MECHANOCHEMICAL ANION-TEMPLATED SYNTHESIS OF CYCLOPEPTIDES

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Cyclopeptides have emerged as a sought-after class of molecules possessing favorable properties such as proteolytic resistance and binding affinity largely due to their macrocyclic structure [1]. Synthesis of cyclopeptides via head-to-tail macrocyclization of their linear analogues presents a considerable challenge, especially in the case of smaller peptides due to the unfavorable conformation required to bring the reactive termini in spatial proximity [2]. Previously, we have found that anions can act as promoting agents for the lactamization step and, in the case of tetra-, penta- and hexapeptides, the use of salts such as TBACl and TEACl gave the corresponding cyclic peptides in moderate to high yields [3]. To prevent undesired oligomerization and polymerization processes, the reaction had to be carried out in high dilution in DMF over a course of 3 – 5 days, which were the main drawbacks of the method in addition to poor solubility of unprotected peptides in organic solvents. To circumvent these problems, we have envisioned a mechanochemical approach to cyclize oligopeptides by milling the linear peptide precursor with a chloride salt and potassium carbonate as a base, followed by addition of the coupling reagent DEPBT and further milling. Two cyclopeptides, cyclo[Phe3-Gly2) and cyclo[Phe4-Gly2], were prepared by the solution-based and mechanochemical approach. Molecular dynamics simulations gave insight into the role of the chloride salt used [4]. Additionally, the cyclic products were evaluated for biological activity.

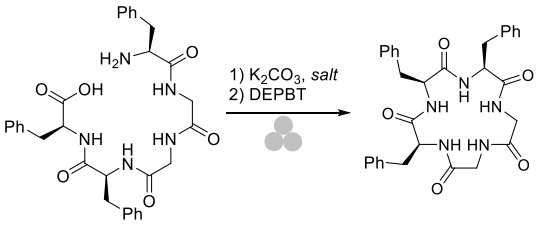

Figure 1. Macrocyclization of linear peptides.

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REFERENCES

[1] X. Ji *et al.*, *Angew. Chem. Int. Ed.* **63** (2024) e202308251
[2] V. Martí-Centelles *et al.*, *Chem. Rev.* **115** (2015), 8736–8834.
[3] N. Vidović *et al.*, *Org. Lett.* **22** (2020) 2129–2134.
[4] M. Duvnjak *et al.*, *ACS Sustainable Chem. Eng.* **13** (2025) 30–35.