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# THE TRANSFORMATION OF α-AMINOACIDS INTO FLUOROACIDS

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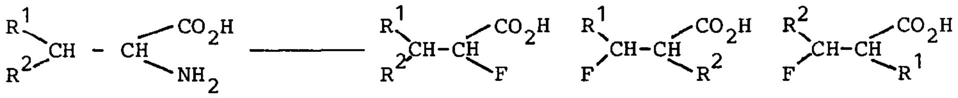
Abstract The reactions of some α-aminoacids with excess sodium nitrite in polyhydrogen fluoride-pyridine are described.

The report by Faustini et al.[1] concerning the reaction of α-aminoacids with sodium nitrite in polyhydrogen fluoride-pyridine prompts us to communicate our own findings. In a previous communication from these laboratories[2] it was reported that in the reaction of a number of α-aminoacids with excess sodium nitrite in 70% hydrogen fluoride in pyridine not only the expected products[3] 1 are obtained, but also rearranged products of types 2 and 3 (see table).



1 2 3

Both the substitution and the rearrangement reactions were shown to be stereospecific. Products of type 1 were shown to be produced with retention of configuration and evidence (ORD measurements) was given which suggests that 2 and 3 are also produced with retention of configuration at C-2. The results of the Italian group support this suggestion and are otherwise in broad agreement with ours.

We now report a number of new results. In the reaction with phenylalanine the formation of product 1 ($R^1$=H, $R^2$=Ph) cannot completely be prevented. This was easily detected using high-field (250 MHz) $^1$H-NMR spectroscopy, but could be overlooked at lower field, because of the complex coupling patterns. When fresh (Aldrich) reagent is used, only 20% of the isolated product is of type 1. This proportion rises a little with ageing of the polyhydrogen fluoride-pyridine.

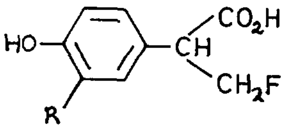
The rearrangement reactions may be completely suppressed (in the cases of phenylalanine and valine) by the use of polyhydrogen fluoride-pyridine containing a lower proportion of hydrogen fluoride.[4] Olah and co-workers have shown this independently for these and other α-aminoacids[5]. High yields of type 1 products are then obtained. These results contrast with those of the Italian group[1].

Table

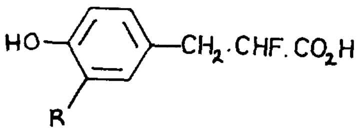
| α-Aminoacid | % Yield (total) | Approximate portions of | | |
|---|---|---|---|---|
| | | 1 | 2 | 3 |
| Glycine<br>$(R^1=R^2=H)$ | 40% | 100% | - | - |
| Alanine<br>$(R^1=Me;\ R^2=H)$ | 81% | 100% | - | - |
| Valine<br>$(R^1=R^2=Me)$ | 42% | 50% | 25% | 25% |
| Isoleucine<br>$(R^1=Et;\ R^2=Me)$ | 54% | 40% | 30% | 30% |
| Threonine<br>$(R^1=H;\ R^2=OH)$ | 20% | - | 100% | - |
| Phenylalanine<br>$(R^1=H;\ R^2=Ph)$ | 80% | 20% | 80% | - |

When concentrated sulphuric acid is added to the reaction medium[6] valine gives rise only to rearrangement products. This reaction is very low yielding (2%) and is thus of no preparative use, though it provides a convenient means of preparing small quantities of pure rearrangement products.

Finally, the reaction with tyrosine is anomalous. When three equivalents of sodium nitrite are used a vigorous reaction takes place, resulting in a 15% yield of products 4[7] and 5[8] in a ratio 7 : 3. When fresh reagent is used neither 6 or 7 is discernible by NMR but with old reagent of lower hydrogen fluoride content, a small quantity of 6 is also formed.



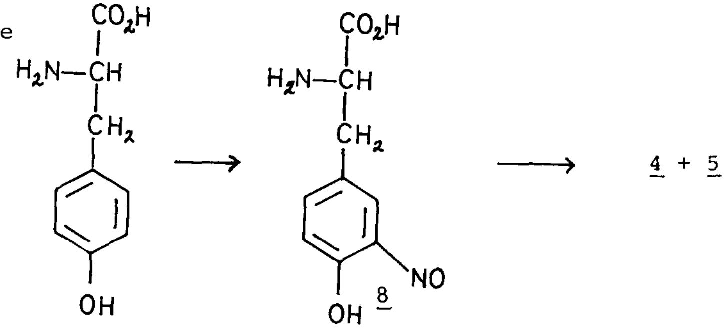
4 $R=NO_2$
6 $R=H$



5 $R=NO_2$
7 $R=H$

Presumably the nitration of the aromatic ring is effected by nitrosation followed by air oxidation during work-up. (The reaction itself is performed under nitrogen). When one equivalent of sodium nitrite is used very small quantities of 4 and 5 are formed but no 6 or 7. Thus the course of the reaction is probably as shown in the scheme.

