Synthetic Reactions by Complex Catalysts. XXVI.[1] The Copper-catalyzed Reaction of α,β-Unsaturated Isocyanide with Active Methylene Compounds

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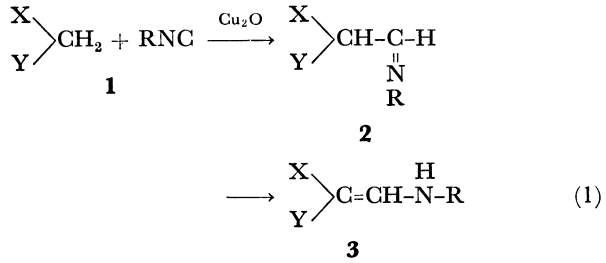
The Cu_2O-catalyzed reaction of α,β-unsaturated isonitrile with active methylene compound is described. Vinyl isocyanide (VIC) and propenyl isocyanide (PPIC) were employed as the isocyanide components. In addition, allyl isocyanide (AIC), which has been known to be rearranged readily to PPIC by Cu_2O, was also used as a precursor of PPIC. Five types of products were isolated and identified. These products were explained by a scheme starting with an intermediate of the organocopper-isonitrile complex (**9**) derived from the active methylene compound.

In a previous communication,[2] we have described a new formimidation of active methylene compounds with isonitrile in the presence of a *catalytic amount* of Cu_2O. In the formimidation, isonitrile is inserted between the C–H bond of active methylene compounds (**1**), thus leading to the transient species (**2**), which then rearranges readily to the tautomeric isomer (**3**) (Eq. (1)).



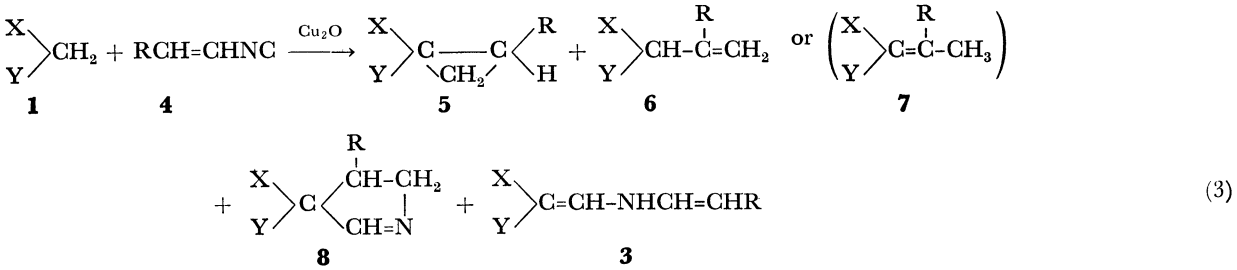
(1)

The formimidation was possible only with aryl and α,β-alkenyl isocyanides. Saturated alkyl isocyanide did not react with active methylene compounds under the conditions of our study.

When the amount of Cu_2O catalyst was increased in the reaction of alkenyl isocyanide with the active methylene compound, some other reactions occurred and the selectivity of the formimidation was lowered. The present paper will describe this reaction as a whole. As the α,β-unsaturated alkenyl isocyanides, vinyl isocyanide (VIP), and propenyl isocyanide (PPIC) were employed. In addition, allyl isocyanide (AIC) was used as a convenient precursor of PPIC, because it was known to be rearranged very readily to PPIC by the Cu_2O catalyst.[3]

$$CH_2{=}CHCH_2NC \rightarrow CH_3{-}CH{=}CHNC \qquad (2)$$

The types of products are **3**, **5**, **6** (or **7**), and **8**. The relative amounts of these products are dependent upon the nature of the active methylene compound.



