Synthetic Reactions by Complex Catalysts. XIX. Copper-Catalyzed Cycloaddition Reactions of Isocyanides. Novel Synthesis of Δ^1-Pyrroline and Δ^2-Oxazoline

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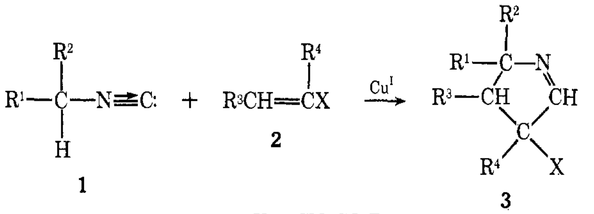
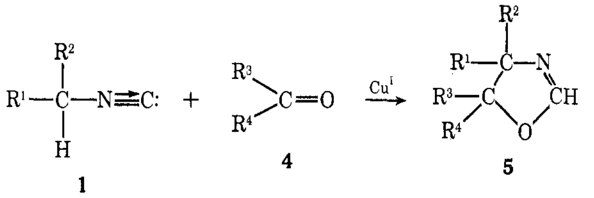
Isonitriles having an acidic hydrogen at the α-carbon atom such as benzyl isocyanide and carbethoxymethyl isocyanide have been found to react with the carbon–carbon double bond of α,β-unsaturated nitriles and carbonyl compounds in the presence of Cu_2O catalyst to produce Δ^1- (or Δ^2-) pyrroline derivatives in high yields. With Cu_2O catalyst, these isocyanides reacted also with the carbon–oxygen double bond of the carbonyl compound to produce Δ^2-oxazoline derivatives. Because of the high selectivity of the reaction in high yields, these two cycloaddition reactions are conveniently employed for synthetic purposes. Reaction schemes have been presented for these two reactions. An organocopper–isonitrile complex is first formed by the abstraction of the hydrogen of isonitrile by Cu_2O, and the organocopper complex adds to the C=C double bond and to the C=O double bond, respectively. The copper organic species thus formed react with the isonitrile group at the γ position to accomplish the ring closure.

For some years, we have been exploring the catalytic activity of copper–isocyanide complexes and have found several versatile reactions.[1–4] This paper describes novel and useful cycloaddition reactions of isocyanides containing acidic α hydrogen to the carbon–carbon double bonds of α,β-unsaturated carbonyl and nitrile compounds **2** (eq 1) and with the carbon–oxygen double bonds of carbonyl compound **4** (eq 2).


(1)

X = CN, CO$_2$R

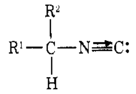
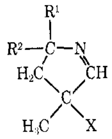

(2)

The reactions catalyzed by copper–isocyanide complexes, which have been hitherto found by us, are the dimerization of α,β-unsaturated carbonyl and nitrile compounds[2–4] and Michael addition reactions.[5] In the mechanistic scheme of the dimerization reaction,[3,4] an organocopper–isocyanide complex is first formed from the polar olefin and copper–isocyanide complex, and the addition of the organocopper complex to the second molecule of olefin is the essential step. In Michael addition reaction,[5] an organic complex of copper having an isocyanide ligand is formed from the acidic hydrogen component and copper–isocyanide complex, and the organic complex of copper–isocyanide then adds to the olefin. In both cases, isocyanide serves as a necessary ligand of the catalyst complex, but it is not incorporated into the products. The isocyanide component of the cycloaddition of the present study, however, has an acidic hydrogen and it is incorporated into the product. It assumes also the role of the essential ligand of the catalyst.

Reaction of Isocyanide with α,β-Unsaturated Carbonyl and Nitrile Compounds.—The results of the reaction of isocyanide having an active α hydrogen with α,β-unsaturated carbonyl and nitrile compounds by means of copper catalyst are shown in Tables I and II. Table I shows the results of the reactions with methacrylonitrile and methyl methacrylate. The products **3** are derivatives of Δ^1-pyrroline, and product yields are fairly high. (Identification data of the products are summarized in Table IV.) The products were obtained as mixtures of the two isomers due to the 3-C and 5-C configurations in **3**. Some of these isomer

TABLE I

Cu_2O-CATALYZED REACTION OF ISOCYANIDE WITH α-METHYL α,β-UNSATURATED ESTERS AND NITRILES[a]

 $R^1-C(R^2)(H)-N\equiv C:$ R¹	R²	$CH_2=C(CH_3)X$ X	 3 Yield, %	Isomer ratio[b]
Ph	H	CN	**3a**, 70	1.0/1.0[c]
		CO_2CH_3	**3b**, 94	1.0/1.0[d]
Ph	CH_3	CO_2CH_3	**3c**, 95	0.85/1.0[c]
		CN	**3d**, 85	1.0/1.0[c]
CO_2Et	H	CO_2CH_3	**3e**, 85	1.5/1.0[d]
		CN	**3f**, 31	0.4/1.0[d]

[a] A mixture of isocyanide (10 mmol), olefin (10 mmol), and Cu_2O (0.20 mmol) in benzene (3 ml) was heated under nitrogen at 80° for 3 hr. [b] The ratio of two configurational isomers due to C-3 and C-5 configuration. [c] Isomer ratio based on glpc and nmr analyses. [d] Isomers were not separated, and the ratios were based on nmr.

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[1] (a) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and H. Yoshioka, *Tetrahedron Lett.*, 6121 (1966); *Bull. Chem. Soc. Jap.*, **42**, 3310 (1969); (b) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and N. Takeda, *Tetrahedron Lett.*, 521, 1273 (1967); *Can. J. Chem.*, **47**, 1217 (1969); (c) T. Saegusa Y. Ito, and S. Kobayashi, *Tetrahedron Lett.*, 935 (1968); (d) T. Saegusa, S. Kobayashi, Y. Ito, K. Hirota, and Y. Okumura, *Bull. Chem. Soc. Jap.*, **41**, 1638 (1968); (e) 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.*, 273 (1968).

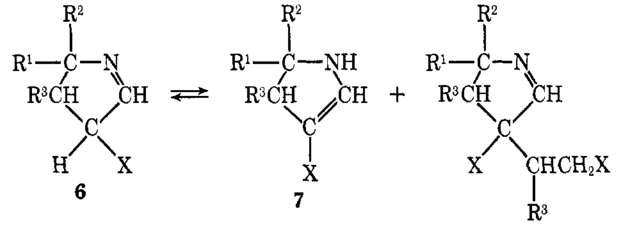
[3] T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, *J. Org. Chem.*, **35**, 670 (1970).

[4] T. Saegusa, Y. Ito, H. Kinoshita, and S. Tomita, *Bull. Chem. Soc. Jap.*, **43**, 877 (1970).

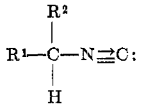
[5] T. Saegusa, Y. Ito, S. Tomita, and H. Kinoshita, unpublished work.

