Peptide Ligation between α-Amidonitrile and N-terminal Cysteine

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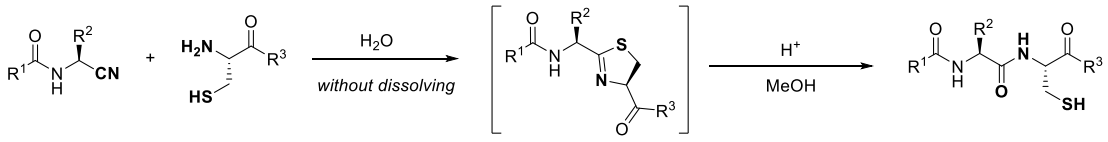
Peptides and proteins are essential components in living organisms and play unparalleled central functions. Chemical synthesis represents one of the most reliable access to obtain the desired peptides and proteins with respect to quality and quantity. Native chemical ligation originated by Kent's group in 1994 is one of the most widely used synthetic methods.[1] It leads to a native cysteine amide bond by reacting one peptide bearing a carboxylic end with the other having a cysteine terminal. Even though this method requires a N-terminal cysteine and additional thiol to form thiol ester first from the carboxy end, native chemical ligation still holds its practically useful position. As continued interests of oxidative amide synthesis using dicyano compounds,[2] we recently extended this method to an efficient synthesis of tripeptides and tetrapeptides with formation of glycine amino amide bond at the ligation site in aqueous media. During this investigation, we found a rapid and selective reaction of cyano group and cysteine methyl ester. We then focused on a more general peptide ligation method inspired by this discovery.

α-Amidonitrile was found to react efficiently with cysteine-terminated peptide using water as the only dispersing media, even though the two substrates do not dissolve completely. This organic solvent-free coupling reaction affords thiazoline as an intermediate and it can be further hydrolyzed to give a cysteine amide linked peptide. Gratifyingly, the two-step sequence can be conducted in one pot. As like the native chemical ligation, a cysteine residue is necessary to achieve the ligation. However, this method realizes a much simpler reaction system by exempting additional thiol additive, which is a green and atom-economical synthetic method and provides an alternative to native chemical ligation.



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