crystallized from pentane to give 19.4 g (50%) of **6** as a white solid, mp 52.5–55 °C. Anal. Calcd for $C_8H_8F_2OS$: C, 50.5; H, 4.2; F, 20.0. Found: C, 50.4; H, 4.2; F, 19.9.

Benzyl Difluoromethyl Sulfone (7). A solution of 10.0 g (0.057 mol) of **4** in 75 mL of HOAc was treated with 20 g (0.176 mol) of 30% H_2O_2, resulting in an exothermic reaction. Dilution with H_2O gave **7** as a white solid, which was recrystallized twice from benzene–hexane to give 8.4 g (71%), mp 57.5–59 °C. NMR ($CDCl_3$) showed CHF_2 at δ 6.08 (triplet, J = 52 Hz), CH_2 at δ 4.37, and ArH at δ 7.4. Anal. Calcd for $C_8H_8F_2O_2S$: C, 46.5; H, 4.9. Found: C, 46.6; H, 3.8. This material failed to react with Cl_2 in H_2O at 0 and 25 °C (2.0 g gave 1.7 g recovery).

2-Fluoromethyl *tert*-Butyl Sulfide (8). A mixture of 180 g (2.0 mmol) of *tert*-butyl mercaptan, 200 mL of THF, and 480 g (6.0 mol) of 50% NaOH formed a paste. Another 600 mL of H_2O was added, and the mixture was warmed at 60–65 °C while adding 185 g (2.15 mol) of CHF_2Cl. Extraction with 200 mL of CH_2Cl_2 and fractional distillation twice yielded 21.9 g (11%) of **8**, bp 99–102 °C. The low yield was thought to be due in part to codistillation with THF. To avoid this, dimethylacetamide was used. A mixture of 21.1 g (0.50 mol) of 57% NaH–mineral oil (washed well with hexane) in 200 mL of DMAC was stirred with 50 g (0.56 mol) of *tert*-butyl mercaptan. Treatment with 70 g (0.81 mol) of CHF_2Cl and distillation under ~60 mm pressure via two dry ice cooled traps gave **8**. Redistillation gave 15.5 g (22%) of pure material, bp 106 °C. Anal. Calcd for $C_5H_{10}F_2S$: C, 42.8; H, 7.2. Found: C, 43.0; H, 7.2.

Chlorination of 8.75 g (0.062 mol) in 100 mL of H_2O at 0 °C and workup as usual yielded 5.7 g (61%) of **2**.

Registry No.—**1**, 42497-69-8; **2**, 1512-30-7; **3**, 2924-74-5; **4**, 68965-44-6; **5**, 58932-27-7; **6**, 68965-45-7; **7**, 68965-46-8; **8**, 68965-47-9; benzyl mercaptan, 100-53-8; difluorochloromethane, 75-45-6; thiourea, 62-56-6; benzyl chloride, 100-44-7; chlorofluoromethane, 593-70-4; *tert*-butyl mercaptan, 75-66-1.