Table II

Cu_2O-Catalyzed Reaction of Isocyanide with α-Unsubstituted α,β-Unsaturated Esters and Nitriles[a]



6 **7** **8**



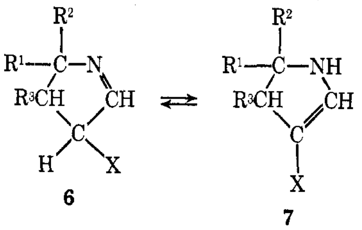
$$R^1-\underset{H}{\overset{R^2}{C}}-N\rightleftarrows C:$$

R^1	R^2	$R^3CH=CHX$		Yield, %	Tautomer ratio,[b]	Yield, %
		R^3	X (mmol)	(**6** + **7**)	**6**/**7**	(**8**)
Ph	H	H	CO_2Me (20)	(**6a** + **7a**) 5		**8a**, 75
Ph	Me	H	CO_2Me (20)	(**6b** + **7b**) 2~3	Mostly **6**	**8b**, 80
		H	CO_2Me (10)	(**6b** + **7b**) 22	Mostly **6**	**8b**, 39
		CH_3	CO_2Me (10)	(**6c** + **7c**) 60	2/1	c
		CO_2Me	CO_2Me (20)	(**6d** + **7d**) 28	4/5	c
CO_2Et	H	H	CO_2Me (20)	(**6e** + **7e**) 19	1/3	**8e**, 70
		H	CO_2Me (10)	(**6e** + **7e**) 57		**8e**, 2~3
		CH_3	CO_2Me (10)	(**6f** + **7f**) 30	1/4	c
		H	CN (10)	(**6g** + **7g**) 37	Trace/1	c
		CO_2Me	CO_2Me (20)	(**6h** + **7h**) 75	1/8	c

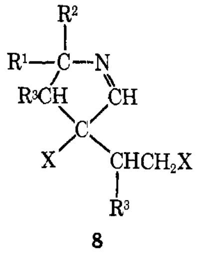
[a] A mixture of isocyanide (10 mmol), olefin, and Cu_2O (0.20 mmol) in benzene (3 ml) was heated under nitrogen at 80° for 3 hr. [b] The tautomer ratio was determined by nmr analysis. [c] Could not be isolated by distillation.

mixtures were separated by preparative glpc. The comparison of the nmr spectra of two isomers clearly indicates that they are configurational isomers.

The results of the reaction with α-unsubstituted α,β-unsaturated carbonyl and nitrile compounds are given in Table II, in which two kinds of products were obtained. The first one is a tautomeric mixture of Δ^1- and Δ^2-pyrroline derivatives (**6** and **7**) due to the migration of the 3-C hydrogen of **6**. The second one consists of 1 mol of isocyanide and 2 mol of olefin. The second product, shown to be **8**, arises by the secondary Michael addition of **6** (or **7**) to the second molecule of olefin. This was confirmed by a reference experiment in which **8e** ($R^1 = CO_2Et$; $R^2 = H$; $R^3 = H$; and $X = CO_2CH_3$) was produced in Michael addition of **6e** (= **7e**) with methyl acrylate in the presence of the Cu_2O–isocyanide catalyst. The alternative species **9** was not isolated. The relative ratio of the amounts of the products, **6** (or **7**)/**8** is controlled by the olefin/isocyanide ratio of the initial feed of the reaction. As expected, the production of **8** is favored when the olefin/isocyanide ratio is increased.



6 **7**



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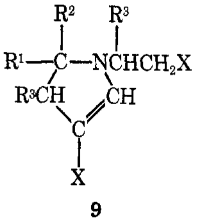

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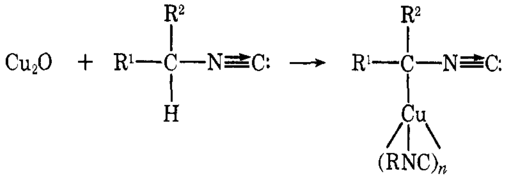
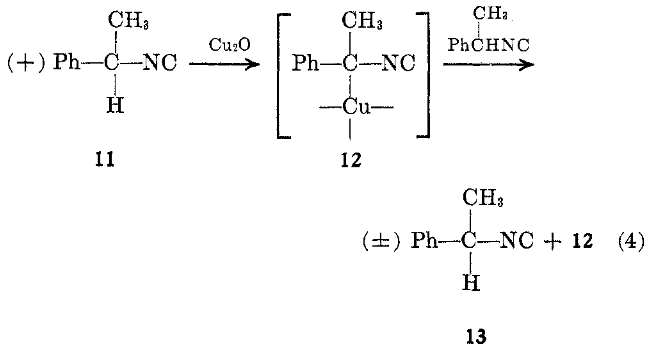
For the cycloaddition reactions in Tables I and II, Cu_2O was the most active among metal salts and oxides so far as examined. Copper(II) acetylacetonate and CuO showed considerable activity. Other copper compounds such as cupric and cuprous halides or acetate were inactive. Moreover, oxides of Ag, Fe(II), and Hg(II) were also inactive.

The key intermediate of the cycloaddition reaction is assumed to be an organocopper–isocyanide complex **10**, which is formed from isocyanide and Cu_2O. The α-acidic hydrogen is replaced by copper(I) having the ligand of other isocyanide molecules (eq 3). The isocyano group of the parent isocyanide whose acidic hydrogen has been replaced by copper may also coordinate to another copper. The formation of an intermediate organocopper–isocyanide complex **10** is supported by the finding that optically active α-phenylethyl isocyanide (**11**) is racemized readily at room temperature by Cu_2O (eq 4). It is reasonable to assume that racemization takes place by inversion of the carbanion of the organocopper–isocyanide complex **12**. Furthermore, the racemization rate of para-substituted phenylethyl isocyanide was dependent upon the nature of the substituent. The order of the racemization rate was p-Cl > H > p-MeO. This order is consistent with the assumption that the α-acidic hydrogen of phenyl-



$$Cu_2O + R^1-\underset{H}{\overset{R^2}{C}}-N\equiv C: \longrightarrow R^1-\underset{\underset{(RNC)_n}{Cu}}{\overset{R^2}{C}}-N\equiv C: \quad (3)$$

