Tag-Assisted Peptide Synthesis (TAPS) – Development of a Continuous Liquid-Phase Process

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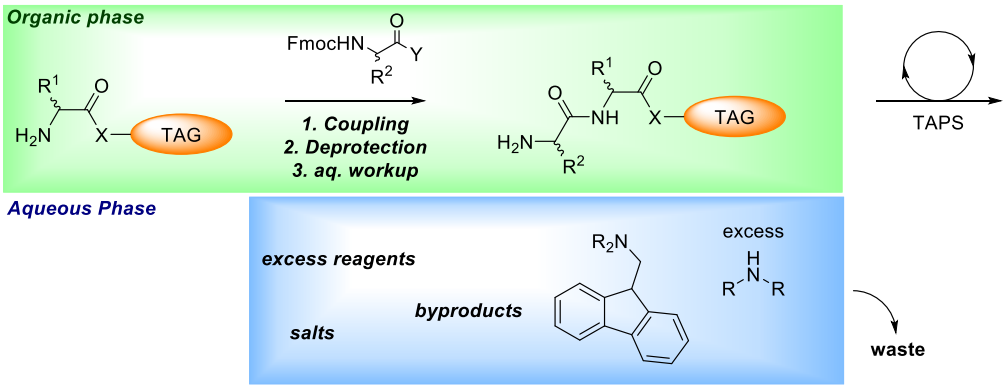
Solid Phase Peptide Synthesis (SPPS), invented by Merrifield in 1963,[1] is the current state of the art for manufacturing of peptide therapeutics. The peptide chain is built up by iterative coupling and deprotection steps using the Fmoc-protected amino acids on solid-support, enabling the removal of reagents and byproducts by washing the resin with excess solvent. However, in the context of green chemistry the enormous amount of waste and the high consumption of hazardous solvents, such as DMF, NMP and DCM, leads to a low PMI of SPPS and demands a more sustainable alternative.[2] In contrast, Tag-Assisted Peptide Synthesis (TAPS) represents an approach which is compatible with these requirements, since the reactions are carried out in solution using soluble tags as anchor molecules, which are attached to the growing peptide chain. TAPS can be carried out using less solvent and excess of reagents, since the reactions are similar to classic solution-phase chemistry. Previous examples of this technology mainly used precipitation[4] or nanofiltration[5] to purify the tagged peptide after each coupling/deprotection cycle, leading to a discontinuous labour-intensive process. Attempts to design a more continuous process, using liquid-liquid extraction for intermediate purification, however used halogenated solvents[6] or DMF mixtures[7] as process solvents.



In our continuous TAPS process the TAG-peptide is maintained in the organic phase (green solvent mixture) for coupling/deprotection cycles, while excess reagents and byproducts are removed by simple aqueous wash steps. The amount of organic solvent used in this process could be reduced by 90% compared to SPPS, while the excess of amino acids and coupling reagents could also be decreased by 50%, leading to a comparable quality of the target molecule. Therefore, TAPS can be considered as a highly efficient and sustainable alternative to classic SPPS.

[1] Merrifield, R. B., J. Am. Chem. Soc. 1963, 85 (14), 2149-2154.
[2] Kekessie et. al., *J. Org. Chem.* **2024**, *89*, 4261-4282.
[3] Albericio, F. et. al. Chem. Rev. 2022, 16, 13516-13546.
[4] Chiba et. al., *Org. Process Res. Dev.* **2019**, *23,* (11) 2576–2581.
[5] Livingston et. al. *Angew. Chem. Int. Ed.* **2021**, *60,* 7786–7795.
[6] Takahashi et. al. *Angew. Chem. Int. Ed.* **2017**, *56*, 7803.
[7] Kubota et. al. *Molecules* **2021**, *26* (12), 3497.