The Formation of Tetrazoles by the Condensation of Organic Azides with Nitriles

WAYNE R. CARPENTER

Organic Chemistry Branch, U. S. Naval Ordnance Test Station, China Lake, Calif.

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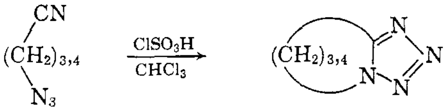
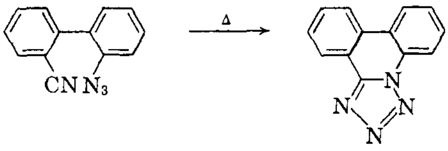
Various 1,5-disubstituted tetrazoles have been synthesized by the thermal condensation of alkyl and aryl azides with electronegative nitriles. This reaction provides a new approach to synthesis in the tetrazole series.

The conversion of nitriles to 5-substituted tetrazoles by reaction with azide ion or hydrazoic acid is well established.[1] However, the analogous reaction between nitriles and organic azides has remained a challenge to investigators in this field. Only two examples of successful condensation are described in the literature. von Kereszty describes the acid-catalyzed cyclization of γ-azidobutyronitrile and δ-azidocapronitrile to form bicyclic tetrazoles.[2] Smith describes the thermal cyclization of



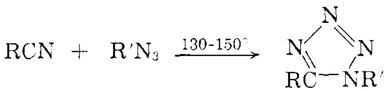
2-azido-2′-cyanobiphenyl to form tetrazolophenanthridine.[3]

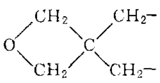
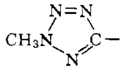


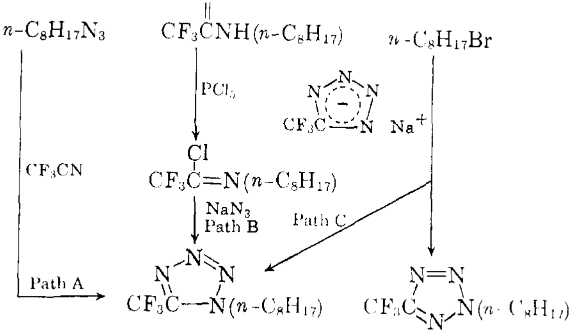
Inasmuch as both of these examples involved intramolecular condensation, it was of interest to discover a method of extending the reaction to intermolecular condensation. It has now been found that intermolecular condensation can be made to occur without catalyst if the nitrile is sufficiently activated by electron-withdrawing groups. With unactivated nitriles, the reaction failed even with the use of various catalysts. Table I describes the results obtained with various azides and activated nitriles.

In each instance where condensation was successful only one of the two possible isomeric tetrazoles was isolated. The products of two of the reactions were shown by independent syntheses to be 1,5-disubstituted tetrazoles. The product obtained from trifluoroacetonitrile and octyl azide was synthesized by two other methods. One method (path B) is specific for 1,5-disubstituted tetrazole synthesis. The other method (path C) affords a mixture of the 1,5- and 2,5-disubstituted tetrazoles, which can be separated by fractional distillation. The three samples of 1-octyl-5-trifluoromethyltetrazole were identical. An independent synthesis of the tetrazole obtained from phenyl azide and perfluorobutyronitrile was carried out *via* a method analogous to path B, thus determining the product to be 1-phenyl-5-perfluoropropyltetrazole.

TABLE I



R	R′	Yield, %
CF_3—	n-C_8H_{17}—	96
C_3F_7—	C_6H_5—	22
CCl_3—	n-C_8H_{17}—	69
—CCl_2—	n-C_8H_{17}—	20
C_3F_7-		95
	n-C_8H_{17}—	76
C_3F_7—	$C_3F_7CH_2$—	64



It was hoped that activation of the nitrile group might be achieved without the use of electronegative substitution. Boron trifluoride etherate has been used with success in the catalysis of hydrazoic acid condensation with nitriles.[1] Therefore, it was felt that Lewis acids or protic acids might catalyze the corresponding condensation with organic azides and nitriles. Of various Lewis acids and protic

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(1) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958) and references contained therein.

