

Radical Reaction of Isocyanide with Thiol

TAKEO SAEGUSA, SHIRO KOBAYASHI, AND YOSHIHIKO ITO

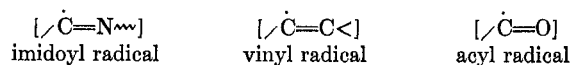
Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan

Received September 28, 1969

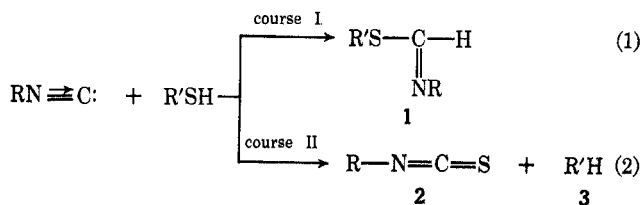
The reaction of an isocyanide with a thiol proceeds in two courses. Course I is regarded as α,α additions of the thiyl group and hydrogen to the isocyanide carbon atom to produce a thioformimidate (1). Course II forms an isothiocyanate (2) from the isocyanide and an alkane (3) from the alkyl group of the thiol. First, experimental results supporting the radical chain mechanism involving the thiyl radical are given. Radical reactions of primary and aromatic thiols take course I, whereas those of α -toluenethiol as well as tertiary thiols take course II. The reaction with a secondary thiol takes both courses. The copper-catalyzed reaction, however, takes course I predominantly, regardless of the nature of the thiol alkyl group.

We have reported a set of reactions of isocyanide, which are the insertions of the isocyanide carbon atom into the nitrogen-hydrogen bond of amine,¹ the oxygen-hydrogen bond of alcohol,² the sulfur-hydrogen bond of thiol,³ the phosphorus-hydrogen bond of phosphine,⁴ and the silicon-hydrogen bond of silanes.⁵ All these reactions are catalyzed by copper compounds and produce the corresponding derivatives of formimidic acid in high yields.

Among these reactions, the isocyanide-thiol reaction differs from the others; *i.e.*, the isocyanide-thiol reaction is also induced by a radical initiator. This paper describes the radical reaction of an isocyanide with a thiol which involves an intermediate imidothiyl radical. It is of interest to note that the imidothiyl radical is iso-electronic with vinyl and acyl radicals of σ character.



The reaction of isocyanide with thiol proceeds in two courses. Course I (eq 1) is regarded as α,α additions of the thiyl group and hydrogen to the isocyanide carbon atom carrying lone-pair electrons, which produces a thioformimidate (1). In course II (eq 2), an isothio-



cyanate (2) and an alkane (3) are formed. The course of the reaction is determined by the nature of the thiol alkyl group; *i.e.*, primary and aromatic thiols take course I exclusively, whereas α -toluenethiol as well as tertiary thiols take course II. The reaction with secondary thiols proceeds along both courses.

In the present studies, experimental evidence to support the radical chain mechanism is given. The difference between the radical reaction of an isocyanide with a thiol and the copper-catalyzed one is also mentioned. So far as we know, the present study is the first to de-

scribe useful reactions of isocyanides *via* radical chain mechanism.

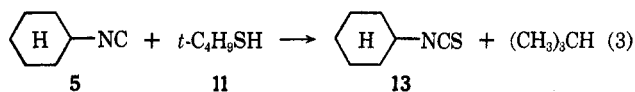
Results and Discussion

Support for a Radical Chain Mechanism.—When a mixture of thiol and isocyanide is heated without any added catalyst, a reaction occurs between them. This reaction can be shown to be a radical chain reaction by the following results: (i) the reaction is accelerated by radical initiators, such as azobisisobutyronitrile (AIBN), and by ultraviolet irradiation and (ii) the reaction is suppressed by radical inhibitors such as hydroquinone (HQ), *t*-butylcatechol, and *p*-benzoquinone (*p*-BQ).

Table I illustrates the radical-initiated reaction of an isocyanide with a thiol. The reactions of primary and aromatic thiols induced by radical initiators proceed *via* course I. Copper-catalyzed reactions of these combinations take the same course. The isocyanide-secondary thiol reactions, both copper-catalyzed and photoinduced ones, give the products of the two courses. The course of the reactions of α -toluenethiol and tertiary thiols, however, is determined by the nature of catalyst; *i.e.*, those induced by radical initiators take course II, whereas those catalyzed by a copper compound take course I.