(3)

a. X=Y=CO_2Et, R=H b. X=Y=CO_2Et, R=CH_3 c. X=COMe, Y=CO_2Me, R=H
d. X=COMe, Y=CO_2Et, R=H e. X=Y=COMe, R=H
f. X=C_6H_5, Y=CO_2Me, R=H g. X=C_6H_5, Y=CO_2Me, R=Me

Results and Discussion

In the reactions of alkenyl isocyanides (VIC, PPIC and AIC) with diethyl malonate in the presence of increasing amounts of the Cu_2O catalyst, cyclopropane derivatives of **5a** and **5b** were obtained in significant yields. Both PPIC and AIC gave the same product of **5b**. This fact can be well explained by the rapid isomerization of AIC to PPIC by Cu_2O (Eq. (2),) which takes place prior to the reaction with diethyl malonate. The amounts of olefinic products, **7a** and **6b**, were small. Presumbaly, **7a** was formed by the double-bond isomerization of **6a**.[4] Under the present reaction conditions, saturated alkyl isocyanide does not react with the active methylene compound.[1] The reactions of VIC with some other active methylene compounds (*i.e.*, methyl acetoacetate, ethyl acetoacetate and acetylacetone) were also examined. The results are shown in Table 1.

The relative ratios of **5** to the combined yield of the four products decrease as the acid strength of the active methylene compound is increased; *i.e.*, $CH_3COCH_2COCH_3$ — $CH_3COCH_2CO_2C_2H_5$ — $C_2H_5O_2C$-

1) Part XXV. T. Saegusa, I. Murase, and Y. Ito, This Bulletin, **45**, 830 (1972).

2) T. Saegusa, I. Murase, and Y. Ito, *Synthetic Commun.*, **1** (3), 145 (1971).

3) T. Saegusa, I. Murase, and Y. Ito, *Tetrahedron*, **27**, 3795 (1971).

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

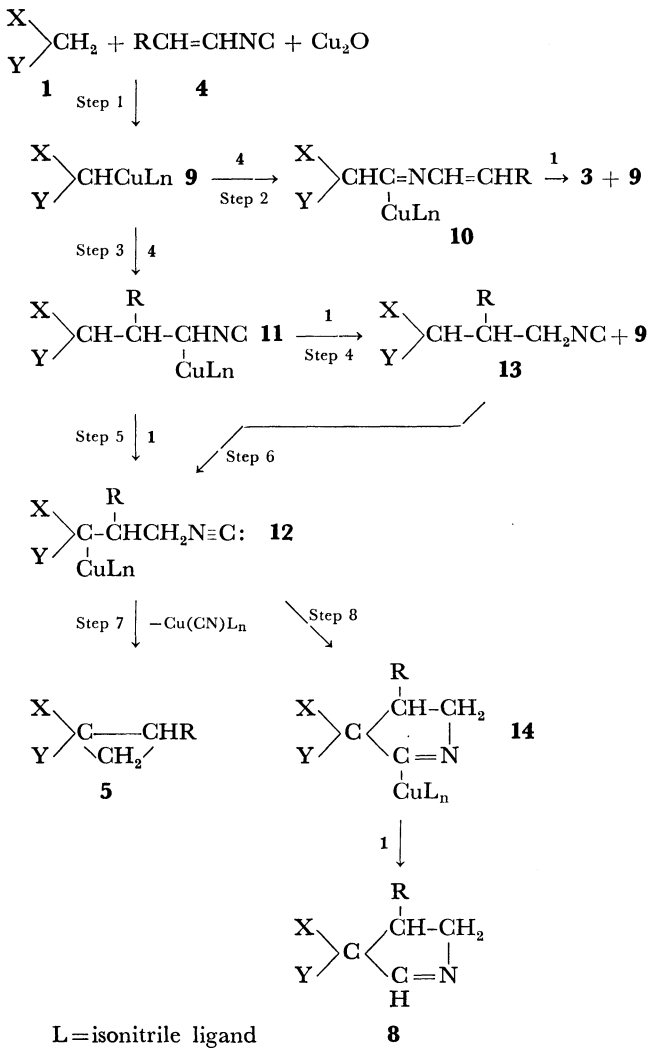
TABLE 1. Cu_2O-CATALYZED REACTION OF ISOCYANIDE WITH ACTIVE METHYLENE COMPOUNDS

Active methylene[a] compd.	Isocyanide (mmol)	Cu_2O (mmol)	Benzene (ml)	Time (hr)	Temp. (°C)	Yields[b] (%) 5	6 (or 7)	8	3
$CH_2(CO_2Et)_2$	VIC (12)	0.5	3	12	80	6	—	—	—
	AIC (12)	0.35	3	12	80	4.5	—	—	—
	VIC (15)	15	20	7	80	17	5[d]	—	—
	AIC (12)	12	20	7	80	47	3	—	5
	PPIC (12)	12	20	7	80	31	14	—	—
$MeCOCH_2CO_2Me$	VIC (15)	7.7	10	24	90	29	trace	14	14
$MeCOCH_2CO_2Et$	VIC (15)	7.7	10	3	80	17	trace	5	21
$MeCOCH_2COMe$	VIC (24)	12	20	48	r. t.	—	—	12	22
$PhCH_2CO_2Me$	VIC (15)	7.7	10[c]	12	80	14	—	18	—
	AIC (12)	6	10	8	80	—	3	—	—
							15b ≈ 27		

