Active Heteromethylene Compounds. I. Hindered Halomethyl Amides

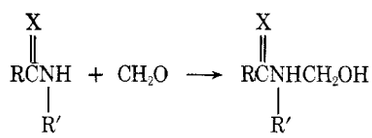
K. W. Ratts* and John P. Chupp

Monsanto Commercial Products Company, Agricultural Division, Research Department, St. Louis, Missouri 63166

Received May 13, 1974

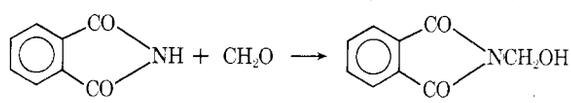
A novel series of hindered *N*-halomethyl- or oxymethyl-α-haloacetanilides (**1**) have been shown to react *via* sulfuric acid catalysis with nitriles to give *N*-acylaminomethyl-α-haloacetanilides (**2**). Some of the limitations and scope of this sequence are outlined. Structural implications in these hindered compounds are discussed based on nmr spectra.

N-Halomethyl or oxymethyl amides and imides are readily prepared classes of active heteromethylene compounds which constitute attractive intermediates for a variety of synthetic transformations. Condensation of amides with formaldehyde produces *N*-hydroxymethyl amides in a general sequence as outlined.[1]



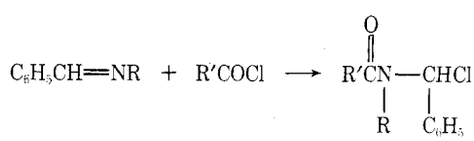
X = O, S
R′ = H, alkyl

Similarly imides condense to give *N*-hydroxymethyl imides, *e.g.*, the reaction of phthalimide and formaldehyde.[1a]



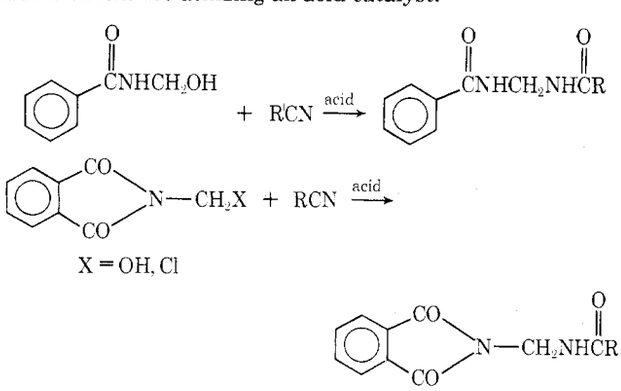
N-Halomethyl derivatives are readily made by hydrogen chloride or thionyl chloride treatment of the corresponding hydroxymethyl compounds mentioned above.[2]

Alternatively such derivatives have, in certain specific instances, been prepared by the addition of acid chlorides to Schiff bases.[3]



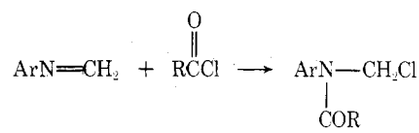
The varied reactivity of *N*-halomethyl or oxymethyl amides and imides is due to activation of the halogen or oxy substituent by the attached amide functionality.[2] Often in such systems the compounds possess this special reactivity due to carbonium ion character which can be induced *via* such systems.[4]

A specific illustration of the above-described reactivity is the reaction of *N*-hydroxymethylbenzamide and phthalimides with nitriles utilizing an acid catalyst.[5]



X = OH, Cl

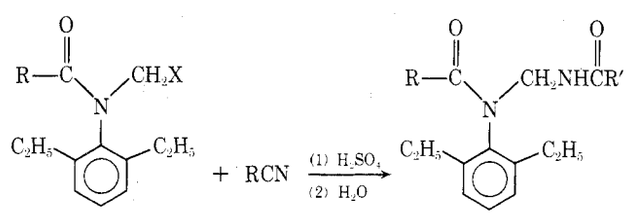
A recently developed procedure for the reaction of hindered azomethines with acid chlorides constitutes a new attractive method of producing a novel series of stable, hindered *N*-halomethyl amides (**1**).[6]



1

Since compounds of type **1** are hindered chloromethyl amides and as such possess some stability, they are useful intermediates for study.

We wish to describe the utilization of hindered *N*-chloromethyl amides in carbonium ion type reactions similar to those described above. A variety of nitriles, *via* acid catalysis, react with **1** to give methylene bis amides (**2**) in good yields.