The mechanism of a radical-initiated reaction of an isocyanide with a thiol obviously differs from that of copper-catalyzed one. The copper-catalyzed reaction of cyclohexyl isocyanide (5) with 2-propanethiol (11) is not affected by the addition of hydroquinone. On the other hand, the radical-initiated reaction of an isocyanide with a thiol is suppressed by the so-called radical inhibitors, as will be described in the following parts of this paper. The difference in the products (Table I, runs 3 and 4) also distinguished the radical-initiated reaction from the copper-catalyzed one.

The effects of radical initiators and inhibitors upon the reaction of 5 with 2-methyl-2-propanethiol (11) giving cyclohexyl isothiocyanate (13) and isobutane are shown in Figure 1. The progress of reaction was followed



by the glpc determination of 13 at several times of reaction. The reaction of an equimolar mixture (neat) of 5 and 11 at 60° under nitrogen is shown by curve a, in which a small amount of oxygen due to incomplete exclusion of air may cause the radical reaction. The addition of AIBN (1 mol %) much enhanced the reaction

(1) T. Saegusa, Y. Ito, S. Kobayashi, K. Hirota, and H. Yoshioka, *Tetrahedron Lett.*, 6121 (1966).


(2) T. Saegusa, Y. Ito, S. Kobayashi, and K. Hirota, *ibid.*, 521 (1967); T. Saegusa, Y. Ito, S. Kobayashi, N. Takeda, and K. Hirota, *ibid.*, 1273 (1967).

(3) T. Saegusa, S. Kobayashi, K. Hirota, Y. Okumura, and Y. Ito, *Bull. Chem. Soc. Jap.*, 41, 1683 (1968).

(4) T. Saegusa, Y. Ito, and S. Kobayashi, *Tetrahedron Lett.*, 935 (1968).

(5) T. Saegusa, Y. Ito, S. Kobayashi, and K. Hirota, *J. Amer. Chem. Soc.*, 89, 2240 (1967).

TABLE I
 RADICAL AND CUPRIC OXIDE CATALYZED REACTIONS OF THIOLS WITH ISOCYANIDES

No.	R-NC (mmol)	R'SH (mmol)	Additive (mmol)	Reaction		Product yield, % ^a		
				Temp, °C	Time, hr	1	2	3
1	<i>t</i> -C ₄ H ₉ NC (4) (5.0)	C ₂ H ₅ SH (7) (5.0)	AIBN (0.01)	35	4.0	60	0	0
2	4 (5.0)	C ₆ H ₅ SH (8) (5.0)	AIBN (0.01)	80	2.0	82	0	0
3	4 (12.0)	C ₆ H ₅ CH ₂ SH (9) (10.0)	AIBN (0.02)	100	0.2	0	93	96
4	4 (12.0)	9 (10.0)	CuO (0.1)	100	2.0	91	0	0
5	 (5) (5.0)	<i>sec</i> -C ₄ H ₉ SH (10) (5.0)	<i>b</i>	0	0.1	83	11	N.d. ^c
6	C ₆ H ₅ NC (6) (6.0)	<i>t</i> -C ₄ H ₉ SH (11) (20.0)	AIBN (0.05)	75	0.2	0	97	N.d. ^c
7	5 (5.0)	11 (7.0)	CuO (0.1) and <i>p</i> -BQ (0.5)	90	3.0	64	6	N.d. ^c

^a Determined by glpc. ^b Irradiated by uv in 2 ml of diethyl ether under nitrogen. ^c N.d., not determined.

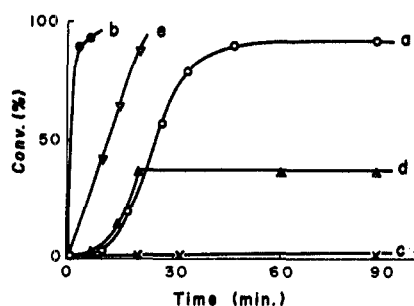
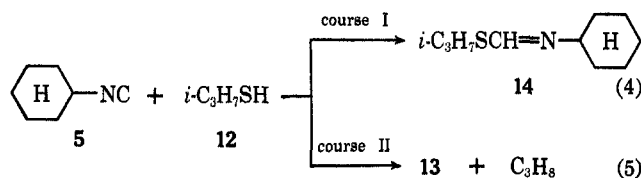


Figure 1.—Reaction of cyclohexyl isocyanide with 2-methyl-2-propanethiol. Effects of radical initiator and inhibitor: (a) without added catalyst at 60°, (b) with 1 mol % of AIBN at 60°, (c) with 5 mol % of hydroquinone at 60°, (d) with addition of 2 mol % of hydroquinone after 20 min at 60°, (e) irradiated in diethyl ether at 0°.

