Aprotic Diazotization[1] of Arylamines in Aromatic Solvents. The Effect of Addition of Strong Acid[2]

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The reaction of arylamines with amyl nitrite in aromatic solvents gives moderate yields of biaryl products. Substrate and positional selectivity, as well as the iodine-abstracting ability of the intermediate generated, indicate that a phenyl radical is the attacking species. The addition of strong acid to the system results in a change in the reaction scheme wherein partial participation of a phenyl cation or diazonium ion is involved. The reaction has been adapted for synthetic use to give biaryl products, supplementing the work of previous investigators.

The reaction of aromatic amines with amyl nitrite in aromatic solvents gives moderate yields of biaryl products.[4] While the present investigation, initiated to determine the mechanism(s) involved and the synthetic scope of the reaction, was in progress, it was reported[5] that phenyl radicals are involved in this reaction. The nature of the results reported herein further supports the intermediacy of radicals and complements the proposed mechanistic scheme for the course of biaryl formation by diazotization coupling[6] reactions.

To determine optimum reaction conditions, *o*-chloroaniline was diazotized with a slight excess of amyl nitrite in a 30-fold molar excess of benzene. Order and method of addition of reagents, temperature, and nitrite concentration were varied without affecting the biaryl yield (Table I). The choice of conditions was then based on convenience; the reagents were added to excess solvent at room temperature and reaction was effected at reflux or 120°, whichever temperature was lower. Nitrogen evolution, a means of observing the decomposition process, ceased within 2 hr.

TABLE I

DIAZOTIZATION OF *o*-CHLOROANILINE IN BENZENE

Technique[a]	Temperature, °C	Time, hr	% yield
Nitrite added to amine–benzene	80[b]	4	38
Amine added to nitrite–benzene	80	4	40
Nitrite, amine, benzene mixed directly	~27	4	39
Nitrite, amine, benzene mixed directly	80	3	40
Nitrite,[c] amine, benzene mixed directly	80	3	40

[a] 1.2 molar equiv of nitrite present. [b] Solution reflux temperature. [c] 2.0 molar equiv of nitrite present.

The extent of nitrogen evolution was measured in two reactions to determine whether the limited formation of biaryl product was due to incomplete diazotization and/or subsequent decomposition of the intermediate. In both cases, more than 90% of the theoretical gas yield was observed, indicating that the low biaryl yield is a result of competition from side reactions.

Utilization of this method for preparative purposes (~1 *M*) was successful. For example, *m*- and *p*-methylbiphenyl were obtained in 30 and 40% yield, respectively, from reaction of the appropriate toluidines in benzene. The isomeric chlorobiphenyls were prepared in 30% yield from the chloroanilines and a 12% yield of 2,5-dimethylbiphenyl was isolated on diazotization of aniline in *p*-xylene.

The reaction was conducted in a variety of aromatic solvents under the conditions described above. The isomer distributions, high *ortho* and *para* and low *meta* substitution, are characteristic of radical attack[7] (Table II).

TABLE II

COMPOSITION OF BIARYL PRODUCTS FROM APROTIC DIAZOTIZATION OF ANILINE IN SUBSTITUTED BENZENE

Substrate	% yield	Substituted biphenyl *o*	*m*	*p*
Toluene[a]	28.8	57.1	28.0	14.0
Nitrobenzene[b]	36.0	44.9	15.4	39.8
Chlorobenzene[b]	40.7	55.0	27.5	17.5
Bromobenzene[b]	47.8	48.1	33.9	17.9
Methyl benzoate[b]		51.4	18.6	29.7

[a] At reflux. [b] At 120°.

Recently, the ability of aryl radicals, generated from benzoyl peroxide, to abstract iodine from aryl iodides was demonstrated.[8] Thus, this is an additional device to determine the amount of radical intermediates generated from the aprotic diazotization of an arylamine. The excellent correlation of yield of aryl iodide from both aprotic diazotization and aroyl peroxide decomposition not only supports the presence of phenyl radicals in the amine–amyl nitrite system but confirms that these are the major arylating agents (Table III). Aryl cations do not display this abstracting ability; *e.g.*, decomposition of benzenediazonium tetrafluoroborate under these conditions does not give any iodine abstraction product.[9]

To determine the nature of the arylating agent generated from the diazotization of aniline in the presence of an equivalent of strong acid, the isomer

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[1] Aprotic refers to solvents that are not proton donors. Other examples of such diazotization are summarized by D. Y. Curtin, J. A. Kampmeier, and B. R. O'Connor, *J. Amer. Chem. Soc.*, **87**, 863 (1965).

