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Supplementary Material Available. Experimental procedures for these reactions will appear following these pages in the microfilm edition of this volume of this journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3807.

References and Notes

(1) S. Danishefsky and R. K. Singh, *J. Am. Chem. Soc.*, **97**, 3239 (1975).
(2) S. Danishefsky, G. Rovnyak, and R. Cavanaugh, *J. Chem. Soc., Chem. Commun.*, 636 (1969).
(3) S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.* 820 (1972).
(4) J. M. Stewart and G. K. Pagenkopf, *J. Org. Chem.*, **34**, 7 (1969).
(5) R. W. Kierstead, R. P. Linstead and B. C. L. Weedon, *J. Chem. Soc.*, 3616 (1952).
(6) For predominant terminal attack upon **3** by cuprates in possible electron transfer processes, see (a) G. Daviaud and P. Miginak, *Tetrahedron Lett.*, 997 (1972); (b) P. A. Grieco and R. Finkelhor, *J. Org. Chem.*, **38**, 2100 (1973). For a recent "cuprate" addition to a monoactivated vinylcyclopropane, see N. Miyaura, M. Itoh, N. Sasaki, and A. Suzuki, *Synthesis*, 316 (1975).
(7) (a) The formula of this compound is established by (a) combustion analysis and (b) spectral properties. The data are provided in the Experimental section which appears in the microfilm edition.
(8) (a) S. Danishefsky and G. Rovnyak, *J. Chem. Soc., Chem. Commun.*, 821 (1972); (b) G. Rovnyak, Ph.D. Thesis, University of Pittsburgh, 1970.
(9) Unfortunately we are unable to measure the rates for **4*** and **6*** at the same temperature. While the temperature dependence of k_{rac} has not been measured, the minimum ratio would appear to be 10^4.
(10) Cf. A. B. Chmurny and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 4237 (1973), and papers cited therein.
(11) The possibility that this type spiroactivation arises from additional strain imposed on the three-membered ring seems to us unlikely but has not been disproven.
(12) K. Pihalaja and M. Seilo, *Acta. Chem. Scand.*, **23**, 3003 (1969).
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Selective Fluorination of Hydroxy Amines and Hydroxy Amino Acids with Sulfur Tetrafluoride in Liquid Hydrogen Fluoride

Summary: At −78° and atmospheric pressure sulfur tetrafluoride in liquid hydrogen fluoride selectively replaces alcoholic hydroxyl groups in hydroxy amines and hydroxy amino acids by fluorine.

Sir: Sulfur tetrafluoride, SF_4, is the most frequently employed reagent for transforming organic compounds containing certain oxygen functionalities into the corresponding organofluorine compounds. It is regarded as the standard reagent for converting aldehydes, ketones, and carboxylic acids into difluoro and trifluoro compounds, respectively.[1,2] However, fluorination of alcohols by SF_4 was found to be restricted to those containing "acidified" hydroxyl groups.[3] Owing to its low reactivity, SF_4 is employed in high pressure apparatus, generally at temperatures of 50–200°.

We have found that the reactivity of SF_4 toward a variety of alcohols is dramatically and selectively increased when employing liquid hydrogen fluoride (HF) as solvent. Surprisingly, the reactivity of SF_4 with carbonyl compounds and carboxylic acids is not concomitantly increased and thus the SF_4–HF solution becomes a selective fluorinating system toward alcohols.[4] Moreover, the protection of amino groups against electrophilic reagent by use of liquid HF solvent, observed in the C-chlorination[5] and C-fluorination[6] of amines and amino acids, also obtains in this system. (In the absence of this protection amino groups react with SF_4 to form imino sulfur difluorides.[7])

Sulfur tetrafluoride, taken as a gas from a cylinder and measured as a liquid in a graduated trap at −78° (dry ice–acetone bath, ≃2.5 ml, 0.042 mol) was bubbled into 40 ml of liquid HF, kept at −78°. (The HF was taken as a gas from a cylinder, liquefied directly by passing into the cooled reactor, made of polyethylene or KEL-F®.[5]) Threo-β-phenylserine monohydrate (1.99 g, 0.01 mol) was added. (Throughout slight positive pressure of N_2 was maintained.) After a 45-min reaction period at −78°, the solvent was blown off by a stream of N_2, concentrated HCl was added, and the solution was evaporated to dryness in vacuo to give the HCl salt of β-fluorophenylalanine. The free amino acid was liberated in water–pyridine (mp 173–74° dec, yield 65%). Spinco amino acid analysis showed a single symmetrical peak.[8] Also, by a similar procedure, L-threonine was transformed into L-2-amino-3-fluorobutyric acid. The results on free amino acids indicated that there was no protection needed for –COOH groups.[9,10]

The mechanism of the SF_4–ROH reaction has been extensively discussed and it is commonly felt that an alkoxysulfur trifluoride, $ROSF_3$, is the key intermediate and that this intermediate collapses to product via an SNi or SN2 pathway.[1] However in the liquid HF–SF_4 system a carbonium ion mechanism is suggested by the following: (1) The product from the most stable carbonium ion seems to be obtained [the quantitative rearrangement of 3-hydroxypiperidine to 4-fluoropiperidine was observed (indicating a shift of the carbonium ion away from the positive $-NH_2^+-$)]; (2) 2-methylserine affords in addition to a 23% yield of the expected 2-fluoromethylalanine, a 40% yield of 1-aminocyclopropane carboxylic acid (this type of insertion into a C–H bond has been well documented in the literature of carbonium ions[11,12]); (3) in the case of simple alcohols (*n*-hexanol), the products are complex (branched chain fluorides, olefins, and dimers). Since fluorination is not observed in the absence of HF (choline chloride afforded no 2-fluoroethyl trimethyl ammonium product when it was reacted with SF_4 in diglyme at −5°), it is important to consider the role of this acid. It is proposed that HF not only induces the well-known dissociation of SF_4 to the much more electrophilic SF_3^+ (eq 1)[13] but also plays an important role in the ionization of the alkoxysulfur trifluoride (eq 3) by providing a solvent of high dielectric constant and possibly engendering an ionization analogous to the one in eq 1. The latter would provide a better leaving group (eq 4).