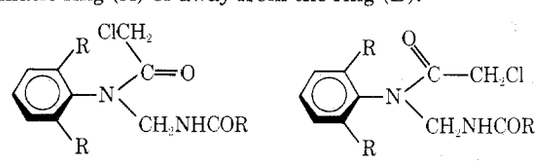


1a, X = Cl
b, X = OCH_3
c, X = $OCOCH_2Cl$

2

A tabulation of the compounds prepared is given in Table I. The replaceable group may be halogen, alkoxyl, or acyloxy, all of which should generate carbonium ion species under acidic conditions. The nitrile can be quite widely varied with the exception of compounds containing acid sensitive groups.

The nmr spectra characteristically exhibit the N–CH_2–NH–methylene at approximately δ 5.0 as a doublet (J = 7 Hz) due to splitting by the adjacent NH proton. Infrared spectra show the presence of two amide carbonyl groups and analytical data are consistent with the proposed structures. Due to the hindered rotation present in such amides two conformations are possible dependent upon the positioning of, for example, the chloromethyl carbonyl over the aromatic ring (A) or away from the ring (B).



A B

In view of the often observed presence of both rotomers in other closely related tertiary substituted α-chloroacetanilides,[6,7] it is perhaps surprising that **2** appears to exist in

Table I
N-Acylaminomethylacetanilides[a]

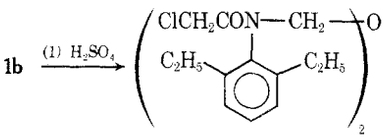
No.	R	R′	Yield, %	Mp, °C	Elemental analysis, % Calcd C	Calcd H	Found C	Found H
2a	Cl	CH_3	79	121–124	59.46	6.77	59.63	6.74
2b	CH_3	CH_3	68	112–115	68.67	8.45	68.88	8.36
2c	CH_3	$ClCH_2$	46	129–130	58.80	7.09	58.79	7.10
2d	$ClCH_2$	H	72	85–89	59.46	6.77	59.64	6.69
2e	$ClCH_2$	CH_3	71	148–149	60.5	7.13	60.68	7.22
2f	$ClCH_2$	n-C_3H_7	72	122–123	62.85	7.76	63.10	7.99
2g	$ClCH_2$	C_6H_5	82	132	66.97	6.46	67.74	6.46
2h	$ClCH_2$	CH_2=CH–	65	174–175	62.23	6.85	62.23	6.72
2i	$ClCH_2$	$ClCH_2$–CH_2–	65	133–136	55.66	6.42	55.55	6.39
2j	$ClCH_2$	C_2H_5S	75	107	56.04	6.76	56.20	6.87
2k[b]	$BrCH_2$	CH_3	57	152–154	54.09	6.53	53.93	6.69
2l[c]	$ClCH_2$	CH_3		145–146	56.58	5.94	56.89	6.10

[a] 2,6-Diethylanilide unless otherwise noted. [b] 6-*tert*-butyl-o-toluidide. [c] o-Toluidide.

solution at room temperature, only in form A. This configuration is assigned from the upfield (δ 3.6) shift of the chloromethylene protons arising from their shielding by the aromatic ring.

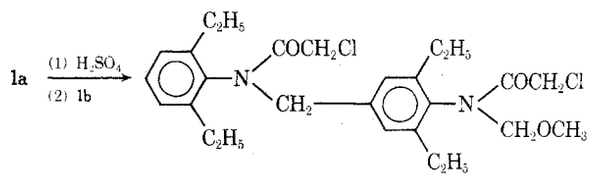
Noteworthy also is the presence of AB coupling observed in the methylene amido protons in **21** which possesses only one aromatic ortho substituent. Only A_2 character is observed in either symmetrical or asymmetrical (*i.e.*, **2k**) di-ortho-substituted amides. Nonequivalence in this instance may arise from the greater differences in magnetic environments of these two protons when the amide plane is allowed to become nearly coplanar to a single ortho-substituted phenyl ring. Lessened methylene proton nonequivalence might be expected when the more usual orthogonal orientation of these two planes occurs in di-ortho-substituted materials.

