

ORGANIC AND BIOLOGICAL CHEMISTRY

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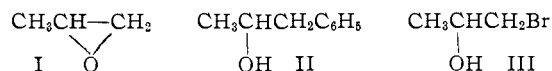
Factors Influencing the Course and Mechanisms of Grignard Reactions. XXIII.
The Reactions of Propylene Oxide and Related Compounds with Grignard Reagents¹BY M. S. KHARASCH,² L. BIRITZ, W. NUDENBERG, ANIMA BHATTACHARYA³ AND N. C. YANG⁴

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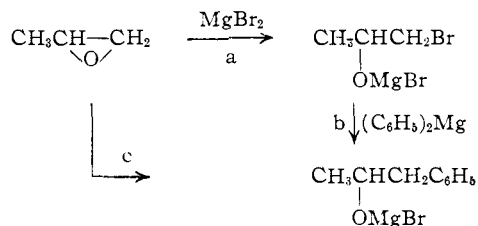
Propylene oxide reacts with phenylmagnesium bromide to give a mixture of 1-phenyl-2-propanol and 1-bromo-2-propanol. When this reaction was carried out in the presence of a catalytic amount of ferric chloride, an entirely different reaction took place. The main products were propylene and biphenyl with smaller amounts of 2-propanol and 1-phenyl-2-propanol; no 1-bromo-2-propanol could be isolated. When 1-propylmagnesium bromide was used instead of phenylmagnesium bromide, the yield of propylene was increased. 1-Bromo-2-propanol, 1-bromo-2-*n*-butoxypropane and isomeric propylene chlorohydrins behaved similarly when treated with phenylmagnesium bromide in the presence of certain transition metal salts. The reaction of propylene oxide with phenyllithium was not modified by the addition of ferric chloride. Possible mechanisms of these reactions are discussed.

The course of Grignard reactions may often be modified by additions of traces of metal salts, notably those of transition series.⁵ A combination of Grignard reagents and certain metal salts are efficient catalysts for the polymerization of simple olefins.⁶ In order to achieve a better understanding of the nature of these "modified" reactions, the reactions of Grignard reagents with ethylene oxides, halohydrins and their derivatives in the presence of transition metal salts were investigated. The products thus obtained were analyzed carefully and compared with those from the "conventional" Grignard reactions.

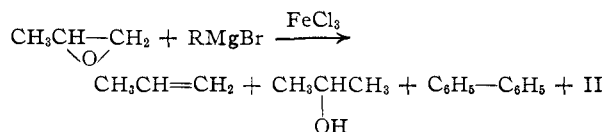
Ethylene oxides react with Grignard reagents to give a mixture of alcohols and halohydrins. The relative yields of these two products depend on the nature of the reactants and on the experimental conditions. At elevated temperatures, the main product is an alcohol. Around the boiling point of ether, a mixture of the two products is obtained. At low temperature with short contact time, the halohydrin is the only isolable product.⁷ Propylene oxide (I) reacts with phenylmagnesium bromide in ether to give 1-phenyl-2-propanol (II) and 1-bromo-2-propanol (III) in approximately equal amounts.⁵ The result of this reaction (when phenylmagnesium bromide prepared from sublimed magnesium is used) corresponds closely to that reported by the previous workers; the order of addition is of no effect. Grignard reagents, as has been demonstrated recently, are best represented as a complex of magnesium halide and organo-magnesium compounds.⁹ Even at low temperature,¹⁰ magnesium halides are known to



cleave ethylene oxides instantaneously to halohydrins, and it has been suggested that 1-bromo-2-propanol (III) is formed from the reaction of propylene oxide and the magnesium bromide in the Grignard reagent (step a). The bromohydrin thus formed reacts at elevated temperature with the phenylmagnesium compound to give 1-phenyl-2-propanol (II) (step b). However, formation of II by a direct attack of the Grignard reagent on the propylene oxide cannot be ruled out (step c).



When propylene oxide was treated with phenylmagnesium bromide in the presence of a catalytic amount of ferric chloride, there was an entirely different reaction. The main product was a gas, propylene (41%), together with smaller amounts of 2-propanol (15%), biphenyl and 1-phenyl-2-propanol (II); no 1-bromo-2-propanol (III) could be isolated. Since the yield of 1-phenyl-2-propanol (II) is not significantly changed, the bromohydrin III was probably reduced by the modified Grignard reagent; propylene and 2-propanol thus were formed. This conclusion is supported by the fact that under the reaction conditions the bromohydrin III was converted (in good yields) into propylene and 2-propanol.