[2] Financial support (Grant No. GP-3976) from the National Science Foundation is gratefully acknowledged.

[3] National Science Foundation Graduate Trainee.

[4] (a) J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962). (b) Previous reports on the use of the method in preparative applications (*cf.* ref 4a) is limited to reactions at <0.1 mol scale. This investigation extends the scale to 1 mol with appropriate modifications of conditions and isolation techniques.

[5] J. I. G. Cadogan, D. A. Roy, and D. M. Smith, *J. Chem. Soc., Sect. C*, 1249 (1966).

[6] C. Rüchardt and E. Merz, *Tetrahedron Lett.*, **36**, 2431 (1964).

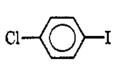
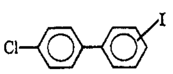
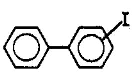
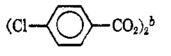
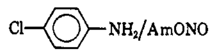
[7] H. Zollinger, "Azo and Diazo Chemistry," Interscience Publishers, Inc., New York, N. Y., 1961, p 157.

[8] (a) D. L. Brydon and J. I. G. Cadogan, *Chem. Comm.*, 744 (1966); (b) J. F. Bunnett and C. C. Wamser, *J. Amer. Chem. Soc.*, **88**, 5534 (1966).

[9] (a) Decomposition of benzenediazonium tetrafluoroborate was also carried out in ethylene chloride and glyme with either iodine or *m*-chloroiodobenzene present. In no case was iodobenzene observed. However, from the reaction in glyme significant amounts of the ether cleavage products, anisole and β-methoxyethyl phenyl ether, were obtained, indicating that the cation becomes free of the gegenion: P. Caruso and L. Friedman, unpublished data. (b) For examples of alkyl diazonium ions, see A. T. Jurewicz, J. H. Bayless, and L. Friedman, *ibid.*, **87**, 5788 (1965).

TABLE III

EXTENT OF IODINE ABSTRACTION BY REACTION INTERMEDIATES[a]

Precursor	% yield 		
 [b]	76	8	39
	75		21

[a] The ratio of the precursor to iodobenzene was 1.0:22.4. [b] Data from ref 8b.

distributions of biaryl products formed on reaction of a variety of precursors in nitrobenzene and bromobenzene were obtained. The reactions studied ranged from the decomposition of benzoyl peroxide (radical intermediate) to the decomposition of benzenediazonium tetrafluoroborate (cationic arylating species).[10] In addition, the relative reactivity of several of these intermediates in benzene–nitrobenzene mixtures was determined (Table IV).

TABLE IV

RELATIVE REACTIVITY AND ISOMER DISTRIBUTIONS FROM REACTIONS IN NITRO- AND BROMOBENZENE AT 78°

Precursor	K_{NO_2}/K_H	Nitrobiphenyls *o*	*m*	*p*	Bromobiphenyls *o*	*m*	*p*
$C_6H_5NH_2$/AmONO	3.04	51	13	36	53	28	19
$C_6H_5N(NO)COCH_3$		50	13	37	58	25	18
$C_6H_5N_2{}^+BF_4{}^-/C_6H_5N$[a]	2.72	53	14	33	55	26	19
$(C_6H_5CO_2)_2$	2.90[a]	60	10	30	54	28	18
$C_6H_5N_2{}^+Cl^- \cdot H_2O$		27	58	15	47	18	35
$C_6H_5NH_3{}^+Cl^-$/AmONO	0.58	25	58	17			
$C_6H_5N_2{}^+Cl^-$		26	55	19			
$C_6H_5N_2{}^+BF_4{}^-$ [a]	0.35	20	80	0	56	20	24

[a] Data from ref 10.