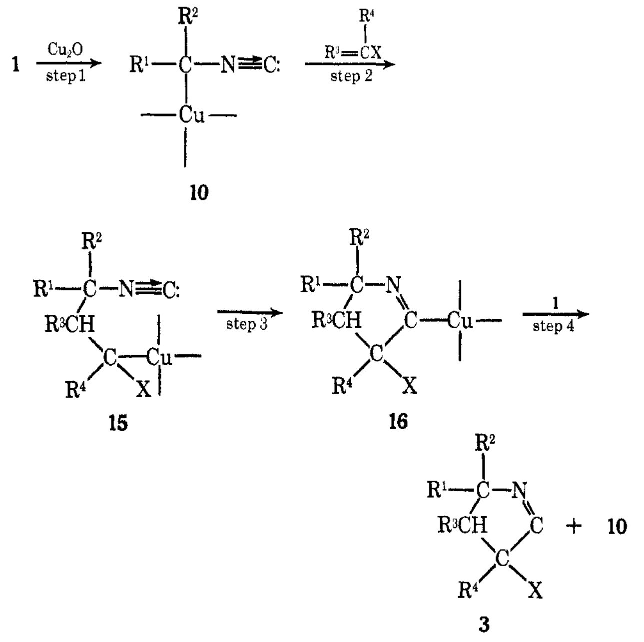
10



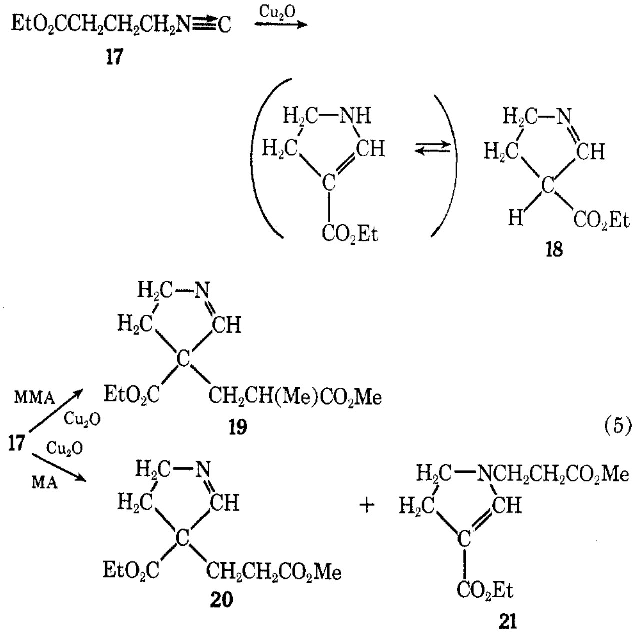
ethyl isocyanide is removed as proton to form an organocopper complex **12**. An organocopper–isocyanide complex has been assumed as the key intermediate in the reactions catalyzed by the copper–isocyanide complexes, *i.e.*, dimerization of α,β-unsaturated carbonyl and nitrile compounds[2-4] and in Michael addition reaction.[5] Especially the cyclopentadienyl-copperisocyanide complex **14**, which has been assumed in the Michael addition reaction of the cyclopentadiene homologs, was prepared and isolated from cyclopentadiene, *tert*-butyl isocyanide, and Cu_2O[6] [$(C_5H_5)Cu(I)$-(CN-*tert*-Bu) (**14**)].

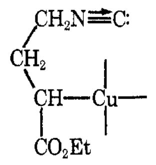
Scheme I, including the organocopper–isocyanide intermediate, may be presented for the copper-catalyzed cycloaddition of isocyanide with olefin. The organocopper–isocyanide complex **10** adds to the polar olefin to produce an intermediate **15**. In the complex **15**, a cyclization between the isocyanide group and the alkyl copper linkage gives rise to **16** (step 3), and the abstraction of a proton by **16** from the second molecule of **1** produces the final product **3** and **10** (step 4). From **10** thus produced, the second reaction cycle is initiated.

SCHEME I



Step 3 is worthy of particular attention; *i.e.*, the isocyanide group may have possibly been activated by coordination to another copper. An alternative reaction proceeding *via* the complex **15** has been realized, in which γ-carbethoxypropyl isocyanide **17** was cyclized by the treatment with Cu_2O. A tautomer mixture of 3-carbethoxy-Δ^1- and -Δ^2-pyrroline (**18**) was isolated in a yield of 19%. Further, when this reaction was carried out in the presence of methyl methacrylate (MMA) or methyl acrylate (MA), Δ^1- or Δ^2-pyrroline derivatives of **19–21**, which was regarded as secondary Michael addition products of **18** with MMA or with MA, were isolated in fairly good yields (eq 5). The hydrogen on the γ-carbon atom of **17** has an acidic character due to the carbethoxy group which is replaced by copper to produce organocopper complex **22**. The cyclization of the complex **22** is the same elementary reaction of step 3 in Scheme I. In the cyclization of **22**, the isocyanide group may have been coordinated to another copper.





22

The cyclization of **17** to **18** by copper catalyst is formally an insertion of the isocyanide group into the carbon–hydrogen bond. A series of copper-catalyzed insertion reactions of isocyanide have been found by us. The insertions of isocyanide into the N–H bond of amine,[1a] O–H bond of alcohol,[1b] P–H bond of phosphine,[1c] S–H bond of thiol,[1d] and Si–H bond of silane[1e] constitute a general reaction of "formimidation." The cyclization of **17** is an "intramolecular formimidation" and affords a significant extension of the isocyanide insertion. The isocyanide insertion into the carbo-hydrogen bond is possible only when the isocyanide group and active hydrogen are appropriately situated in a single molecule. The reaction between ethyl propionate and cyclohexyl isocyanide with Cu_2O catalyst did not occur. In addition, β-carbethoxyethyl isocyanide in which an acidic hydrogen is at the β position from the isocyanide group was not cyclized under the same conditions with Cu_2O catalyst.

Reaction of Isocyanides with Carbonyl Compounds.—The results of the reaction of isocyanide having an ac-

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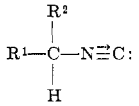
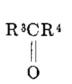
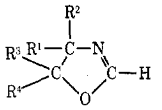
(6) T. Saegusa, Y. Ito, and S. Tomita, *J. Amer. Chem. Soc.*, in press.

tive hydrogen with the carbon–oxygen double bond of carbonyl compounds by means of copper catalyst are shown in Table III. The structure of the products of Δ^2-oxazoline derivatives were convincingly determined by ir and nmr spectra as well as elemental analysis. Except for the oxazoline obtained from benzyl isocyanide and acetone, all the products are mixtures of the configurational isomers due to the 4-C and 5-C configurations.

TABLE III

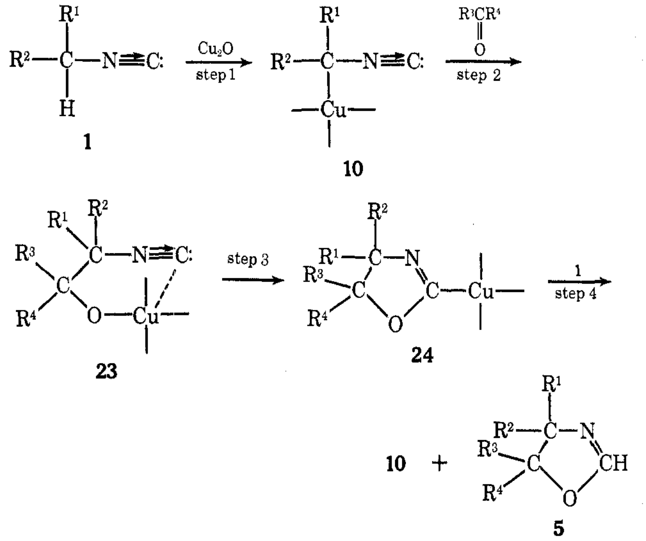
Cu_2O-CATALYZED REACTION OF ISOCYANIDE WITH CARBONYL COMPOUNDS[a]

 $R^1C(R^2)(H)N\equiv C{:}$ (10 mmol)		 $R^3C(=O)R^4$ (20 mmol)		Reaction time, hr	 **5** Yield, %	Isomer ratio
R^1	R^2	R^3	R^4			
Ph	H	Me	Me	3	**5a**, 60	
Ph	H	Ph	Me	3	**5b**, 75[b]	1.5/1.0[b]
Ph	H	$-(CH_2)_4-$		15	**5c**, 82	
Ph	H	*i*-Pr	H	1	**5d**, 85[b]	*d*
Ph	Me	Et	Me	15	**5e**, 41[b]	0.6/1.0[c]
CO_2Et	H	Ph	Me	3	**5f**, 75[b]	1.0/1.0[b]
CO_2Et	H	*i*-Pr	H	1	**5g**, 73[b]	*d*
CO_2Et	H	$-(CH_2)_4-$		15	**5h**, 57	

[a] A mixture of isocyanide (10 mmol), carbonyl compound (20 mmol), and Cu_2O (0.20 mmol) in benzene was heated under nitrogen at 80° for the indicated time. [b] Isomer ratio was determined by glpc. [c] Isomer ratio was determined by nmr. [d] Isomer ratio could not be determined.

