

transformed to dihydrojasnone (**5a**)^{2f,8,9b,13} and allylrethronone (**5b**),^{8,14} respectively.

We are currently studying further improvements in the synthetic method here outlined as well as a number of other, quite different approaches to 2-cyclopentenone derivatives.

Acknowledgment. We thank Dr. Kiitiro Utimoto for helpful discussions.

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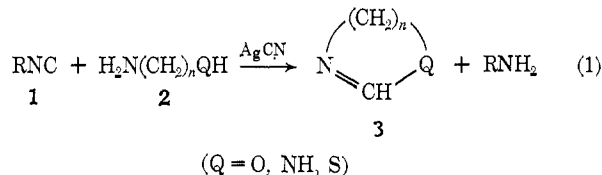
(14) L. Crombie, A. J. B. Edgar, S. H. Harper, M. W. Lowe, and D. Thompson, *J. Chem. Soc.*, 3552 (1950); T. Mukaiyama, S. Kobayashi, K. Kamio, and H. Takei, *Chem. Lett.*, 237 (1972).

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Synthetic Reactions by Complex Catalysts. XXXI. A Novel and Versatile Method of Heterocycle Synthesis

Sir:

To date, the preparation of cyclic imidates (**3**, Q = oxygen) which are unsubstituted in the 2 position has been done with some difficulty. Especially, to our best knowledge, the synthetic method of a six-membered cyclic imidate, 5,6-dihydro-4*H*-1,3-oxazine, has not been known. Now, we wish to report a new general method for the synthesis of heterocycles which include 2-oxazoline¹ and dihydro-1,3-oxazine as well as 2-imidazoline,² tetrahydro-2-pyrimidine,² and 2-thiazoline.³ The synthesis is readily accomplished by a single-step reaction of isonitrile (**1**) with amino alcohol, with diamine, or with aminothiols in the presence of a small amount of silver cyanide. The reactions are expressed by the following general equation.



The efficiency and generality of the reaction coupled with the ready availability of the starting materials render it very useful in the preparation of heterocycles containing the $-\text{N}=\text{CHQ}-$ unit. A typical experimental procedure is illustrated by the reaction of γ -aminopropanol with *tert*-butyl isocyanide in the presence of silver cyanide leading to the formation of 5,6-dihydro-4*H*-1,3-oxazine. A mixture of 1.5 g (20 mmol) of γ -aminopropanol, 1.7 g (20 mmol) of *tert*-butyl isocyanide, and 0.13 g (1 mmol) of silver cyanide was heated at 90° for 12 hr with stirring under nitrogen. The reaction mixture was subjected to distillation directly. 5,6-Dihydro-4*H*-1,3-oxazine, bp 85° (70 mm), was obtained in 66% yield (ir (neat) 1650 cm^{-1} ($\nu_{\text{C}=\text{N}}$), 1150 ($\nu_{\text{C}-\text{O}}$); nmr (CDCl₃) τ 8.18 (m, 2 H), 6.72 (t, 2 H), 5.87 (t, 2 H), 3.15 (s, 1 H)). As a by-product, *tert*-butylamine (bp 45°) derived from the isonitrile component was isolated and identified. Some results are

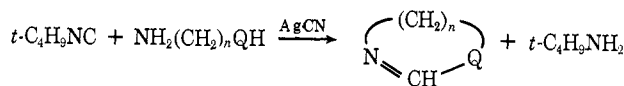
(1) P. J. Edge, D. R. Marshall, and L. A. Mulligan, *Chem. Ind. (London)*, 203 (1969).