(curve b), whereas the addition of hydroquinone suppressed it (curve c). The addition of hydroquinone at a halfway point (at 20 min) to the reaction system without any added catalyst interrupted the reaction completely (curve d). In addition, the reaction was accelerated by uv irradiation. A mixture of 5, 11, and diethyl ether (solvent) in a Pyrex tube was irradiated at 0° under nitrogen (curve e). Here, no reaction was observed at all in the dark at 0° in diethyl ether solvent.

In the combination of isocyanide and secondary thiol, two modes of reaction, courses I and II, take place. The reaction of 5 with 2-propanethiol (12) was carried out under various conditions (Figure 2). The total



yield of the two products, 13 and 14, and the yield of 13 at several times of reaction without any added catalyst at 100° are shown by curves a and a', respectively. The addition of 2 mol % of hydroquinone at a time of 2.5 hr interrupted both courses of reaction (curves b and b'). The reaction was accelerated by AIBN (reaction at 70°, curves c and c'). It is quite significant that

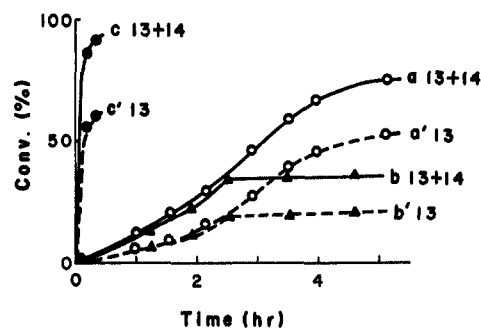


Figure 2.—Reaction of cyclohexyl isocyanide with 2-propanethiol: (a and a') without added catalyst at 100°, (b and b') with addition of 2 mol % of hydroquinone after 2.5 hr at 100°, (c and c') with 0.5 mol % of AIBN at 70°.

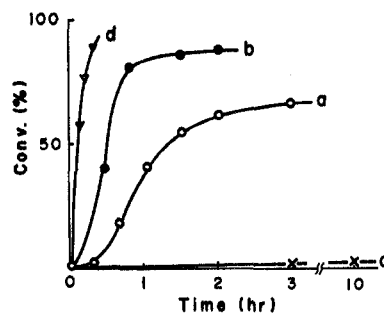
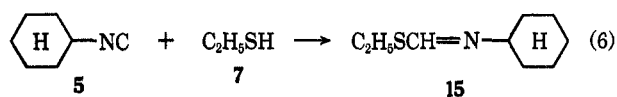


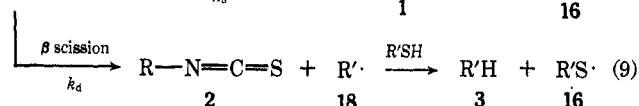
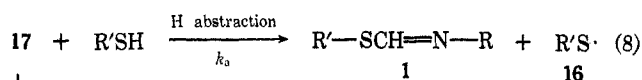
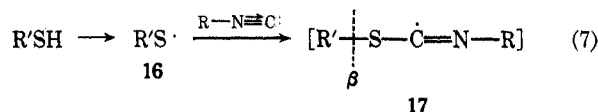
Figure 3.—Reaction of cyclohexyl isocyanide with ethanethiol: (a) without added catalyst at 40°, (b) with 0.1 mol % of AIBN at 40°, (c) with 10 mol % of *p*-BQ at 40°, (d) irradiated in diethyl ether at 0°.

the ratio of the final yields of the two products, 13/14, was 3/2 in each of these three reactions. Furthermore, 1 mol % of *t*-butylcatechol was enough to inhibit the reaction completely.

The reaction with a primary thiol proceeds through course I. In Figure 3, the acceleration by AIBN (curve b) and by uv irradiation (curve d), as well as the inhibition by *p*-benzoquinone, are demonstrated in the reaction of 5 with ethanethiol (7).