When an alkyl Grignard reagent (e.g., 1-propylmagnesium bromide) is used instead of phenylmagnesium bromide, the yield of propylene is higher (71%). This result is in agreement with

(1) (a) Supported by a grant from the National Science Foundation, No. NSF G-2624. (b) A portion of this work was presented at the 135th Meeting of the American Chemical Society, Boston, Mass., April, 1959; Abstracts of Papers, p. 73-O.

(2) Deceased.

(3) U. S. Rubber and Tire Co. Postdoctoral Fellow, 1956-1957.

(4) To whom inquiries of this paper may be sent; Alfred P. Sloan Fellow.

(5) M. S. Kharasch, J. W. Hancock, W. Nudenberg and P. O. Tawney, *J. Org. Chem.*, **21**, 322 (1956), and earlier papers.

(6) J. K. Stille, *Chem. Revs.*, **58**, 541 (1958).

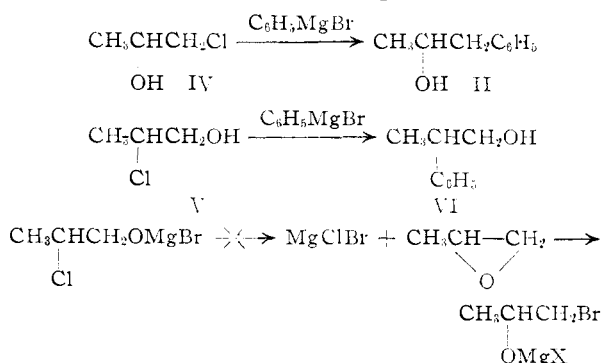
(7) N. G. Gaylord and E. J. Becker, *ibid.*, **49**, 413 (1950).

(8) R. C. Huston and C. O. Bostwick, *J. Org. Chem.*, **13**, 331 (1948).

(9) R. E. Desc- et al., *J. Am. Chem. Soc.*, **79**, 3476 (1957).

(10) C. A. Stewart and C. A. VanderWerf, *ibid.*, **76**, 1259 (1954).

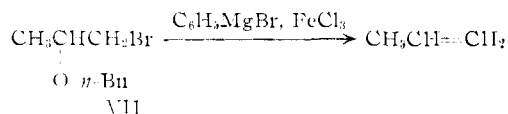
the fact that alkyl Grignard reagents react with ethylene oxides to give higher yields of halo-hydrins than aryl Grignard reagents.⁷



Isomeric chloropropanols, 1-chloro-2-propanol (IV) and 2-chloro-1-propanol (V), react with phenylmagnesium bromide in the presence of FeCl₃ to give propylene as the main product. The formation of 1-phenyl-2-propanol (II) from IV and 2-phenyl-1-propanol (VI) from V clearly demonstrated that phenylpropanol formation from a halo-hydrin is due to a direct displacement of the halide by the Grignard reagent. The magnesium salt of the halo-hydrin does not recycle appreciably to give propylene oxide under the reaction condition (reverse of step b); otherwise, the same phenyl propanol or same mixture of phenylpropanols would be formed from the two isomeric chloropropanols IV and V.

Phenyllithium reacts with propylene oxide in ether to give a moderate yield of 1-phenyl-2-propanol.¹¹ If the foregoing conclusion is valid, that the formation of propylene in the reaction of propylene oxide, phenylmagnesium bromide and ferric chloride is due to the intermediate formation of 1-bromo-2-propanol, the reaction of phenyllithium and propylene oxide cannot be modified by the addition of ferric chloride, and this is verified experimentally.

Finally, when a β-haloether, 1-bromo-2-*n*-butoxypropane (VII), is treated with phenylmagnesium bromide in the presence of FeCl₃, CrCl₃ or TiCl₄, an excellent yield of propylene is obtained. However, MnCl₂ has no effect on the reaction.