Scheme II may be presented to explain the isocyanide–carbonyl reaction, in which the organocopper–isocyanide complex **10** is a key intermediate as in the isocyanide polar olefin reaction. The addition of **10** to the carbonyl group produces a copper alkoxide complex **23** (step 2), and the intramolecular reaction between the copper alkoxide and isocyanide groups in **23** is a cyclization process (step 3). The copper complex of the cyclized species **24** will abstract a hydrogen from the second molecule of **1** to afford the product of the Δ^2-oxazoline derivative and **10** (step 4). The reaction cycle is repeated from **10**.

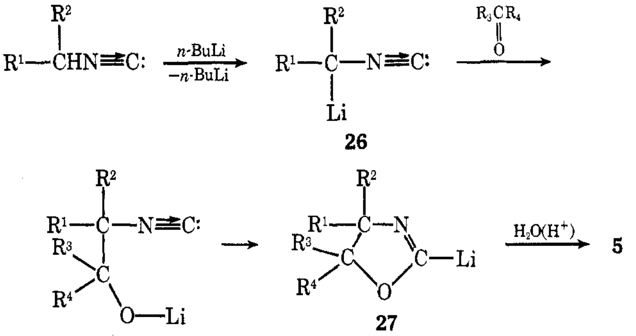
SCHEME II



Step 3 is regarded as the insertion of isocyanide into the copper–oxygen bond. This process may be taken to correspond to the copper-catalyzed reaction of isocyanide with alcohol[1b] in which the copper alkoxide–isocyanide complex **25** from Cu_2O, alcohol, and isocyanide plays an important role.

$$\mathrm{ROH + Cu_2O + R'NC \longrightarrow \underset{\mathbf{25}}{ROCu(R'NC)_{\it n}}}$$

The copper-catalyzed cycloaddition of isocyanides with carbonyl compounds is interestingly compared with the base-induced reaction of the same pattern. Schöllkopf, *et al.*,[7,8] reported two procedures. One was performed by means of alkyllithium. Alkyllithium abstracts the α hydrogen of isocyanide to give the α-lithio isocyanide **26** whose addition to the carbonyl compound followed by cyclization forms the lithio compound of oxazoline **27**. By this procedure, the usual alkyl isocyanides were allowed to react with carbonyl compounds. The second procedure was due to the use of the NaCN–EtOH system, which was applied only to carbethoxymethyl isocyanide. The reactions proceed catalytically in this case. Comparison between the copper-catalyzed cycloaddition and the usual base-catalyzed one is the subject of future studies.



Experimental Section

Reagents.—Benzyl isocyanide, α-phenylethyl isocyanide, and carbethoxymethyl isocyanide were prepared by Ugi's procedure using phosgene.[9] Cyclohexyl isocyanide was prepared by a method using phosphorus oxychloride.[10]

Reaction of Isocyanides with α-Methyl α,β-Unsaturated Carbonyl and Nitrile Compounds.—A mixture of isocyanide (10 mmol), olefin (20 mmol), and Cu_2O (0.2 mmol) in 3 ml of benzene was heated at 80° for 3 hr. The product was isolated by fractional distillation. The olefins employed were methyl methacrylate and methacrylonitrile. The products were a mixture of two configurational isomers. Some of these isomers were separated by glpc. The identifications are summarized in Table IV.

Reaction of Isocyanides with α,β-Unsaturated α-Unsubstituted Carbonyl and Nitrile Compounds.—The reactions were carried out under the same conditions as above. In the reactions of methyl acrylate with $PhCH_2NC$, with $PhCH(Me)NC$, and with EtO_2CCH_2NC, the glpc analysis of the reaction mixture showed two peaks, A and B, of products. The retention time of A was shorter than that of B. Analysis of the isolated sample showed that fraction A contains Δ^1- and Δ^1-pyrroline derivatives **6** and **7** and fraction B was the Michael adduct **8** of **6** with methyl acrylate. In the reactions of other olefins shown in Table II, only one glpc peak was observed, which corresponded to a tautomeric mixture of **6** and **7**. The identification data of the products are summarized in Table V.

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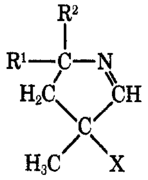
[7] F. Gerhart and U. Schöllkopf, *Tetrahedron Lett.*, 6231 (1968).
[8] D. Hoppe and U. Schöllkopf, *Angew. Chem.*, **80**, 290 (1970).
[9] I. Ugi, U. Fetzer, H. Knupfer, and K. Offermann, *ibid.*, **77**, 492 (1965).
[10] I. Ugi and R. Meyer, *Ber.*, **93**, 239 (1960).

TABLE IV

PRODUCTS FROM ISOCYANIDES AND α-METHYL α,β-UNSATURATED CARBONYL AND NITRILE COMPOUNDS[a]



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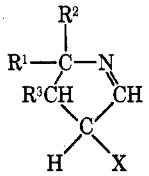
Compd	R^1	R^2	X	Bp, °C (mm)	Calcd (found)			Principal ir bands, cm^{-1}	Nmr, τ (in $CDCl_3$)	Isomer ratio
					C, %	H, %	N, %			
3a	Ph	H	CN	104–105 (2)	78.23 (78.18)	6.57 (6.66)	15.21 (14.94)	1615 (w), 2215 (w)	8.48 (s, CH_3), 7.80 and 7.46 (2 q, CH_2), 4.76 (t, each was d, $>$CH), 2.71 (s, Ph), 2.46 (d, N=CH)[a] 8.45 (s, CH_3), 8.27 and 7.02 (2 q, CH_2), 4.62 (t, each was d $>$CH), 2.71 (s, Ph), 2.51 (d, N=CH)[a]	1/1
3b	Ph	H	CO_2Me	101–102 (2)	71.86 (72.02)	6.96 (7.12)	6.45 (6.38)	1618 (w), 1724 (s)	8.59 and 8.56 (2 s, CH_3), 8.60–6.80 (m, CH_2), 6.32 and 6.31 (2 s, CO_2CH_3), 4.82 and 4.71 (2 t, each was d $>$CH), 2.78 (s, Ph), 2.48 and 2.38 (2 d, N=CH). A set of absorptions due to isomers are equal intensity	1/1
3c	Ph	CH_3	CO_2Me	86–88 (0.1)	72.70 (72.74)	7.41 (7.33)	6.06 (6.03)	1625 (w), 1732 (s)	8.49 and 8.36 (2 s, CH_3), 8.00 and 7.25 (2 d, CH_2), 6.42 (s, CO_2CH_3), 2.71 (s, Ph), 2.49 (s, N=CH)[a] 8.70 and 8.44 (2 s, CH_3), 8.00 and 7.25 (2 d, CH_2), 6.22 (s, CO_2CH_3), 2.71 (s, Ph), 2.49 (s, N=CH)[a]	0.85/1.0
3d	Ph	CH_3	CN	107–110 (0.7)	78.75 (78.66)	7.12 (7.11)	14.13 (14.02)	2226 (w), 1628 (w)	8.60 and 8.37 (2 s, CH_3), 7.89 and 7.25 (2 d, CH_2), 2.70 (s, Ph), 2.60 (s, N=CH)[a] 8.60 and 8.77 (2 s, CH_3), 7.89 and 7.25 (2 d, CH_2), 2.70 (s, Ph), 2.60 (s, N=CH)[a]	1/1
3e	CO_2Et	H	CO_2Me	85–87 (1)	56.32 (56.11)	7.09 (7.11)	6.57 (6.51)	1620 (w), 1720 (s)	8.66 (t, CH_3CH_2), 8.56 (minor) and 8.50 (major) (2 s, CH_3), 8.25–7.00 (m, CH_2), 6.22 (s, CO_2CH_3), 5.73 (q, CH_3CH_2), 5.15 (t, each of t was d, $>$CH), 2.46 (major) and 2.37 (minor) (2 d, N=CH)[b]	1.5/1.0
3f	CO_2Et	H	CN	112–113 (5)	59.98 (59.45)	6.71 (6.85)	15.55 (15.30)	1627 (w), 1720 (s), 2222 (w)	8.67 (minor) and 8.59 (major) (2 t, CH_3CH_2), 8.47 (s, CH_3), 8.20–7.00 (m, CH_2), 5.60 (q, CH_3CH_2), 5.10 (t, each of t was d, $>$CH), 2.45 (major) and 2.39 (minor) (2 d, N=CH)[b]	0.4/1.0