Treatment of the derivative **1b** with acid in the absence of nitrile gave the bis ether **3**.[4]



3

The intermediate carbonium ion species may alkylate activated aromatic rings in certain instances if no nitrile is added. Indeed it might be considered somewhat surprising



4

that **1a** does not prefer self condensation even in the presence of other nucleophilic species. These low yield reactions do, however, illustrate alternate reactivity of the "carbonium ion species" with other substrates than nitriles. The mechanism for the above reactions is undoubtedly similar to that for the Ritter reaction with the halo or oxymethylene amide compound **1** serving as a carbonium ion precursor.[2,4,8]

N-Acylaminomethyl-α-haloacetanilides, in particular the formamido compound (**2**, R′ = H), provide a series of intermediates of interest for synthesis of a variety of new compounds. These results will be published in future papers.

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus. Nuclear magnetic resonance spectra were recorded on Varian A-60 and T-60 spectrometers while infrared spectra were recorded on a Perkin-Elmer Infracord. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

The following preparations of materials **2** are illustrative of the procedures used to make the materials appearing in Table I. Minor variations in procedure are not critical for good yields and product purity.

Acetamidomethyl(2′,6′-diethylphenyl)carbamoyl Chloride (2a). Chloromethyl-*N*-(2,6-diethylphenyl)carbamoyl chloride was prepared by the simple addition of equimolar amounts of phosgene to 2,6-diethyl-*N*-methyleneaniline.[9] This adduct (15 g, 0.058 mol) was mixed with acetonitrile (2.5 g, 0.06 mol) and added to 40 ml of 96% sulfuric acid. The mixture was heated to 50° for *ca.* 15 min, then the mixture was stirred at ambient temperatures for a further hour. The material was then poured into *ca.* 300 ml of ice–water and after 15 min the granular solid (12.9 g) filtered off. The material was recrystallized from ethyl acetate to give 4.7 g, with an additional 3.2 g recovered from the mother liquors: nmr ($CDCl_3$) δ 1.30 (t, 6, J = 7 Hz, $ArCH_2CH_3$), 2.0 (s, 3, CH_3CO), 2.60 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 5.06 (d, 2, J = 6 Hz, NCH_2N), 6.92–7.4 (m, 3, ArH), 8.3 (broad, 1, NH).

***N*-Acetamidomethyl-2′,6′-diethylacetanilide (2b).** *N*-Chloromethyl-2′,6′-diethylacetanilide (prepared by procedures described in ref 9, from addition of acetyl chloride to 2,6-diethyl-*N*-methyleneaniline) (8.0 g, 0.0334 mol) in a mixture with 1.47 g of acetonitrile (0.0358 mol) was added to 35 ml of concentrated sulfuric acid, and the whole was heated with stirring at 55° for 1.5 hr. The homogeneous mixture was then poured into 300 ml of ice–water. No product separated; so the aqueous solution was extracted with 300 ml of methylene chloride; the solution was washed twice with water and then dried over magnesium sulfate. After filtering off the drying agent and removing the solvent under vacuum, the residual oil solidified and was recrystallized from heptane to give a 6.0-g yield: nmr ($CDCl_3$) δ 1.20 (t, 6, J = 6 Hz, $ArCH_2CH_3$), 1.68 (s, 3, $CH_3C(O)N$), 1.91 (s, 3, $CH_3C(O)N$), 2.48 (quartet, 4, $ArCH_2CH_3$), 4.80 (d, 2, J = 7 Hz, $-NCH_2NH$), 7.1–7.4 (m, 4, ArH and N–H).

***N*-(α-Chloroacetamidomethyl)-2′,6′-diethylacetanilide (2c).** The adduct used in the preparation of **2b** (10.0 g, 0.042 mol) was mixed with 3.4 g of chloroacetonitrile (0.045 mol) and added with stirring to 40 ml of concentrated sulfuric acid. The mixture was then heated at 50° for 1 hr, cooled to room temperature, and poured into *ca.* 300 ml of ice–water. The material was permitted to stand for 54 hr and the granular solid was filtered off and slurried well with water, filtered, and washed once again with water, followed by air drying. The solid was then recrystallized from heptane to give 5.8 g: nmr ($CDCl_3$) δ 1.20 (t, 6, J = 6 Hz, $ArCH_2CH_3$), 1.68 (s, 3, CH_3CO), 2.45 (quartet, J = 6 Hz, $ArCH_2CH_3$), 3.9 (s, 2, $ClCH_2CO$), 4.86 (d, 2, J = 7 Hz, $HNCH_2N$), 7.1–7.3 (m, 3, ArH), 7.9 (broad, 1, N–H).