Both the relative reactivity and positional selectivity of the intermediate generated in the aniline–amyl nitrite system compare favorably with the values obtained from acknowledged radical sources.[11] However, the results obtained from the reaction of aniline hydrochloride cannot be easily interpreted. Although the relative reactivity (less than unity) and the isomer distribution (high *meta* product) indicate participation by a cationic arylating agent, there is only partial correspondence with results obtained from the benzenediazonium tetrafluoroborate decomposition. Involvement of phenyl radical can partially account for this discrepancy. However, it is not possible to compute the observed isomer distribution exactly by attributing fractions of the phenylation to radical and cationic intermediates.[12]

Chemical evidence for the intermediacy of phenyl radicals is shown by the minor iodine abstracting ability of intermediates generated in the decomposition of the diazonium chloride monohydrate[13] in the presence of *m*-chloroiodobenzene. In contrast, decomposition of the diazonium tetrafluoroborate shows no trace of abstraction product (Table V).

The variation of product composition in the decomposition of N-nitrosoacetanilide, benzenediazonium chloride, and benzenediazonium tetrafluoroborate in the presence of molecular iodine supplements the above observation. Aryl radicals, generated from N-nitrosoacetanilide react predominatly with iodine, whereas aryl cations, formed from benzenediazonium tetrafluoroborate, are insensitive to the added halogen. The intermediate(s) generated from benzenediazonium chloride give a product composition intermediate between these extremes, showing a significant fraction of reaction with iodine (Table VI).

These results are consistent with the mechanism postulated for the Gomberg reaction.[6] Reaction of amyl nitrite with aniline gives diazohydroxide which combines with itself to form the diazoanhydride ultimately decomposing to yield phenyl radicals. In the presence of strong acid, the diazohydroxide is converted into the diazochloride which then decomposes heterolytically and homolytically to give both radical and cation intermediates (Scheme I). The good agreement of data from reaction of aniline hydrochloride, benzenediazonium chloride, and the hydrated form of the diazonium salt support this scheme.

The presence of complex radical intermediates, acting as hydrogen-abstracting agents, is neither necessitated nor excluded by the available data. However, there is no evidence to suggest that such a species, similar to that recently postulated in the decomposition

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[10] (a) R. A. Abramovitch and J. G. Saha, *Tetrahedron*, **21**, 3297 (1965). (b) The comparison of data from the literature (*cf.* ref 10a) was made only where all reaction conditions were similar. In addition, the decomposition of benzenediazonium tetrafluoroborate with pyridine added was performed under the conditions described giving results identical with those reported.

[11] C. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press Inc., London, 1960, pp 29, 34.

[12] Calculation of the theoretical isomer distribution was done by using the percentage of *para* substitution as a measure of the extent of radical participation; *i.e.*, no yield of *para* indicates a completely cationic process (data from benzenediazonium tetrafluoroborate), whereas 36% indicates a predominantly radical process (N-nitrosoacetanilide). This approach gives the partitioning of the decomposition of benzenediazonium chloride as 43% radical and 57% cationic. Calculations of the remaining isomer percentage on this basis predicts *ortho*, 33%; *meta*, 51%; and *para*, 16%. This deviates from the observed distribution by 6%. However, this method cannot be applied to the results obtained in bromobenzene.

[13] Diazotization of aniline hydrochloride with amyl nitrite in ether was presumed to yield the anhydrous salt. However, decomposition in benzene gave in addition to the expected products (biphenyl and chlorobenzene) phenol, diphenyl ether, the isomeric chlorobiphenyls, and *o*- and *m*-phenylphenol. (*p*-Phenylphenol was not detected under the analysis conditions.) These spurious products comprised >60% of the product composition and were identified by a correlation of gas chromatographic and mass spectral data. To measure the amount of water present, freshly prepared benzenediazonium chloride was dissolved in deuterium oxide. Decomposition takes place in solution presumably to form phenolic and azo coupling products and hydrochloric acid. Nuclear magnetic resonance analysis of the mixture shows a complex multiplet(s) centered at τ 1.77 which is attributed to the aromatic protons of the diazonium salt and any products formed in solution. There is also a sharp singlet at τ 5.41 which, in the acidic medium, can be attributed to the water, phenolic, and hydrochloric acid protons in the system. Integration of these regions gives an aromatic/"aqueous" ratio of 5.00:2.06. Since the only source of proton in the system is the diazonium salt, the integration is strong evidence for the presence of the hydrate, whose theoretical aromatic/"aqueous" ratio would be 5.00:2.00.

