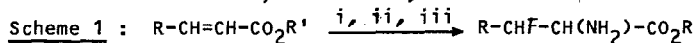


SYNTHESIS OF FLUORINATED PEPTIDES

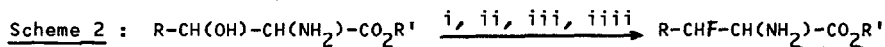
M. L. Martos Alcaniz, N. Patino, R. Condom, A. I. Ayi* and R. Guedj

Laboratoire de Chimie Structurale Organique, Université de Nice, Parc Valrose, 06034 Nice (France)

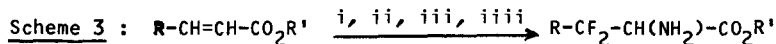
We have described the preparation of monofluorinated or difluorinated amino-acid derivatives^{1,2} by two routes, summarized in the following schemes :



i : Br₂/CCl₄ ; ii : NH₃/DMSO ; iii : HF/Py (70%30 w/w)/CH₂Cl₂



i : TrCl/Et₃N ; ii : MsOCl/pyridine ; iii : N-ethylpiperidine/benzene ;
iiii : HF/Py (70/30 w/w)/CH₂Cl₂



i : NaN₃/ICl/CH₃CN ; ii : DABCO ; iii : pyrolysis ; iiiii : 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 enkephalin 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-(F₂)Thr-OH ; H-Gly-(F₂)Thr-OH ; H-Gly-(F₂)Phe-OMe ; H-Ala-(F₂)Phe-OMe.

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

1 T.N. Wade, F. Gaynard and R. Guedj, Tetrahedron Lett., 1979, 2681

2 A. Barama, R. Condom and R. Guedj, J. Fluorine Chem., 1980, 16, 183