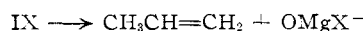
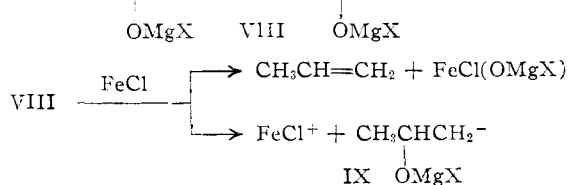
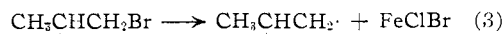
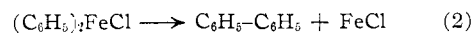
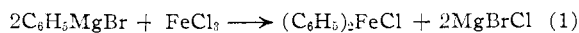
Discussion

Phenylmagnesium bromide gives with ferric chloride an unstable organoiron intermediate (step 1) which then decomposes to give biphenyl and a reduced iron salt (step 2).¹² Transition metal salts in the reduced form are known to be reactive intermediates which attack organic halides to give a radical (VIII) and to regenerate the salt in its higher oxidation state (step 3). The reaction is thus a chain reaction with reactions 1 to 3 as the propagating steps. The formation

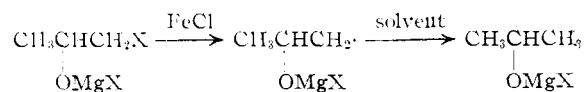
(11) S. J. Cristol, J. R. Douglass and J. S. Meek, *J. Am. Chem. Soc.*, **73**, 816 (1951).

(12) G. Champetier, *Bull. soc. chim.*, [4] **47**, 1131 (1930).

of free radicals from organic halides and modified Grignard reagents has been demonstrated in many instances¹³ and, specifically, the presence of a β-oxyalkyl radical in a modified Grignard reaction of halo-hydrin derivative already has been demonstrated.^{13a} The method of subsequent formation of propylene from the radical VIII thus generated is not clear. Two alternative routes are here suggested: (1) The radical may be further attacked by a reactive iron intermediate and propylene directly formed or (2) the attack by the intermediate gives a carbanion (IX) which eliminates an OMgX group to give propylene.¹⁴



From the reaction of phenylmagnesium bromide and ferric chloride with propylene oxide, 1-halo-2-propanol and 2-halo-1-propanol, isomeric propanols are obtained in small but appreciable amounts. These products were obtained from the reaction mixture by analytical distillation; they were identified by their derivatives and by gas chromatography. In all probability propanols are formed by the attack of the intermediate radical VIII on the solvent.



Among the catalysts investigated FeCl₃, being ether soluble, seems to be more satisfactory than other transition metal salts. The failure of MnCl₂ as a catalyst⁵ for the reaction between phenylmagnesium bromide and 1-bromo-2-butoxypropane probably is due to the formation of a relatively stable phenylmanganese compound.¹⁵ Since no reactive manganese intermediate is formed (step 2), no chain reaction may take place.

The reactions of epoxides, halo-hydrins and β-haloethers with a Grignard reagent in the presence of ferric chloride thus offer a convenient alternative method for the conversion of these compounds into the corresponding olefins. The yields of these reactions compare favorably with those obtained from existing methods.¹⁶

(13) (a) M. S. Kharasch, R. D. Mulley and W. Nudenberg, *J. Org. Chem.*, **19**, 1477 (1954); (b) M. S. Kharasch and W. H. Urry, *ibid.*, **13**, 101 (1948); and (c) R. O. C. Norman and W. A. Waters, *J. Chem. Soc.*, 950 (1957).

(14) E. D. Amstutz, *J. Org. Chem.*, **9**, 310 (1944).

(15) C. Beermann and K. Clauss, *Angew. Chem.*, **71**, 627 (1959).

(16) (a) H. O. House and R. S. Ro, *J. Am. Chem. Soc.*, **80**, 182 (1958); (b) J. W. Cornforth, R. H. Cornforth and K. K. Mathew, *J. Chem. Soc.*, 112 (1950); and (c) C. B. Scott, *J. Org. Chem.*, **22**, 1118 (1957).