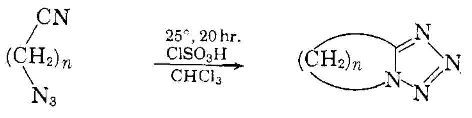
(2) von Kereszty and Wolf, German Patent 611,692; *Chem. Abstr.*, **29**, 5994⁹ (1935).

(3) P. A. S. Smith, J. M. Clegg, and J. H. Hall, *J. Org. Chem.*, **23**, 524 (1958).

acids ($AlCl_3$, BF_3, $BF_3 \cdot (C_2H_5)_2O$, HSO_3Cl, CF_3COOH, $FeCl_3$, $ZnCl_2$, $PtCl_2$, CH_3SO_3H) and various azides (phenyl azide, *p*-dimethylaminophenyl azide, cyclohexyl azide, octyl azide, butyl azide) and various nitriles (acetonitrile, butyronitrile, benzonitrile, *p*-nitrobenzonitrile, terphthalonitrile) no combination was found which would furnish a tetrazole. Either the components failed to react at all or else the azide would decompose to nitrogen and a complex mixture of amines, imines, and uncharacterizable materials. It is not too surprising that acidic materials fail to catalyze the reaction when one considers the relative basicities of nitriles and azides. In order to be effective the catalyst must complex with the nitrile, but because of the greater basicity of the azide it is complexed preferentially.

A wide variation was found to exist between the thermal stabilities of organic azides. Whereas *n*-octyl azide was recovered nearly unchanged after forty-eight hours at 150°, *p*-dimethylaminophenyl azide was completely decomposed after a few hours at 110°. Phenyl azide is also unstable above 100°. Hence, in the thermal condensation of phenyl azide with perfluorobutyronitrile only a 32% yield of the corresponding tetrazole was obtained, whereas *n*-octyl azide affords a 96% yield with trifluoroacetonitrile, the difference being due to the extensive decomposition of phenyl azide.

An effort was made to extend von Kereszty's cyclization to higher members of the series by treating a series of ω-azidoalkyl cyanides under identical conditions with chlorosulfonic acid in chloroform. It was found that von Kereszty's reactions were readily duplicated where *n* equals 3 and 4, but where *n* equals 5 or 6 no tetrazoles (either monomeric or polymeric) could be detected by careful chromatographic analysis of the products. In fact, much of the starting material was recovered. Under the same conditions butyronitrile and butyl azide also failed to produce a tetrazole. The implication of these results is that in the transition state of the cyclization process a high degree of orientation of the cyano and azido groups is required, resulting in a high negative entropy of activation. Where *n* equals 3 and 4, the entropy factor is lowered, thus enabling the reaction to proceed. In certain respects the azide–nitrile condensation is similar to the Diels-Alder condensation. A high degree of orientation is required in the transition state; electronegative substitution on the dienophile (the nitrile) assists the reaction; and where two modes of addition are possible, one mode is usually predominant.



n	Yield, %
3	89
4	79
5	0
6	0

Experimental

Alkyl Azides.—The alkyl azides employed in this study [with the exceptions of 3,3-bis(azidomethyl)oxetane and 1,1-dihydroperfluorobutyl azide] were conveniently prepared by stirring a mixture of the alkyl halide, excess sodium azide, and diethylene glycol at 95–100° for 20–24 hr. The product was steam distilled from the mixture and then redistilled under reduced pressure. It appeared to make little difference whether the halide was chloride, bromide, or iodide. Yields were usually in the 70–80% range. This method was also used in the preparation of the ω-azidoalkyl cyanides from the corresponding ω-haloalkyl cyanides (Aldrich Chem. Co.). α-Azidobutyronitrile and δ-azidovaleronitrile were reported previously by von Kereszty.[3] ε-Azidocapronitrile was previously prepared.[4] ω-Azidoheptanonitrile is a new compound, b.p. 101°/0.25 mm.

Anal. Calcd. for $C_7H_{12}N_4$: C, 55.71; H, 7.81; N, 36.71. Found: C, 55.24; H, 7.95; N, 36.81.

