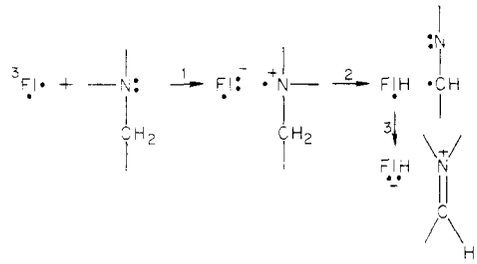
of one electron from tertiary amines to the lowest (triplet) excited state of 3-MLF is thermochemically favorable even for the formation of discrete radical cations and anions (Table I). Subsequent steps involving proton transfer within the radical pair (step 2) and electron transfer (step 3) would produce the reduced flavin–imine (redox) couple.



We speculate that the formation of distinct enzymatic and photoadducts from **5** with flavins may be traced to the forces that determine binding at the active site of the enzyme (and thus site-specific attack on the flavin prosthetic group), which are certain to be different from those forces that determine the structure of molecular complexes generated from amines and photoexcited flavins. The fact that little is known regarding the nature of such photochemical or enzymatic complexes should make this a target of future research.

Experimental Section

Melting points were determined in open glass capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer Model 727 spectrophotometer. NMR spectra were recorded with Varian Associates EM-360 and HFT-80 instruments and a Bruker 360-MHz spectrometer, using tetramethylsilane as the internal standard.

Photolyses of 3-Methyllumiflavin with Amines (5, R′ = CH_3) and 9. Typically, 3-methyllumiflavin was irradiated with Pyrex-filtered light in the presence of a tenfold excess of amine (0.5×10^{-3} M) in 20% acetonitrile–80% (0.1 M) phosphate buffer, pH 7.2, under argon, and the reaction mixture was worked up according to Gärtner.[1] With *N,N*-dimethyl-2,3-butadienylamine (**5**, R′ = CH_3), we obtained >90% yields (conversions range from 80–90%) of a yellow brown powder which was characterized as 5-[3-(dimethylimino)-1-methylpropenyl]-3-methyl-1,5-dihydrolumiflavin betaine (**7**): mp 207–210 °C dec; NMR ($CDCl_3$) δ 2.22 (3 H, s) and 2.28 (3 H, s) (7,8-CH_3), 2.36 (3 H, s, 1′ CH_3), 2.94 (3 H, s, 10-NCH_3), 3.28 (3 H, s, 3-NCH_3), 3.34 (3 H, s) and 3.39 (3 H, s) ($N(CH_3)_2$), 5.27–5.42 and 5.75–5.89 (br, 2′-H, two olefinic resonances split in a ratio of 2:1), 6.82 (1 H, br s, 9-H), 6.97 (1 H, br, 6-H), 7.53 (1 H, d, $J_{2,3}$ = 12 Hz, 3′-H); UV λ_{max} (ε, mM^{-1} cm^{-1})($CHCl_3$) 413 nm (13.0), 313 (12.6); UV (CH_3OH) 387 nm (16.6), 301 (15.3); UV [pH 7.2 (phosphate buffer)] 374 nm (17.3), 299 (15.8); UV [pH 2.0 (HCl)] 368 nm (19.0), 299 (12.7); UV (CF_3CO_2H) 368 nm (19.0), 299 (12.7); IR ($CHCl_3$) ν_{max} 1640 cm^{-1} (2,4-C=O); pK_a = 4.9. The solvent dependence of the electronic spectrum of **7** is very typical of flavocyanines,[1-3] as is the value of the pK_a. Whereas **5** (R′ = CH_3) gives almost exclusively the flavocyanine **7** (80% aqueous acetonitrile, pH 7.2, 0.1 M phosphate buffer; Figure 1), the irradiation of 3-MLF with the isomeric acetylenic amine, *N,N*-dimethyl-2-butynylamine (**9**, R = CH_3) under essentially identical conditions gives two major isolable photochemical products, the flavocyanine **7** in 20% yield and, following Hemmerich,[1] 1-hydroxy-3,5,8,10,11-pentamethyl-1*H*,8*H*-benzo[*g*]pyrrolo[2,1-*e*]pteridine-4,6-dione (**10**): 32%; yellow crystals (ether); mp 194 °C; NMR ($CDCl_3$) δ 1.79 (3 H, s, 3-CH_3), 2.19 (6 H, s, 10,11-CH_3), 3.27 (3 H, s, NCH_3), 3.57 (3 H, s, NCH_3), 4.47 (1 H, disappears in D_2O, d, $J_{1,OH}$ = 11.6 Hz, 1-OH), 5.60 (1 H, d, collapses with D_2O, 1-H), 5.84 (1 H, s, 2-H), 6.72 and 6.99 (2 s, 2 H, 9,12-H); IR ν_{max} ($CHCl_3$) 1665 (6-C=O), 1705 (4-C=O), 3450 (1-OH) cm^{-1}; UV λ_{max} (ε, mM^{-1} cm^{-1}) (CH_3OH) 368 nm (4.0), 300 (sh, 5.7), 279 (13.0), 234 (17.3), 214 (20.0).

