250. Synthetic Methods and Reactions. Part 106. Suppression of Anchimerically Assisted Rearrangement Products in the Synthesis of α-Fluorocarboxylic Acids from α-Amino Acids with 48:52 (w/w) Hydrogen Fluoride/Pyridine [1]

by **George A. Olah**[1]), **G. K. Surya Prakash** and **Yah Li Chao**

Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, California-90007

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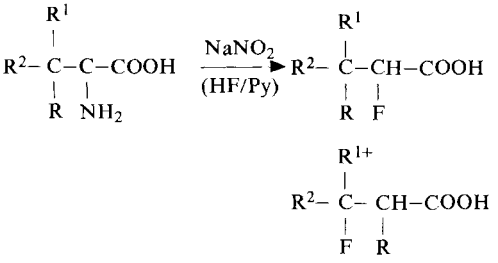
Summary

Anchimerically assisted rearrangement, observed in the fluorination of some α-amino acids with 70:30 (w/w) hydrogen fluoride/pyridine (by weight) in the presence of $NaNO_2$, is substantially or fully suppressed by using the less acidic reagent 48:52 (w/w) hydrogen fluoride/pyridine.

Pyridinium polyhydrogen fluoride (pyridine/hydrogen fluoride 30:70 (by weight) was developed [2] as a convenient fluorinating agent in place of anhydrous hydrogen fluoride. The reagent has gained wide use in a variety of organic fluorination reactions due to its thermal stability (decomposition at +55°). The broad scope of its application in organic synthesis has recently been shown [3].

The reagent was reported, *inter alia*, to be useful for the preparation of α-fluorocarboxylic acids from α-amino acids by *in situ* nitrosation in the reagent media [4]. α-Fluorocarboxylic acids are important synthons and are of substantial biological interest as enzymatic blocking agents. In using our method [4], however, difficulties were experienced [5] [6] in the case of fluorinating some α-amino acids such as valine, isoleucine, phenylalanine, tyrosine and threonine. It was found [6] that total or partial rearrangement to β-fluorocarboxylic acid took place due to anchimeric



[1]) To whom correspondence should be addressed.

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Table 1. *Preparation of α-fluorocarboxylic acids (R-CHFCOOH) from α-amino acids (R-CH(NH$_2$)COOH) in 48:52 (w/w) hydrogen fluoride/pyridine*

α-Amino Acid	R	Reaction Time [h]	Yield[a] [%]	B.p. (m.p.)
Glycine	H	5	41	162–164°/760 Torr
Alanine	CH_3	5	76	64–66°/13 Torr
2-Aminobutanoic acid	C_2H_5	5	82	90°/12 Torr
Valine	i-C_3H_7	5	75	(38–40°)
Phenylalanine	$C_6H_5CH_2$	5	86	(73–75°)
Isoleucine	sec-C_4H_9	5	71	97–99°/10 Torr
Tyrosine[b]	$HOC_6H_4CH_2$	6	58 (80% α and 15% β)	56°/0.5 Torr 56°/0.5 Torr
Threonine[b][c]	$CH_3CH(OH)$	6	43 (80% α and 20% β)	

[a] α-Fluorocarboxylic acids showed the characteristic ^{1}H-, ^{13}C-, ^{19}F-NMR. and IR. data.
[b] Based on integrating ^{1}H-NMR. spectrum.
[c] Crude yield.

Table 2. *Proton decoupled ^{13}C-NMR. data of some selected α-fluorocarboxylic acids*[a]