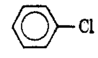
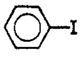
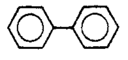
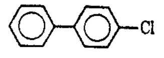
Decomposition of benzenediazonium chloride monohydrate in the solid state leads to the same products, with the exception of biphenyl, which are observed from decomposition in benzene. The product composition—phenol, 3%; chlorobenzene, 5%; diphenyl ether, 17%; chlorobiphenyls, 15%; and phenylphenols, 4%—is similar to that observed in the solution reaction. It was subsequently found that the rate of stirring of the heterogeneous benzene–diazonium ion mixture had a decided effect on the yield of these products. These observations suggest that only reaction in the solid state, prior to extraction into solution, gives rise to these aromatic materials.

This is supported by the following observations. Decomposition of benzenediazonium chloride, prepared from the reaction of phenyl isocyanate and nitrosyl chloride,[14] under the same conditions shows a marked diminution in products resulting from the reaction of phenyl cation and water. For example, the ratio of diphenyl ether to biphenyl drops from 4.0 to 1.0. (Water uptake during isolation of the salt can account for the occurrence of the products.) Moreover, these products are not observed on diazotization of aniline hydrochloride which involves *in situ* formation of the diazonium chloride.

[14] We thank Professor K. Scherer for supplying us with experimental details.

TABLE V

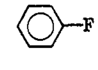
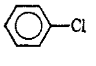
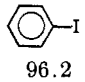
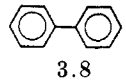
EXTENT OF IODINE ABSTRACTION BY REACTION INTERMEDIATES[a]

	% yield			
				
$(C_6H_5CO_2)_2$[b]	4.0	43	23	17
$C_6H_5N_2^+Cl^- \cdot H_2O$	41	2.4	6.2	2.0
$C_6H_5NH_3^+Cl^-$/AmONO	13	0.4	0.8	1.3
$C_6H_5N_2^+BF_4^-$		0.0		0.0

[a] Precursor/*m*-chloroiodobenzene/benzene = 1.0:1.0:16.9. [b] Data *cf.* ref. 8b.

TABLE VI

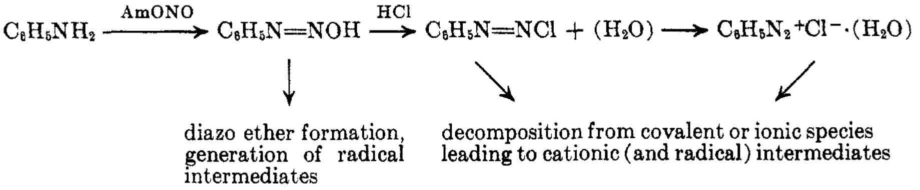
REACTION OF RADICAL AND CATION PRECURSORS WITH IODINE[a]

		Product composition, %			
Precursor	% yield				
$C_6H_5N(NO)COCH_3$	18.3			96.2	3.8
$C_6H_5N_2^+Cl^- \cdot H_2O$	66.2		26.2	61.0	12.8
$C_6H_5N_2^+BF_4^-$	69.6	94.1		0.1	5.8

[a] Benzene/precursor/I_2 = 30:1:0.5.

SCHEME I

EFFECT OF STRONG ACID



$$C_6H_5NH_2 \xrightarrow{AmONO} C_6H_5N{=}NOH \xrightarrow{HCl} C_6H_5N{=}NCl + (H_2O) \longrightarrow C_6H_5N_2^+Cl^- \cdot (H_2O)$$

of N-nitrosoacetanilide,[15] plays a major function in the formation of the aryl radical.

Experimental Section

Reagents.—N. F. grade Mallinckrodt amyl nitrite was used without purification.

N-Nitrosoacetanilide was prepared from acetanilide and nitrosyl chloride according to the method of DeTar.[16]

Benzenediazonium chloride and benzenediazonium tetrafluoroborate were prepared from the appropriate aniline acid salt by diazotization with amyl nitrite in ethanol. This is a modification of the Knoevenagel preparation of diazonium ion salts.[17]

***m*-Chloroiodobenzene** was prepared *via* aqueous diazotization of *m*-chloroaniline in the presence of potassium iodide, a modification of the method of Lucas and Kennedy[18] for the preparation of iodobenzene.