References and Notes

(1) (a) G. G. I. Moore, J. K. Harrington, and K. F. Swingle, *J. Med. Chem.*, **18**, 386 (1975); (b) G. G. I. Moore in "Antiinflammatory Agents", R. A. Scherrer and M. W. Whitehouse, Eds., Academic Press, New York, 1974, p 160.
(2) G. G. I. Moore, L. R. Lappi, J. E. Bachhuber, and A. C. Conway, 160th National Meeting of the American Chemical Society, Chicago, Ill., 1970, Abstracts, MEDI.
(3) E. H. Banitt, W. E. Coyne, K. T. McGurran, and J. E. Robertson, *J. Med. Chem.*, **17**, 116 (1974).
(4) (a) R. D. Trepka, J. K. Harrington, J. E. Robertson, and J. T. Waddington, *J. Agric. Food Chem.*, **18**, 175 (1970); (b) R. D. Trepka, J. K. Harrington, J. W. McConville, K. T. McGurran, A. Mendel, D. R. Pauly, J. E. Robertson, and J. T. Waddington, *ibid.*, **22**, 1111 (1974).
(5) M. V. Farrar, *J. Chem. Soc.*, 3058 (1960).
(6) J. K. Harrington and G. M. Kaufman, 3M Co., unpublished work.
(7) (a) L. N. Sedova, *Zh. Obshch. Khim.*, **39**, 2057 (1969); *Chem. Abstr.*, **72**, 3166q (1970); (b) J. Hine and J. J. Porter, *J. Am. Chem. Soc.*, **79**, 5493 (1957); (c) J. Hine and K. Tanabe, *ibid.*, **80**, 3002 (1958); (d) L. Soboronskii, *Zh. Obshch. Khim.*, **29**, 1144 (1959); *Chem. Abstr.*, **54**, 8603 (1960); (e) W. A. Shephard and C. M. Sharts, "Organic Fluorine Chemistry", W. A. Benjamin, New York, 1969.
(8) H. R. Davis and R. J. Loer, 3M Co., unpublished work.
(9) A material claimed to be **3** was isolated by K. A. Petrov and G. A. Sokolskii, *Zh. Obshch. Khim.*, **27**, 2711 (1957) [*Chem. Abstr.*, **51**, 7198c (1957)], on treatment of $ClCH_2SCH_2Ph$ with HF. However, the low boiling point cited (25 °C at 0.1 mm vs. our 65 °C at 0.1 mm) and the instability (decomposed at 50–60 °C) argue against this.
(10) J. Hine, "Divalent Carbon", Ronald Press, New York, 1964, p 39.
(11) E. E. Gilbert, "Sulfonation and Related Reactions", Interscience, New York, 1965, p 201.
(12) W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, **36**, 3145 (1971).
(13) J. S. Grossert, W. R. Hardstaff, and R. F. Langer, *J. Chem. Soc., Chem. Commun.*, 50 (1973).

Notes

Reaction of Unsaturated Compounds with Hypofluorous Acid[1a]

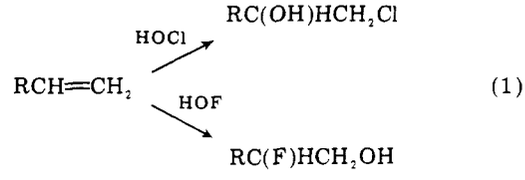
K. G. Migliorese,*[1b] E. H. Appelman, and M. N. Tsangaris[1c]

Chemistry Division, Argonne National Laboratory, Argonne, Illinois 60439

Received December 21, 1978

The successful synthesis of hypofluorous acid by Studier and Appelman[2] has prompted the study of the reactions of this novel molecule with organic substrates. Appelman and Bonnett have recently reported the hydroxylation of aromatic compounds[3] by hypofluorous acid. The fact that hydroxylation rather than fluorination was observed in this system supports the hypothesis that HOF is polarized in the sense $HO^{\delta+}$–$F^{\delta-}$. This unique polarization was initially suggested by NMR spectral data.[4] Among the hypohalous acids, only HOF would be expected to be polarized in this way since all of the other halogen atoms are less electronegative than oxygen.[5] We would thus expect the Markownikoff addition of hypofluorous acid to alkenes to yield halohydrins of an orientation opposite to that resulting from the well-known Markownikoff addition of hypochlorous acid ($HO^{\delta-}$–$Cl^{\delta+}$).[6,7] We have therefore decided to investigate the reaction of HOF with unsaturated molecules.

The hypofluorous acid used in this work was prepared in ~50-mg quantities by the reaction of fluorine with ice at ca. −40 °C in a recirculating flow system as described by Appelman.[8] The HOF prepared in this way was invariably contaminated with substantial amounts of HF and with traces of water. The HF was present in amounts comparable to the HOF. Hypofluorous acid decomposes spontaneously to oxygen and hydrogen fluoride,[2,3] and in the course of this work several minor detonations occurred. Adequate shielding is therefore needed whenever HOF is being handled. The reactions were carried out by warming a U-tube containing the HOF to −50 °C and sweeping the HOF from the U-tube with dry nitrogen into a cold solution of the alkene or alkyne in dichloromethane or carbon tetrachloride. In general, immediate reaction was evidenced by a darkening of the solution. The reaction mixtures were concentrated by evaporation under vacuum and were analyzed by gas chromatography. The major products were characterized by gas chromatography–mass spectrometry, infrared spectrophotometry, and $^{19}F/^{1}H$ nuclear magnetic resonance spectrometry. Some volatile products may have been lost during the concentration. Our results are summarized in Table I.



