COMMUNICATIONS

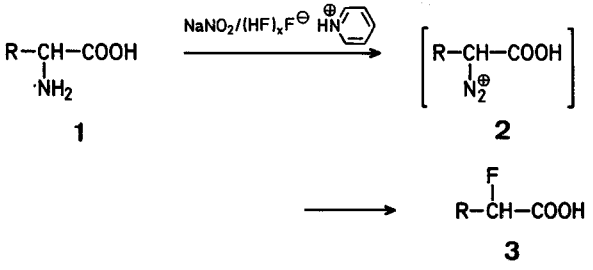
Synthetic Methods and Reactions XII[1]. Preparation of α-Fluorocarboxylic Acids from α-Amino Acids via Diazotization in Polyhydrogen Fluoride/Pyridine Solution.

George A. OLAH and John WELCH

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, U.S.A.

α-Fluorocarboxylic acids are of substantial biological interest as enzymatic blocking agents and also as synthetic intermediates. Their preparation, however, so far was tedious. 2-Fluorocarboxylic acids were prepared by exchange reaction of 2-halocarboxylate esters with silver, potassium or sodium fluoride, generally including pressure with optimum yields of less than sixty percent[2]. Coupling reactions of fluorinated carboxylates such as α-fluoromalonates, with either aldehydes[3], ketones[4], or bromides[5,6] gave 2-fluorocarboxylic acids in generally low yields. Other preparations involving the use of hydrogen fluoride[5] or perchloryl fluoride[5,7] gave 2-fluorocarboxylic acids in low (less than twenty percent) yield. Most of these methods are inconvenient and the yields are modest.

We wish to report now a convenient, simple preparation of 2-fluorocarboxylic acids from easily available α-amino acids via diazotization in 70% polyhydrogen fluoride/pyridine reagent at room temperature. The amino acid, dissolved in polyhydrogen fluoride/pyridine, is diazotized using excess sodium nitrite and is subsequently dediazonized in the same solution at atmospheric pressure to form the corresponding 2-fluorocarboxylic acid. The carboxylic acids formed were readily purified by distillation at reduced pressure, and gave the correct analytical data (including N.M.R. and I.R. spectra).

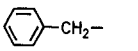
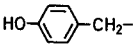
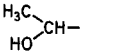


The compounds prepared in this way are summarized in the Table. Typical are the preparations of 3-(4-hydroxyphenyl)-2-fluoropropanoic acid and 2-fluorobutanoic acid.

3-(4-Hydroxyphenyl)-2-fluoropropanoic Acid:
Sodium nitrite (2.1 g, 0.03 mol, previously dried at 140° for 72 h) was added to racemic tyrosine – 3-(4-hydroxyphenyl)-2-aminopropanoic acid – (3.2 g, 0.02 mol) magnetically stirred in 70% polyhydrogen fluoride/pyridine (50 ml) in a polyethylene flask. After being stirred for 1 h, the reaction mixture was quenched with ice/water and extracted with diethyl ether. The ether layer was neutralized with 5% sodium hydrogen carbonate solution and dried with magnesium sulfate. The ether was evaporated off and 3-(4-hydroxyphenyl)-2-fluoropropanoic acid obtained by distillation; yield: 3.34 g (90%); b.p. 57°/0.5 torr.

$C_9H_9FO_3$	calc.	C 58.70	H 4.89	F 10.33
(184.05)	found	58.51	4.92	10.51

Table. Preparation of α-Fluorocarboxylic Acids (R—CHF—COOH) from α-Amino Acids (R—CH(NH_2)—COOH) in 70% Polyhydrogen Fluoride/Pyridine Solution

α-Amino Acid	R	Yield (%)[a]
glycine	H	38
alanine	CH_3	96
2-aminobutanoic acid	C_2H_5	80
valine	i-C_3H_7	84
leucine	i-C_4H_9	88
isoleucine	sec-C_4H_9	75
phenylalanine		98
tyrosine		90
serine	$HOCH_2$–	80
threonine		54
aspartic acid	HOOC–CH_2–	52
glutamic acid	HOOC–CH_2–CH_2–	12
glutamine	H_2N–CO–CH_2–CH_2–	60

[a] All α-fluorocarboxylic acids showed the expected ^1H- and ^{19}F-N.M.R. spectra.

2-Fluorobutanoic Acid:
Sodium nitrite (2.1 g, 0.03 mol, treated as above) was added to a magnetically stirred mixture of 2-aminobutanoic acid (2.1 g, 0.02 mol) in 70% polyhydrogen fluoride/pyridine. After being stirred for 1 h, the reaction mixture was quenched and extracted as described above. The ether was evaporated off and 2-fluorobutanoic acid obtained by distillation; yield: 1.79 g (80%); b.p. 90–90.5°/12 torr.

$C_4H_7FO_2$	calc.	C 50.00	H 7.29	F 19.79
(106.01)	found	49.20	7.38	19.58

Support of our work by the National Institute of Health is gratefully acknowledged.

Received: June 2, 1974

[1] Part XI. G. A. Olah, H. C. Lin, *Synthesis* **1974**, 444.
[2] B. C. Saunders, G. J. Stacey, *J. Chem. Soc.* **1948**, 1773.
F. Gryszkiewicz-Trochimowski, A. Sporzynski, J. Wnuk, *Rec. Trav. Chim. Pays-Bas* **66**, 413 (1947).
W. Bockemüller, *Liebigs Ann. Chem.* **506**, 20 (1933).
F. D. Bergmann, I. Shahak, *Chem. & Ind.* **1958**, 157.
F. L. M. Pattison, J. E. Millington, *Can. J. Chem.* **34**, 757 (1956).
[3] F. D. Bergmann, I. Shahak, *J. Chem. Soc.* **1960**, 5261; **1961**, 4033.
[4] G. Schmidt, H. Jahn, *Liebigs Ann. Chem.* **644**, 43 (1961).
[5] F. L. M. Pattison, et al., *Can. J. Chem.* **43**, 1700 (1965).
[6] F. D. Bergmann, S. Sinzai, *J. Chem. Soc.* **1956**, 1521.
[7] H. Gershow, S. G. Schulman, A. D. Spevack, *J. Med. Chem.* **10**, 536 (1967).