Acknowledgment is made to Drs. T. P. Singer and J. Salach (Molecular Biology Division, VA Hospital, San Francisco, CA) for their encouragement to A. Krantz during the initial stages of this project. This work was supported by Grant No. 1 R01 NS13220 from the National Institutes of Health to A. Krantz, Biomedical Research Support Grant No. 2S07RR057-3607, and a stipend from the donors of the Petroleum Research Fund, administered by the American Chemical Society, to B. Kokel, for which we express our deep gratitude. Support (A.C.) from IF:s Stiftelse för farmaceutisk forskning, Apotekare C.D. Carlssons stiftelse, and Lennanders fond is also gratefully acknowledged.

Registry No. **1**, 18636-32-3; **5** (R′ = CH_3), 42574-40-3; **7**, 74592-22-6; **9** (R = CH_3), 14731-37-4; **10**, 74592-23-7.

A New Route to the Acridizinium Ion[1]

Charles K. Bradsher* and David A. Hunt

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received May 29, 1980

The acridizinium (benzo[*b*]quinolizinium) ion (**4a**)[2,3] has been of interest because of its ability to react with alkenes to form cycloadducts,[4-6] some of which have proved to be of importance as synthetic intermediates.[5,7,8] With the exception of a few 6-alkyl derivatives,[9] all acridizinium salts have been prepared by the acid-catalyzed cyclization of 1-benzyl-2-formyl- (or acyl-) pyridinium salts (**3**) or a suitable carbonyl derivative[10] of these. To date the most severe limitations of this method have been those imposed by steric hindrance. For example, the reaction of benzyl bromide (**1**) for 1 month with the acetal of 6-methyl-2-formylpyridine (**2c**) followed by hydrobromic acid catalyzed cyclization of the resulting salt (**3c**) afforded only a 9% yield of the expected 4-methylacridizinium salt (**4c**).[10]

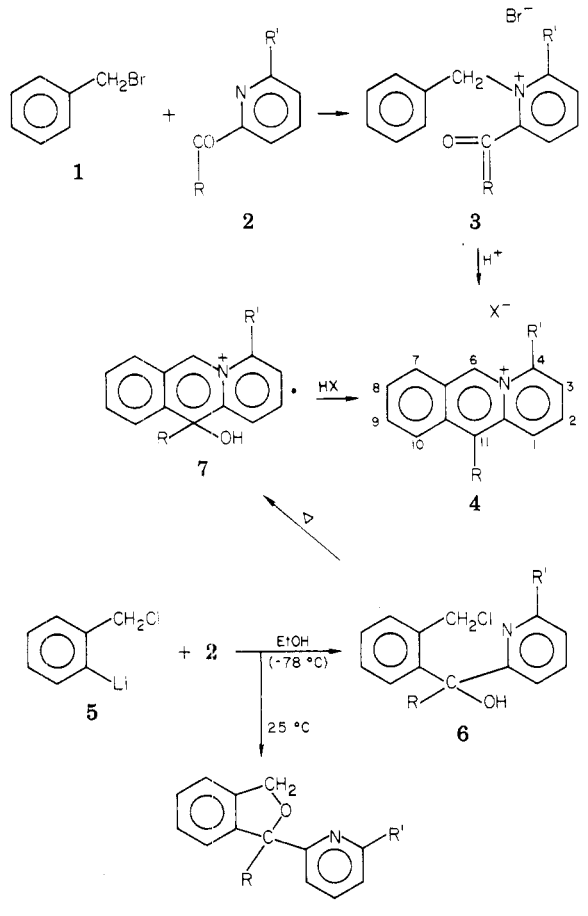
The discovery by Parham et al.[11] that *o*-bromobenzyl chloride will undergo selective bromine–lithium exchange with butyllithium at −100 °C opened the possibility for another approach to the synthesis of the acridizinium ion. If the carbinol (**6**) to be expected from the reaction of *o*-lithiobenzyl chloride (**5**) with pyridine-2-carboxaldehyde or the corresponding ketone (**2**) could be obtained, it might, on heating, afford an 11-hydroxy-6,11-dihydroacridizinium salt (**7**) (Scheme I). While no such salt had ever been isolated, it is clear from much earlier observations[12] that compounds similar to **7** must be formed in the transformation **3** → **4** and would undergo transannular dehydration in hydrobromic acid.

