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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

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Selective Fluorination of Hydroxy Amines and Hydroxy Amino Acids with Sulfur Tetrafluoride in Liquid Hydrogen Fluoride

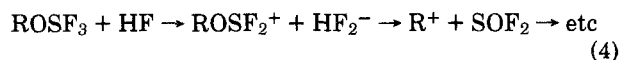
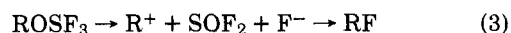
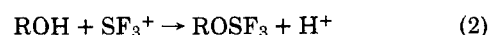
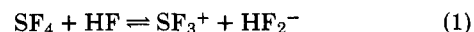
Summary: At -78° and atmospheric pressure sulfur tetrafluoride in liquid hydrogen fluoride selectively replaces alcoholic hydroxyl groups in hydroxy amines and hydroxy amino acids by fluorine.

Sir: Sulfur tetrafluoride, SF₄, 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 SF₄ was found to be restricted to those containing "acidified" hydroxyl groups.³ Owing to its low reactivity, SF₄ is employed in high pressure apparatus, generally at temperatures of 50–200°.

We have found that the reactivity of SF₄ toward a variety of alcohols is dramatically and selectively increased when employing liquid hydrogen fluoride (HF) as solvent. Surprisingly, the reactivity of SF₄ with carbonyl compounds and carboxylic acids is not concomitantly increased and thus the SF₄-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-chlorination⁵ and C-fluorination⁶ of amines and amino acids, also obtains in this system. (In the absence of this protection amino groups react with SF₄ 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[®].) Threo- β -phenylserine monohydrate (1.99 g, 0.01 mol) was added. (Throughout slight positive pressure of N₂ was maintained.) After a 45-min reaction period at -78° , the solvent was blown off by a stream of N₂, 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 SF₄-ROH reaction has been extensively discussed and it is commonly felt that an alkoxy-sulfur trifluoride, ROSF₃, is the key intermediate and that this intermediate collapses to product via an S_Ni or S_N2 pathway.¹ However in the liquid HF-SF₄ 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 -NH₂⁺); (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 SF₄ 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 SF₄ to the much more electrophilic SF₃⁺ (eq 1)¹³ but also plays an important role in the ionization of the alkoxy-sulfur 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).



This method for the C-OH \rightarrow C-F transformation¹⁴ (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 SF₄-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 hydro- chloride		32
4-Methyl-5-(2-fluoroethyl)thiazole hydrochloride	116-117	29

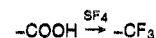
^a Elemental (C, H, N, F) analyses and NMR spectra were in accord with product structures. The substrates were the hydroxy congeners except where otherwise noted. ^b Yields are those of pure isolated products unless otherwise noted; NMR analysis of reaction mixtures indicated much higher yields (75-100%).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

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

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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-SF₄ at 120° common α-amino acids have been transformed to the corresponding -CF₃ derivatives [M. S. Raasch, *ibid.*, **27**, 1406 (1962)]. The modest yields (averaging 11.6% of theory) imply a rather ineffective degree of protection of -NH₂ groups by HF at 120°.

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