[a] Each of two configurational isomers was isolated by glpc. Their nmr absorptions are given here separately. Isomer ratio was calculated from glpc peaks and from the intensity ratio of the corresponding isomer absorptions by nmr of the isomer mixture. [b] Two isomers were not separated by glpc. Nmr data of a mixture of two isomers are given here. Isomer ratio was calculated from the nmr intensity ratio of the corresponding isomer absorptions.

TABLE V

PRODUCTS FROM ISOCYANIDES AND α-UNSUBSTITUTED α,β-UNSATURATED CARBONYL AND NITRILE COMPOUNDS



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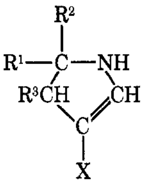

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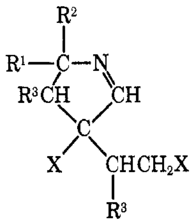


8

Compd, major (minor)	R^1	R^2	R^3	X	Bp, °C (mm)	Calcd (found)			Principal ir bands, cm^{-1}	Nmr, τ (in $CDCl_3$)[a]	Tautomer ratio[b]
						C, %	H, %	N, %			
6a (**7a**)	Ph	H	H	CO_2Me	Preparative glpc				1595 (s), 1675 (s), 1730 (s), 3310 (s)		
8a	Ph	H	H	CO_2Me	161–163 (0.1)	66.42 (66.17)	6.62 (6.74)	4.84 (4.98)	1615 (w), 1726 (s)	8.00–7.50 (m, CH_2), 6.33, 6.29 (2 s, CO_2CH_3), 4.83 (t, each of t was d, $>$CH), 2.72 (s, Ph), and 2.37 (d, N=CH)	No isomer from nmr

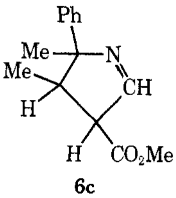
TABLE V

(*Continued*)

Compd, major (minor)	R^1	R^2	R^3	X	Bp, °C (mm)	Calcd (found)			Principal ir bands, cm^{-1}	Nmr, τ (in $CDCl_3$)[a]	Tautomer ratio[b]
						C, %	H, %	N, %			
6b (**7b**)	Ph	Me	H	CO_2Me	Preparative glpc 150–170 (0.1)				1595 (w), 1625 (m), 1730 (s), 3300 (m)	8.34 (s, CH_3, 3 H), 7.60 (d, CH_2, 2 H), 6.32 (s, CO_2CH_3, 3 H), 6.2–6.5 (m, ⩾CH, 1 H), 2.4–2.8 (m, Ph and N=CH, 6 H), >NH absorption could not be detected	Almost exclusively **6b**[c]
8b	Ph	Me	H	CO_2Me		67.31 (67.68)	6.98 (7.26)	4.62 (4.65)	1625 (w), 1730 (s)	8.46, 8.34 (equal intensity) (2 s, CH_3), 8.70–7.10 (m, CH_2), 6.46, 6.40, 6.31, 6.24 (equal intensity) (4 s, CO_2Me), 2.76 (s, Ph), and 2.76, 2.50 (equal intensity) (2 s, N=CH)	1/1 configurational isomer
6c (**7c**)	Ph	Me	CH_3	CO_2Me	143–145 (0.9)	72.10 (72.55)	7.41 (7.50)	6.06 (5.90)	1595 (m), 1660 (s), 1740 (s), 3310 (s)	9.41 (d, ⩾$CHCH_3$, **6** isomer, 2 H), 8.88 (d, >$CHCH_3$, **7** isomer, 1 H), 8.50, 8.42, 8.25 (*ca.* equal intensity) (3 s, $PhCCH_3$, 3 H), 7.0–8.0 (m, ⩾CH, $^5/_3$ H), 6.43 6.30, 6.20, 6.10 (4 s, CO_2CH_3, 3 H), 5.46 (broad s, NH, $^1/_3$ H), and 2.4–3.0 (m, Ph, CH=CN<, HC=N, 6 H)	**6c**/**7c** = 2/1
7d (**6d**)	Ph	Me	CO_2Me	CO_2Me	150–155 (0.5)	65.44 (65.75)	6.22 (6.33)	5.09 (5.15)	1590 (m), 1662 (s), 1720 (s), 3310 (s)	8.56–7.86 (6 s, CH_3, 3 H), 7.60 (⩾CH, **7** isomer $^5/_9$ H), 6.85 (d, ⩾CH, **6** isomer $^8/_9$ H), 6.0–6.4 (6 s, CO_2CH_3, 6 H), 4.6–5.2 (broad s, NH, **7** isomer $^5/_9$ H), 2.3–2.9 (m, Ph NCH=, N=CH, 6 H)	**6d**/**7d** = 4/5
7e (**6e**)	CO_2Et	H	H	CO_2Me	128–130 (0.7)	54.26 (54.39)	6.85 (6.59)	7.03 (6.93)	1590 (m), 1660 (s), 1725 (s), 3310 (s)	8.66 (t, CH_3CH_2, 3 H), 7.8–6.7 (m, CH_2, ⩾CH, 3 H), 6.28 (s, CO_2Me, 3 H), 5.75 (q, CH_3CH_2, 2 H), 5.0–5.5 (broad s, >NH, $^3/_4$ H), 2.75 (m, >C=CH, $^3/_4$ H), 2.30 (m, N=CH, $^1/_4$ H)	**6e**/**7e** = 1/3
8e	CO_2Et	H	H	CO_2Me	133–134 (0.7)	54.73 (54.67)	6.71 (6.86)	4.91 (4.96)	1619 (w), 1729 (s)	8.70 (t, CH_3CH_2), 8.00–7.00 (m, CH_2), 6.25, 6.23 (2 s, CO_2Me), 5.75 (q, CH_3CH_2), and 2.32 (broad s, N=CH)	
7f (**6f**)	CO_2Et	H	CH_3	CO_2Me	120–122 (4)	56.32 (56.18)	7.09 (7.04)	6.57 (6.28)	1590 (m), 1662 (s), 1727 (s), 3350 (s)	8.50–8.95 (overlap of t for isomer, CH_2CH_3 and d for CH_3CH<, 6 H), 7.8–7.1 (m, CH_3CH<, 1 H), 6.8–6.4 (q, EtO_2CCH<, 1 H), 6.28 (s, major peak), 5.96–6.26 (4 s, minor peak) (CO_2CH_3, total 3 H), 5.4–5.96 (overlap q, CH_2CH_3, 2 H), 5.1 broad s, >NH, $^4/_5$ H), 2.73 (d, NHCH=C<, $^4/_5$ H), and 2.20 (m, >N=CH, $^1/_5$ H)	**6f**/**7f** = 1/4
7g (**6g**)	CO_2Et	H	H	CN	128–130 (0.4)	57.82 (57.75)	6.07 (6.19)	16.86 (16.97)	1595 (m), 1731 (s), 2195 (w), 3355 (s)	8.69 (t, CH_3CH_2, 3 H), 6.96 (d, CH_2, 2 H), 5.75 (q, CH_3CH_2, 2 H), 5.56 (t, ⩾CH, 1 H), 4.82 (s, >NH, 1 H), 2.99 (m, >C=CH, 1 H), and 2.40 (m, N=CH, trace)	Almost **7g**[d]
7h (**6h**)	CO_2Et	H	CO_2Me	CO_2Me	164–165 (1)	51.36 (50.96)	5.88 (5.90)	5.45 (5.23)	1590 (m), 1670 (s), 1730 (s), 3345 (s)	8.70 (t, CH_3CH_2, 3 H), 6.31, 6.21 (2 s, CO_2Me, 6 H), 5.76 (q, CH_3CH_2, 2 H), 5.34 (d, >$CHCO_2Me$, 1 H), 4.75 (s, >NH, $^8/_9$ H), 2.68 (m, >C=CH, $^8/_9$ H), and 2.35 (m, N=CH, $^1/_9$ H)	**6h**/**7h** = 1/8