3,3-Bis(azidomethyl)oxetane.—Thirty-one grams of 3,3-bis(chloromethyl)oxetane, 50 g. of sodium azide, and 200 ml. of diethylene glycol were stirred and heated on a steam bath for 30 hr. The product was steam distilled and then separated from the distillate with the help of ether. The organic phase was dried over anhydrous magnesium sulfate, filtered, and then distilled. The product was collected at 88.5–91.5°/1.0 mm.; yield, 7.3 g. or 25%.

Anal. Calcd. for $C_5H_8ON_6$: C, 35.71; H, 4.79; N, 49.98. Found: C, 35.98; H, 4.69; N, 49.82.

Caution: This compound can explode violently if heated above 200°.

1,1-Dihydroperfluorobutyl Azide.—Fifteen grams of sodium azide and 35.4 g. of 1,1-dihydroperfluorobutyl tosylate were added to 150 ml. of diethylene glycol in a 300-ml. flask equipped with stirrer and a simple distillation apparatus. The mixture was stirred and at the same time heated to 180°, at which temperature the product began to be evolved along with some water and ammonium azide. The product (8.6 g., 38%) consisted of the lower layer of the two phase distillate. The azide was redistilled at 72°/700 mm. It was found to be shock-insensitive. Its refractive index is 1.3150 at 30°.

Anal. Calcd. for $C_4H_2N_3F_7$: C, 21.34; H. 0.90; N, 18.67; F, 59.10. Found: C, 21.15; H, 1.23; N, 18.81; F, 58.90.

Preparation of Perfluoro- and Perchloronitriles.—Trichloromethyl-, trifluoromethyl-, and perfluorobutyronitrile were prepared from the corresponding amides by thoroughly mixing the amide with an equal weight of phosphorus pentoxide and heating the mixture to 160°–170° for 4 hr. The volatile nitriles were trapped at −70° and then redistilled. The boiling points of the nitriles are as follows: CCl_3CN, 78°; CF_3CN, −64°; C_3F_7CN, −1 to 5°. Dichloromalononitrile, b.p. 97°, was prepared according to the method of Ott by chlorination of an aqueous solution of malonitrile at 5°.[5]

1-Octyl-5-trifluoromethyltetrazole.—Octyl azide (8.66 g.) and trifluoroacetonitrile (3.76 g.) were sealed in a glass tube at −70°. The tube was heated in a reaction bomb at 150° for 17.5 hr. and then cooled before being opened. Distillation of the liquid product yielded 2.17 g. of octyl azide in the forerun and 6.20 g. of 1-octyl-5-trifluoromethyltetrazole (96% conversion), b.p. 81.5–85°/0.25 mm; $n^{25}D$ 1.4172.

1-Phenyl-5-perfluoropropyltetrazole.—Phenyl azide (10.17 g.) and perfluorobutyronitrile (19.64 g.) were sealed in a glass tube at 0° and heated in a reaction bomb at 130° for 17 hr. The tube was cooled to −70° before being opened be-

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[4] E. Gryszkiewicz-Trochemowski and A. Sporzynski, *Roczniki Chem.*, **16**, 37 (1936).

[5] E. Ott and B. Löpmann, *Ber.*, **55**, 1255 (1922).

hind a barricade to release internal pressure. The dark, oily product was dissolved in 150 ml. of ether. This solution was hydrogenated with hydrogen (platinum catalyst) to convert azides, azo compound, etc., to amines. These amines were then removed by extraction with dilute sulfuric acid. The ether layer was dried over anhydrous magnesium sulfate, then filtered and concentrated to yield 4.97 g. (22% yield) of brown solid, 1-phenyl-5-perfluoropropyltetrazole, m.p. 66–69° after recrystallization from ethanol–water and sublimation at 75°/0.1 mm.

Anal. Calcd. for $C_{10}H_5N_4F_7$: C, 38.23; H, 1.60; N, 17.83; F, 42.33. Found: C, 38.34; H, 1.46; N, 17.84; F, 41.98.

1-Octyl-5-trichloromethyltetrazole.—Trichloroacetonitrile (10.98 g.) and *n*-octyl azide (8.69 g.) were sealed in a glass tube and heated in a reaction bomb at 150° for 20 hr. The tube was cooled to −70° before being opened behind a barricade to release internal pressure. The dark, oily product was fractionated to obtain 11.5 g. (69% yield) of 1-octyl-5-trichloromethyltetrazole, b.p. 152–5°/0.75 mm., n^{25}_D 1.4922.