(1)

Under our conditions, alkenes gave α-fluoro alcohols as the major products, while acetylenes gave mixtures of aldehydes, ketones, and acyl fluorides, which presumably resulted from

0022-3263/79/1944-1711$01.00/0

Table I. Products Formed in the Reaction of Alkenes and Acetylenes with HOF

starting material	registry no.	product	registry no.	yield,[a] %
	110-83-8		656-60-0	80
$(CH_3)_2C{=}C(CH_3)_2$	563-79-1	$(CH_3)_2CFCOH(CH_3)_2$	661-63-2	81
$(CH_3)_2C{=}CHCH_3$	513-35-9	$(CH_3)_2CFCHOHCH_3$	1998-77-2	91
$(CH_3)_2C{=}CHCH_2CH_3$	625-27-4	$(CH_3)_2CFCHOHCH_2CH_3$	69429-53-4	64
		$(CH_3)_2COHCHFCH_2CH_3$	69429-54-5	16
$C_6H_5CH{=}CH_2$	100-42-5	$C_6H_5CHFCH_2OH$	2932-58-3	80
	693-89-0		69429-55-6	90
$C_6H_5C{\equiv}CH$	536-74-3	$C_6H_5COCH_2F$	450-95-3	30
		$C_6H_5CH_2COF$	370-84-3	45
$(CH_3)_3CC{\equiv}CH$	917-92-0	$(CH_3)_3CCHFCHO$	69429-56-7	60

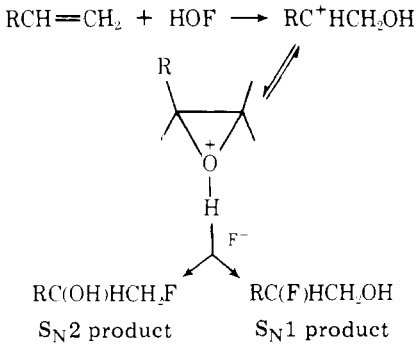
[a] Calculated from gas chromatographic data as percentage of product mixture.

tautomerization of the initially formed α-fluoro enol adducts. In most cases, the expected Markownikoff addition products (based on the polarization $HO^{\delta+}$–$F^{\delta-}$) were formed. Unexpectedly, however, a number of anti-Markownikoff addition products were also formed in these reactions. For example, the reaction of 2-methyl-2-pentene with HOF gave a 16% yield of the anti-Markownikoff addition product, 2-methyl-3-fluoro-2-pentanol. Similarly, the reaction of ethynylbenzene with HOF yielded 30% of the anti-Markownikoff product, α-fluoroacetophenone, and produced no Markownikoff product (2-fluoro-2-phenylacetaldehyde).

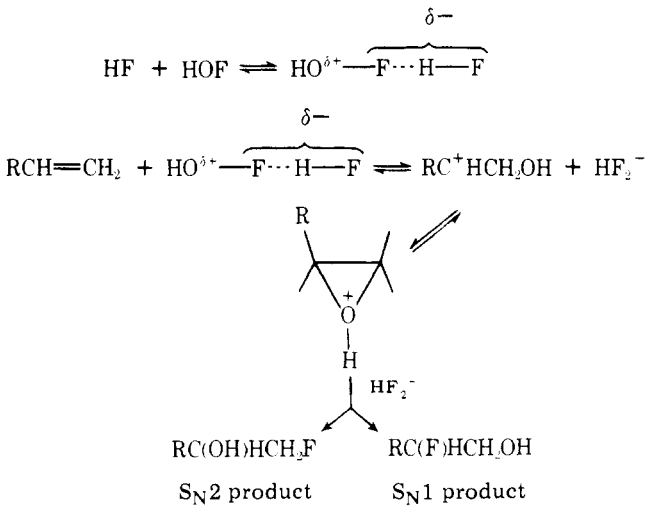
These results strongly suggest that the addition of hypofluorous acid to unsaturated compounds does not always occur by a simple Markownikoff electrophilic addition mechanism, since this would give rise solely to Markownikoff addition products.[9] In order to explain this anomaly, we propose the mechanism outlined in Scheme I. Equivalently, since HF is always present along with the HOF, the HF may catalyze the addition as outlined in Scheme II.

