



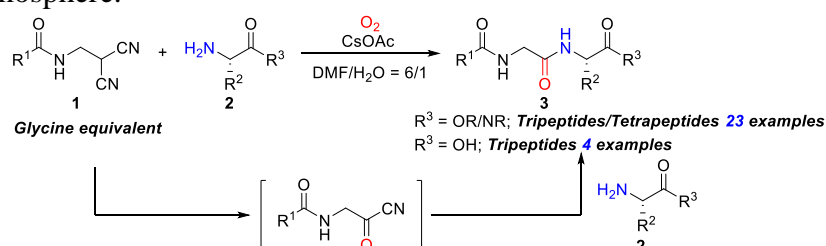
2- (アミノメチル) マロノニトリルを用いるグリシン-アミノ酸の
酸化的ペプチド結合生成

**Oxidative peptide bond formation of glycine-amino acid using 2-
(aminomethyl)malononitrile as a glycine unit**

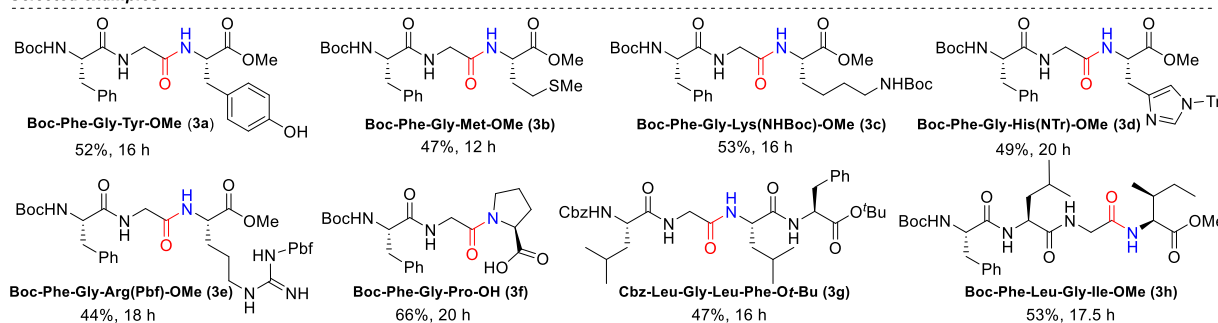
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Recently, peptides and proteins have gained growing attention both in fundamental research and drug discovery, making a great demand in an efficient access to these molecules. However, the current state of the art of peptide synthesis involves usually expensive coupling reagents and has little focus on atom efficiency. An ideal synthesis of peptides proceeds without coupling reagents, with minimum waste generation and in aqueous condition. Because of our continuous interests of oxidative amide synthesis using dicyano compounds,¹ we extend it to an efficient assembly of tripeptides and tetrapeptides with a formation of a glycine amino amide bond at the coupling site in aqueous media.²

When 2-(aminomethyl)malononitrile **1** is treated with amine **2** in the presence of CsOAc under O₂ atmosphere using DMF/H₂O in 6/1 ratio as solvent, amide bond formation occurs to afford the peptide **3** in good yield without coupling reagents or catalyst. The reaction is thought to proceed via an acyl cyanide intermediate. The reaction has a wide generality, which is effective for the preparation of tripeptides and tetrapeptides with various side chains on the amine substrates having a protected or unprotected carboxylic acid group. It is not necessary to protect the phenol moiety of tyrosine (**3a**). The methyl sulfide moiety of methionine (**3b**) is inert even under an O₂ atmosphere.



Selected examples



<参考文献>

- 1) J. Li, M. Lear, Y. Hayashi, *Angew. Chem. Int. Ed.* **2016**, *55*, 9060.
- 2) X. Wang, J. Li, Y. Hayashi, *Chem. Commun.* **2021**, *57*, 4283.

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