Anal. Calcd. for $C_{10}H_{17}N_4Cl_3$: C, 40.08; H, 5.72; N, 18.70; Cl, 35.50. Found: C, 40.06; H, 5.93; N, 18.69; Cl, 35.66.

Dichlorobis(1-octyl-5-tetrazolyl)methane.—Dichloromalononitrile (15.71 g.) and excess octyl azide (29.68 g.) were sealed in a glass tube and heated in a reaction bomb at 150° for 23 hr. The tube was chilled to −70° before being opened behind a barricade to release internal pressure. The black, viscous product was dissolved in 200 ml. of benzene. An equal volume of hexane was added to precipitate tarry materials, which were then removed by filtration. The dark filtrate was passed through an alumina column containing 400 g. of alumina. The product was eluted with a 20-vol. % solution of methylene chloride in hexane. The product, 8.8 g. (19.8%), a dark solid, was purified by recrystallization from ethanol–water, followed by recrystallization from toluene–hexane. The white crystals thus obtained melted at 56–57.5°.

Anal. Calcd. for $C_{19}H_{34}N_8Cl_2$: C, 51.34; H, 7.69; N, 25.16; Cl, 15.92. Found: C, 51.59; H, 7.17; N, 25.30; Cl, 15.38.

3,3-Bis(5-perfluoropropyl-1-tetrazolyl)oxetane.—3,3 Bis-(azidomethyl)oxetane (4.92 g.) and excess perfluorobutyronitrile (18.6 g.) were sealed in a glass vial at 0° and heated in a reaction bomb at 150° for 20 hr. After being cooled to −70°, the vial was opened behind a barricade. The excess perfluorobutyronitrile was allowed to boil off upon warming to ambient temperature. The yellow, waxy, crystalline product weighed 15.63 g. (95% yield based on the azide) and melted at 130–133°. It was purified by recrystallization from benzene–ethanol, ethanol–water, and benzene, m.p. 136.5–138.5°.

Anal. Calcd. for $C_{13}H_8F_{14}O$: C, 27.97; H, 1.44; N, 20.07; F, 47.65. Found: C, 28.01; H, 1.48; N, 20.03; F, 49.14.

1-Octyl-5-(2-methyl-5-tetrazolyl)tetrazole.—2-Methylcyanotetrazole (5.53 g.) and 7.72 g. of octyl azide were heated in a reaction bomb at 150° for 24 hr. The light yellow liquid product was removed from the bomb and heated to 150°/0.4 mm. to remove the starting materials. The residue solidified on cooling and consisted of nearly pure 1-octyl-5-(2-methyl-5-tetrazolyl)tetrazole (10.1 g., 76% yield). The material was recrystallized once from ethanol–water and once from ether–pentane, from which transparent, white scales were obtained, m.p. 34.5–36°.

Anal. Calcd. for $C_{11}N_8H_{20}$: C, 49.98; H, 7.63; N, 42.39. Found: C, 50.18; H, 7.04; N, 42.67.

***N*-Octyltrifluoroacetamide.** Methyl trifluoroacetate (50.0 g.) was added slowly to a flask containing 43.6 g. of octylamine. An efficient reflux condensor was used to return the methyl trifluoroacetate to the flask as the mixture became warm. After the addition was complete, the mixture was allowed to stand overnight before being distilled. The fraction boiling at 109–113°/4.0 mm. crystallized upon long standing, m.p. 26–28°, wt. 59.0 g., 78% yield. A portion of the material was redistilled to obtain an analytical sample, b.p. 86°/0.3 mm.

Anal. Calcd. for $C_{10}H_{18}NF_3O$: C, 53.32; H, 8.05; N, 6.22; F, 25.30. Found: C, 53.30; H, 8.20; N, 6.68; F, 25.97.

