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STEREOSPECIFICITY IN THE TRANSFORMATION OF α-AMINOACIDS INTO FLUOROACIDS

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Abstract. In the reaction of α-aminoacids with excess $NaNO_2$ in polyhydrogen fluoride-pyridine, stereospecific substitution(i.e. retention of configuration) is observed with $C_6H_{11}CH_2CHNH_2COOH$, while a stereospecific rearrangment occurs in the case of phenylalanine.

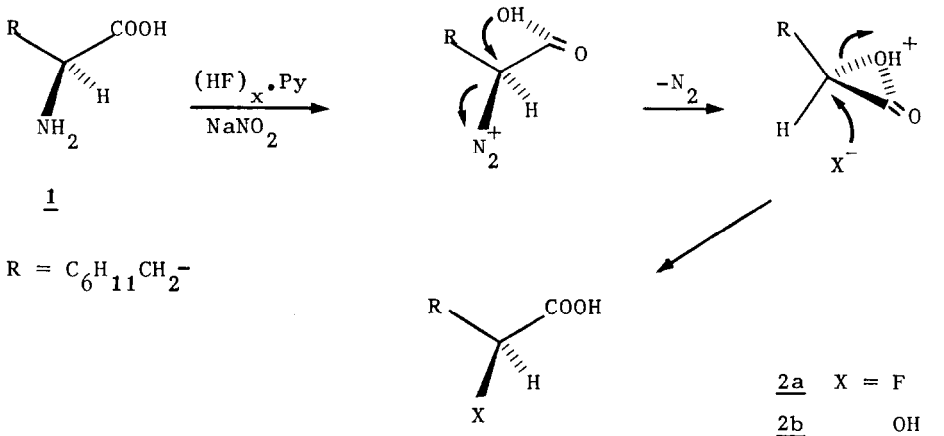
Optically active organofluorine compounds are of wide biological interest. In particular, 16-fluoro-13,14-didehydro-$PGF_{2\alpha}$ has shown a high luteolytic activity, strongly related to the 15R-16S absolute configuration[1].

In the synthetic approach to the epimerically pure final compounds developed in our laboratories[2], a key role is played by 2-fluorocarboxylic acids.

Stereospecific synthesis of ethyl (S)- and (R)-2-fluoropropionate has been reported from (S)-lactic acid[3], but the stereospecific approach from α-aminoacids, based on Olah's method[4], can as well be of great interest and it is receiving particular attention. Recently this method has been applied to (S)-aspartic acid and (S)-fluorosuccinic acid was obtained with presumably a little racemization[5].

We wish to report our results obtained by reacting (S)-2-amino-3-cyclohexyl propionic acid 1[6] and (S)-phenylalanine 3 in 70% polyhydrogen fluoride-pyridine with excess of $NaNO_2$ at 0°C.

1 gave the corresponding 2-fluoro-3-cyclohexylpropionic acid 2a, whose methyl ester showed in the CD spectrum in MeOH a positive maximum at 212 nm ($\Delta\varepsilon$ +1.04; c 5.15 g/l), characteristic for the S configuration[5,7].