These several findings are taken to support a radical chain mechanism, which may be explained by the scheme (reactions 7–9) involving thiyl radical 16. The thiyl radical 16 is first formed from the thiol by a



radical initiator or by irradiation, and then attacks the isocyanide to produce the intermediate imidothiyl radical 17. The imidothiyl radical 17 may undergo two reactions, *i.e.*, hydrogen abstraction from thiol (eq 8) and β scission (eq 9). The hydrogen abstraction gives thioformimidate 1 and 16. On the other hand, the β scission at the alkyl- (or benzyl-) sulfur bond leads to isothiocyanate 2 and alkyl (or benzyl) radical 18. The second hydrogen abstraction of 18 from thiol produces hydrocarbon 3 and 16. These two reactions are competitive ones. The relative degrees of participation of the two reactions are determined by the stability of R'-S bond of 17 and the steric hindrance to the approach of a thiol to 17 in the H abstraction (eq 8). Preference of β scission in the case of a tertiary thiol is ascribed to these two factors. In the reaction of α -toluenethiol, the stability of the resultant benzyl radical may predominate in the determination of the direction of reaction. On the other hand, when R' is less stable as a radical and the steric hindrance is less significant, 17 prefers to abstract hydrogen from the thiol (eq 8). The reactions with primary and aromatic thiols take this course.

The case of secondary thiol is between these two extremes. The reaction of 5 with 12 gives the two products 13 and 14. On the basis of the above equations (8 and 9), the molar ratio of the two products is expressed by eq 10 where k_a is the rate constant of hydro-

$$\frac{14}{13} = \frac{k_a}{k_d} [\text{R'SH}] \quad (10)$$

gen abstraction of 17 from the thiol and k_d is the rate constant of β scission of 17.

In accord with eq 10, the molar ratio of 14/13 was gradually decreased as the reaction proceeds to decrease the concentration of 12 (Figure 2).

In addition, a series of experiments was conducted in which the initial concentration of 12 was varied. The ratios of 14/13 at a low conversion (below 10%) were found to vary linearly with the concentration of 12 as shown in Figure 4.

In the above scheme, both courses involve thiyl radical as the common chain carrier. The coupling of two thiyl radicals constitutes the chain termination, which produces the corresponding disulfide. A small amount of dialkyl disulfide was actually detected in the reaction mixture. For instance, 3.5×10^{-5} mol of di-*t*-butyl disulfide was detected by glpc in the mixture of the 5–11 reaction (Figure 1, curve a). Assuming that di-*t*-butyl disulfide is formed only by the termination reaction, the chain length is calculated to be 140.

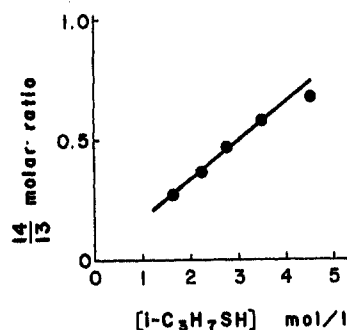
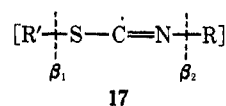
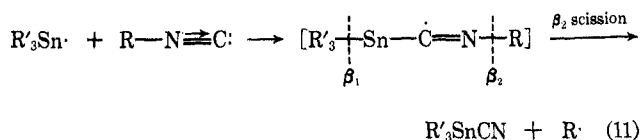


Figure 4.—Dependency of the molar ratio of 14/13 on the concentration of 2-propanethiol.

In the intermediate imidothiyl radical 17, the R-N bond is located at another β position (β_2), which may possibly be involved in a β -scission reaction especially when R is



a good leaving group as a free radical. The isocyanide-thiol reaction, however, does not involve β_2 scission at the R-N bond; *i.e.*, in the first two reactions of Table I using *t*-butyl isocyanide (4), no product derived from the β_2 scission of 17 was detected. This is quite different from the radical reaction of isocyanide with trialkylstannane, which involves scission at β_2 position (eq 11).⁶



Experimental Section

Materials.—All thiols were commercial samples of pure grade, which were purified by rectification under nitrogen prior to use. Isocyanides were prepared from the corresponding formamides according to Ugi's procedure.⁷

Reactions of Cyclohexyl Isocyanide (5) with 2-Methyl-2-propanethiol (11) (Figure 1).—Curve a reaction: A mixture of 0.90 g (10 mmol) of 11 and 1.08 g (10 mmol) of 4 was heated at 60° in a nitrogen atmosphere without added catalyst. The progress of the reaction was followed by glpc determination of 13 at several times of reaction (column, silicon DC 550 and PEG 20000). Curve b reaction: A ternary mixture of 0.90 g (10 mmol) of 11, 1.08 g (10 mmol) of 5, and 17 mg (0.1 mol) of AIBN was heated at 60°. Curve c reaction: As a radical inhibitor, 55 mg (0.5 mmol) of hydroquinone was added at the beginning of the curve a reaction. Curve d reaction: After the reaction proceeded for 20 min under the same conditions as those of the curve a reaction, 22 mg (0.2 mmol) of hydroquinone was added to the reaction system. Curve e reaction: A solution of 0.45 g (5 mmol) of 11, 0.54 g (5 mmol) of 5, and 2 ml of diethyl ether (solvent) in a Pyrex test tube cooled in an ice bath was irradiated using a high-pressure mercury lamp under nitrogen atmosphere.