Reaction of *N*-Octyltrifluoroacetimidoyl Chloride with Sodium Azide. The *N*-octyltrifluoroacetimidoyl chloride was prepared by heating a mixture of 25.0 g. of phosphorus pentachloride and 25.2 g. of *N*-octyltrifluoroacetamide at 100° for 1 hr. Phosphorus oxychloride was removed at 100°/20 mm. The residue was then distilled. The imidoyl chloride (6.0 g.) was obtained as a fraction boiling at 41–45°/0.15 mm. This fraction was redistilled to obtain 1.77 g. of purified product, b.p. 44–45°/0.5 mm. This material was added to a suspension of 5.0 g. of finely powdered sodium azide in 50 ml. of dry acetonitrile. The resulting mixture was stirred 65 hr. at ambient temperature under anhydrous conditions and refluxed for 1 hr. before being filtered. Evaporation of the filtrate yielded 1.81 g. of a clear, colorless oil (1-octyl-5-trifluoromethyltetrazole). The infrared spectrum and refractive index showed it to be identical to the material formed by condensation of trifluoroacetonitrile and octyl azide.

Reaction of the Sodium Salt of 5-Trifluoromethyltetrazole with Octyl Bromide. A solution of 20 ml. of octyl bromide, 150 ml. of acetonitrile and 14.7 g. of the sodium salt of 5-trifluoromethyltetrazole was heated under reflux for 18 hr. on the steam bath. The mixture was filtered and the filtrate was concentrated to an oil. Fractionation of the oil produced three fractions. Fraction I, b.p. 66–82°/40 mm., consisted mainly of octyl bromide (4.85 g.). Fraction II, b.p. 82–112°/4.0 mm., consisted mainly of 2-octyl-5-trifluoromethyltetrazole (16.24 g.). Fraction III (0.90 g.) was obtained by reducing the pressure to 0.2 mm. to distill the residue. This fraction consisted mainly of 1-octyl-5-trifluoromethyltetrazole, which was identified by its infrared spectrum. Fraction II was redistilled to obtain an analytical sample, b.p. 108–111°/4 mm. Refractive index of pure material, n^{25}_D 1.4090.

Anal. Calcd. for $C_{10}H_{17}N_4F_3$: C, 47.99; H, 6.85; N, 22.39; F, 22.77. Found: C, 47.91; H, 6.57; N, 23.31; F, 23.08.

Preparation of 1-Phenyl-5-perfluoropropyltetrazole from Heptafluorobutyranilide. Heptafluorobutyranilide (17.5 g.), phosphorus pentachloride (13.6 g.), and 50 ml. of dry toluene were heated to reflux under anhydrous conditions for 6 hr. Toluene and phosphorus oxychloride were then removed by heating on the steam bath under vacuum. Sodium azide (12.0 g.) and 150 ml. of dry acetonitrile were then added and the mixture was stirred magnetically for 3 days at ambient temperature under anhydrous conditions. The mixture was heated to reflux for 1 hr., cooled, and then filtered. The filtrate was treated with an excess of 10% sodium hydroxide solution and then extracted twice with 200-ml. portions of ether. The ether extract was dried with anhydrous magnesium sulfate, filtered, and concentrated to 7.8 g. of tan oil, which solidified on standing; m.p. 40–68°. Three recrystallizations from ethanol-water were required to rid the tetrazole of anilide impurity. The melting point of the pure, dry product is 58–62° and is not depressed by admixture with the material produced by condensation of phenyl azide with perfluorobutyronitrile. The infrared spectra of the two samples of 1-phenyl-5-perfluoropropyltetrazole prepared by different methods are identical.

1-(1,1-Dihydroperfluorobutyl)-5-perfluoropropyltetrazole.—A mixture of 5.33 g. of 1,1-dihydroperfluorobutyl azide and 8.39 g. of perfluorobutyronitrile was sealed in a glass vial and heated in a bomb reactor at 155° for 27 hr. The vial was then cooled and opened. Excess nitrile and azide were removed by placing the vial in hot water. The pale, yellow residue was solidified by chilling in ice, wt. 6.36 g., 64%. The material was crystallized from ether–pentane as long, fibrous, white needles, m.p. 25.5–26.5°. The material has a strong tendency to sublime even at room temperature. Hence, it was further purified by sublimation at room temperature under vacuum.

Anal. Calcd.: C, 22.87; H, 0.48; N, 13.37; F, 63.31. Found: C, 22.64; H, 0.39; N, 13.19; F, 63.36.