The major problem faced in applying the new synthesis was that the reaction of *o*-lithiobenzyl chloride with al-

(1) This research was supported in part by Grant No. DAAG-29-77-G-0170 from the Army Research Office.
(2) Bradsher, C. K.; Beavers, L. E. *J. Am. Chem. Soc.* **1955**, *77*, 4812.
(3) Bradsher, C. K. *Acc. Chem. Res.* **1969**, *2*, 181.
(4) Bradsher, C. K.; Solomons, T. W. G. *J. Am. Chem. Soc.* **1958**, *80*, 933.
(5) Fields, D. L.; Regan, T. H.; Dignan, J. *J. Org. Chem.* **1968**, *33*, 390.
(6) Bradsher, C. K. *Adv. Heterocycl. Chem.* **1974**, *16*, 289.
(7) Fields, D. L.; Regan, T. H. *J. Org. Chem.* **1971**, *36*, 2995 and references contained therein.
(8) Fields, D. L. *J. Org. Chem.* **1971**, *36*, 3002.
(9) Bradsher, C. K.; Jones, J. H. *J. Org. Chem.* **1960**, *25*, 293.
(10) Bradsher, C. K.; Parham, J. C. *J. Org. Chem.* **1963**, *28*, 83.
(11) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1976**, *41*, 1184.
(12) Bradsher, C. K.; Smith, E. S. *J. Am. Chem. Soc.* **1943**, *65*, 854.

0022-3263/80/1945-4248$01.00/0

Scheme I



a, R = H, R′ = H; b, R = Ph, R′ = H; c, R = H, R′ = Me

dehydes or ketones, followed by warming to room temperature, had been found to afford good yields of dihydroisobenzofurans[11] (for example 8). While each of three pyridine carbonyl compounds did indeed afford good yields (68–72%) of dihydroisobenzofurans (8) when allowed to react with 5 and warm to room temperature, it was found that this cyclization could be at least partially avoided if the anion formed in the initial reaction was quenched at −78 °C with ethanol. From 2-formylpyridine (**2a**) the carbinol **6a** was obtained as an oil which was not purified but dissolved in benzene and the solution was refluxed until the salt (presumably 7) had separated. After removal of the benzene layer, the salt was refluxed with 48% hydrobromic acid to afford acridizinium bromide (**4a**) in only 40% yield.

When the synthesis was repeated with 2-benzoylpyridine (**2b**), the yield (11%) of 11-phenylacridizinium perchlorate (**4b**) was also disappointing. With the sterically hindered 6-methyl-2-formylpyridine (**2c**) the yield of 4-methylacridizinium perchlorate **4c** was 34%, which is low but more than three times better than that reported[10] for the aromatic cyclodehydration method (1 → 4).

Although no effort was made to optimize reaction conditions for the new acridizinium ion synthesis, it appears likely that the route involving cycloquaternization (5 → 7 → 4) generally will prove inferior to that involving cyclodehydration (1 → 4) except in those syntheses in which steric factors are critical, as in the synthesis of **4c**.

Experimental Section

General. All reactions involving organolithium reagents were conducted under an atmosphere of dry nitrogen. Tetrahydrofuran was distilled from either lithium aluminum hydride or calcium hydride before use. Reaction temperatures of −100 °C were achieved by use of a liquid nitrogen–ether bath. The drying agent for organic solutions was magnesium sulfate. ^{1}H NMR data was obtained by using a JEOL Model JNM-MH-100 100-MHz spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR data was from a JEOL Model FX-60 15-MHz Fourier transform spectrometer with $CDCl_3$ lock and with tetramethylsilane as internal standard. IR data was from a Perkin-Elmer Model 297 spectrometer. Microanalyses were by MHW Laboratories, Phoenix, AZ. Melting points were determined by using a Mel-Temp melting-point block and are uncorrected.