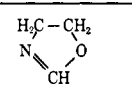
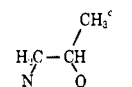
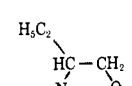
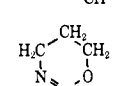
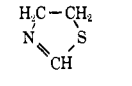
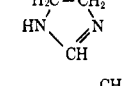
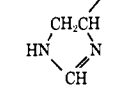
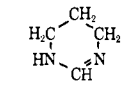
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summarized in Table I. Spectral data and elemental analyses supported the assigned structures of all prod-

Table I. Preparation of Heterocycles by the Reactions of Isonitrile with Amino Alcohol, Diamine, and Aminothiols



NH ₂ (CH ₂) _n QH	Reaction ^{a,b}		Product (%)
	Temp, °C	Time, hr	
NH ₂ CH ₂ CH ₂ OH	90	13	 (67)
NH ₂ CH ₂ CH(CH ₃)OH	90	13	 (72)
NH ₂ CH(C ₂ H ₅)CH ₂ OH	90	12	 (63)
NH ₂ CH ₂ CH ₂ CH ₂ OH	90	12	 (66)
NH ₂ CH ₂ CH ₂ SH	90	19	 (88)
NH ₂ CH ₂ CH ₂ NH ₂	90	11	 (80)
NH ₂ CH ₂ CH(CH ₃)NH ₂	90	23	 (80)
NH ₂ CH ₂ CH ₂ CH ₂ NH ₂	90	15	 (94)

^a Reaction: NH₂(CH₂)_nQH 20 mmol, isonitrile 20 mmol, and silver cyanide 1 mmol. ^b The optimum conditions have not been explored. ^c When cyclohexyl isocyanide was employed instead of *tert*-butyl isocyanide, the product of 5-methyl-2-oxazoline was produced in 70% yield.

ucts. The nmr of all cyclic products exhibited a singlet in the region of τ 2–3 which is characteristic of a $-\text{N}=\text{CHQ}-$ unit. Cuprous chloride can also be employed as a catalyst which is, however, less effective than silver cyanide.

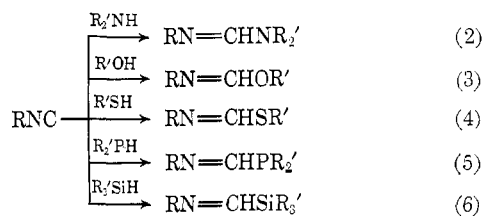
The present reaction is also applied to *o*-aminophenol,⁴ *o*-phenylenediamine,⁵ and *o*-aminothiophenol,⁴ resulting in the formation of benzoxazole (54%), benzimidazole (64%), and benzothiazole (93%), respectively.

The present synthesis of heterocycles is closely related to the formimidation reaction in which isonitrile is inserted into a heteroatom-hydrogen linkage of

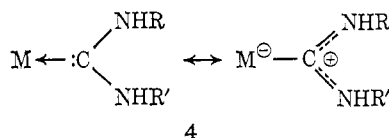
(4) G. L. Jenkins, A. M. Knevel, and S. S. Davis, *J. Org. Chem.*, **26**, 274 (1961).

(5) (a) E. C. Wagner and W. H. Millett, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 65; (b) E. C. Taylor and W. Ehrhart, *J. Amer. Chem. Soc.*, **82**, 3138 (1960).

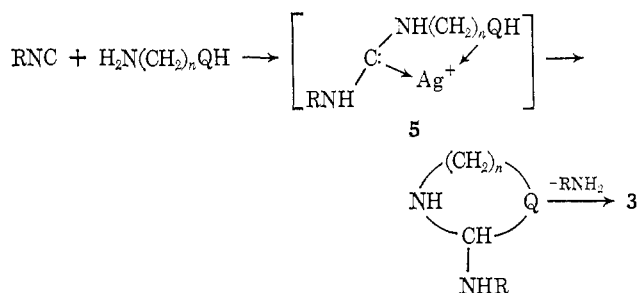
amine,⁶ alcohol,⁷ thiol,⁸ phosphine,⁹ and silane¹⁰ in the presence of a catalytic amount of group IB and IIB metal compounds, *e.g.*, Cu, Ag, and Zn.



The insertion of a carbon atom *via* an isonitrile by means of a metal catalyst in these formimidation reactions (eq 2-6) is mechanistically intriguing. Recently, Balch and Miller¹¹ reported the formation of an iron complex (4) having a coordinated carbene ligand in the reaction of the iron isonitrile complex with amine.



The heterocycle synthesis in the present study may well be interpreted by assuming a silver complex having a carbene-type ligand (5) as a key intermediate. Fur-



ther studies are in progress to extend the potential of this synthetic method and to investigate the reaction mechanism.

