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Propargyl-Assisted Selective Amidation Applied in C-terminal Glycine Peptide Conjugation

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Abstract

© 2016 Wiley-VCH Verlag GmbH & Co. KGaA, WeinheimAlkyl esters, such as propargyl esters, typically lack the electron-withdrawing inductive effects needed to participate in nucleophilic acyl substitution reactions. Herein, we report an unusual observation in which glycine propargyl ester derivatives displayed selective, base-independent reactivity towards linear alkylamines under mild, metal-free conditions. Through global reaction route mapping (GRRM) modeling calculations, it is predicted that these observations may be governed by factors related to hydrogen-bonding and intermolecular interactions, rather than electron-withdrawing inductive effects. Based on this concept of propargyl-assisted selective amidation, a direct application was made to develop a novel site-specific C-terminal glycine peptide bioconjugation technique as a proof-of-concept, which relies upon the selective reactivity of glycine propargyl esters over that of aspartate and glutamate side-chain-linked propargyl esters.

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Keywords

amides, hydrogen bonds, peptides, propargyl esters, selective amidation