Synthesis of Acridizinium Salts. General Procedure. A solution of *o*-lithiobenzyl chloride (**5**) was prepared at −100 °C[11] and 1 mol equiv of the pyridyl aldehyde or ketone (**2**) was added. The mixture was allowed to warm to −78 °C and remain at this temperature for 45 min. The mixture was quenched at −78 °C by addition of 15 mL of ethanol followed by addition of 200 mL of water. The organic layer was separated and the aqueous phase extracted three times with ether. The combined organic solution was dried and concentrated (rotary evaporator). The crude carbinol (**6**) which showed the presence of hydroxyl and absence of carbonyl absorption in the IR was taken up in benzene and the resulting solution refluxed until an oil separated from the solution. The benzene layer was decanted and the residue taken up in approximately 5 mL of 48% hydrobromic acid per gram of oil. The acid solution was heated on the steam bath for 1 h. The hydrobromic acid was removed under reduced pressure (rotary evaporator) and the resulting glass crystallized from ethanol or ethanol–water. Positive identification of each of the salts was made by mixture melting points with authentic samples and by comparison of IR spectra.

Acridizinium Bromide (4a). *o*-Lithiobenzyl chloride **5** was prepared from 4.11 g (20 mmol) of *o*-bromobenzyl chloride and 2.14 g (20 mmol) of pyridine-2-carboxaldehyde (**2a**) was added. By the general procedure, 2.06 g (40%) of yellow needles was obtained: mmp 248–249 °C (lit.[2,13] mp 239–240 °C); IR (KBr) 3450, 3070, 3020, 1630, 1465, 1410, 1390, 1370, 1340, 1330, 1150, 890, 770 cm^{-1}.

11-Phenylacridizinium Perchlorate (4b). From *o*-lithiobenzyl chloride (**5**, prepared from 10 mmol of *o*-bromobenzyl bromide) and 1.83 g (10 mmol) of 2-benzoylpyridine (**2b**), following the general procedure except that the crude product was precipitated by addition of 35% perchloric acid before crystallization, was obtained 0.39 g (11%) of **4b** as yellow needles: mp and mmp 244–246 °C (lit.[14] mp 246–248 °C); IR (KBr) 3090, 1645, 1610, 1560, 1400, 1370, 1340, 1310, 1090, 760, 710 cm^{-1}.

4-Methylacridizinium Bromide (4c). By the general procedure with 6-methyl-2-picolinaldehyde (**2c**), **4c** was obtained in 34% yield as yellow needles, mp and mmp 237–244 °C dec (lit.[10] mp 233–239 °C).

The **perchlorate** was obtained from the bromide as yellow plates; mp and mmp 178–181 °C (lit.[10] mp 180–180.5 °C); IR (KBr) 3040, 2950, 1640, 1470, 1410, 1330, 1080, 760 cm^{-1}.

Synthesis of 1,3-Dihydroisobenzofurans (8). The general procedure for the preparation of acridizinium salts was followed except that after addition of the pyridyl ketone or aldehyde (**2**) to the *o*-lithiobenzyl chloride (**5**) the temperature of the mixture was allowed to rise to room temperature and to remain there for 12–16 h.

Water was then added, the organic layer was separated, and the aqueous layer was extracted repeatedly with ether. The combined organic solutions were dried and concentrated (rotary evaporator); oils were purified by vacuum distillation and solids were recrystallized.

1-(2-Pyridyl)-1,3-dihydroisobenzofuran (8a) was obtained in 72% yield as a yellow oil: bp 96–98 °C (0.05 torr); IR (film) 3050, 2920, 2860, 1590, 1570, 1460, 1440, 1050, 745 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.68 (sym t (ABX), 2, CH_2), 6.31 (sym t (ABX), 1, CH), 6.80–7.43 (m, 7, Ar H), 8.52–8.68 (m, 1, Ar H); ^{13}C NMR ($CDCl_3$)

(13) The significantly higher melting point observed in the present work probably arises from more complete dehydration of acridizinium bromide which normally crystallizes as the monohydrate.

(14) Bradsher, C. K.; Solomons, T. W. G. *J. Am. Chem. Soc.* **1959**, *81*, 2550.

δ 73.75, 86.42, 120.20, 120.85, 122.54, 127.48, 127,80, 136.84, 138.46, 140.86, 149.05, 161.79.

The **picrate**, mp 145–145.5 °C, was prepared for analysis.

Anal. Calcd for $C_{19}H_{14}N_4O_8$: C, 53.52; H, 3.29; N, 13.15. Found: C, 53.52; H, 3.26; N, 12.96.

