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SYNTHESIS OF FLUORINATED PEPTIDES

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We have described the preparation of monofluorinated or difluorinated amino-acid derivatives[1,2] by two routes, summarized in the following schemes :

Scheme 1 : $R\text{-}CH{=}CH\text{-}CO_2R' \xrightarrow{i,\ ii,\ iii} R\text{-}CHF\text{-}CH(NH_2)\text{-}CO_2R$

i : Br_2/CCl_4 ; ii : NH_3/DMSO ; iii : HF/Py (70%30 w/w)/CH_2Cl_2

Scheme 2 : $R\text{-}CH(OH)\text{-}CH(NH_2)\text{-}CO_2R' \xrightarrow{i,\ ii,\ iii,\ iiii} R\text{-}CHF\text{-}CH(NH_2)\text{-}CO_2R'$

i : TrCl/Et_3N ; ii : MsOCl/pyridine; iii : N-ethylpiperidine/benzene ; iiii : HF/Py (70/30 w/w)/CH_2Cl_2

Scheme 3 : $R\text{-}CH{=}CH\text{-}CO_2R' \xrightarrow{i,\ ii,\ iii,\ iiii} R\text{-}CF_2\text{-}CH(NH_2)\text{-}CO_2R'$

i : NaN_3/ICl/CH_3CN ; ii : DABCO ; iii : pyrolysis; iiii : HF/Py.

The fluorinated amino acid derivatives have been used for the synthesis of peptides in order to point out :

- some synthetic methods which avoid losing the fluorine atom ;
- the obtention of biologically active peptides and the influence on the activity due to the introduction of the fluorine atom in the molecules.

Thus many peptides containing a mono- or a difluorinated aminoacid have been prepared, especially some fluorinated encephalin derivatives.

The following fluorinated peptides have been prepared :

- Monofluorinated series : H(F)Phe-Met-OMe ; Boc-F*(Ala)-Thr-OMe ; Boc-F*(Ala)-Thr-OMe ; Boc-leu-(F)Thr*-OMe ; H-Ala-(F)Thr*-OMe ; Boc-Gly-(F)Phe-OMe ; Boc-Ala-(F)Phe-OMe ; N-Z-OtBu Tyr-Gly-Gly-(F)Phe-leu-OMe ; Boc-Tyr-Gly-Gly-(F)Phe-Met-OMe ; Boc-Tyr-Ala-Gly-(F)Phe-Met-OMe ; Boc-Tyr-Gly-Gly-(F)Phe-OMe ; Boc-Tyr-Dala-Gly-(F)Phe-OMe.
- Difluorinated series : H-Phe-(F_2)Thr-OH ; H-Gly-(F_2)Thr-OH ; H-Gly-(F_2)Phe-OMe ; H-Ala-(F_2)Phe-OMe.

* -(F)X indicates a fluorinated aminoacid with optical activity.

1 T.N. Wade, F. Gaymard and R. Guedj, Tetrahedron Lett., 1979, 2681
2 A. Barama, R. Condom and R. Guedj, J. Fluorine Chem., 1980, 16, 183