

## Poster Presentation

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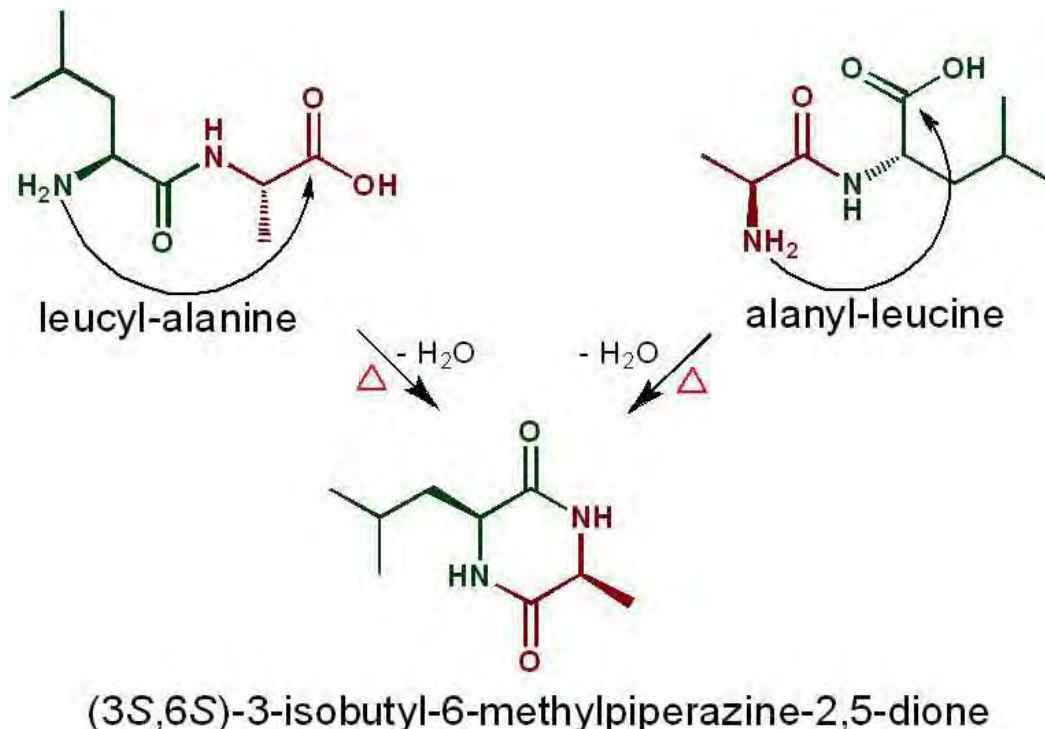
### Solid state intramolecular cyclization of leucyl-alanine and alanyl-leucine

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Solid state organic synthesis is a future alternative to traditional, solution-based laboratory and industrial synthetic procedures. Solvent-free synthetic methods allow for quantitative yields, high stereospecificity, need no solvent, and are easy to conduct. They may contribute to green economy by reducing pollution, cutting the consumption of energy, and lowering the cost of production of various organic compounds. Although solid state reactions have been reported for almost all main classes of organic compounds and reaction types[1], the reactivity of peptides in the solid state has not been well explored. One potential product of the solid state transformation of dipeptides is 2,5-diketopiperazines (DKPs), the cyclic forms of dipeptides. They have attracted attention due to their high biological activity and use in medicinal chemistry[2,3]. In this study, we investigated the thermally induced intramolecular cyclization of leucyl-alanine and alanyl-leucine in the solid state. The reaction was conducted in a range of experimental conditions using thermogravimetric analyzer (TGA), differential scanning calorimeter (DSC), and gas chromatograph - mass spectrometer (GC-MS). The progress of the reaction was observed in situ through monitoring the release of water (mass loss and infra-red spectra) as well as the characterization of the solid residue (1H and 13C NMR, powder and single crystal XRD). The scalability of the reaction was tested with larger samples using a ventilation oven, and a microwave reactor. We found that the both dipeptides easily undergo the cyclization reaction upon mild heating, to give a stereospecific product with ~100% yield. However, the study was complicated with polymorphism displayed by the cyclic product. The solid state reaction yielded an orthorhombic form of the cyclic dipeptide, while its recrystallization produced a triclinic polymorph. The crystal structure and relative stability of the forms were investigated with XRD and DSC techniques. When the solid-state reaction was conducted at higher temperature, partial racemization and distereomerization were observed which led to new crystal structures. The degree of racemization was evaluated by a polarimeter and the NMR analysis.

[1] F. Toda (ed), *Organic solid-state reactions* (Dordrecht: Springer), 2002, VII, 275 p, [2] M. Martins, I. Carvalho, *Tetrahedron*, 2007, 63, 9923–9932, [3] A. Borthwick, *Chem. Rev.*, 2012, 112, 3641-3716



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