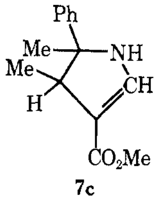
[a] Nmr absorption for a mixture of **6** and **7** isomers. [b] Tautomer ratio of **6**/**7** was calculated from the intensity ratio of >NH absorption and from the intensity ratio of N=CH/>C=CHNH absorptions. Configurational isomer ratio of **8b** was calculated from the PhCMe intensity ratio of each isomer. [c] The tautomer is present mostly as **6b** from nmr, but the ir spectrum shows the presence a small amount of **7b** by ν_{NH} absorption. [d] Ir and nmr spectra show that the tautomer is present almost as **7g**, but a weak N=CH group in the nmr spectrum shows the presence a small amount of **6g**.

The constituent parts of the peak A fraction were examined by nmr and ir spectra. For example, the ir spectrum of the reaction product (**6c**–**7c**) of PhCH(Me)NC with metyl crotonate showed four characteristic absorptions at 3310 (s, ν_{NH} of **7c**), 1740 (s, $\nu_{C=O}$ of **6c**), 1660 (s, $\nu_{C=O}$ of **7c**), and 1595 cm^{-1} (m, $\nu_{C=C}$ of **7c**). An expected absorption of $\nu_{C=N}$ of **6c** was included in the strong absorption at 1660 cm^{-1}. The nmr spectrum of **6c**–**7c** was as follows: τ 9.41 (d, 2 H) and 8.88 (d, 1 H, both were >CHCH$_3$), 8.50, 8.42, and 8.25 (three singlets of equal intensity, PhCCH$_3$, total 3 H), 7.0–8.0 (m, ⪢CH, $^5/_3$ H), 6.43–6.10 (four singlets, CO$_2$CH$_3$, total 3 H), 5.46 (broad s, >NH, $^1/_3$ H), and 2.4–3.0 (m, C$_6$H$_5$, CH=CN<, CH=N, 6 H). The peak at τ 5.46 disappeared by D$_2$O treatment. In other cases, the analysis of the peak A fraction gave the same conclusion, *i.e.*, it consists of **6** and **7**. These nmr spectrum fitted a mixture of **6c** and **7c**.



6c

four configurational isomers



7c

two configurational isomers

The formation of four isomers of these six isomers was suggested by the four singlets of CO$_2$CH$_3$ in the case of **6c**–**7c**. The nmr spectrum of **6d**–**7d** showed the formation of all six isomers.

In addition, the doublet or multiplet peaks of NHCH=C< of **7e** (**6e**) and **7h** (**6h**) were decoupled and became singlets by D$_2$O treatment. This observation supports the above conclusion.

The composition of **6c**–**7c** was given by nmr; *i.e.*, the intensity of >NH was $^1/_3$ H, and, thus, **6c**/**7c** = 2/1. In accordance with this value, the intensity ratio of >CHCH$_3$ absorptions at τ 9.41 and 8.88 was 2/1.

Preparation of γ-Carbethoxypropyl Isocyanide and β-Carbethoxyethyl Isocyanide.—To a solution of 10 ml of ammonia in 450 ml of chloroform 120 g of the HCl salt of ethyl γ-aminobutyrate was added. The mixture was stirred at 0° for 10 min. The chloroform solution was filtered in order to remove ammonium chloride; to this filtrate 150 ml of ethyl formate was added and the mixture refluxed for 24 hr. *N*-(γ-Carbethoxypropyl)formamide was distilled at 146° (0.7 mm). From *N*-(γ-carbethoxypropyl)formamide, γ-carbethoxypropyl isocyanide [bp 82–83° (4 mm)] was prepared according to the phosgene method.[9] β-Carbethoxyethyl isocyanide [bp 60–62° (0.9 mm)] was prepared by the same procedure.[9]

Cyclization of γ-Carbethoxypropyl Isocyanide.—A mixture of 1.41 g (10 mmol) of γ-carbethoxypropyl isocyanide and 29 mg (0.20 mmol) of Cu$_2$O in 3 ml of benzene was heated at 80° for 1 hr. Complete consumption of the isocyanide was shown by glpc analysis. The reaction mixture was subjected to vacuum distillation. The fraction boiling at 50–90° (1 mm) was collected. The major product of this distillate was a tautomer mixture of 3-carbethoxy-Δ^1- and -Δ^2-pyrroline (**18**). From the nmr intensity ratio of the absorptions of >NH, N=CH, and >NC=CH, the tautomer ratio of Δ^1/Δ^2 was shown to be about 4/3. The yield was 19%: nmr (in CDCl$_3$) (**18**) τ 8.72, 8.70 (2 t, CH$_3$CH$_2$), 7.85–7.00 (m, CH$_2$), 5.84, 5.82 (2 q, CH$_3$CH$_2$), 5.25 (d, >NH, $^3/_7$ H), 2.72 (m, CH=C, $^3/_7$ H), and 2.45 (m, N=CH, $^4/_7$ H); principal ir bands (neat) 3310 (s), 1720, (s), 1670 (s), 1620 (w), and 1591 cm^{-1} (m).