2-Chloro-2′,6′-diethyl-*N*-formamidomethylacetanilide (2d). 2-Chloro-*N*-chloromethyl-2′,6′-diethylacetanilide (200 g, 0.73 mol) was placed in 250 ml of concentrated sulfuric acid and 30 g of (1.04 mol) cooled, liquified hydrogen cyanide was added drop-

wise over 15–20 min at 5–20°. The mixture was then allowed to warm, with final heating at 55–60° for 1 hr. The cooled reaction mixture was then poured into 1.2 l. of ice–water with stirring, and the mixture was allowed to stand for 3 hr. The granular precipitate was then filtered off, washed thoroughly with water, air dried, then recrystallized from methylcyclohexane to give 161 g: nmr ($CDCl_3$) δ 1.21 (t, 6, J = 7 Hz, $ArCH_2CH_3$), 2.51 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 3.62 (s, 2, $ClCH_2$), 4.88 (d, 2, J = 7 Hz, NCH_2N), 7.1–7.4 (m, 3, ArH) 7.65 (broad, 1, NH), 8.2 (s, 1, CHO).

N-Acetamidomethyl-2-chloro-2′,6′-diethylacetanilide (2e). To 17.7 g (0.104 mol) of chloroacetic anhydride contained in a minimum amount of hot benzene was slowly added 16.8 g (0.104 mol) of N-methylene-2,6-diethylaniline in an equal volume of benzene. Concentration and cooling of the mixture gave crystals, mp 57–58°; elemental analysis and nmr and ir spectra were consistent for the adduct **1c** (R = $ClCH_2$). Material **1c** (7.96 g, 0.025 mol) was mixed with 100 ml of acetonitrile and 5 drops of 10% sulfuric acid was added. The mixture was heated on the steam bath for 70 min then permitted to stand overnight. After an additional reflux period of 90 min, the mixture was poured into 900 ml of ice–water. The solid was filtered off and air dried to give 6.0 g, mp 114–125°. Recrystallization of the material from methanol gave 2.4 g (32%) of **2e.** Better yields (see Table I) of **2e** could be obtained from reaction of **1a** (R = $ClCH_2$) with equimolar amounts of acetonitrile in concentrated sulfuric acid, as described for **2d** above: nmr ($CDCl_3$) δ 1.2 (t, 6, J = 7 Hz, $ArCH_2CH_3$), 1.96 (s, 3, CH_3CO), 2.52 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 3.63 (s, 2, $ClCH_2$), 4.95 (d, 2, J = 6 Hz, NCH_2N), 7.0–7.5 (m, 4, ArH and NH).

N-Acrylamidomethyl-2-chloro-2′,6′-diethylacetanilide (2h). 2-Chloro-N-(methoxymethyl)-2′,6′-diethylacetanilide[9] (0.05 mol, 13.5 g) was mixed with 2.7 g of (0.05 mol) acrylonitrile and then added at 15–20° to 30 ml of concentrated sulfuric acid. The mixture was heated at 55° for 1 hr, cooled, and poured into 300 ml of ice–water. After standing 15 min with occasional stirring, the solid granules were filtered off, washed on the filter with more water, then recrystallized from 2-propanol to give 10.0 g of product. If **1a** (R = $ClCH_2$) was used in place of **1b** (R = $ClCH_2$), addition takes place with the formation of **2i** in good yield: nmr (**2h**) ($CDCl_3$) δ 1.20 (t, 6, J = 7 Hz, $ArCH_2CH_3$), 2.51 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 3.62 (s, 2, $ClCH_2$), 5.02 (d, 2, J = 6 Hz, NCH_2N), 5.4–6.3 (m's, 3, =CH), 7.1–7.5 (m, 4, ArH, NH).

