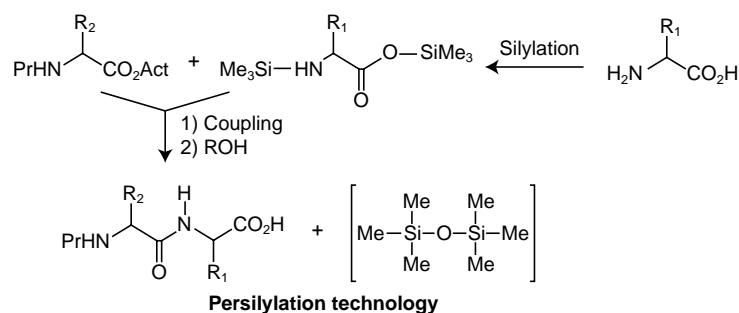


INNOVATIVE PEPTIDE PRODUCTION

Large volume, custom-synthesis of customer-owned peptides often includes the incorporation of non-natural amino acid residues

Roland Callens • Peptisyntha et Cie

PEPTISYNTHA was founded in 1987 following a successful demonstration at the research laboratories of SOLVAY which proved that large-scale synthesis of technology licensed from the University of Ghent was feasible. It currently produces several tens of kilos of peptide per year in a plant inspected by the US Food and Drug Administration (FDA). Expansion of PEPTISYNTHA's major production facility was completed in 1998, having received FDA in March 1999.



Pr = any protective group
"Act" = most of the activation methods
ROH = a hydroxylic solvent including water

Technology

At the heart of the production technology is a solution-phase process, based on extensive use of persilylated amino acids. Free amino acids are undoubtedly the least expensive components with which peptide synthesis is performed. Since they are only soluble in water, they are not compatible with most coupling methods. Upon conversion to a fully silylated derivative, they become highly soluble in organic solvents. Trimethylsilylester offers the required protection and the reactivity of the trimethylsilylamino function is sufficiently high to permit peptide bond formation. Once the reaction mixture has been worked-up, the TMS groups split off and the intermediates are recovered in a minimally protected form.

Process advantages include :

- Lower cost of goods - in certain cases even bi-functional amino acids can be used instead of their expensive, differentially protected counterparts
- Reduction in the number of process stages - the persilylation

step itself consists of a short pre-treatment

- High solubility of the silylated amino acids and peptides - an advantage of particular importance for fragment coupling
- Reduced danger of racemisation related to the attenuated basicity of the amino function, together with the possibility of working in apolar solvents
- Mild conditions during the final deprotection.

Another patent-protected asset in Peptisyntha's portfolio of technologies relates to the use of side-chain unprotected arginine residues which are put into reaction and/or isolated in the form of their highly lipophilic tetraphenylborate salts. Peptide couplings can thereby be run in high concentration with easy recovery procedures.

Much of the company's activities lie in the large volume, custom-synthesis of customer-owned peptides, often incorporating non-natural amino acid residues. As several generic peptides have attracted the interest of drug delivery

companies, upon request scale-up of laboratory processes to industrial level can be arranged (for example, TRH, LHRH, SRIF, Calcitonin).

Product Quality

PEPTISYNTHA product quality meets the strictest FDA and European requirements. A great deal of attention is given to the establishment of the analytical dossier - the identification of trace impurities and stability tests are routinely included.

The proximity of Solvay's large analytical department allows access to the most sophisticated analytical techniques : HPLC, FAB-MS, ICP-MS for trace metals, ion chromatography, GC-MS for optical purity, and multi-nuclear NMR spectroscopy. •



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