Both of these mechanisms involve initial Markownikoff addition of electrophilic HOF to the unsaturated system, followed by cyclization of the oxycarbonium ion to a protonated epoxide. This protonated epoxide intermediate then undergoes a nucleophilic ring opening to yield the final fluorohydrin product. The last step in the proposed mechanism is identical with the acid-catalyzed nucleophilic ring opening of an epoxide. Acid-catalyzed ring-opening reactions of substituted epoxides normally yield a mixture of S_N1 and S_N2 products. The product distributions are known to be quite sensitive to reaction conditions, as well as to epoxide structure.[10,11] This is particularly true in the cases in which hydrogen fluoride[12] and its salts[13] are involved. The balance of factors favoring the S_N1 mechanism over the S_N2 mechanism for ring opening is quite delicate[14] and usually unpredictable.[15,16] Recent efforts to use the entropy of activation as a criterion for mechanism type have been only partially successful.[17,18] It is therefore not surprising that mixtures of products result from the addition of HOF to alkenes if, in fact, the reaction involves the postulated intermediates. This proposed mechanism is similar to the arene oxide mechanism postulated for the hydroxylation of aromatic compounds by hypofluorous acid.[3] It is also similar to the pathway involved in enzyme-catalyzed oxidation of alkenes.[19]

Scheme I. Proposed Mechanism for Reaction of Alkenes with HOF



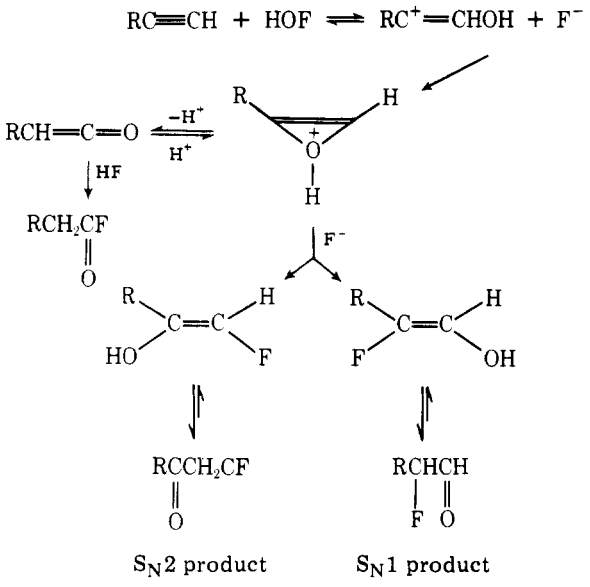
Scheme II



An alternative possibility arises from the fact that HOF reacts with water to give hydrogen fluoride and hydrogen peroxide.[2] Since small amounts of water are inevitably present in HOF preparations, it is conceivable that HF and H_2O_2 are responsible for our observed results. However, this possibility seems to be remote. Halohydrins can, indeed, be prepared from olefins by reaction with hydrogen peroxide and hydrogen halides in aqueous solution, but the process requires relatively long reaction times and elevated temperature.[20] Hydrogen peroxide alone cannot form epoxides in the absence of an appropriate activating carrier such as selenium dioxide.[21] Thus, it is quite unlikely that our low concentrations of hydrogen peroxide and hydrogen fluoride could give rise to the observed products under our relatively mild reaction conditions. We therefore conclude that our results are attributable to addition of HOF by the mechanisms suggested in Schemes I and II.

In our hands, certain alkenes underwent telomerization rather than simple electrophilic addition. Isobutylene and 1-pentene gave only higher molecular weight products, which mass spectrometric analysis indicated to contain neither

Scheme III



fluorine nor oxygen. Indene gave only dimers under our reaction conditions.[22] The rationale for these results is not entirely clear, and further work on these systems was not carried out.