S-Ethyl N-[2-Chloro-N-(2,6-diethylphenyl)acetamidomethyl]thiocarbamate (2j). Material **1b** (R = $ClCH_2$) (0.0222 mol, 6.0 g) was mixed with 2.06 g (0.0238 mol) of ethyl thiocyanate to which *ca.* 5 ml of glacial acetic had been added to help effect the dissolution of the amide. The mixture was then added *via* dropping funnel with stirring to 25 ml of concentrated sulfuric acid at 5–10°. After the addition, the material was allowed to warm to 15° and then was poured into *ca.* 200 ml of ice–water. The insolubles thus obtained gradually hardened overnight to a granular solid. This material was filtered off and air dried to give a 5.7 g yield. The technical material could be further purified by recrystallization from methylcyclohexane–toluene (charcoal): nmr ($CDCl_3$) δ 1.22 (t, 9, J = 7 Hz, $-CH_2CH_3$), 2.52 (quartet, 4, J = 7 Hz, $ArCH_2CH_3$), 2.81 (quartet, 2, J = 7 Hz, SCH_2CH_3), 3.61 (s, 2, $ClCH_2$), 4.92 (d, 2, J = 7 Hz, NCH_2N), 7.2–7.35 (m, 4, ArH and NH).

N-Acetamidomethyl-2-bromo-6′-*tert*-butylaceto-*o*-toluidide (2k). 2-Bromo-N-(methoxymethyl)-6′-*tert*-butyl-*o*-acetotoluidide (6.5 g, 0.0197 mol) was mixed with 5 ml of glacial acetic acid and 0.87 g (0.021 mol) of acetonitrile. The mixture was added to 30 ml of concentrated sulfuric acid at 10–20° and then heated at 55° for 1.5 hr. After cooling, the mixture was stirred into 300 ml of ice–water. The granular precipitate was separated by filtration, washed with water, and air dried to give 5.75 g. The material was recrystallized from 2-propanol to give 4.0 g: nmr ($CDCl_3$) δ 1.35 (s, 9, $(CH_3)_3C-$), 1.95 (s, 3, $ArCH_3$), 2.2 (s, 3, CH_3CO), 3.58 (s, 2, $ClCH_2$), 4.90 (d, 2, J = 6 Hz, NCH_2N), 7.1–7.6 (m's, 4, ArH and NH).

N-Acetamidomethyl-2-chloro-*o*-acetotoluidide (21). 1a (R = $ClCH_2$) (23.6 g, 0.1 mol) was mixed with 4.5 g of acetonitrile, and this mixture was added to 60 ml of cold, concentrated sulfuric acid. After addition, the mixture was heated at 70–80° for 2 hr, cooled, and poured into 600 ml of ice–water. The material was made basic with NaOH and then permitted to stand 2 days. The solid, consisting of product and sodium sulfate, was separated, air dried, and then recrystallized from toluene: nmr ($CDCl_3$) δ 1.95 (s, 3, $ArCH_3$), 2.23 (s, 3, CH_3CO), 3.71 (s, 2, $ClCH_2$), 4.90 (AB quartet, 1, J = 14 Hz), 5.00 (AB quartet, 1, J = 14 Hz) (4.90 and 5.00 for NCH_2N), 7.1–7.7 (m's, 5, ArH and NH). Deuteration of the sample with D_2O to form the N–D material reduced the absorption in this region to a single AB quartet (J = 14 Hz).

N,N'-(Oxydimethylene)bis(2-chloro-2′,6′-diethylacetanilide) (3). Material **1b** (R = $ClCH_2$) (9.7 g, 0.036 mol) was mixed with 2.9 g of (0.04 mol) N-methylacetamide, and the contents were added dropwise to 10 ml of concentrated sulfuric acid at 10–15°. After addition, the mixture was heated 1 hr at 45–48° and then stirred an additional 3 hr at room temperature. The material was poured into 300 ml of ice–water and the sticky solid was extracted with methylene chloride, washed twice with water, filtered through clay, and dried over $MgSO_4$. On evaporation, an oil was obtained which solidified overnight. The material was recrystallized from ethyl acetate to give product, mp 145–147°: nmr ($CDCl_3$) δ 1.15 (t, 12, J = 7 Hz, CH_2CH_3), 2.48 (quartet, 8, J = 7 Hz, $ArCH_2CH_3$), 4.6 (s, 4, $ClCH_2$), 5.11 (s, 4, NCH_2O), 7.2–7.4 (m, 4, ArH and NH). The mass spectra displayed the parent ion at 492 and base peak at 238 (carbonium ion resulting from ether oxygen–carbon cleavage of 3).

Anal. Calcd for $C_{26}H_{34}Cl_2N_2O_3$: C, 63.28; H, 6.94. Found: C, 62.84; H, 6.93.

