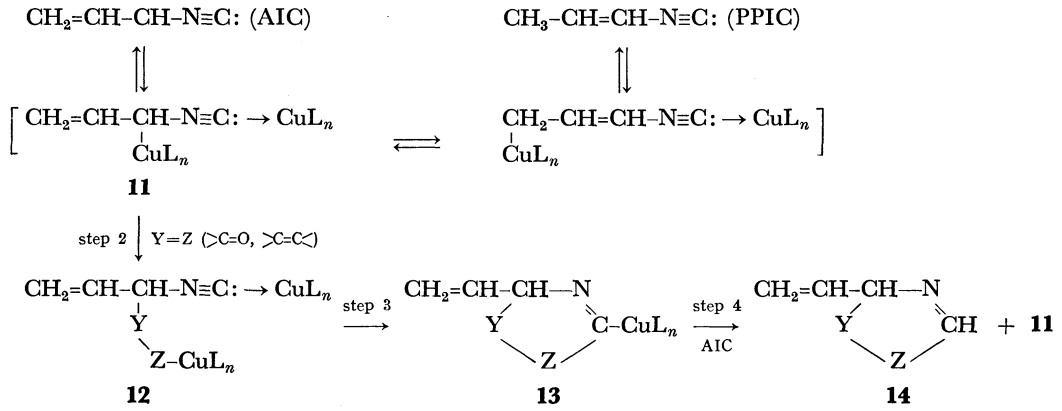
15

Experimental

Reagents. AIC was prepared according to Ugi's procedure,[8] while PPIC was prepared by the isomerization of AIC by the Cu_2O catalyst.[5] The carbonyl compounds were all commercial reagents and were purified by distillation under nitrogen. The α,β-unsaturated esters and nitriles were all commercial reagents which has been purified by distillation under nitrogen. The cuprous oxide was a commercial reagent of an analytical reagent grade and was dried under a nitrogen atmosphere prior to use.

Reactions with Carbonyl Compounds. An equimolecular mixture of isonitrile and carbonyl compounds and catalytic amounts of Cu_2O in benzene was reacted in a sealed test tube under nitrogen under the conditions shown in Table 1. The products were then isolated by vacuum distillation and purified by preparative glpc. The product structures were determined by IR, NMR, and elementary analysis. The identification data of the products are summarized in Table 3.

Reactions with Olefins. The reactions were carried out by a procedure similar to those used with carbonyl com-



11 **12** **13** **14**

6) a) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and H. Yoshioka, *Tetrahedron Lett.*, **1966**, 6121. b) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and H. Yoshioka, This Bulletin, **42**, 3310 (1969).

7) T. Saegusa, S. Horiguchi, and H. Fujii, Presented at the 19th Symposium of Polymer Science, Oct. 1970, Kyoto.

8) I. Ugi, *Angew. Chem.*, **77**, 492 (1965).

Table 3. Identifications of 2-oxazoline derivatives (**1**)

