

PROCESS FOR THE PREPARATION OF PEPTIDES

The invention relates to a new and versatile process for the preparation of compounds containing one or more amide bonds, in particular peptides, especially for processes performed in solution.

Peptides are synthesized either in solution or on a solid support. In both approaches coupling and deprotection steps repetitively alternate and may be separated by intermittent purifications. An excess of an activated carboxylic component is preferably used in each coupling step to ensure quantitative coupling to an amino component; thus the occurrence of deletion sequences in the final product can be avoided. In solid phase peptide synthesis residual activated carboxylic component is usually removed by filtration at the end of each coupling step. In solution phase synthesis it is usually assumed that the residual activated carboxylic component is destroyed and removed during the intermittent aqueous work-up. Insertion peptide sequences, however, are often encountered in solution phase synthesis as impurities of the final peptide due to incomplete removal of residual (activated) carboxylic component after a coupling step, which subsequently has coupled following deprotection. In order to avoid the occurrence of said side-reactions a scavenging step may be introduced directly after the coupling step to scavenge (inactivate) the residual activated carboxylic functions. Amines are usually applied as scavengers. The use of polyamines as scavengers leads to scavenged compounds which may be actively extracted into a - preferably acidic - aqueous phase, depending on their polarity [e.g. Kisfaludy, L. *et al.* (1974) *Tetrahedron Lett.* 19, 1785-1786]. This extraction is usually performed before the deprotection step to avoid loss of the growing peptide into the aqueous phase. However, this procedure has in numerous cases been found to result in incomplete intermittent purification due to the hydrophobicity of the scavenged compound: the intrinsic hydrophobicity of the amino acyl part of the carboxylic component is enhanced by the still present amino-protecting group. Aqueous extraction is thus not completely effective.

Recently, Carpino, L.A. *et al.* [(1999) *J. Org. Chem.* 64, 4324-4338] reported an improvement of the scavenging method. In addition to the use of a polyamine as a scavenger the amino-protecting group 1,1-dioxobenzo[*b*]thiophene-2-ylmethoxycarbonyl (Bsmoc) was applied in the process. The Bsmoc function has very high lability towards base. As a result thereof, residual