Reaction Procedure.—The following general procedure was followed in carrying out reactions. Amyl nitrite (1.4 g, 0.012 mol) was added to a stirred solution of aniline (0.93 g, 0.01 mol) and 30 ml of aryl solvent in a 50-ml, round-bottom flask equipped with a reflux condenser and bubbler. The flask was then placed in an oil bath and gradually heated to reflux. When a high-boiling solvent or solvent mixture was used, reaction temperature was maintained at 120°. Reaction was allowed to continue until gas evolution ceased. The mixture was allowed to cool and an internal standard was added. Analysis was performed *via* gas–liquid partition chromatography.

The reaction of benzenediazonium chloride, aniline hydrochloride, and N-nitrosoacetanilide were carried out in the same manner, substituting the appropriate reagent for aniline. No amyl nitrite was added in the decomposition of benzenediazonium chloride.

In the series of reactions run at 78°, temperature control was maintained by performing the reactions in a double-walled reaction vessel. Benzene was heated to reflux in the outer jacket, providing a constant temperature environment.

Competition Reactions.—Relative reactivity factors were obtained by performing the reaction(s) in solvent mixtures (~30 ml) which varied in composition.

Iodine abstraction reactions were carried out following the general procedure with those reagent concentrations described by Bunnett.[8b]

Synthetic scale reactions were generally carried out in the following manner. Amyl nitrite (70 g, 0.59 mol) was added to a stirred mixture of aniline (46.5 g, 0.5 mol) and 750 ml of aromatic solvent in a 2-l., three-necked flask, fitted with a reflux condenser and gas bubbler. The reaction mixture was heated to solvent reflux or 120°, whichever temperature was lower, and maintained at that temperature until gas evolution ceased.

Larger scale reactions can be performed using this technique. However, it is advisable that the specific system be tested at the 0.1-mol level. The rate of nitrogen evolution is sensitive to the specific solvent and amine and may become violent.

The reaction flask was then fitted with a Claisen head and condenser and solvent was distilled from the reaction mixture. Stannous chloride (200 g, 1.05 mol) in 150 ml of concentrated hydrochloric acid was then added to the mixture. The flask was then heated on a steam cone overnight. This treatment was found to be effective in removing colored by-products.

The mixture was then steam distilled and the organic layer was taken up in petroleum ether (30–60°). The extracted material was then placed on a rotary evaporator to remove the solvent and the residue was vacuum distilled. Isolated yields ranged from 12 to 40% of biaryl product.

Analysis.—The products of these reactions were analyzed by gas chromatography. Compounds were identified by comparison of their retention times to those of authentic materials. In some cases further authentication was made by collecting samples *via* glpc and comparing infrared spectra and melting points.

Analyses were carried out on either a gas chromatography instrument constructed at Case Western Reserve or a Varian Hy-Fi instrument. The quarter inch columns described below were used on the former instrument; the eighth inch columns were used on the latter.

Column A was a 5 ft × 0.25 in. copper column packed with G.E.-SF-96 (20%) on Chromosorb P operated at 210° with a

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[15] G. R. Chalfont and M. J. Perkins, *J. Amer. Chem. Soc.*, **89**, 3054 (1967).

[16] D. F. DeTar, *ibid.*, **73**, 1448 (1951).

[17] E. Knoevenagel, *Ber.*, **23**, 2995 (1890).

[18] H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 351.

He inlet pressure of 32 psi. Column B was a 7 ft × 0.125 in. stainless steel column packed with Apiezon L (15%) on Chromosorb W operated at 210° with a N_2 inlet pressure of 15 psi. Column C was a 5 ft × 0.125 in. stainless steel column packed with SE-30 (5%) on Chromosorb W operated at 167° with a N_2 inlet pressure of 15 psi. Column D was a 10 ft × 0.25 in. copper column packed with Apiezon L (25%) on Chromosorb W operated at 195° with a He inlet pressure of 40 psi.