$$SF_4 + HF \rightleftharpoons SF_3^+ + HF_2^- \quad (1)$$

$$ROH + SF_3^+ \rightarrow ROSF_3 + H^+ \quad (2)$$

$$ROSF_3 \rightarrow R^+ + SOF_2 + F^- \rightarrow RF \quad (3)$$

$$ROSF_3 + HF \rightarrow ROSF_2^+ + HF_2^- \rightarrow R^+ + SOF_2 \rightarrow \text{etc} \quad (4)$$

This method for the C–OH → C–F transformation[14] (formally "fluorodehydroxylation") is considered a promising tool of antimetabolite synthesis. The physicochemical similarity of the C–OH and C–F bonds has been recognized

Table I
Products from Reaction of SF_4–HF with Various Hydroxy Amino Compounds at −78°

Product[a]	Mp, °C	Yield, %[b]
3-Fluoro-D-alanine[c]	168 dec	51
3-Fluoro-L-2-aminobutyric acid hydrochloride		85
β-Fluoro-DL-phenylalanine	173–174 dec	65
2-*tert*-butylaminoethyl fluoride hydrochloride	214–215	38
2-Fluoroethyltrimethylammonium chloride[c]	255–257	75[d]
4-Fluoropiperidine hydrochloride	163–164	64
4-Fluoropiperidine hydrochloride[e]	163–164	46
2-Fluoromethylimidazole hydrochloride		32
4-Methyl-5-(2-fluoroethyl)thiazole hydrochloride	116–117	29

[a] Elemental (C, H, N, F) analyses and NMR spectra were in accord with product structures. The substrates were the hydroxy congeners except where otherwise noted. [b] Yields are those of pure isolated products unless otherwise noted; NMR analysis of reaction mixtures indicated much higher yields (75–100%). [c] Known compounds. [d] NMR yield. [e] The substrate was 3-hydroxypiperidine.

in regard to bond length, electronegativity, and crystal lattice geometry.[15]

References and Notes

(1) G. A. Boswell, Jr., W. C. Ripka, R. M. Scribner, and C. W. Tullock, *Org. React.*, **21**, 1–124 (1974).
(2) R. D. Chambers, "Fluorine in Organic Chemistry", Wiley, New York, N.Y., 1973, pp 48 et seq.
(3) Reference 1, pp 12–20.
(4) Benzaldehyde, α-aminoacetophenone, and glycine are recovered unchanged after treatment with SF_4 in liquid HF at −78°. Cf. also ref 9.
(5) J. Kollonitsch, G. A. Doldouras, and V. F. Verdi, *J. Chem. Soc. B*, 1093 (1967).
(6) J. Kollonitsch, L. Barash, and G. A. Doldouras, *J. Am. Chem. Soc.*, **92**, 7494 (1970).
(7) O. Glemser, *Endeavour*, **28**, 86 (1969). However, see W. A. Sheppard, *J. Am. Chem. Soc.*, **87**, 2410 (1965).
(8) For an attempted synthesis, see E. D. Bergmann and A. M. Cohen, *Israel J. Chem.*, **8**, 925 (1970).
(9) Catalysis of the

$$-COOH \xrightarrow{SF_4} -CF_3$$

reaction by HF was recognized [D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962)]. This catalysis apparently is not operative with amino acids at −78°. Note, however, that in HF–SF_4 at 120° common α-amino acids have been transformed to the corresponding $-CF_3$ derivatives [M. S. Raasch, *ibid.*, **27** 1406 (1962)]. The modest yields (averaging 11.6% of theory) imply a rather ineffective degree of protection of $-NH_2$ groups by HF at 120°.
(10) Recently we noticed an abstract (R. S. Loy and M. Hudlicky, Abstracts of Papers, 170th National Meeting of the American Chemical Society, Chicago, Ill., 8/24–29, 1975, FLUO 12) describing the synthesis of a mixture of *threo*- and erythro-L-2-amino-3-fluorobutyric acids via hydrolysis of the ethyl esters which in turn were obtained from ethyl L-threoninate in HF–SF_4 at 60°.
(11) L. R. C. Barclay and M. C. MacDonald, *Tetrahedron Lett.*, 881 (1968).
(12) M. H. Knight, T. Putkey, and H. S. Mosher, *J. Org. Chem.*, **36**, 1483 (1971).
(13) M. Azeem, M. Brownstein, and R. J. Gillespie, *Can. J. Chem.*, **47**, 4159 (1969).
(14) This method complements other novel methods for C–OH → C–F transformation: G. A. Olah, M. Nojima, and I. Kerekes, *Synthesis*, 786 (1973); G. A. Olah, M. Nojima, and I. Kerekes, *J. Am. Chem. Soc.*, **96**, 925 (1974); W. J. Middleton, *J. Org. Chem.*, **40**, 574 (1975).
(15) N. F. Taylor in "Carbon–Fluorine Compounds", Elsevier-Excerpta Medica-North Holland, New York, N.Y., 1972, p 216. Analogous stereospecific action of phosphokinase on glycerol and 2-fluoro-2-deoxyglycerol served dramatic proof for this: P. A. Briley, R. Eisenthal, and R. Harrison, *Biochem. J.*, **145**, 501 (1975).

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