Investigation into the Effect of Tertiary Amine and Brønsted Acid for Rapid Formation and Amidation of Mixed Anhydride Using a Micro-Flow Reactor

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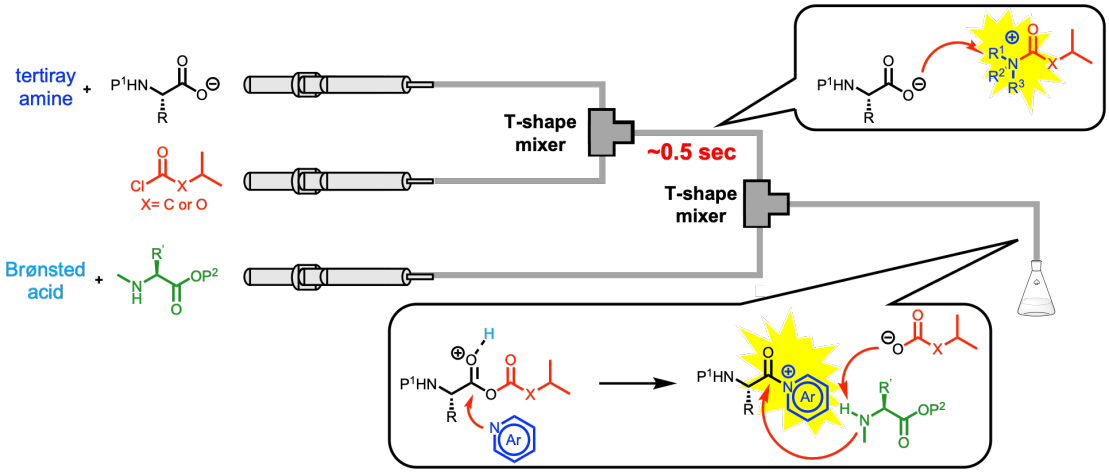
In recent years, there has been a growing interest in therapeutic peptides. Development of efficient synthetic processes for peptides has become increasingly important. The first chemical peptide synthesis, reported by Curtius in 1882 includes generation of a mixed anhydride from a carboxylic acid and benzoyl chloride, and its use for following peptide bond formation. In 1951, generation of a mixed carbonic anhydride from a carboxylic acid and an alkyl chloroformates, and its use for following peptide bond formation was reported by three independent groups. Because of the advantage in short reaction time, ease of purification, and low cost, this methodology is very useful, although it has a high risk of epimerization.

We have reported micro-flow peptide syntheses via formation of mixed carbonic anhydrides,[1)-2)] and the undesired reaction was successfully avoided by precise control of reaction time and temperature by micro-flow technology. We observed that the tertiary amines and/or Brønsted acids have a great effect on mixed carbonic anhydride formation and amidation.[2)] On the other hand, those effects for mixed anhydride formation and amidation has not been well studied. In this study, we examined the effect of tertiary amines and Brønsted acids on the formation of mixed anhydride and mixed carbonic anhydride, and the following peptide bond formation in a micro-flow reactor.



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