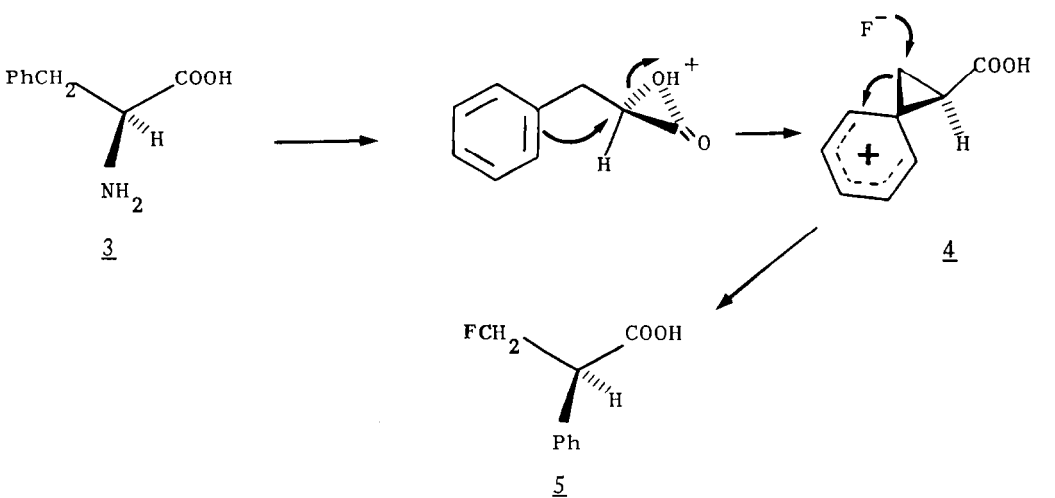


1

The retention of configuration can be safely ascribed to the anchimeric assistance of the carboxylate group: in fact, by premature quenching of the reaction mixture with water, the corresponding 2-hydroxy acid 2b ($[\alpha]_D$ -9.7°, c 10 g/l in $CHCl_3$) was also isolated. Its absolute configuration was determined by CD measurement on the methyl ester ($\Delta\varepsilon$ +1.57 at 210 nm; c 0.15 g/l in MeOH), the positive value indicating S configuration[7].

However, in the case of phenylalanine 3 we did not obtain the expected 2-fluoro-3-phenylpropionic acid[8]: the only isolated product was (-)-(R)-3-fluoro-2-phenylpropionic acid 5[9]. Also in this case the CD spectrum of the methyl ester ($\Delta\varepsilon$ -2.26 at 210 nm, c 0.24 g/l in MeOH) allowed the assignment of the absolute configuration[10].

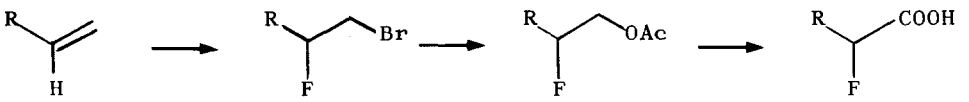
The formation of this compound can be tentatively explained by the following mechanism:



3 4 5

in which the easy expulsion of nitrogen assisted from the rear by the carboxylate group, is followed by a participation of the phenyl ring to give the more stabilized phenonium ion 4. Finally the attack by the fluoride ion on the monosubstituted β-carbon leads to 5 with R configuration.

(RS)-2-fluoro-3-phenylpropionic acid was prepared after the following general scheme[11] (R = benzyl):



Optical separation was then achieved by classical methods and confirmed by DSC (Differential Scanning Calorimetry) analysis on the diastereoisomeric salts obtained with (+)-ephedrine.

(RS)-2-fluoro-3-cyclohexylpropionic acid was also prepared from 3-cyclohexyl-1-propene and then resolved as above. From α_D and CD values, and by comparison of the DSC analysis carried out on the (+)-ephedrine salts, we could therefore evaluate the optical purity of the compound obtained in the diazotization-substitution reaction: we have found that no racemization occurred.

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References and footnotes.

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4. G.A. OLAH and J. WELCH, Synthesis, 1974, 652.
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6. Prepared by reduction of (S)-phenylalanine (H_2/Rh-C, 5%; HCl 2N): $[\alpha]_D$ +11.4° (NaOH 1N, c 10 g/l).
7. J.C. CRAIG, S-Y.C. LEE and A. FREDGA, Tetrahedron 33, 183 (1977).
8. This contrasts with the results obtained by Olah with (±)-phenylalanine[4]. Modifications of the reaction conditions also according to Olah's suggestions (private communication) were unsuccessful. We thank Prof. Olah for providing us with an authentic sample of 2-fluoro-3-phenylpropionic acid.
9. ^{1}H-NMR ($CDCl_3$/TMS) data of $Ph\text{-}CH_X\ (CH_AH_BF)COOCH_3$: δ 4.04 (dd, 1H, $\underline{H}_X$); 4.60 (ddd, 1H, $\underline{H}_A$); 4.98 (dt, 1H, $\underline{H}_B$); $^3J_{XF}$ 19.5, $^3J_{AX}$ 5.5, $^3J_{BX} = {}^2J_{AB}$ 9.0, $^2J_{AF} = {}^2J_{BF}$ 47.0 Hz.

^{13}C-{^{1}H}NMR (C_6D_6/TMS): δ_C 52.5 (d, $^3J_{CF}$ 20 Hz, $\underline{C}_2$); 83.0 (d, $^2J_{CF}$ 174 Hz, $\underline{C}_3$).
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