Anal. Calcd for C$_7$H$_{11}$NO$_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.62; H, 7.91; N, 9.90.

Reaction of γ-Carbethoxypropyl Isocyanide with Methyl Methacrylate.—A mixture of 1.41 g (10 mmol) of γ-carbethoxypropyl isocyanide and 2.00 g (20 mmol) of methyl methacrylate and 29 mg (0.20 mmol) of Cu$_2$O in 3 ml of benzene was heated at 80° for 3 hr. The product, 3-(β-carbomethoxypropyl)-3-carbethoxy-Δ^1-pyrroline (**19**) was isolated in 61% yield by fractional distillation [bp 99–105° (0.4 mm)] along with a small amount of 1-(β-carbomethoxypropyl)-3-carbethoxy-Δ^2-pyrroline: nmr (in CDCl$_3$) (**19**) τ 8.80 (d, CH$_3$CH<), 8.72, 8.70 (2 t, CH$_3$CH$_2$), 8.30–7.30 (m, CH$_2$), 6.37, 6.25 (2 s, CO$_2$CH$_3$), 5.92, 5.90 (2 q, CH$_3$CH$_2$), and 2.57 (t, N=CH); principal ir bands (neat) 1725 (s) and 1621 cm^{-1} (w).

Anal. Calcd for C$_{12}$H$_{19}$NO$_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.65; H, 7.80; N, 6.04.

Reaction of γ-Carbethoxypropyl Isocyanide with Methyl Acrylate.—The reaction was carried out under the same conditions as those of the reaction with methyl methacrylate. From the reaction mixture, two products were isolated by fractional distillation. The first product boiling at 108–109° (0.4 mm) was 3-(β-carbomethoxyethyl)-3-carbethoxy-Δ^1-pyrroline (**20**). The yield was 39%. The second fraction boiling at 150–160° (0.5 mm) was 1-(β-carbomethoxyethyl)-3-carbethoxy-Δ^2-pyrroline (**21**). The yield was 17%.

Identification data of **20**: nmr (in CDCl$_3$) τ 8.72, 8.70 (2 t, CH$_3$CH$_2$), 8.50–7.30 (m, CH$_2$), 6.30, 6.25 (2, s, CO$_2$CH$_3$), 5.92, 5.90 (2 q, CH$_3$CH$_2$), and 2.55 (t, N=CH); principal ir bands (neat) 1612 (w) and 1722 cm^{-1} (s).

Anal. Calcd for C$_{11}$H$_{17}$NO$_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 57.93; H, 7.70; N, 6.18.

Identification data of **21**: nmr (in CDCl$_3$) τ 8.80 (t, CH$_3$CH$_2$), 7.80–7.20, 6.80–6.50 (m, CH$_2$), 6.33 (s, CO$_2$CH$_3$), 5.90 (q, CH$_3$CH$_2$), and 3.10 (m, >C=CH); principal ir bands (neat) 1736 (s), 1673 (s) and 1595 cm^{-1} (m).

Anal. Calcd for C$_{11}$H$_{17}$NO$_4$: C, 58.13; H, 7.54; N, 6.16. Found: C, 58.11; H, 7.72; N, 6.40.

An Attempt of Cyclization of β-Carbethoxyethyl Isocyanide.—A mixture of 1.27 g (10 mmol) of β-carbethoxyethyl isocyanide and 29 mg (0.2 mmol) of Cu$_2$O in 3 ml of benzene was heated at 80° for 15 hr. No reaction was observed by glpc analysis.

An Attempt of Reaction of Cyclohexyl Isocyanide with Methyl Propionate.—A mixture of 1.09 g (10 mmol) of cyclohexyl isocyanide, 0.88 g (10 mmol) of methyl propionate, and 29 mg (0.2 mmol) of Cu$_2$O in 3 ml of benzene was heated at 80° for 16 hr. By glpc analysis it was found that the two reagents of isocyanide and propionate remained unreacted in the reaction mixture.

Michael Addition Reaction of 3-Carbomethoxy-5-carbethoxy-Δ^1- and -Δ^2-pyrroline Tautomer Mixture with Methyl Acrylate.—A tautomer mixture of 3-carbomethoxy-5-carbethoxy-Δ^1-pyrroline and its tautomer (0.40 g, 2 mmol) was allowed to react with methyl acrylate (0.17 g, 2 mmol) in the presence of Cu$_2$O (6 mg, 0.04 mmol) and cyclohexyl isocyanide (0.22 g, 2 mmol) in benzene (1 ml) at 80° for 3 hr. By comparison of the glpc retention time with the authentic sample, the products were identified. The main product was 3-(β-carbomethoxyethyl)-3-carbomethoxy-5-carbethoxy-Δ^1-pyrroline, and a by-product was 1-(β-carbomethylethyl)-3-carbethoxy-5-carbethoxy-Δ^2-pyrroline. In the absence of Cu$_2$O, no reaction was observed.

Preparation of Optically Active Isocyanides.—The following three isocyanide were prepared, *i.e.*, α-phenylethyl isocyanide, α-(*p*-chlorophenyl)ethyl isocyanide, and α-(*p*-methoxyphenyl)ethyl isocyanide. α-Phenylethylamine was commercially available, and α-(*p*-chlorophenyl)ethylamine and α-(*p*-methoxyphenyl)ethylamine were prepared according to the Leukert reaction.[11] α-Phenylethylamine and α-(*p*-chlorophenyl)ethylamine were optically resolved by means of *l*-malic acid.[11] Optical resolution of α-(*p*-methoxyphenyl)ethylamine was carried out by means of *l*-tartaric acid. Optically active amines were converted into the corresponding formamide by treatment with ethyl formate, and then the formamide derivatives were employed to prepare optically active isocyanides by the phosgene method:[9] (+)-α-phenylethylamine, $[\alpha]^{15}\mathrm{D}$ +38.9° (*c* 3.37, C$_6$H$_6$); (+)-α-(*p*-chlorophenyl)ethylamine, $[\alpha]^{15}\mathrm{D}$ +25.3° (*c* 4.46, C$_6$H$_6$); (+)-α-(*p*-methoxyphenyl)ethylamine, $[\alpha]^{15}\mathrm{D}$ +16.7° (*c* 5.96, C$_6$H$_6$); (+)-α-phenylethyl isocyanide, $[\alpha]^{15}\mathrm{D}$ +24.4° (*c* 8.75, C$_6$H$_6$); (+)-α-(*p*-chlorophenyl)ethyl isocyanide, $[\alpha]^{15}\mathrm{D}$ +13.5° (*c* 10.47, C$_6$H$_6$), bp 50–53° (0.5 mm); (+)-α-(*p*-methoxyphenyl)ethyl isocyanide, $[\alpha]^{15}\mathrm{D}$ +19.6° (*c* 9.71 C$_6$H$_6$), bp 90–92° (0.4 mm).

Racemization of Optically Active Isocyanide.—A mixture of 2 mmol of isocyanide and 104 mg (0.4 mmol) of copper(II) acetylacetonate in 3 ml of chloroform was allowed to stand at 20° for 5 hr. The racemization degrees of α-phenylethyl isocyanide, α-(*p*-chlorophenyl)ethyl isocyanide, and α-(*p*-methoxyphenyl)ethyl isocyanides were 39, 49, and 17%, respectively.

