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Development of a solid-phase catch-release linker system for cysteine alkylation

Manal Alanazi[1], **Sam Butterworth**[2] and **Francisco Fernandez-Trillo**[1]
[1]University of Birmingham, UK
[2]University of Manchester, UK

The modification of proteins with chemical species provides a wide range of opportunities to study, alter or exploit protein function. For example, antibody drug conjugates are currently receiving significant attention as tools to allow the selective delivery of therapeutic agents to specific cell types. The selective modification of proteins represents a significant chemical challenge because the reaction must modify the targeted residue selectively in the presence of other competing unprotected polypeptide side chains. Developing a solid phase catch release system could provide clean products of alkylated cysteine thiols, based on liberation of the alkylated protein under mild conditions. We have developed a novel system containing a thiol reactive group (iodoacetamide) attached to the standard solid support (agarose) *via* a linker that can be readily cleaved in the presence of the catalytic palladium. Initial studies focused on allyl deprotection reaction scope using catalytic palladium under mild conditions. An allyl carbamate was selected as the linker due to its general stability and relatively straightforward deprotection with catalytic palladium in aqueous conditions. Based on this we have developed a synthesis of the completed catch-release linker system in six steps. Having the allyl carbamate alkylating linker in hand we turned our attention to immobilize it into the solid support. The allyl carbamate alkylating linker immobilized into NHS-agarose by amide linker. This system has been studied using standard proteins (BSA) to evaluate the use of catch-release methodology to selectively cysteine alkylation in combine with a second solid phase reducing agent to allow the direct reduction and alkylation of the protein (scheme 1). BSA has been alkylated and separated from the unreacted protein simply by filtration. Unfortunately, the release of alkylated BSA from the solid support by using catalytic palladium has not proceeded as expected from the model system, this step is currently under investigation.

MMA361@STUDENT.BHAM.AC.UK