a) An equimolecular mixture of active methylene compounds and isonitrile was employed. VIC=vinyl isocyanide, AIC=allyl isocyanide, PPIC=propenyl isocyanide
b) The yield was based upon the amount of the product isolated by distillation.
c) The reaction was carried out in *N,N*-dimethylformamide.
d) The type of product was **7a**.

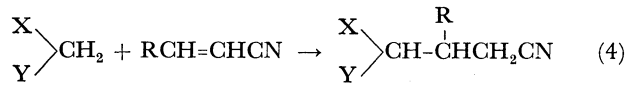
$CH_2CO_2C_2H_5$. Probably, active methylene compounds with more acidic hydrogen undergo formimidation more readily.

These products may be explained by the following reaction scheme.



The first step is the formation of an organocopper complex (**9**)[5], which possibly has the ligand of isonitrile (Step 1). The hydrogen abstraction from the active methylene compound (**1**) by Cu_2O-isonitrile has been proposed and well supported in the Michael-type addition reaction induced by the Cu_2O-isonitrile system.[5,6] The α,α-addition of organocopper of **9** to the terminal carbon atom of the isonitrile group gives **10**, which then abstracts a hydrogen atom from another molecule of **1** to produce the formimidation product, **3**, and the key intermediate of organocopper (**9**)[2] (Step 2).

The α,β-addition of organocopper of **9** to the olefinic double bond of alkenyl isocyanide affords **11** (Step 3), and the subsequent step of the hydrogen abstraction by **11** (Step 5) gives rise to the adduct, **13**, and the intermediate, **9**. The combination of Steps 3 and 4 corresponds to the addition of the active methylene compound to α,β-unsaturated isonitrile, which may interestingly be compared with the corresponding Michael addition to α,β-unsaturated nitrile[6] (Eq. (4)):



(4)

It has been reported[7] that the terminal carbon atom of the vinyl group of VIC has an increased electron density due to a canonical form of $^-CH_2-CH=\overset{+}{N}=C:$. The polarization character of VIC is opposite to that of acrylonitrile. Consequently, the nucleophilic addition to VIC may not be a favorable reaction. The addition of diethyl malonate to VIC was not observed in the presence of the *tert*-BuOK catalyst under the

5) T. Saegusa, Y. Ito, and S. Tomita, *J. Amer. Chem. Soc.*, **93**, 5656 (1971).
6) T. Saegusa, Y. Ito, S. Tomita, and G. Kinoshita, This Bulletin, **45**, 496 (1972).
7) a) D. S. Matteson and R. A. Baiely, *Chem. Ind.* (London), 191 (1967); b) D. S. Matteson and R. A. Bailey, *J. Amer. Chem. Soc.*, **90**, 3762 (1968).