Reaction of Isocyanides with Carbonyl Compounds.—A mixture of isocyanide (10 mmol), carbonyl compound (20 mmol), and Cu$_2$O (0.20 mmol) in benzene (3 ml) was heated at 80°. The reaction product, a derivative of Δ^2-oxazoline, was isolated by fractional distillation. The reaction time and the product yield

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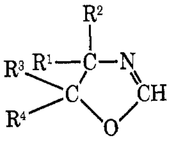
[11] "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 506.

TABLE VI

PRODUCTS FROM ISOCYANIDES AND CARBONYL COMPOUNDS



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Compd	R¹	R²	R³	R⁴	Bp, °C (mm)	—Calcd (found)— C, %	H, %	N, %	Principal ir bands, cm⁻¹	Nmr, τ (in $CDCl_3$)	Isomer ratio
5a	Ph	H	Me	Me	79–80°(7)	75.40 (74.81)	7.48 (7.47)	7.99 (7.94)	1618 (w)	9.15 and 8.42 (2 s, CH_3), 5.17 (d, $>CH$), 3.01 (d, $N{=}CH$), and 2.75 (s, Ph)	No isomer
5b	Ph	H	Ph	Me	116–117°(3)	80.98 (81.27)	6.37 (6.41)	5.90 (6.02)	1618 (w)	8.81 (s, CH_3), 4.80 (d, $>CH$), 2.74 and 2.64 (2 s, Ph and overlap $N{=}CH$)[a] 8.16 (s, CH_3), 4.92 (d, $>CH$), and 2.84 broad s, Ph and $N{=}CH$)[a]	2.0/1.3
5c	Ph	H	$\left(CH_2\right)_4$		106–107°(0.8)	77.58 (77.34)	7.51 (7.62)	6.96 (6.81)	1630 (s)	9.00–7.60 (m, H-1 of cyclopentyl), 5.30 (d, $PhCH<$), 2.96 (d, $N{=}CH$), and 2.74 (m, Ph)[b]	No isomer
5d	Ph	H	*i*-Pr	H	77°(3)	76.15 (76.05)	7.99 (8.21)	7.40 (7.44	1620 (w)	9.00, 8.98 (2 d, Me_2CH), 8.12 (m, Me_2CH), 5.87 (t, $Me_2CHCH<$), 5.21 (d, $PhCH<$), 3.00 (d, $N{=}CH$), and 2.75 (s, Ph)[b]	*c*
5e	Ph	Me	Me	Et	79–80°(6)	76.81 (77.11)	8.43 (8.67)	6.89 (7.16)	1618 (w)	9.30 (s, CH_3CEt), 8.54 (major), 8.46 (minor) (2 s, $PhCCH_3$), 7.7–9.3 (m, CH_3CH_2), 3.18 (s, $N{=}CH$), and 2.70 (m, Ph)[b]	3/5
5f	CO_2Et	H	Ph	Me	107–113°(0.2)	66.93 (66.63)	6.48 (6.54)	6.01 (5.76)	1625 (w), 1735 (s)	9.20 (t, CH_3CH_2), 8.15 (s, CH_3), 6.38 (q, CH_3CH_2), 5.40 (s, $>CH$), 2.68 (s, Ph), and 2.60 (d, $N{=}CH$)[a] 8.65 (2 t, CH_3CH_2), 8.36 (s, CH_3), 5.66 (q, CH_3CH_2), 5.35 (s, $>CH$), 2.68 (s, Ph), and 2.60 (d, $N{=}CH$)	1.0/1.0
5g	CO_2Et	H	*i*-Pr	H	110°(6)	58.36 (58.46)	8.16 (8.44)	7.56 (7.30)	1615 (w), 1730 (s)	9.00 (d, each peak is d, $(CH_3)_2CH$), 8.66 (t, CH_3CH_2), 8.10 (m, Me_2CH), 5.70 (q, CH_3CH_2), and 3.04 (d, $N{=}CH$)[b]	*c*
5h	CO_2Et	H	$\left(CH_2\right)_4$		81–84°(0.5)	60.89 (60.13)	7.67 (7.81)	7.10 (7.11)	1630 (m), 1750 (s)	8.65 (t, CH_3), 8.66 (broad s, H-1 on cyclopentyl), 5.73 (q, CH_3CH_2), 5.43 (d, $>CH$), and 3.02 (d, $N{=}CH$)	No isomer

[a] Each of the two configurational isomers were separated by glpc. Their nmr absorptions are given here separately. Isomer ratio was calculated from the glpc peak areas and confirmed by the corresponding nmr absorption intensity ratio of the isomer mixture. [b] Two isomers were not separated by glpc. Nmr absorption of a mixture of the two isomers are given here. The isomer ratio of **5e** was determined by the Me intensity of the nmr spectrum. [c] Two isomers could not be separated by glpc. There nmr spectra show the presence of two isomers, but the ratio could not be determined due to close peaks of isomers.

are shown in Table III. Identification data of the products are summarized in Table VI.

Registry No.—**3a,** 31385-48-5 (isomer a), 31339-14-7 (isomer b); **3b,** 31339-15-8 (a), 31339-16-9 (b); **3c,** 31385-49-6 (a), 31339-17-0 (b); **3d,** 31339-18-1 (a), 31339-19-2 (b); **3e,** 31339-20-5 (a), 31339-21-6 (b); **3f,** 31339-22-7 (a), 31339-23-8 (b); **5a,** 31339-24-9; **5b,** 31385-50-9 (a), 31339-25-0 (b); **5c,** 31339-26-1; **5d,** 31339-27-2 (a), 31339-28-3 (b); **5e,** 31339-29-4 (a), 31339-30-7 (b); **5f,** 31339-31-8 (a), 31339-32-9 (b); **5g,** 28082-06-6 (a), 28082-01-1 (b); **5h,** 31339-35-2; **6a,** 31339-36-3; **6b,** 31385-51-0; **6c,** 31428-84-9; **6d,** 31339-37-4; **6e,** 31339-38-5; **6f,** 31339-39-6; **6g,** 31339-40-9; **6h,** 31339-41-0; **7a,** 31339-42-1; **7b,** 31339-43-2; **7c,** 31339-44-3; **7d,** 31339-50-1 (a), 31339-51-2 (b); **7e,** 31339-45-4; **7f,** 31339-46-5; **7g,** 31339-47-6; **7h,** 31339-48-7; **8a,** 31385-52-1; **8b,** 31339-49-8 (a), 31339-52-3 (b); **8e,** 31339-53-4; **Δ¹-18,** 31339-54-5; **Δ²-18,** 31339-55-6; **19,** 31339-56-7; **20,** 31339-57-8; **21,** 31328-34-4; (+)-α-phenylethylamine, 3886-69-9; (+)-α-(*p*-chlorophenyl)ethylamine, 27298-99-3; (+)-α-(*p*-methoxyphenyl)ethylamine, 22038-86-4; (+)-α-phenylethyl isocyanide, 21872-33-3; (+)-α-(*p*-chlorophenyl)ethyl isocyanide, 31328-39-9; (+)-α-(*p*-methoxyphenyl)ethyl isocyanide, 31328-40-2.