1-(2-Pyridyl)-1-phenyl-1,3-dihydroisobenzofuran (8b) crystallized from ethyl acetate–hexane as colorless needles (68% yield): mp 98–98.5 °C; IR (KBr) 3020, 2900, 2850, 1580, 1470, 1440, 1025, 980, 770, 760, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.32 (s, 2, CH_2), 7.08–7.92 (m, 11, Ar H), 8.40–8.52 (m, 2, Ar H).

Anal. Calcd for $C_{19}H_{15}NO$: C, 83.52; H, 5.49; N, 5.13. Found: C, 83.61; H, 5.50; N, 4.95.

1-(6-Methyl-2-pyridyl)-1,3-dihydroisobenzofuran (8c) was obtained as a yellow oil in 70% yield: bp 104–109 °C (0.05 torr); IR (film) 3070, 2970, 2925, 2860, 1600, 1580, 1460, 1060, 810, 775, 750, 680, 645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.69 (s, 3, CH_3), 5.28 (sym t (ABX), 2, CH_2), 6.23 (sym t (ABX), 1 CH), 6.86–7.70 (m, 7, Ar H); ^{13}C NMR ($CDCl_3$) δ 24.43, 73.68, 86.55, 109.16, 116.95, 120.85, 122.02, 122.80, 127.35, 127.74, 128.65, 137.10, 138.52, 141.12.

The **picrate**, mp 157–158 °C, was prepared for analysis.

Anal. Calcd for $C_{19}H_{15}NO$: C, 54.55; H, 3.64; N, 12.73. Found: C, 54.78; H, 3.61; N, 12.58.

Registry No. 2a, 1121-60-4; **2b**, 91-02-1; **2c**, 1122-62-9; **4a**, 7547-88-8; **4b**, 6634-51-1; **4c**·bromide, 74808-18-7; **4c**·perchlorate, 74808-20-1; **5**, 74824-35-4; **6a**, 74808-21-2; **6b**, 74824-36-5; **6c**, 74808-22-3; **8a**, 74808-23-4; **8a**·picrate, 74808-25-6; **8b**, 74808-26-7; **8c**, 74808-27-8; **8c**·picrate, 74808-28-9.

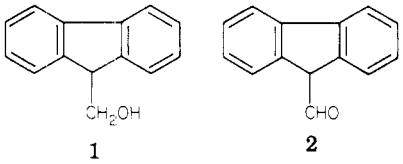
Convenient Preparation of (9-Fluorenyl)methanol and Its 2,7-Dihalo Derivatives

Louis A. Carpino

Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003

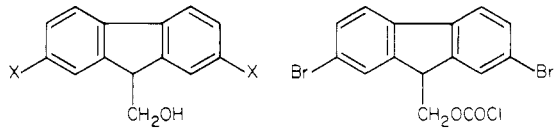
Received June 26, 1980

With the ever-increasing use[1-3] of the base-sensitive 9-fluorenylmethyloxycarbonyl (Fmoc) amino-protecting group there is a current need for a convenient, large-scale synthetic route to (9-fluorenyl)methanol (1), the key precursor of all Fmoc derivatives. A previously described[4] simple modification of the tedious Wislicenus–Brown[5,6] procedure, while a marked improvement over earlier methods, still suffers from the necessity to separate 1 from significant quantities of polymeric byproducts with consequent mediocre yields (50–60%). These remaining difficulties can be eliminated and 1 readily obtained in quantity by substitution of sodium borohydride for formalin in the conversion of 2 to 1. By this method 1 is obtained in 80% yield in a form pure enough for further use directly from the reaction mixture.



1 2

This simple method was not, however, satisfactory for the synthesis of the 2,7-dibromo and 2,7-dichloro derivatives of (9-fluorenyl)methanol, the corresponding Fmoc derivatives of which are of potential interest as amino-protecting groups of greater base sensitivity than the parent system. Fortunately a return to the classic procedure of Wislicenus–Brown[5,6] in the case of the dichloro derivative (3, X = Cl) and use of potassium ethoxide al-



