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Design and synthesis of a hydrogen peroxide-responsive amino acid that induces peptide bond cleavage after exposure to hydrogen peroxide

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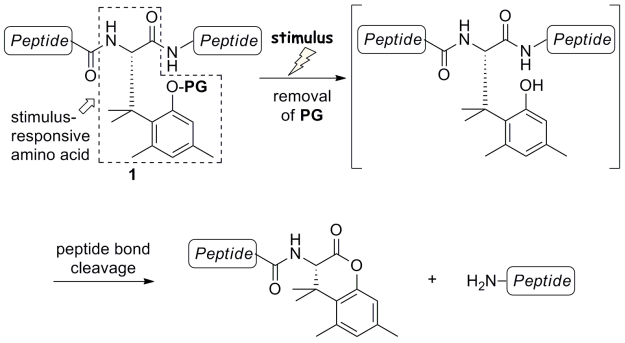
ABSTRACT

Oxidative stress-responsive compounds are attracting significant attention in the field of medicinal chemistry and chemical biology. Here, we disclose the development of a hydrogen peroxide (H_2O_2)-responsive amino acid that induces peptide bond cleavage in the presence of H_2O_2 that closely relates to the oxidative stress. The H_2O_2-responsive amino acid possessing a boronate or boronic acid moiety was incorporated into a peptide using Fmoc-based solid-phase peptide synthesis or that with minor modification, respectively, and the peptide bond cleavage of the obtained peptide was successfully triggered by the addition of H_2O_2.

1. Introduction

Reactive oxygen species (ROS) play a wide variety of roles in health and disease.[1] Hydrogen peroxide (H_2O_2) is one of the ROS and its controlled generation is essential for living organisms, e.g., cellular signalling[2] and removal of invading pathogens.[3] Loss of ROS regulation, however, can cause oxidative damage to cellular components, and thereby H_2O_2 is thought to be involved in numerous diseases and aging.[4] Cancer is an oxidative stress related disease and production of ROS in most cancer cells is known to be elevated.[5] For example, the intracellular concentration of H_2O_2 in cancer cells was estimated to be much higher than that in normal cells (in cancer cells: 10 to 100 μM; in normal cells: up to 0.7 μM).[6] Therefore, it is of interest to develop H_2O_2-responsive fluorophores,[7] prodrugs,[6a,8] and drug carriers[9] to detect and treat cancer. With these in mind, we decided to prepare an H_2O_2-responsive amino acid that induces peptide bond cleavage in the presence of H_2O_2, because it would potentially be applicable to the development of oxidative stress-responsive peptidyl prodrugs and drug carriers.



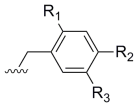
stimulus	PG	R_1	R_2	R_3
ultraviolet		NO_2	H	H
near-infrared two-photon excitation		NO_2	OMe	OMe
fluoride		H	OTBDPS	H
hypoxia		H	NO_2	H
thiol	4-nitrobenzenesulfonyl	-	-	-
phosphatase	phosphate	-	-	-

Figure 1. Stimulus-responsive peptide bond cleavage system (**PG**: a protective group that can be removed by an appropriate stimulus; TBDPS: *t*-butyldiphenylsilyl).

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