Site-selective Tyrosine modification using hypervalent iodine(V) reagents

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The emerging interest in chemical modifications of peptides in pharmaceutical and bio-material science has shown the need to develop an effective method for site-selective or residue specific transformations. Classical approaches focus on the modification of lysine or cysteine residues, often leading to selectivity issues due to the abundance of such motifs in proteins. Therefore, there has recently been a shift to the development of new methods targetting other amino acid residues. Among them, tyrosine has emerged as a good target due to its low abundance and its relatively low surface-exposure, making it an ideal target for site-selective modifications.[1,2] While there are numerous enzymatic methods to modify tyrosine,[3] synthetic chemical modifications to introduce new functionalities on tyrosine residues remains a challenge.

Herein, we report a site-selective tyrosine modification strategy under mild conditions. Tyrosine was selectively oxidised with hypervalent iodine reagents to generate highly reactive *o*-quinones *in situ*,[4] which were trapped with diamine in a one-pot process to yield quinoxalines. The quinoxalines on a peptide framework have the ability to function as fluorescent probes, imitate natural amino acids, and display a wide range of pharmacological properties. The reaction proceeds with excellent selectivity for tyrosine residues in di-, tri-, and oligopeptides under mild conditions, tolerating potentially problematic functionalities.

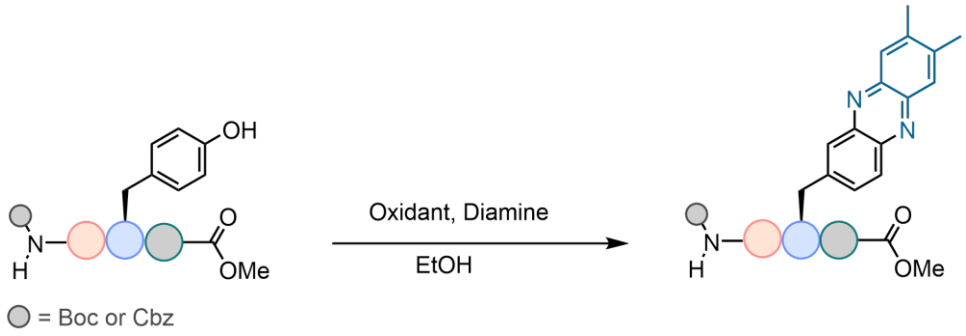

Figure 1. Tyrosine containing peptide modifications.

[1] N. Declas, S. Götze, J. L. Sprague, P. Stallforth, S. Matile, J. Waser, Chemical science **2022**, 13, 12808.
[2] W. Zeng, Q. Zhu, Biotechnology and bioengineering **2024**, 121, 799.
[3] A. J. Gross, I. W. Sizer, Journal of Biological Chemistry **1959**, 234, 1611.
[4] R. Bernini, R. Saladino, Tetrahedron Letters **2009**, 50, 6519.