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Sterically Crowded Amines. III. β-Chloroamines and Aziridines[1]

G. F. HENNION AND PETER E. BUTLER[2]

Chemical Laboratories of the University of Notre Dame, Notre Dame, Ind.

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Tetra-substituted aziridines, $R^1R^2C—CH(CH_3)—N—R^3$, were prepared by cyclization of β-chloroamines, $R^1R^2C(NHR^3)—CHCl—CH_3$. The chloroamines of indicated structure were obtained by treatment of the corresponding β-amino alcohols with thionyl chloride. Methods are described for the preparation of sterically crowded aziridines.

Mention was made in a previous paper[3] that 1,2,2,3-tetra-substituted aziridines may be prepared from certain sterically crowded β-amino alcohols *via* the intermediate β-chloroamines. The synthesis involves the steps A→B→C→II→XI shown in Fig. 1. These transformations and the nature of the various products were studied in detail in the case of 1-isopropyl-2,2,3-trimethylaziridine (XI) and related compounds correlated as shown. The fact that the amines A,D,E, and XVIII and their hydrochlorides were already known aided significantly in the assignment of the structures II, XI, XVI, and XVII.

Treatment of 3-isopropylamino-3-methyl-2-butanol[3] (preferably as the hydrochloride[3] in chloroform) with thionyl chloride yielded a chloroamine

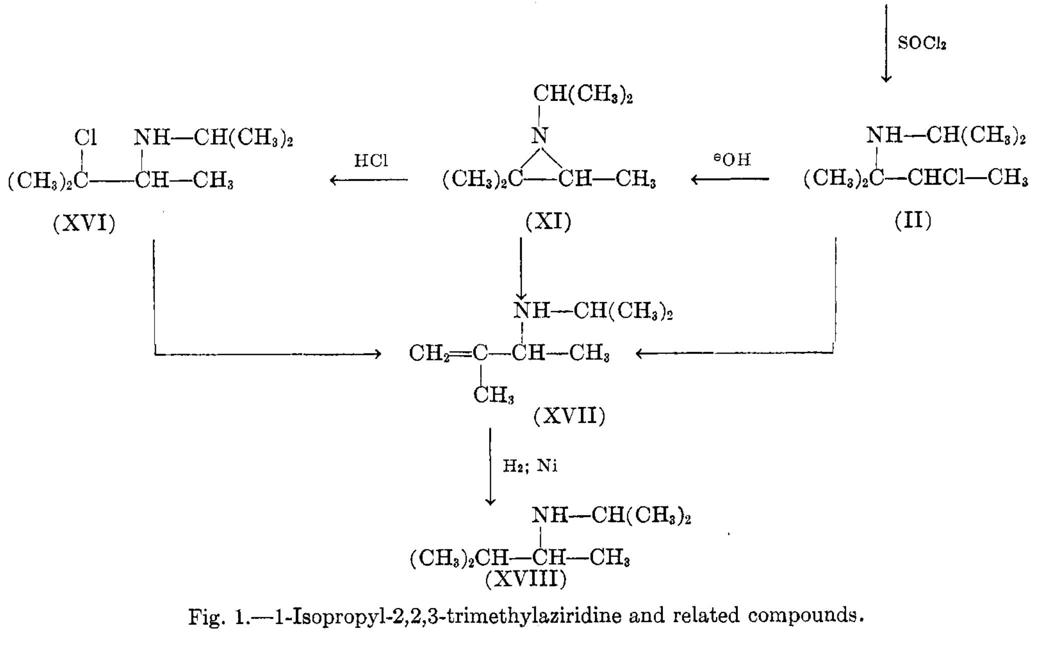

Fig. 1.—1-Isopropyl-2,2,3-trimethylaziridine and related compounds.

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[1] Paper no. 78 on substituted acetylenes; previous paper, G. F. Hennion and Leonard Price, *J. Org. Chem.*, **27**, 1587 (1962).

[2] Eli Lilly Company Fellow, 1959-1961. Abstracted in part from the Ph.D. dissertation of P. E. B.

[3] G. F. Hennion and P. E. Butler, *J. Org. Chem.*, **26**, 3341 (1961).