α-fluorocarboxylic acid	^{13}C-NMR. chemical shifts in ppm[b]
CH_3CH_2–CH(F)–COOH	175.1 ($^2J_{C,F}$ = 24.0 Hz), 88.7 ($^1J_{C,F}$ = 184.2 Hz), 24.5 ($^2J_{C,F}$ = 21.2 Hz), 8.0 (4.2 Hz)
$(CH_3)_2$CH–CH(F)–COOH	175.3 ($^2J_{C,F}$ = 25.1 Hz), 92.6 ($^1J_{C,F}$ = 186.9 Hz), 31.2 ($^2J_{C,F}$ = 20.5 Hz), 18.2 ($^3J_{C,F}$ = 3.1 Hz), 15.9 ($^3J_{C,F}$ = 5.4 Hz)
$CH_3CH_2CH(CH_3)$–CH(F)–COOH	173.2 ($^2J_{C,F}$ = 25.9 Hz), 92.5 ($^1J_{C,F}$ = 186.0 Hz), 37.6 ($^2J_{C,F}$ = 20.3 Hz), 23.6 ($^3J_{C,F}$ = 4.0 Hz), 14.9 ($^3J_{C,F}$ = 3.8 Hz), 11.4
$CH_3CH(OH)$–CH(F)–COOH	170.9 ($^2J_{C,F}$ = 23.8 Hz), 93.4 ($^1J_{C,F}$ = 186.0 Hz), 72.1 ($^2J_{C,F}$ = 21.2 Hz), 12.8 ($^3J_{C,F}$ = 5.1 Hz)
$C_6H_5CH_2$–CH(F)–COOH	175.5 ($^2J_{C,F}$ = 23.9 Hz), 136.8, 131.1, 130.3, 129.0, 90.5 ($^1J_{C,F}$ = 186.7 Hz), 40.1 ($^2J_{C,F}$ = 20.8 Hz)
$HOC_6H_4CH_2$–CH(F)–COOH	171.1 ($^2J_{C,F}$ = 24.2 Hz), 151.9, 136.5, 123.1, 117.9, 85.7 ($^1J_{C,F}$ = 188.1 Hz), 34.6 ($^2J_{C,F}$ = 20.1 Hz)

[a] In $CDCl_3$ solution.
[b] Chemical shifts are in ppm from external capillary tetramethylsilane.
[c] The methyl groups are non equivalent in the prochiral isopropyl group.

assistance by alkyl, aryl or hydroxy group during diazotization reaction. These reports lead us to reinvestigate these fluorinations. We report now that such anchimerically assisted rearrangement can be suppressed by carrying out the reaction in a reagent media of lower HF-concentration (pyridine/hydrogen fluoride 52:48 (by weight)).

The rearrangement was totally circumvented in the case of phenylalanine, valine and isoleucine, whereas in the case of tyrosine and threonine 15–20% rearrangement to the β-product could not be avoided. Decreasing the HF-concentration of the reagent further did not remedy the problem but drastically affected the yield of the α-fluoro product. The results of the present work are summarized in *Table 1*.

The use of the less acidic mixture 48:52 (w/w) hydrogen fluoride/pyridine extends the utility of the pyridinium polyhydrogen fluoride reagent in cases where the potentially higher acidity of the latter can cause rearrangement or other side-reactions.

Experimental Part

Reagent. The pyridinium polyhydrogen fluoride (52% pyridine, 48% HF, by weight) was prepared by condensing 73 g (3.85 mol) of anhydrous HF into 79 g (1 mol) of pyridine at $-78°$ as previously described [4], or by diluting the reagent HF pyridine 7:3 with pyridine to achieve the appropriate concentration.

General procedure for the preparation of α-fluorocarboxylic acids. To 20 mmol of the α-amino acid dissolved in 50 ml of above prepared pyridinium polyhydrogen fluoride in a polyolefin bottle with good stirring at 0° are added 2.1 g (0.03 mol) of predried sodium nitrite in three portions over a period of 30 min. Stirring is continued at room temp. till the end of the reaction (s. *Table 1* for the optimum time). After the reaction is complete, the mixture is quenched with 100 ml of ice water and extracted with diethyl ether (3 times 100 ml) in a polyolefin separatory funnel. The ether layer is washed with sat. NaCl solution (3 times 100 ml) and dried over anh. $MgSO_4$. The ether layer on evaporation gives the crude product which is further purified by recrystallization or distillation. The ^{13}C-NMR. data of the prepared α-fluoroacids are listed in *Table 2.*

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