3, X = Cl, Br 4

lowed facile formylation, and the formyl derivative was easily reduced to the alcohol. In the case of the dibromo analogue (3, X = Br) this method was not completely satisfactory because the presence of colored impurities (possibly the dibenzofulvene or products derived therefrom) made purification of the initial product exceptionally tedious. A far simpler approach to the dibromo derivative involved direct bromination of (9-fluorenyl)methanol by means of *N*-bromosuccinimide in acetic acid in the presence of hydrogen bromide. This method was developed from a related simple technique newly devised for the halogenation of fluorene. Direct bromination of (9-fluorenyl)methyl chloroformate was also noted to give the corresponding chloroformate, 4. However, the yield was not high (37%), and the chloroformate would probably be best prepared from the alcohol by reaction with phosgene. Curiously, chlorination of 1 by means of *N*-chlorosuccinimide in acetic acid by the same method as that used for the dibromo derivative gave not the alcohol but the corresponding acetate. Although this could be avoided by chlorination in dioxane–water, there was no particular advantage to this technique since the Wislicenus–Brown method proved satisfactory for the preparation of 3 (X = Cl).

That 2,7-dihalo substitution greatly accelerates base-catalyzed deblocking was shown by comparison of the ease of cleavage by piperidine and pyridine of the urethanes derived from 1 and 3 by reaction with *p*-chlorophenyl isocyanate. Deblocking rates were greatly dependent on the concentration of reactants. Under standardized conditions in dilute solution the dihalo derivatives were deblocked by a 10 molar excess of piperidine in toluene within 45–85 min, whereas the unsubstituted compound

(1) For a polymeric deblocking system for Fmoc derivatives see L. A. Carpino, J. R. Williams, and A. Lopusinski, *J. Chem. Soc., Chem. Commun.*, 450 (1978). Further work has shown that commercial polymers used as supports for piperazino deblocking agents as described in this reference are inconsistently effective even though obtained from the same suppliers (Dow Chemical Co., Rohm and Haas, Inc.). Although the deblocking step occurred readily, the scavenging of dibenzofulvene by piperazino polymers obtained from the new samples of commercial resins was more sluggish. These differences, which may have arisen because of the presence of traces of additives left over from the polymerization process, are now under study.

(2) For the unique advantages of Fmoc protection in connection with both solid-phase and solution peptide synthesis, see: (a) E. Atherton, H. Fox, D. Harkiss, C. J. Logan, R. C. Sheppard, and B. J. Williams, *J. Chem. Soc., Chem. Commun.*, 537, 539 (1978); (b) C.-D. Chang and J. Meienhofer, *Int. J. Pept. Protein Res.*, 11, 246 (1978); (c) C.-D. Chang, M. Waki, M. Ahmad, J. Meienhofer, E. O. Lundell, and J. D. Haug, *ibid.*, 15, 59 (1980); (d) M. Bodanszky, S. S. Deshmane, and J. Martinez, *J. Org. Chem.*, 44, 1622 (1979); (e) A. Bodanszky, M. Bodanszky, N. Chandramouli, J. Z. Kwei, J. Martinez, and J. C. Tolle, *ibid.* 45, 72 (1980); (f) J. Martinez, J. C. Tolle, and M. Bodanszky, *ibid.*, 44, 3596 (1979); (g) E. Atherton, C. Bury, R. C. Sheppard, and B. J. Williams, *Tetrahedron Lett.*, 3041 (1979); (h) R. Arshady, E. Atherton, and R. C. Sheppard, *ibid.*, 1521 (1979); (i) "Chemalog Hi-Lites", Chemical Dynamics Corp., South Plainfield, NJ, June 1978, Apr 1980.

(3) R. B. Merrifield and A. E. Bach, *J. Org. Chem.*, 43, 4808 (1978).

(4) (a) L. A. Carpino and G. Y. Han, *J. Am. Chem. Soc.*, 92, 5748 (1970); (b) L. A. Carpino and G. Y. Han, *J. Org. Chem.*, 37, 3404 (1972); 38, 4218 (1973); (c) L. A. Carpino, *Acc. Chem. Res.*, 6, 191 (1973).

(5) W. Wislicenus and M. Waldmuller, *Ber. Dtsch. Chem. Ges.*, 42, 785 (1909).

(6) W. G. Brown and B. A. Bluestein, *J. Am. Chem. Soc.*, 65, 1082 (1943). The conversion of 2 to 1 by means of alkaline aqueous formaldehyde was previously referred to erroneously as a cross-Cannizzaro reaction. The mechanism of this reaction was established by Burr [J. G. Burr, Jr., *J. Am. Chem. Soc.*, 73, 823 (1951)] as involving hydroxymethylation followed by base-catalyzed deformylation.

0022-3263/80/1945-4250$01.00/0