Reactions of Cyclohexyl Isocyanide (5) with 2-Propanethiol (12), Ethanethiol (7), and 2-Butanethiol (10).—The time-conversion curve of the reactions of 5 with 12 (Figure 2) and 5 with 7 (Figure 3) were made by the same procedures as the above. The structures of 14 and 15 were established already.³ *sec*-Butyl N-cyclohexylthioformimidate was produced in the 5–10 reaction: bp 99–100° (4 mm), n_D^{20} 1.5012.

(6) T. Saegusa, S. Kobayashi, Y. Ito, and N. Yasuda, *J. Amer. Chem. Soc.*, **90**, 4182 (1968).

(7) I. Ugi and R. Meyr, *Chem. Ber.*, **93**, 239 (1960).

Anal. Calcd for $C_{11}H_{21}NS$: C, 66.27; H, 10.62; N, 7.03. Found: C, 66.03; H, 10.51; N, 7.11.

Nmr and ir (ν_{C-N} at 1595 cm^{-1}) spectra supported its structure.

Reaction of *t*-Butyl Isocyanide (4) with Benzenethiol (8).—A mixture of 0.55 g (5 mmol) of 8 and 0.42 g (5 mmol) of 4 was heated in the presence of 1.7 mg (0.01 mmol) of AIBN at 80° for 2 hr. Distillation gave 0.65 g (67%) of phenyl *N-t*-butylthioformimidate: bp $99-101^\circ$ (3 mm), n_D^{25} 1.5514.

Anal. Calcd for $C_{11}N_2S$: C, 68.34; H, 7.82. Found: C, 68.22; H, 7.95.

The structure was further confirmed by nmr and ir (ν_{C-N} at 1597 cm^{-1}) spectra.

Reaction of *t*-Butyl Isocyanide (4) with Ethanethiol (7).—Similarly, the 4-7 reaction by AIBN was carried out at 35° for 4 hr, which gave ethyl *N-t*-butylthioformimidate: bp $75-76^\circ$ (70 mm), n_D^{25} 1.4654.

Anal. Calcd for $C_7H_{15}NS$: C, 57.90; H, 10.34. Found: C, 57.60; H, 10.20.

Dependency of the Molar Ratio of 14/13 on the Concentration of 2-Propanethiol (12).—A series of five reactions was carried out, in which the initial concentration of 2-propanethiol was varied. A typical run was as follows. A mixture of 0.43 g (5.6 mmol) of 12 and 1.34 g (12.4 mmol) of 5 (concentration of 12, 2.8 mol/l.) was heated without radical initiator at 100° for 20 min. The total conversion for 12 was 8% and the molar ratio of 14/13 was determined to be 0.48 by glpc analysis.

Reactions of *t*-Butyl Isocyanide (4) with α -Toluenethiol (9).—The radical reaction of 4 with 9 by AIBN at 80° gave 93% *t*-butyl isothiocyanate and 96% toluene.

To a mixture of 1.24 g (10 mmol) of 9 and 1.00 g (12 mmol) of 4 was added 8.0 mg (0.1 mmol) of cupric oxide as a catalyst. The reaction system soon became homogeneous at room temperature. When the reaction mixture was heated at 100° for 2.0 hr, 91% of 9 disappeared. Benzyl *N-t*-butylthioformimidate was isolated by preparative glpc, n_D^{25} 1.5435.

Anal. Calcd for $C_{12}H_{17}NS$: C, 69.51; H, 8.26; N, 6.76. Found: C, 69.78; H, 8.37; N, 6.52.

Reaction of Cyclohexyl Isocyanide (5) with 2-Methyl-2-propanethiol (11) in the Presence of Cupric Oxide and *p*-Benzoquinone.—A mixture of 0.63 g (7 mmol) of 11, 0.54 g (5 mmol) of 5, 8 mg (0.1 mmol) of cupric oxide, and 55 mg (0.5 mmol) of *p*-benzoquinone was refluxed at 90° for 3 hr. By glpc analysis of the reaction mixture, *t*-butyl *N*-cyclohexylthioformimidate⁹ (64%) and 13 (6%) were formed.