Table 2. Identification data of products

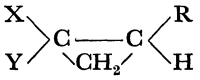
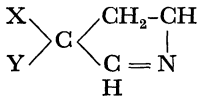
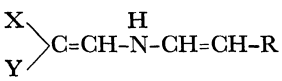
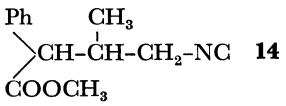
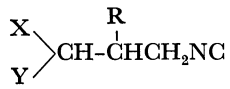
Compd.	Mass (*m/e*)	IR spectrum, neat (cm^{-1})	NMR absorption (τ)	Anal.
		 **5**		
5a bp. 65°C(6)	186(M^+), 159, 158, 141, 130, 114, 113, 112	3098, *ca.* 1730 1030	Ethyl proton, 8.56(s, 4H)	Authentic.[12]
5b bp. 63°C(4)	200(M^+), 172, 155, 144, 127, 126, 125	3098, *ca.* 1730 1034	Ethyl proton, *ca.* 8.10 (m, 1H), *ca.* 8.63(5H)	Found: C, 60.28; H, 8.25. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05.
5c bp. 60°C(5)	142(M^+), 127, 110, 111, 95, 82, 69, 59	3095, 1720, 1040	6.21(s, 3H), 7.52(s, 3H), 8.56(4H)	Found: C, 59.29; H, 7.07. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.07.
5d bp. 82°C(7)	156(M^+), 141, 128, 113, 111, 110, 86, 69	3098, 1720, 1030	Ethyl protons, 7.51(s, 3H), 8.48(4H)	Found: C, 60.91; H, 7.69. Calcd for $C_8H_{12}O_3$: C, 61.51; H, 7.75.
5f	176(M^+), 144, 117, 116, 115, 91	1715, 1603, 1300	Phenyl protons, 6.35(s, 3H), 8.35(m, 2H), 8.76(m, 2H)	
		Olefins		
7a	186(M^+), 171, 141, 140, 113, 95, 85	1729, 1650, 1450, 1059, 1030	2.90(q, 1H), 8.02(d, 3H), Ethyl protons	
6b	200(M^+), 155, 154, 149, 127, 108	1732, 1650, 1460, 1062, 1038, 925	3.02(t, 1H), 7.72(m, 2H), Ethyl protons, 8.82(q, 3H)	Found: C, 59.72; H, 8.17. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05.
6g	190(M^+), 158, 131, 130, 129, 115, 91	1722, 1638, 1050	Phenyl protons, 2.85(t, 1H), 6.24(s, 3H), 7.85(m, 2H), 8.92(q, 3H)	Found: C, 75.58; H, 7.47. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42.
				
8c	169(M^+), 138, 137, 110, 109, 96, 95	1738, 1643, 1518, 935	3.25(s, 1H), 6.33(s, 3H), 7.29(4H), 7.73(s, 3H)	Found: C, 56.47; H, 6.79; N, 8.08 Calcd for $C_8H_{11}NO_3$: C, 56.76; H, 6.55; N, 8.28.
8d	183(M^+), 138, 110, 109, 96	1738, 1640, 1515, 1120, 935	2.35(s, 1H), Ethyl protons, 7.25(4H), 7.70(s, 3H)	Found: C, 58.86; H, 7.30; N, 7.74. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65.
8e	153(M^+), 126, 111, 110, 96, 69	1715, 1670, 1610, 1512, 1125, 940	2.30(s, 1H), 7.21(4H), 7.70(s, 3H), 7.83(s, 3H)	Found: C, 62.25, H, 7.44; N, 9.30. Calcd for $C_8H_{11}NO$: C, 62.72; H, 7.24; N, 9.14
8f	203(M^+), 176, 144, 117, 116, 115, 103	1738, 1621, 1500, 1492, 1249, 700	2.18(s, 1H), Phenyl protons, 6.02(t, 2H), 7.2(m, 1H), 7.8(m, 1H), 6.28(s, 3H)	Found: C, 70.72; H, 6.36; N, 7.70. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89.
				
3b		1730, 1678, 1635, 1595, 1245, 1153, 1103, 1070, 912	−0.8(1H), 2.0(d, 1H, J=13.1 Hz), 3.81(t, 1H), 5.07(m, 1H), Ethyl protons, 8.30(3H)	

Table 2. (continued)

Compd.	Mass (*m/e*)	IR spectrum, neat (cm^{-1})	NMR absorption (τ)	Anal.
3c bp. 88°C(3)		3180, 1708, 1640, 1589, 1250, 1179, 1080, 980	−2.2(1H), 1.98(d, 1H, J=12.5 Hz), *ca.* 3.6, 5.2 (vinyl protons, 3H), 6.25 (s, 3H), 7.55 s, 3H)	
3d bp. 114°C(2)		3180, 1705, 1635, 1589, 1245, 1178, 1071, 980	−2.2(1H), 2.01(d, 1H, J=12.5 Hz), *ca.* 3.6, 5.4 (vinyl proton, 3H), ethyl protons, 7.50 (s, 3H)	Found: C, 59.24; H, 7.38; N, 7.43. Calcd for $C_9H_{13}NO_3$: C, 59.00; H,7.15; N, 7.65.
3e bp. 113—115°C(2)		1665, 1640, 1610, 1200, 1120, 1025, 971, 921	−2.25(1H), 2.12(d, 1H, J=12.5 Hz), vinyl proton, 7.50(s, 3H), 7.72(s, 3H)	Found: C, 62.51; H, 7.48; N, 9.12. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14.
		 **14**		
15g	217(M^+), 202, 190, 158	2148, 1735, 1610	2.61(5H, phenyl protons), 6.22(d, 1H), 6.35(s, 3H), 6.5—6.6(2H), 7.5(m, 1H), 8.8—9.4(3H)	Found: C, 71.99; H, 7.18; N, 6.36. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45.