TABLE I
 THE REACTION OF PROPYLENE OXIDE AND RELATED COMPOUNDS WITH GRIGNARD REAGENTS

Reactant	Mole	Grignard	Mole	Transition metal salt	Mole	Reaction Products			
						Alcohol ^a CH ₃ -CH(OH)-CH ₂ Ph	Halohydrin ^b CH ₃ CH(OH)-CH ₂ X	Pro- pylene	Pro- panol
	0.2	PhMgBr	0.44	None	...	40	40	0	0
	.2	PhMgBr	.44	None ^c	...	37	44	0	0
	.3	PhMgBr	.8	FeCl ₃	0.01	30	0	41	16 ^d
	.2	PhMgBr	.6	FeCl ₃	.01	13	0	78	4.5 ^d
	.3	<i>n</i> -PrMgBr	.7	FeCl ₃	.01	17 ^e	0	72	...
	.22	PhMgBr	.8	FeCl ₃	.01	12	0	82	4.5 ^d
	.21	PhMgBr	.8	FeCl ₃	.01	27 ^f	0	62	7 ^g
	.1	PhMgBr	.22	FeCl ₃	.005	95	...
	.1	PhMgBr	.4	TiCl ₄	.005	84	...
	.1	PhMgBr	.4	CrCl ₃	.005	92	...
	.1	PhMgBr	.4	MnCl ₂	.005	No gas ev.	...

^a 1-Phenyl-2-propanol, b.p. 120–121° (20 mm.), *n*_D²⁰ 1.5205–1.5208; α -naphthylurethan, m.p. 88.5–90°; phenylurethan, m.p. 91–92°. ^b 1-Bromo-2-propanol, b.p. 46–53° (15 mm.), *n*_D²⁰ 1.4832; α -naphthylurethan, m.p. 115–116°. ^c Inverse addition. ^d 2-Propanol, α -naphthylurethan, m.p. 105°. ^e 2-Hexanol, 60–65° (20 mm.), *n*_D²⁵ 1.4120; α -naphthylurethan, 60–61°; 3,5-dinitrobenzoate, 37–38°. ^f 2-Phenyl-1-propanol, b.p. 121° (26 mm.), *n*_D²⁵ 1.5220; *p*-nitrobenzoate, 64°; α -naphthylurethan, 103.5–104°. ^g 1-Propanol; phenylurethan, m.p. 78–79.5°.

Experimental¹⁷

The Grignard reagents were prepared under nitrogen by the reaction of freshly distilled halides with a 10% excess of sublimed magnesium in dry ether. The Grignard reagents were filtered, and their respective concentrations were determined by the addition of a 2-ml. aliquot to an excess of standard hydrochloric acid and back-titration with standard sodium hydroxide. Aliquots of the reagents were used for the various reactions unless otherwise stated. The alkyl Grignard reagents thus prepared are transparent and colorless solutions and the aryl Grignard reagents are clear brown solutions. Phenyllithium was prepared by the usual procedure using chlorobenzene or bromobenzene. Propylene oxide (Eastman Kodak Co.) was dried over anhydrous sodium sulfate and distilled through a column packed with glass helices (1.6 × 45 cm.); b.p. 35°. 1-Bromo-2-propanol was prepared by the reaction of anhydrous hydrogen bromide and propylene oxide in absolute ether at 0–5°; b.p. 52° (18 mm.), *n*_D²⁰ 1.4799; 1-chloro-2-propanol was prepared by the same method using hydrogen chloride; b.p. 65–67° (75 mm.), *n*_D²¹ 1.4380. No isomeric 2-halo-1-propanols were detected in these 1-halo-2-propanols by infrared spectroscopy.⁶ 1-Chloro-2-propanol was prepared by lithium aluminum hydride reduction of α -chloropropionyl chloride¹⁸; b.p. 70–71° (76 mm.), *n*_D²⁰ 1.4385. 2-*n*-Butoxy-1-bromopropane was prepared according to the procedure of Nesmeyanov, Lutsenko and Vereschagin¹⁹; b.p. 74–75° (17 mm.), *n*_D²⁰ 1.4450.