Compds	Bp (°C/mmHg)	Formula	Anal Calcd C	H	N	Found C	H	N	IR spectrum (neat) cm^{-1}	NMR, τ, ($CDCl_3$)
1a	85— 90/170	$C_7H_{11}NO$	67.17	8.86	11.19	66.91	8.93	11.39	3075, 1640 (C=C) 1625 (N=C) 930 (C=C)	8.56, 8.80(s, 6H, $-CH_3$), 5.86(d, 1H, >CH–N=), *ca.* 4.7(m, 3H), 3.2(broad s, 1H, –N=CH–)
1b	114/8	$C_{12}H_{13}NO$	76.96	7.00	7.48	76.88	7.03	7.35	1645 (C=C) 1628, 1630 (N=C)	8.21, 8.42(s, 3H, $-CH_3$), 5.45(broad d, 1H, >CH–N=), *ca.* 4.7(m, 3H), 2.9(1H, –N=CH–)
1c	65— 69/11	$C_9H_{13}NO$	71.49	8.63	9.26	71.56	8.73	9.34	3075 (C=C) *ca.* 1630 (C=C, N=C)	5.72(broad, d, 1H, >CH–N=), *ca.* 4.7(m, 3H), 3.15(1H, –N=CH–)
1d	75— 80/3	$C_{10}H_{15}NO$	72.69	9.15	8.48	72.24	9.46	8.50	3075, 1645, 935 (C=C), 1625 (N=C)	5.96(d, 1H, >CH–N=), *ca.* 4.6(m, 3H), 3.17(1H, –N=CH–)
1e	115—121/10	$C_{11}H_{11}NO$	76.27	6.40	8.09	75.80	6.61	7.94	1642 (C=C), 1608 (N=C)	5.60(broad, t, 1H) *ca.* 4.8 (m, 2H, $-CH=CH_2$), *ca.* 4.2 (m, 1H, $-CH=CH_2$), 3.05 (1H, –N=CH–)
1f	66— 70/46	$C_8H_{13}NO$	69.03	9.41	10.06	68.51	9.74	10.63	3075, 1645 (C=C) 1630 (NC)	5.75(broad, t, 1H) *ca.* 4.8, 4.2(m, 3H), 3.15(d, 1H, –CH=N–)

Table 4. Identifications of pyrroline derivatives

Compds	Bp (°C/mmHg)	Formula	Anal Calcd C	N	H	Found C	H	N	IR spectrum (neat) cm^{-1}	NMR, τ, ($CDCl_3$)
4a	50— 55/1	$C_9H_{13}NO$	64.65	7.84	8.38	64.67	8.12	8.50	3080, 645 (C=C) 1735 (C=O) 1635 (N=C)	8.57(d, 3H, >CH–CH_3), 6.25 (s, 3H, –O–CH_3), *ca.* 5.21(m, 1H, >CH–N=), *ca.* 4.8(m, 2H, $-CH=CH_2$), *ca.* 4.15(m, 1H, $-CH=CH_2$), 2.55(1H, –N=CH)
4b	55— 63/4	$C_8H_{10}N_2$	71.61	7.51	20.88	71.72	7.78	20.78	3080, 645 (C=C) 2232 (N≡C) 1628 (N=C)	8.57(d, 3H, >CH–CH_3), *ca.* 5.35(m, 1H, >CH–N=), *ca.* 4.85(m, 2H), *ca.* 4.20(m, 1H), 2.65(1H, –N=CH–)
5	135—136/2.5	$C_{12}H_{17}NO_4$	60.28	7.16	5.85	59.84	7.29	6.50	3080, 645 (C=C) 1738 (ester) 1625 (N=C)	7—8(m, 6H, $-CH_2-$), 6.62, 6.72(s, 6H, $-COOCH_3$), *ca.* 5.35(m, 1H, >CH–N=), *ca.* 4.8 (m, 2H, $-CH=CH_2$), *ca.* 4.1(m, 1H, $-CH=CH_2$), 2.52 (d, 1H, >CH=N–)
6	IR (neat) ; 3080 (C=C), 2202 (C≡N), 1650 (C=C), 1600 (N=C)									
	NMR ($CDCl_3$ τ); 8.69 (d, 3H, >CH–CH_3), 8.15 (d, 3H, CH_3–CH=), 7.06 (q, 1H, CH_3–CH<), 5.70 (t, 1H, >CH–N=), 4—5 (m, 4H, olefin protons), 3.45 (d, 1H, =N–CH=C<^{CH_3}), 2.60 (s, 1H, >N–CH=C(CN)–), 2.41 (s, 1H, N–CH=N)									
10	IR (neat) ; 3090, 1662, 985, 908 (C=C), 2200 (C≡N), 1630 (N=C)									

pounds under the conditions indicated in Table 2. The structures of **4a**, **4b**, and **5** were determined by IR, NMR, and elementary analyses. The identification of **8** was made by a comparison of its IR and NMR with those of an authentic sample.[2] The identification of **6** was made by means of its IR and NMR, while the structure of **10** was assumed on the basis of its IR spectra. The identification data of the AIC-olefin reaction products are summarized in Table 4.