Determination of product yields was made by comparing peak areas with that of an internal standard. Adjustment was made for differences in thermal conductivity and applied to correct the observed areas.

Notes

Aprotic Diazotization of Aniline in the Presence of Iodine[1,2]

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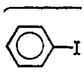
The reaction of arylamines with amyl nitrite in aromatic solvents has been conclusively demonstrated to generate aryl radicals.[4] The presence of a radical intermediate in this reaction suggested the use of iodine, which might serve as the radical trap,[5] to give a facile method for the formation of aryl iodides. When aniline was treated with amyl nitrite in benzene in the presence of an equivalent of iodine,[6] iodobenzene was formed in 50% yield with small amounts of biphenyl. However, in addition to the expected products, a significant amount of *p*-diiodobenzene was found.[7]

To investigate the source of the diiodinated product, the relative amounts of aniline, iodine, and amyl nitrite were varied (Table I). When aniline is present in excess relative to amyl nitrite, the product composition is insensitive to excess iodine. When amyl nitrite is in excess the expected increase in diiodinated product with increasing iodine concentration is observed. Biphenyl formation does not become significant until less than an equivalent of iodine is present. Iodine acts as a more effective radical trap than benzene by a factor of ~2 × 10^3.

These results do not, however, uncover the source of *p*-diiodobenzene. Addition of iodobenzene to an aprotic diazotization reaction had no effect on the yield of diiodinated product. Diazotization of aniline hydroiodide and decomposition of N-nitrosoacetanilide and benzenediazonium chloride under conditions similar to those employed in the reaction system gave no *p*-diiodobenzene (Table II). Since these compounds are analogous to either suggested intermediates or transient oxidation states in the diazotization sequence, the iodination process must occur prior to the diazotization reaction. Thus, *p*-iodoaniline is postulated as the precursor of *p*-diiodobenzene. When the isomeric iodoanilines are diazotized under reaction conditions, high yields of the respective diiodobenzenes are formed without side products within the limits of detection (glpc). Isolation of *p*-iodoaniline from reactions where an excess of aniline relative to amyl nitrite was employed conclusively demonstrates the intermediacy of this species as precursor of *p*-diiodobenzene.

TABLE I

PRODUCT COMPOSITION AS A FUNCTION OF REAGENT RATIOS

Relative concn of reagents			%	% product compn		
$C_6H_5NH_2$	AmONO	$^1/_2I_2$	yield			
2	1	2	56	89	10	1
2	1	1	47	86	11	3
1	1	1	60	78	21	1
1	3	1	77	85	13	2
1	1.2	3	63	57	39	4
1	1.2	2	60	64	33	3
1	1.2	1	60	82	16	2
1	1.2	0.7	38	77	14	9
1	1.2	0.5	41	77	2	21

The direct reaction of aniline and molecular iodine cannot account for the formation of *p*-iodoaniline in this system. When an aniline–benzene mixture was refluxed for 3 hr with an equivalent amount of iodine, iodination of aniline did occur. However, the yield was low, and a mixture of isomers (20% *ortho*, 80% *para*) was obtained. This is not consistent with the relatively high yields and isomer distribution of diiodobenzenes (*ortho* <1%, *para* >99%) obtained from the diazotization reaction. Iodination of aniline in aqueous bicarbonate solution,[8] involving hypoiodous acid as the iodinating agent,[9] gives almost exclusively the *para* isomer (4% *ortho*) in high yield. Other examples of electrophilic iodination have also shown great *para* selectivity.[10,11] Thus, a cationic species is postulated as the iodinating agent in this system. An attractive mechanism for the generation of such a species is the oxidation of iodine by alkoxyl or hydroxyl radical. These oxidizing agents are generated in the diazotization process and could react with iodine to

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[1] Aprotic refers to solvents that are not proton donors. Other examples of such diazotizations are summarized by D. Y. Curtin, J. A. Kampmeier, and B. R. O'Connor, *J. Amer. Chem. Soc.*, **87**, 863 (1965).

[2] Financial support (Grant No. GP 3976) from the National Science Foundation is gratefully acknowledged.

[3] National Science Foundation Graduate Trainee.

[4] L. Friedman and J. F. Chlebowski, *J. Org. Chem.*, **33**, 1633 (1968).

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