The Reactions of Propylene Oxide and Related Compounds with Grignard Reagents in the Presence of Transi-

tion Metal Halides.—The apparatus for these reactions consisted of a three-neck flask equipped with a Tru-Bore stirrer, a Friederichs condenser and a dropping funnel. Before the reaction, the apparatus was flame-dried and flushed with nitrogen. The exit of the condenser then was connected to a gas collecting bottle containing a saturated solution of sodium chloride. Ice-water was circulated through the condenser to exclude ether from the evolved gas. If the rate of gas evolution did not exceed 5 l. per hour, no additional trap was necessary. The propylene oxide or the halohydrins (0.1–0.3 mole) in 50–100 ml. of absolute ether was added dropwise through the dropping funnel to the Grignard mixture (0.22–0.8 mole) containing a small amount of transition metal halide (0.005–0.01 mole). The time of addition varied between 1 and 2 hours. It was seldom necessary to reflux the mixture for more than 1 hour following the addition. Usually, after the first 20 minutes of reflux no more gas was evolved.

The reaction mixture was hydrolyzed with saturated ammonium chloride.²⁰ The ethereal solution was decanted and concentrated by distillation at atmospheric pressure. The propanol was removed from the residue at room temperature under reduced pressure (20 mm.) and collected in a Dry Ice trap. The residue was analyzed by chromatography over alumina (Activity 111), using petroleum ether as the eluent to separate the biphenyl from the phenylpropanol. The phenylpropanol was eluted with ether. After removal of the ether, the phenylpropanol was isolated by distillation under reduced pressure. To recover propanol quantitatively, the distilled ether was carefully fractionated with a Heliapak column rated at 50 theoretical plates. The residue was combined with the material previously collected in the Dry Ice trap and fractionated on an analytical column. The distillate consisted of the azeotrope of benzene (from Grignard reagent) and the propanol and intermediate

(17) The boiling points and melting points are uncorrected.

(18) W. Fickett, H. K. Garner and H. J. Lucas, *J. Am. Chem. Soc.*, **73**, 5066 (1951).

(19) A. N. Nesmeyanov, I. F. Lutsenko and N. I. Vereschagin, *Bull. Acad. Sci. U.S.S.R., Classe Sci. Chim.*, **63** (1947); *C. A.*, **42**, 4148i (1948).

(20) L. F. Fieser, "Experiments in Organic Chemistry," 2nd Edition, D. C. Heath Co., New York, N. Y., 1941, p. 410.

fractions which were analyzed by gas chromatography using a 0.25" × 6' column packed with polypropylene glycol (30%) on firebrick.

The composition of the evolved gases was determined by the method of Kharasch, Lewis and Reynolds²¹ and verified by gas chromatography with a 0.25" × 50' column packed with dimethyl sulfoxide (30%) on firebrick.

The results of these experiments are given in Table I.

Reaction of Phenyllithium and Propylene Oxide in the Presence of Ferric Chloride.—Propylene oxide (17.4 g., 0.3 mole) in 100 ml. of ether was added dropwise into an ethereal solution of phenyllithium (0.77 mole) containing 5.5 g.

(21) M. S. Kharasch, D. W. Lewis and W. B. Reynolds, *J. Am. Chem. Soc.*, **65**, 495 (1943).

(0.0385 mole) of ferric chloride. The mixture was refluxed for 1 hour following the addition. No gas evolution was observed. After being cooled to 0–5°, the mixture was decomposed with a minimum quantity of saturated aqueous ammonium chloride solution. The ethereal layer was decanted and the residue was washed with ether (2 × 10 ml.). The combined ethereal solution was concentrated to a light brown oily residue (29 g.). A portion of the oil (14.5 g.) was chromatographed over alumina (200 g., Woelm Activity II). Biphenyl (0.75 g.) was isolated from the petroleum ether eluent. A yellow liquid (13.1 g.) was isolated from the ether eluent. Distillation of this liquid yielded 1-phenyl-2-propanol (12.6 g., 61%), b.p. 98–100° (15 mm.), n_D^{20} 1.5210; 1-naphthylurethan, m.p. 92° alone or admixed with an authentic sample.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND THE INSTITUTE OF ORGANIC CHEMISTRY, THE UNIVERSITY OF CHICAGO, CHICAGO 37, ILL.]