The reaction of acetylenes with HOF may be considered to proceed in a manner similar to that of the alkenes. The proposed pathway is outlined in Scheme III. Catalysis by HF as outlined in Scheme II may also be involved here. The central intermediate in this scheme is a protonated oxirene, which is likely to be extremely unstable since it is isoelectronic with the antiaromatic cyclopropenyl carbanion.[23] An oxirene has, however, been proposed as an intermediate in the reaction of peracids with alkynes.[24,25] Additionally, Scheme III allows for the rearrangement of the initially formed oxirene to a ketene intermediate,[24,25] which then reacts with hydrogen fluoride to give the observed acyl fluoride product. Since traces of water are present, substituted acetic acids would also be expected to form. In fact, we have observed small amounts of phenylacetic acid in the acidified bicarbonate wash from the reaction of HOF with ethynylbenzene. It is interesting to note that no Markownikoff addition product is formed in this reaction, while in the analogous reaction of HOF with 3,3-dimethyl-1-butyne the only fluorine-containing product results solely from Markownikoff addition. Clearly, the interplay of the various mechanistic factors is quite complex here, and further work is necessary before any definite conclusions can be drawn.

The products of the addition of HOF to alkenes and acetylenes are similar to those obtained with oxygen difluoride, which can react at low temperatures with alkenes to give fluorohydrins and with acetylenes to give α-fluoro aldehydes and ketones.[26] Here the postulated intermediates are α-fluorohypofluorites, which spontaneously hydrolyze to the products. However, the mechanism of OF_2 addition to alkenes and acetylenes has not been entirely delineated.

The question of the role of HF in HOF reactions remains open. No products resulting from the addition of HF to alkenes or acetylenes could be detected in the product mixtures from the HOF addition reactions, suggesting either that HF is complexed with HOF as indicated in Scheme II or that alkenes react much more slowly with HF than with HOF. Current work on HF chemistry does not permit relevant evaluation of these possibilities.[27]

Although it is difficult to do, HOF can be freed from all HF impurity, and this remains as a viable path for future exploration of HOF chemistry.

Experimental Section

Infrared spectra were obtained on a Beckman IR-8 spectrophotometer, using cells with sodium chloride windows. Gas chromatography was done on a Perkin-Elmer Model 900 gas chromatograph equipped with a flame ionization detector and a 22 ft × $\frac{1}{8}$ in. stainless steel column of 2% QF-1 on 80/100 Chrom G (AW/DMCS). Peak areas were calculated by triangulation. GC–MS was done on a Perkin-Elmer Model 270 system operating at 70 eV. ^{19}F NMR spectra were obtained with a Varian A56/60 spectrometer operating at 56.4 MHz, with fluorotrichloromethane as an internal standard. Proton NMR was done on a Perkin-Elmer R-20B spectrometer at 60 MHz, using tetramethylsilane as an internal standard.

Preparation of HOF and Reaction with Alkenes and Alkynes. HOF (1–3 mmol) was prepared as previously described.[8] Reactions were carried out by sweeping the HOF out of its U-tube at −50 °C with dry nitrogen into an ice–salt cooled Kel-F tube containing 10 mL of a 20% (v/v) solution of the alkene or alkyne in carbon tetrachloride (Baker Analyzed Reagent) or dichloromethane (Eastman Spectro Grade). All alkenes and alkynes were initially purified by chromatography through a short column of neutral alumina (Woelm, Grade 1). When all of the HOF had been transferred, the reaction mixture was poured into aqueous 5% sodium bicarbonate solution. The organic layer was removed, and the aqueous layer was further extracted twice with 10-mL portions of dichloromethane. The organic extracts were combined, washed five times with saturated sodium chloride solution, dried over magnesium sulfate, and then concentrated on a rotary evaporator to ~0.2 mL. The products were not isolated further but were characterized by IR, NMR (^1H or ^{19}F), and GC–MS. This procedure may have led to the loss of volatile products, such as alkyl fluorides.

Cyclohexene. The single product formed in 85% yield was 2-fluorocyclohexanol. This material had infrared[12] and ^{19}F NMR[22] spectra identical with those of an authentic sample.

2,3-Dimethyl-2-butene. The only addition product observed (80% yield) was 2,3-dimethyl-3-fluoro-2-butanol. The product was identified from its ^1H NMR and mass spectra, which were identical with the literature spectra.[26]

2-Methyl-2-butene. The only addition product observed (90% yield) was 3-fluoro-3-methyl-2-butanol: mass spectrum, *m/e* (rel intensity) 86 (50), 71 (60), 57 (70), 45 (90), 43 (80), 41 (100). The mass spectrum is consistent with initial loss of HF from the absent molecular ion (*m/e* 106) to give a fragment of *m/e* 86. The ^1H NMR spectrum showed a doublet centered at δ 1.42 (J = 22 Hz), consistent with the $(CH_3)_2CF$ grouping:[28] ^1H NMR ($CDCl_3$) δ 1.0 (d, 3 H), 1.42 (d, 6 H), 3.6 (broad, 1 H), 3.8 (q, 1 H).