N-[4-[2-Chloro-N-(methoxymethyl)acetamido]-3,5-diethylbenzyl]-2′,6′-diethyl-2-chloroacetanilide (4). Equimolar amounts of **1a** and **1b** (R = $ClCH_2$) were mixed together and added dropwise to cold, concentrated sulfuric acid. After addition, the material was heated at 50° for 1 hr, cooled, and then poured into ice–water to give a granular solid. This material was then filtered, washed with water, and air dried. Recrystallization was effected first from methylcyclohexane and then from ethyl acetate, mp 153–156°: nmr ($CDCl_3$) δ 1.0 (triplets, 12, J = 7 Hz, $ArCH_2CH_3$), 2.3 (quartets, 8, J = 7 Hz, $ArCH_2CH_3$), 3.61 (s, 2, $ClCH_2$), 4.10 (s, 2, $ClCH_2$), 4.80 (s, 2, $ArCH_2N$), 7.0 (s, 2, ArH), 7.1–7.3 (m, 3, ArH (A_2B)), 7.9 (broad, 1, NH). The mass spectra gave a parent molecular ion at 464.

Anal. Calcd for $C_{27}H_{36}Cl_2N_2O_3$: C, 64.79; H, 6.96; Cl, 15.30; N, 6.04. Found: C, 65.03; H, 6.97; Cl, 15.89; N, 5.84.

Registry No.—**1a** (R = Cl), 35747-79-6; **1a** (R = CH_3), 52920-49-7; **1a** (R = $ClCH_2$), 40164-69-0; **1b** (R = $ClCH_2$), 15972-60-8; **1c** (R = $ClCH_2$), 40164-65-6; **2a,** 52920-50-0; **2b,** 52920-51-1; **2c,** 52920-52-2; **2d,** 40164-72-5; **2e,** 40164-67-8; **2f,** 40164-95-2; **2g,** 40164-97-4; **2h,** 40164-74-7; **2i,** 40164-93-0; **2j,** 52920-53-3; **2k,** 52920-54-4; **2l,** 52920-55-5; **3,** 52920-56-6; **4,** 52920-57-7; acetonitrile, 75-05-8; chloroacetonitrile, 107-14-2; hydrogen cyanide, 74-90-8; N-methylene-2,6-diethylaniline, 35203-08-8; chloroacetic anhydride, 541-88-8; ethyl thiocyanate, 542-90-5; 2-bromo-N-(methoxymethyl)-6′-*tert*-butyl-*o*-acetotoluidide, 2163-81-7; acrylonitrile, 107-13-1.

References and Notes

(1) (a) J. F. Walker, "Formaldehyde," 2nd ed, Reinhold, New York, N.Y., 1953, pp 290–309; (b) J. P. Chupp and A. J. Speziale, *J. Org. Chem.*, **28,** 2592 (1963); (c) J. Wijma, *et al., J. Agr. Food Chem.*, **18,** 674 (1970).
(2) H. E. Zaugg and W. B. Martin, *Org. React.*, **14,** 52 (1965).
(3) (a) T. C. James and C. W. Judd, *J. Chem. Soc.*, **105,** 1427 (1914). (b) H. Leuchs and A. Schlotzer, *Chem. Ber.*, **67,** 1572 (1934). (c) H. Bohme and K. Hartke, *ibid.*, **96,** 600 (1963). (d) H. Bohme, S. Ebel, and K. Hartke, *ibid.*, **98,** 1463 (1965); (e) German Patent 1,153,756 to Bayer; (f) F. W. Fowler and A. Hassner, *J. Amer. Chem. Soc.*, **90,** 2875 (1968).
(4) S. D. Ross, *et al., J. Org. Chem.*, **31,** 134 (1966).
(5) (a) D. T. Mowry, U.S. Patent 2,529,455 to Monsanto Chem. Co., Dec. 30, 1947; (b) S. Buc, *J. Amer. Chem. Soc.*, **69,** 254 (1947).
(6) J. P. Chupp, J. F. Olin, and H. K. Landwehr, *J. Org. Chem.*, **34,** 1192 (1969).
(7) J. P. Chupp and J. F. Olin, *J. Org. Chem.*, **32,** 2297 (1967).
(8) L. I. Krimen and D. J. Cota, *Org. React.*, **17,** 213 (1969).
(9) J. F. Olin, U.S. Patent 3,630,716 (1971).