Efficient Synthesis of Tag-Modified Peptide Thioester Facilitated by γ-Substituted Proline

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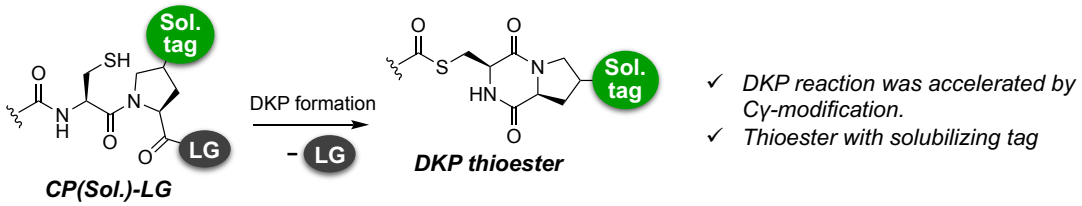
Native chemical ligation (NCL) is an effective strategy to ligate side-chain unprotected peptide segments between an N-terminal cysteine peptide and a C-terminal peptide thioester in neutral aqueous conditions.[1] To introduce a base-liable thioester moiety through Fmoc solid-phase peptide synthesis (SPPS), many thioester surrogates has been designed and reported by peptide chemists. Cysteinyl-prolyl-leaving group (CP-LG) is easily introduced to a peptide in Fmoc Solid-Phase Peptide Synthesis and converts into thioester through diketopiperazine (DKP) formation. The effect of leaving group to reaction rate in DKP formation has been reported intensively.[2–4] However, few studies have reported the effect of other substitutions to DKP formation. Proline substitutions at Cγ position greatly affect the cis-trans conversion of prolyl amide and puckering of pyrrolidine ring of proline.[5] We hypothesized that Cγ-modified proline is an effective tool to investigate the nature of DKP formation.

Herein, we will discuss the effect of γ-substitution of proline of CP-LG on DKP formation using CP-pyrazole peptides. Some modifications indicated a great improvement in the rate of DKP reaction. In addition, we report peptide ligation using peptide thioester with solubilizing tag attached to the γ-position of the proline to ease the handling of peptides in ligation reaction and purification steps.



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