2-Methyl-2-pentene. Two major addition products were observed in a ratio of 4:1. Both products gave identical mass spectra. On the basis of the ^1H NMR spectrum of the mixture, however, the major product was identified as 2-fluoro-2-methyl-3-pentanol while the minor product was identified as 2-methyl-3-fluoro-2-pentanol. The product spectrum was dominated by the large methyl doublet at δ 1.35 (J = 21.6 Hz), which is indicative of the $(CH_3)_2CF$ grouping.[28] These compounds would be expected to have similar mass spectra, based on the known tendency of secondary and tertiary alcohols to fragment via loss of the largest alkyl group attached to the hydroxyl-bearing carbon:[29] mass spectrum, *m/e* (rel intensity) 100 (10), 85 (10), 71 (70), 59 (35), 57 (75), 43 (100), 41 (40), 39 (15).

Styrene. Only one addition product (80%) was observed. On the basis of its mass spectrum, the product was identified as 2-fluoro-2-phenylethanol: mass spectrum, *m/e* (rel intensity) 140 (10), 120 (20), 110 (20), 109 (50), 92 (30), 91 (100).

1-Methylcyclopentene. The only addition product formed (90%) was 2-fluoro-2-methycyclopentanol: mass spectrum, *m/e* (rel intensity) 118 (2), 100 (10), 98 (15), 85 (20), 83 (25), 69 (50), 51 (100), 55 (80), 43 (70), 42 (60); ^{19}F NMR ϕ 144.6 ppm. The ^{19}F chemical shift is in good agreement with that reported for 2-methyl-2-fluorocyclohexanol (ϕ 143.6 ppm).[30]

Ethynylbenzene. Two major products were formed in essentially equal amounts. On the basis of their respective mass spectra, these products were identified as α-fluoroacetophenone and phenylacetyl fluoride. The mass spectrum of the α-fluoroacetophenone is characterized by the loss of the CH_2X fragment to give the base peak at *m/e* 105 ($C_6H_5C^+{\equiv}O$), which is characteristic of α-haloacetophenones:[31] mass spectrum, *m/e* (rel intensity) 106 (95), 105 (100), 77 (80), 43 (60). The mass spectrum of phenylacetyl fluoride is straightforward: *m/e* (rel intensity) 138 (20), 118 (10), 91 (100), 77 (15), 43 (50). Identification of phenylacetyl fluoride was further strengthened by the IR spectrum of the reaction mixture, which, in addition to unreacted ethynylbenzene, showed a carbonyl stretching at 1825 cm^{-1} indicative

of an acyl halide.[32] Acidification of the initial bicarbonate wash liquor followed by extraction with dichloromethane showed the presence of phenylacetic acid (mass spectrum was identical with the literature spectrum[31b]) as well as other organic material.

3,3-Dimethyl-1-butyne. A single product (70%) was formed, which was identified as 2-fluoro-3,3-dimethylbutanal on the basis of the IR (aldehyde carbonyl stretching at 1710 cm^{-1}) and ^1H NMR spectra [^1H NMR ($CDCl_3$) δ 1.1 (*t*-Bu), 3.5 (d, J = 43 Hz, CHF), 10.6 (broad CHO)] of the reaction mixture. The ^1H NMR spectrum is similar to that of the chloro and bromo analogues,[33] and the observed CHF coupling constant is also indicative of this structure.[34] The mass spectrum of the major product also agreed well with the proposed structure: mass spectrum, *m/e* (rel intensity) 118 (1), 98 (35), 83 (10), 69 (70), 55 (98), 41 (100).

Acknowledgments. The authors would like to thank Professor Raymond Bonnett of Queen Mary College, London, and Dr. Randall Winans of Argonne for their continuing interest and helpful discussions. K.G.M. acknowledges the support of the Argonne Center for Educational Affairs as a Faculty Research Participant.