Registry No.—*sec*-Butyl *N*-cyclohexylthioformimidate, 24058-23-9; phenyl *N-t*-butylthioformimidate, 24058-24-0; ethyl-*N-t*-butylthioformimidate, 24058-25-1; benzyl *N-t*-butylthioformimidate, 24058-26-2; 4, 630-18-2; 5, 931-53-3; 6, 100-47-0; 7, 75-08-1; 8, 108-98-5; 9, 100-53-8; 10, 513-53-1; 11, 75-66-1.

Peroxide-Metal Ion Oxidations. II. A Convenient Synthesis of Imides

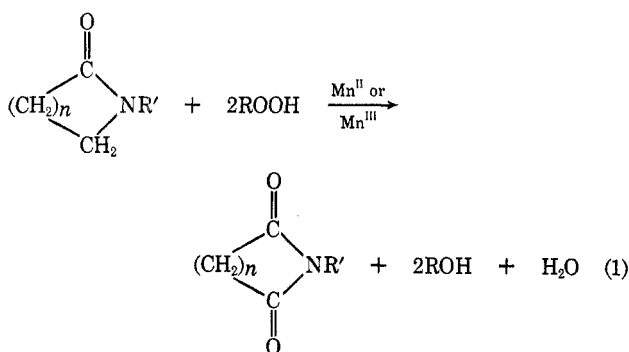
A. R. DOUMAUX, JR., AND D. J. TRECKER

Research and Development Department, Union Carbide Corporation, Chemicals and Plastics, South Charleston, West Virginia 25303

Received October 20, 1969

A novel and highly selective oxidation of lactams and *N*-alkylamides to the corresponding imides has been developed. The oxidant consists of a hydroperoxide or a peroxy acid in combination with a catalytic amount of a manganese(II) or -(III) salt. The extremely mild reaction represents the first convenient method for synthesizing many imides, including adipimide, a polymer intermediate which had previously been preparable only in low yields. The synthetic scope of the oxidation and its limitations are discussed.

A convenient synthesis of imides has been developed, using a novel and particularly mild oxidation procedure.¹ Lactams or *N*-alkylamides treated with a hydroperoxide or a peroxy acid in the presence of a metal ion catalyst such as manganese(II) produced the corresponding imides in excellent yield. The oxidation has proved to be quite general, proceeding under mild conditions to provide imides, many of which have previously been preparable only in poor yields. The general reaction and apparent stoichiometry are indicated below.



Metal ion interactions with hydroperoxides and peroxy acids are well known^{2,3} and have been used to

synthetic advantage in the past. Kharasch, Kochi, and their respective groups prepared 2-alken-1-yl esters and unsymmetrical peroxides by copper(I)-catalyzed treatment of olefins with peroxy esters and hydroperoxides, respectively.⁴ More recently, primary amines have been converted to oximes,⁵ tertiary amines to amine oxides,⁶ and sulfides to sulfoxides and sulfones⁷ by peroxide-metal ion oxidants. These latter reactions are characterized by oxidative transformations at the heteroatom.

The oxidation of amides to imides, a two-electron transformation at the position adjacent to the heteroatom, has been accomplished in low yield by autoxidation⁸ and by treatment with ruthenium tetroxide⁹ and persulfates.¹⁰ The procedure which we describe offers several advantages, the most significant being ease of operation, high selectivity, and generally satisfactory

(3) E. G. E. Hawkins, "Organic Peroxides, Their Formation and Reactions," D. Van Nostrand Co., Inc., Princeton, N. J., 1961, Chapters 1, 3, and 7.

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(6) U. S. Patent 3,274,252 (1966); L. Kuhnen, *Chem. Ber.*, **99**, 3384 (1966); M. N. Sheng and J. G. Zajacek, *J. Org. Chem.*, **33**, 588 (1968).

(7) L. Kuhnen, *Angew. Chem. Int. Ed. Engl.*, **5**, 893 (1966).

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(10) H. L. Needles and R. E. Whitfield, *J. Org. Chem.*, **31**, 341 (1966).

(1) For a preliminary report on the oxidation system, see A. R. Doumaux, Jr., J. E. McKeon, and D. J. Trecker, *J. Amer. Chem. Soc.*, **91**, 3992 (1969).

(2) A. G. Davies, "Organic Peroxides," Butterworth and Co. (Publishers) Ltd., London, 1961, Chapters 12 and 13.