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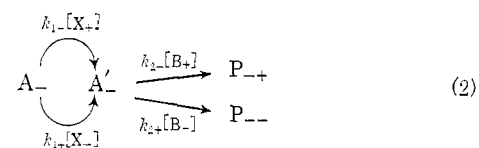
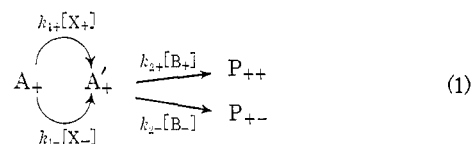
Nonreciprocal Kinetic Resolution. Kinetic Evidence for a Reactive Intermediate without Measurement of Rates

Sir:

We wish to describe a new method for showing the presence of a slowly formed, rapidly consumed intermediate. The reaction of a chiral reagent B_+ with an

excess of a racemic substrate, A_{\pm} , may give two diastereomeric products, P_{++} and P_{--} (from $A_+ + B_+$ and $A_- + B_+$, respectively). In general, kinetic resolution¹ is observed, *i.e.*, the amount of P_{++} formed differs from the amount of P_{--} , and the unreacted A is enriched in the enantiomer corresponding to the less abundant diastereomer.² Most commonly, when the same reaction is performed using excess B_{\pm} and, say A_+ , the per cent stereoselectivity² is the same as that from the reaction of A_{\pm} with B_+ ; we refer to such reactions as showing "reciprocal kinetic resolution."

Such a reciprocal relationship, however, need not always obtain. To illustrate, we take a process $A + X + B \rightarrow P$ reacting by the sequence $A + X \rightarrow A' + X'$ (k_1) and $A' + B \rightarrow P$ (k_2) in which $k_2 \gg k_1$; this is expanded below for the case in which A , A' , B , and X are chiral.



Note particularly that enantiomeric reactions (*e.g.*, A'_+ with B_+ *vs.* A'_- with B_-) have identical rate constants.³

When A_+ reacts with B_{\pm} the ratio of the rates of formation of the products is (rate P_{++})/(rate P_{+-}) = $k_{2+}[B_+]/k_{2-}[B_-]$, whereas with $A_{\pm} + B_+$ (and X_+) the ratio is (rate P_{++})/(rate P_{-+}) = $k_{1+}[A_+]/k_{1-}[A_-]$. The consequences can perhaps be seen most clearly under "pseudo-first-order conditions," when the ratios of the diastereomers upon isolation become $P_{++}/P_{+-} = k_{2+}/k_{2-}$ and $P_{++}/P_{-+} = k_{1+}/k_{1-}$, *i.e.*, the two reaction modes yield different product ratios (or stereoselectivities).⁴ Such a "nonreciprocal kinetic resolution" requires at least one reaction in which a chiral reactive intermediate reacts quickly *via* diastereomeric pathways.⁵ It can readily be seen that nonreciprocal kinetic resolution also occurs in the simpler cases in which X is achiral (including racemic) or the first step, $A \rightarrow A'$, is unimolecular (in which cases $P_{++}/P_{-+} = 1$ for the reaction of A_{\pm} with B_+).

Practical illustration is provided for the case in which $X \equiv B$ by the reaction of camphor-10-sulfonyl

(1) *Cf.* (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 65 ff; (b) K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, New York, N. Y., 1966, p 122 ff; (c) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, p 28 ff.

(2) The extent of the kinetic resolution may be described^{1b} by the "per cent stereoselectivity" = $100(P_{++} - P_{--})/(P_{++} + P_{--})$.

(3) We denote the sign of these rate constants by the sign of the product of the signs of the reacting enantiomers.

(4) It may be recalled that Horeau's ingenious "partial resolution" method for determining optical purity⁵ specifically requires reciprocal kinetic resolution. It therefore cannot be used with reactions showing the nonreciprocal relationship noted here.

(5) A. Horeau, *Bull. Soc. Chim. Fr.*, 2673 (1964).

(6) Note that the mere observation of different product ratios does not in itself establish a nonreciprocal resolution, since they could arise if the reaction, for example, were first order in A and second order in B ; this may be readily distinguished experimentally from a true nonreciprocal resolution.