Scheme



The intermediate 8 is presumably formed in the reaction with one equivalent of sodium nitrite, but remains in the aqueous phase during work-up (dilution with water followed by ether extraction) and is consequently not isolated. The relatively low migratory aptitude of the nitroso substituted ring results in the formation of a higher proportion of unrearranged product than would be expected if nitrosation of the aromatic ring occurred after the fluorination reaction. When the hydrogen fluoride content of the reagent is reduced both nitration and rearrangement are somewhat suppressed and mixtures of 5 and 6 (approximately 1:1), containing small amounts of 4 and 7 may be obtained[4], Olah and co-workers[5] have obtained moderate yields of 7 (with 6 present as a minor product) by using 48% hydrogen fluoride in pyridine.

In conclusion, the reaction of sodium nitrite and polyhydrogen fluoride in pyridine with α-aminoacids is very versatile, but also very sensitive[9]. From phenylalanine either the α- or the β-fluoroacid may be obtained stereospecifically and in good yield depending on the hydrogen fluoride content of the reagent. The utility of these fluoroacids as synthetic intermediates is under investigation.

1. F. Faustini, S. de Munary, A. Panzeri, V. Villa and C.A. Gandolfi, Tetrahedron Letters, 22, (45), 4533, (1981).
2. R. Keck and J. Rétey, Helvetica Chimica Acta 63, 769, (1980).
3. G.A. Olah, J.T. Welch, Y.D. Vankar, M. Nojima, I. Kerekes and J.A. Olah, J. Org. Chem. 44, 3872, (1979).
4. Dry pyridine (3 ml) was added to the amino acid (2-5 mmole), followed by commercial polyhydrogen fluoride-pyridine (5 ml), and finally sodium nitrite.
5. G.A. Olah, G.K.S. Prakash and Y.L. Chao, Helvetica Chimica Acta, 64, 2528, (1981). We thank Professor Olah for communication of results prior to publication.
6. Commercial polyhydrogen fluoride-pyridine (5 ml) was added to the amino acid (500 mg) at -10°. Concentrated sulphuric acid (2 ml) was then added dropwise with stirring. Finally, sodium nitrite (2.5 g) was added.

7. M.p. 124-125$^{\circ}$; $\delta$ 10.54 (2H, bs, O$\underline{\text{H}}$), 8.09 (1H, d, J=2Hz, ArH), 7.58 (1H, dd, J=2Hz, 7.5 Hz, ArH), 7.18 (1H, d, J=7.5 Hz, ArH), 4.90 (1H, ddd, $J_{HF}$= 45 Hz, $J_{HH}$=10 Hz, 7 Hz, C$\underline{\text{H}}$F), 4.71 (1H, ddd, $J_{HF}$= 45 Hz, $J_{HH}$=10 Hz, 6 Hz, C$\underline{\text{H}}$F), 4.04 (1H, ddd, $J_{HF}$=17.5 Hz, $J_{HH}$=7 Hz, 6 Hz, ArC$\underline{\text{H}}$), m/e 229 ($M^{+}$), 209, 184, 164.

8. Not obtained pure; $\delta$ 9.18 (2H, bs, OH), 8.02 (1H, d, J=2 Hz, ArH), 7.50 (1H, dd, J=7 Hz, 2 Hz, ArH), 7.13 (1H, d, J=7 Hz, ArH), 5.16 (1H, ddd, $J_{HF}$=47 Hz, $J_{HH}$=7 Hz, 4 Hz, C$\underline{\text{H}}$FCOOH), 3.06-3.44 (2H, m, $ArCH_2$), m/e 229 ($M^{+}$), 209.

9. Normally the reaction was performed at 0$^{\circ}$C, with a reaction time of 5 hours, other experimental conditions as in reference 2. However, many variables were tested for the phenylalanine and tyrosine reactions. Variations in reaction time (1-24 hours) and in the concentration of the amino acid (0.4-1 M) had no significant effect. The reaction was more easily controlled at 0$^{\circ}$C or -10$^{\circ}$ than at room temperature, but yields and product ratios were unaffected. Provided the amount of sodium nitrite was at least 1.5 equivalents for phenylalanine, and 2.5 equivalents for tyrosine excess of this reagent also had no effect.

   Addition of potassium fluoride to the reaction mixture caused no change. The variations observed are caused only by the acidity of the reagent, and to this the reaction is extremely sensitive.

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