Registry No.—Hypofluorous acid, 14034-79-8.

References and Notes

(1) (a) Based on work performed under the auspices of the Division of Basic Energy Sciences of the U.S. Department of Energy. (b) Present address: Helene Curtis Industries, Inc., Chicago, Ill. 60639. (c) Undergraduate Research Student, Indiana University Northwest, Gary, Indiana 46408.
(2) M. H.Studier and E. H. Appelman, *J. Am. Chem. Soc.*, **93,** 2349 (1971).
(3) E. H. Appelman, R. Bonnett, and B. Mateen, *Tetrahedron*, **33,** 2119 (1977).
(4) J. C. Hindman, A. Svirmickas, and E. H. Appelman, *J. Chem. Phys.*, **57,** 4542 (1972).
(5) L. Pauling, "The Chemical Bond", Cornell University Press, Ithaca, N.Y., 1960, p 63.
(6) E. Muller, *Methoden Org. Chem. (Houben-Weyl), 4th Ed., 1962,* **5,** Part 3, 768 (1962).
(7) A. Detoeuf, *Bull. Soc. Chim. Fr.*, **31,** 169 (1922).
(8) E. H. Appelman and H. Kim, *J. Chem. Phys.*, **57,** 3272 (1972).
(9) V. Markownikoff, *C. R. Hebd. Seances Acad. Sci.*, **82,** 668 (1875).
(10) A. Feldstein and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76,** 1626 (1954).
(11) R. Fuchs and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76,** 1631 (1954).
(12) A. Kergomard and G. Farges, *Bull. Soc. Chim. Fr.*, 51 (1963).
(13) G. Aranda, J. Jullien, and J. A. Martin, *Bull. Soc. Chim. Fr.*, 1890 (1965).
(14) A. Rosowsky in "*Heterocyclic Compounds with Three- and Four-Membered Rings, Part 1*", A. Weissberger, Ed., Wiley-Interscience, New York, 1964, p 1.
(15) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59,** 737 (1959).
(16) S. Patai, Ed., "*The Chemistry of the Ether Linkage*", Interscience, London, 1967.
(17) (a) J. Biggs, N. B. Chapman, and V. Wray, *J. Chem. Soc. B*, 66 (1971); (b) *ibid.*, 63 (1971); (c) *ibid.*, 71 (1971).
(18) J. Novak and J. Antosova, *Collect. Czech. Chem. Commun.*, **35,** 1096 (1970).
(19) M. J. Klug and A. J. Markovetz, *Adv. Microb. Physiol.*, **5,** 1 (1971).
(20) W. Weigert, H. Klebe, A. Meffert, G. Kaebisch, and A. Langenfeld, Ger. Offen. 2 160 613 (June 20, 1973); *Chem. Abstr.*, **79,** 65718f (1973).
(21) N. Matsumura, N. Sonoda, and S. Tsutsumi, *Tetrahedron Lett.*, 2029 (1970).
(22) A. Dansi and C. Pasini, *Gazz. Chim. Ital.*, **81,** 508 (1951).
(23) R. Breslow, J. Brown, and J. J. Gajewski, *J. Am. Chem. Soc.*, **89,** 4383 (1967).
(24) R. N. McDonald and P. Schwab, *J. Am. Chem. Soc.*, **86,** 4866 (1964).
(25) J. K. Stille and D. D. Whitehurst, *J. Am. Chem. Soc.*, **86,** 4871 (1964).
(26) R. F. Merritt and J. K. Ruff, *J. Org. Chem.*, **30,** 328 (1965).
(27) M. Hudlicky, "Chemistry of Organic Fluorine Compounds", 2nd. ed., Ellis Horwood Ltd., Chichester, 1976, p 36–41.
(28) J. A. Martin, *C. R. Hebd. Seances Acad. Sci.*, **261,** 4385 (1965).
(29) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds", Holden-Day, San Francisco, 1967, p 96.
(30) J. Jullien, J. A. Martin, and R. Ramanadin, *Bull. Soc. Chim. Fr.*, 171 (1964).
(31) (a) E. Stenhagen, S. Abrahamsson, and F. W. McLafferty, Eds., Registry of Mass Spectral Data", Wiley, New York, 1974, pp 443, 971; (b) *ibid.*, p 282.
(32) C. J. Pouchert, Ed., "The Aldrich Library of Infrared Spectra", 2nd ed., Aldrich Chemical Co., Milwaukee, Wis., 1975, p 375.
(33) P. Duhamel, L. Duhamel, and J. Gralak, *Bull. Soc. Chim. Fr.*, 3641 (1970).
(34) D. P. Wyman, B. L. Shapiro, and P. R. Kaufman, *Can. J. Chem.*, **43,** 2433 (1965).