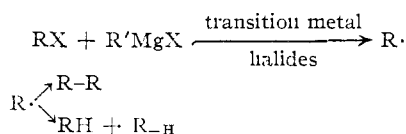
Factors Influencing the Course and Mechanism of Grignard Reactions. XXIV. Reactions of 1,3-Disubstituted Compounds, 1,2-Hydrogen Atom Shift¹

BY M. S. KHARASCH,² M. WEINER, W. NUDENBERG, ANIMA BHATTACHARYA,³ TING-I WANG AND N. C. YANG⁴

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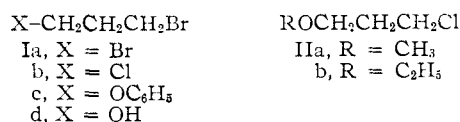
The reactions of 3-substituted 1-alkyl halides with phenylmagnesium bromide in the presence of ferric chloride were investigated. 1,3-Dibromopropane and 1-bromo-3-chloropropane gave cyclopropane; 3-ethoxy-1-chloropropane and 3-methoxy-1-chloropropane gave pure propylene, while 3-phenoxy-1-bromopropane gave a mixture of these two products. The formation of propylene in these reactions is interpreted *via* a 1,2-hydrogen atom shift of the intermediate 3-alkoxy-1-alkyl radical.

Simple alkyl halides react with Grignard reagents in the presence of transition metal halides to give alkanes, alkenes and alkyl dimers in various proportions.⁵ The formation of these products may be rationalized from the disproportionation and dimerization of the intermediate alkyl radicals.



In several instances, the presence of these radicals was detected in appreciable concentration.⁶ The introduction of a second functional group to the alkyl halide molecule has a direct influence on these reactions. In 2-substituted 1-alkyl halides, the main product was an alkene derived from the elimination of both functional groups.⁷ This observation led subsequently to a systematic study of the reactions of modified Grignard reagents, *i.e.*, combinations of Grignard reagents and transition metal salts, and bifunctional organic compounds. The present communication deals with the reactions of modified Grignard reagents

with 3-substituted 1-alkyl halides, such as 1,3-dibromopropane (Ia), 1-bromo-3-chloropropane (Ib), 3-phenoxy-1-bromopropane (Ic), 3-methoxy-1-chloropropane (IIa), 3-ethoxy-1-chloropropane (IIb) and 3-bromo-1-propanol (Id), and trimethylene oxide.



1,3-Dihalopropanes and 3-halopropyl ethers do not react with phenylmagnesium bromide prepared from sublimed magnesium. In the presence of a small amount of ferric chloride, 1,3-dibromopropane (Ia) or 1-bromo-3-chloropropane (Ib) reacts with phenylmagnesium bromide to give a good yield (81–84%) of cyclopropane contaminated with small amount of propylene, while 1-methoxy-3-chloropropane (IIa) or 1-ethoxy-3-chloropropane (IIb) under similar conditions gives exclusively pure propylene (60–78%). In view of this surprising finding, the formation of propylene from 1,3-disubstituted propanes, the reaction of 3-phenoxy-1-bromopropane (Ic) with modified Grignard reagents⁸ was reinvestigated. The result showed that a mixture of cyclopropane and propylene was obtained. The effectiveness of various transition metal salts as modifiers in these reactions were investigated and ferric chloride was found to be the most effective. 3-Bromo-1-propanol (Id) reacts with phenylmagnesium bromide in the presence of ferric chloride to give a moderate yield of propylene (38%); trimethylene oxide is quite

(1) Supported by grants from the National Science Foundation, No. NSF G-2624, and from the Research Corporation.

(2) Deceased.

(3) Firestone Tire and Rubber Co. Postdoctoral Fellow, 1957–1958.

(4) To whom inquiries on this paper may be sent; Alfred P. Sloan Foundation Fellow.

(5) M. S. Kharasch, J. K. Hambling and T. P. Rudy, *J. Org. Chem.*, **24**, 303 (1959), and references therein.

(6) (a) M. S. Kharasch and W. H. Urry, *ibid.*, **13**, 101 (1948); (b) M. S. Kharasch, R. D. Mulley and W. Nudenberg, *ibid.*, **19**, 1477 (1954); and (c) R. O. C. Norman and W. A. Waters, *J. Chem. Soc.*, 950 (1937).

(7) M. S. Kharasch, *et al.*, *J. Am. Chem. Soc.*, **83**, 3229 (1961).

(8) M. S. Kharasch, G. Stampa and W. Nudenberg, *J. Org. Chem.*, **18**, 575 (1953).