conditions shown in Table 1. The polarization character of VIC, however, may be much changed by its coordination through the termical carbon atom of the isocyano group to copper. In each of the reaction mixtures of VIC and AIC with methyl phenylacetate with the Cu_2O catalyst, the Michael addition products, **15f** and **15g**, were actually isolated.



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f. X=C_6H_5, Y=CO_2Me, R=H
f. X=C_6H_5, Y=CO_2Me, R=Me

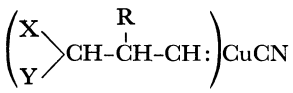
When the reaction of VIC with methyl phenylacetate was carried out in dimethylformamide, **15f** was not formed, but **5f** and **8f** were produced (see Table 1). Complex **12** is formed by the 1,3-rearrangement of **11** (Step 5) or from **13** (Step 6), which has an active hydrogen at the γ-carbon. The elimination of CuCN from **12** gives rise to the formation of **5** (Step 7). Step 7 is closely related to the following reaction of CuCN elimination:[8]

$$EtO_2CCH_2CH_2NC + \frac{1}{2}Cu_2O \rightarrow EtO_2CCH{=}CH_2 + CuCN + \frac{1}{2}H_2O$$

$$EtO_2CCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HNC + \frac{1}{2}Cu_2O \rightarrow EtO_2CCH{=}\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3 + CuCN + \frac{1}{2}H_2O$$

On the other hand, the insertion of the isocyano group into the carbon-copper band in **12** is a cyclization process[9] (Step 8) which produces **14**, which in turn abstracts hydrogen from another molecule of **1** to give **8** and **9**. The olefinic compound, **6**, is a minor product, whose formation has not yet been elucidated.

The production of olefin suggests another possibility for the formation of the cyclopropane derivative.



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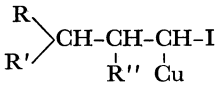
It seems likely that a carbene intermediate (**16**) is formed by the α,α-elimination from α-isocyanoorganocopper (**11**), which may be regarded as a kind of copper carbenoid. Kirmse and Wächtershäuser[10] reported that cyclopropane and olefin were obtained in the reaction of 1,1-diiodoneoalkanes with copper. This reaction has been explained in terms of a process involving a copper carbenoid (**17**).



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Experimental

Reagent. VIC was prepared according to Matteson's procedure.[7] AIC was prepared according to Ugi's procedure,[11] while PPIC was prepared by the isomerization of

8) T. Saegusa, Y. Ito, S. Tomita, and K. Goda, unpublished work.

9) T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *J. Org. Chem.*, **36**, 3316 (1971).

10) W. Kirmse and G. Wächtershäuser, *Tetrahedron*, **22**, 73 (1966).

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

AIC with a Cu_2O catalyst.[4] The active methylene compounds were all commercial reagents and were purified by distillation under nitrogen. The Cu_2O was a commercial reagent of an analytical reagent grade and was dried under nitrogen prior to use.

Reactions of Isonitriles with Active Methylene Compounds. A mixture of equimolecular amounts of isonitrile and an active methylene compound, together with Cu_2O in benzene, was heated under nitrogen. Then, the excess solid Cu_2O was removed by filtration and wahed with CH_2Cl_2. The filtrate and washings were combined and treated with a 4 N KCN aqueous solution. The organic layer was subjected to distillation under reduced pressure. The products were purified by preparative glpc. The product structures were determined by studying the IR, NMR, and Mass spectra and by elemental analysis. The identification data of the products are summarized in Table 2.

12) W. H. Perkin, *J. Chem. Soc.*, **47**, 807 (1885).