Efficient Synthesis of 3-Substituted Aspartic Acids[1]

Yasuhiko Ozaki, Tameo Iwasaki, Muneji Miyoshi, and Kazuo Matsumoto*

Research Laboratory of Applied Biochemistry, Tanabe Seiyaku Co. Ltd., 16-89, Kashima-3-chome, Yodogawa-ku, Osaka, 532, Japan

Received December 5, 1978

3-Substituted aspartic acids are a class of physiologically interesting amino acids. For example, 3-hydroxyaspartic acid,[2] 3-methylaspartic acid,[3] 3-phenylaspartic acid,[4] 3-aminoaspartic acid (2,3-diaminosuccinic acid),[4] and their derivatives are attractive substances as a possible antagonist of aspartic acid, and some of these possess antibacterial activity. Of these, 3-aminoaspartic acid derivatives are also important intermediates for biotin[5] and 3-fluoroaspartic acid,[6] which is a useful precursor of 5-fluorouracil.[7] With regard to the synthesis of 3-aminoaspartic acid, two conventional methods are known: the first method is an amination of dibromosuccinic acid with benzylamine, followed by debenzylation;[8a,b] the second is a newer method by photodimerization of *N*-acylglycinate.[9]

In this regard, we have attempted to exploit the more versatile method for the synthesis of the 3-substituted amino acids in the course of studies on the synthesis of amino acids and related compounds. Most recently, we have found that 2-acetoxyamino acid derivatives were useful cationic synthons, which reacted with various nucleophiles to afford 2-substituted amino acid derivatives in excellent yields.[10] In the present study, this finding has been extended to the C–C bond formation by the reaction with carbanion as a nucleophile; this paper describes that the method has effected a potentially general synthesis of 3-substituted aspartic acids, especially 3-aminoaspartic acid derivatives as shown in Scheme I.

The reaction of ethyl 2-acetoxyglycinate (**1**), which was prepared by the anodic oxidation of ethyl *N*-acetylaminomalonate,[11] with an anionic source possessing the glycine skeleton (**2**) proceeded smoothly in the presence of sodium hydride. After the reaction mixture was worked up in the usual manner, the products were purified by column chromatography on silica gel. The resulting *N*-acetyl-3-substituted-aspartic acid derivatives (**3**) were identified by IR and NMR spectroscopies as described in the Experimental Section. When diethyl *N*-acetylaminomalonate (**2a**), diethyl *N*-formylaminomalonate (**2b**), diethyl *N*-carbobenzoxyaminomalonate (**2c**), and ethyl 2-(*N*-acetylamino)cyanoacetate (**2d**) as the carbanion sources having glycine skeleton were used, the corresponding coupling products (**3a–d**) were obtained in high yields. Of these, the compound **3d** was isolated as crystals in 55% yield, which seemed to be a single isomer; unfortunately, the stereochemistry was not determined in this study. Subsequently, these coupling products were hydrolyzed with hydrochloric acid to afford the desired 2,3-diaminosuccinic acid (**4**), which was a diastereomeric mixture of (±) and meso forms, in a good yield as shown in the Experimental Section.

The synthetic method was further applied to the preparation of other 3-substituted aspartic acid analogues. The reaction of the acetoxyglycinate (**1**) with ethyl acetoacetate and ethyl cyanoacetate afforded diethyl *N*-acetyl-3-acetylaspartate (**5**)[12] and diethyl *N*-acetyl-3-cyanoaspartate (**6**), respectively, in good yields. Further attempts to prepare the 2-methylaspartic acid derivative were carried out using ethyl *N*-acetyl-2-acetoxyalaninate (**1'**). As a typical example, diethyl *N*-acetyl-3-cyano-2-methylaspartate (**6'**) was synthesized in

0022-3263/79/1944-1714$01.00/0